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(54) Title: IMPROVED ANTI-SERUM ALBUMIN BINDING VARIANTS

(57) Abrégé/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.

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(54) **Title**: IMPROVED ANTI-SERUM ALBUMIN BINDING VARIANTS

(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.

# IMPROVED ANTI-SERUM ALBUMIN BINDING VARIANTS

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.

## 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, e.g., ligands comprising an anti-SA dAb and a dAb that specifically binds a target antigen, such as TNFR1. Binding moieties are disclosed that specifically bind serum albumins from more than one species, e.g. human/mouse cross-reactive anti-SA dAbs.

WO05118642 and WO2006/059106 disclose the concept of conjugating or associating an anti-SA binding moiety, 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 new chemical entity (NCE ) drugs are disclosed and exemplified. WO2006/059106 discloses the use of this concept to increase the half-life of insulintropic agents, e.g., 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, pp283-288, 2008.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 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 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-SA 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, e.g., a dAb, that 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 (e.g., TNFR1) on the cell surface, thus increasing the likelihood of receptor agonism and detrimental receptor signaling.

A number of improved dAbs are disclosed in PCT/EP2010/052008 and PCT/EP2010/052007 the disclosures of which are incorporated by reference.

It would also be desirable to provide improved dAbs that have an improved stability. This would be advantageous in allowing a dAb to have a suitable stability profile or shelf-life. In particular, it would be desirable to provide dAbs having an improved ability to resist unfolding upon exposure to elevated temperatures i.e. improved thermostability. It would also be desirable to provide dAbs that have improved stability when formatted into constructs such as multi-specific ligands or when conjugated to proteins, peptides or NCEs.

## SUMMARY OF THE INVENTION

Aspects of the present invention solve these problems.

To this end, the present inventors surprisingly found that mutations can be made to immunoglobulin single variable domain molecules of the DOM7h-11 lineage to give the molecules improved stability as measured by an improved thermostability relative to the parent DOM7h-11 molecules.

In one aspect, there is provided an anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-11 (DOM7h-11 as shown in Figure 1), said

variant having a $T_m$ of at least 54°C. In another aspect, there is provided an anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-11 (DOM7h-11 as shown in Figure 1), said variant having a $T_m$ of greater than 54°C. The transition midpoint ($T_m$) is the temperature where 50% of the protein is in its native conformation and the other 50% is denatured. Suitably said $T_m$ is measured by Differential Scanning Calorimetry.

In one embodiment, said variant comprises at least one mutation in any of positions 22, 42 or 91 (numbering according to Kabat) compared to DOM7h-11. Suitably, an anti-SA immunoglobulin single variable domain variant is a variant of DOM7h-11-15 (DOM7h-11-15 as shown in Figure 1 (SEQ ID NO: 7) and comprises at least one mutation in any of positions 22, 42 or 91 (numbering according to Kabat) compared to DOM7h-11-15. In one embodiment, a variant comprises at least one mutation selected from the following:

Position 22 = Ser, Phe, Thr, Ala or Cys;
Position 42 = Glu or Asp;
Position 91 = Thr or Ser;

In other embodiments, there is provided an anti-SA immunoglobulin single variable domain variant wherein position 22 is Ser or Phe; an anti-SA immunoglobulin single variable domain variant wherein position 42 is Glu and position 91 is Thr; an anti-SA immunoglobulin single variable domain variant wherein position 91 is Thr; an anti-SA immunoglobulin single variable domain variant wherein position 22 is Phe. In one embodiment, position 108 is Trp.

Further embodiments provide a variant comprising an amino acid sequence that is identical to the amino acid sequence of a single variable domain selected from DOM7h-11-56 (SEQ ID NO: 412), DOM7h-11-68 (SEQ ID NO: 416), DOM7h-11-79 (SEQ ID NO:418) and DOM7h-11-80 (SEQ ID NO: 419) (or a variant having an amino acid that is at least 95, 96, 97, 98 or 99% identical to the amino acid sequence of the

selected amino acid sequence) or has up to 4 changes compared to the selected amino acid sequence.

In particular, it has been found that mutations targeted to the FW3 (positions 57 to 88, numbering according to Kabat) and CDR3 regions (positions 89 to 97, numbering according to Kabat) of DOM7h-11 confer improved stability. Accordingly, in another embodiment, there is provided an anti-SA immunoglobulin single variable domain variant in accordance with an aspect of the invention wherein the variant comprises at least one mutation in the FW3 region (positions 57 to 88, numbering according to Kabat) or in the CDR3 region (positions 89 to 97, numbering according to Kabat) compared to DOM7h-11.

Further embodiments provide an anti-SA immunoglobulin single variable domain variant wherein said variant is a variant of DOM7h-11-15 (DOM7h-11-15 as shown in Figure 1) and comprises at least one mutation in the FW3 region (positions 57 to 88, numbering according to Kabat) or in the CDR3 region (positions 89 to 97, numbering according to Kabat) compared to DOM7h-11-15. Suitably, said variant comprises at least one mutation at any of positions 77, 83, 93 or 95 (numbering according to Kabat).

In one embodiment, the variant comprises at least one mutation selected from the following:

Position 77 = Asn, Gln

Position 83 = Val, Ile, Met, Leu, Phe, Ala or Norleucine.

Position 93 = Val, Ile, Met, Leu, Phe, Ala or Norleucine.

Position 95 = His, Asn, Gln, Lys or Arg.

In another embodiment, an anti-SA immunoglobulin single variable domain in accordance with the invention further comprises a mutation at position 106 or 108 (numbering according to Kabat). Suitably, position 106 is Asn or Gln. Suitably position 108 is Trp, Tyr or Phe.

In further embodiments, there is provided an anti-SA immunoglobulin single variable domain variant wherein position 77 is Asn; an anti-SA single variable domain wherein position 83 is Val; an anti-SA single variable domain wherein position 95 is

His; an anti-SA single variable domain wherein position 95 is His; an anti-SA single variable domain wherein position 93 is Val.

In yet further embodiments, there is provided a variant comprising an amino acid sequence that is identical to the amino acid sequence of a single variable domain selected from DOM7h-11-57 (SEQ ID NO: 413), DOM7h-11-65 (SEQ ID NO: 414) or DOM7h-11-67 (SEQ ID NO:415) (or a variant having an amino acid that is at least 95, 96, 97, 98 or 99% identical to the amino acid sequence of the selected amino acid sequence) 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 FW3 or CDR3 region.

In further embodiments, there is provided a variant comprising an amino acid sequence that is identical to the amino acid sequence of a single variable domain selected from DOM7h-11-69 (SEQ ID NO: 417), DOM 7h-11-90 (SEQ ID NO: 420), DOM 7h-11-86 (SEQ ID NO: 421), DOM 7h-11-87 (SEQ ID NO: 422), or DOM 7h-11-88 (SEQ ID NO: 423) (or a variant having an amino acid that is at least 95, 96, 97, 98 or 99% identical to the amino acid sequence of the selected amino acid sequence).

Suitably a variant has a $T_m$ of at least 57°C. In another embodiment, a variant has a $T_m$ of greater than 57°C.

In one embodiment, a variant in accordance with any embodiment of the invention has an increased $T_m$ value compared to DOM7h-11. In another embodiment, said variant has an increased $T_m$ value compared to DOM7h-11-15. In another embodiment, there is provided a variant comprising any combination of any of the mutations listed above. Suitably, $T_m$ is measured by DSC in accordance with the methods described herein.

Suitably, a variant in accordance with the invention comprises a binding site that specifically binds human SA with a dissociation constant (KD) of from about 0.1 to about 10000 nM, optionally from about 1 to about 6000 nM, as determined by surface plasmon resonance. The variant of any preceding claim, wherein the variant comprises a binding site that specifically binds human SA with an off-rate constant ($K_d$) of from about $1.5 \times 10^{-4}$ to about 0.1 $sec^{-1}$, optionally from about $3 \times 10^{-4}$ to about 0.1 $sec^{-1}$ as

determined by surface plasmon resonance. The variant of any preceding claim, wherein the variant comprises a binding site that specifically binds human SA with an on-rate constant ($K_a$) of from about 2 x $10^6$ to about 1 x $10^4$ $M^{-1}sec^{-1}$, optionally from about 1 x $10^6$ to about 2 x $10^4$ $M^{-1}sec^{-1}$ as determined by surface plasmon resonance.

Advantageously, the variant in accordance with the invention is cross-reactive with serum albumin from a number of different species such as, for example, monkey e.g. Cynomolgus monkey, suncus (shrew), marmoset, ferret, rat, mouse, pig and dog SA.

Accordingly, in one embodiment, the variant in accordance with the invention comprises a binding site that specifically binds *Cynomolgus* monkey SA with a dissociation constant (KD) of from about 0.1 to about 10000 nM, optionally from about 1 to about 6000 nM, as determined by surface plasmon resonance. The variant of any preceding claim, 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 x $10^{-4}$ to about 0.1 $sec^{-1}$, optionally from about 3 x $10^{-4}$ to about 0.1 $sec^{-1}$ as determined by surface plasmon resonance. The variant of any preceding claim, wherein the variant comprises a binding site that specifically binds *Cynomolgus* monkey SA with an on-rate constant ($K_a$) of from about 2 x $10^6$ to about 1 x $10^4$ $M^{-1}sec^{-1}$, optionally from about 1 x $10^6$ to about 5 x $10^3$ $M^{-1}sec^{-1}$ as determined by surface plasmon resonance. In another aspect, there is provided a multispecific ligand comprising an anti-SA variant in accordance with the invention and a binding moiety that specifically binds a target antigen other than SA. Suitable target antigens are exemplified herein. In one embodiment, the binding moiety that specifically binds a target antigen may be another single domain immunoglobulin molecule. In another embodiment, the binding moiety that specifically binds a target antigen may be a monoclonal antibody. Suitable formats and methods for making dual specific molecules, such as mAbdAb molecules are described, for example in WO2009/068649.

An aspect of the invention provides a fusion product, e.g., 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. In another aspect, there is provided a fusion protein, polypeptide fusion or conjugate comprising a polypeptide or peptide drug fused to an anti-serum albumin dAb variant in accordance with the invention, optionally wherein the selected variant is DOM7h-11-56 (SEQ ID NO: 412), DOM7h-11-57 (SEQ ID NO: 413), DOM7h-11-65 (SEQ ID NO: 414), DOM7h-11-67 (SEQ ID NO:415), DOM7h-11-68 (SEQ ID NO:416), DOM7h-11-69 (SEQ ID NO: 417), DOM7h-11-79 (SEQ ID NO:418), DOM7h-11-80 (SEQ ID NO: 419), DOM 7h-11-90 (SEQ ID NO: 420), DOM 7h-11-86 (SEQ ID NO: 421), DOM 7h-11-87 (SEQ ID NO: 422), or DOM 7h-11-88 (SEQ ID NO: 423). Suitably, such a fusion protein comprises a linker (e.g., a linker comprising the amino acid sequence TVA, optionally TVAAPS (SEQ ID NO: 437) between the variant and the drug.

In one embodiment, there is provided a polypeptide fusion or conjugate comprising an anti-serum albumin dAb as disclosed herein and an incretin or insulinotropic agent, e.g., exendin-4, GLP-1(7-37), GLP-1(6-36) or any incretin or insulinotropic 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.

In another aspect, there is provided an anti-SA variant single variable domain in accordance with the invention, wherein the variable domain is conjugated to a drug (optionally an NCE drug), optionally wherein the selected variant is DOM7h-11-56 (SEQ ID NO: 412), DOM7h-11-57 (SEQ ID NO: 413), DOM7h-11-65 (SEQ ID NO: 414), DOM7h-11-67 (SEQ ID NO:415), DOM7h-11-68 (SEQ ID NO:416), DOM7h-11-69 (SEQ ID NO: 417), DOM7h-11-79 (SEQ ID NO:418), DOM7h-11-80 (SEQ ID NO: 419), DOM 7h-11-90 (SEQ ID NO: 420), DOM 7h-11-86 (SEQ ID NO: 421), DOM 7h-11-87 (SEQ ID NO: 422), or DOM 7h-11-88 (SEQ ID NO: 423).

In another aspect there is provided a composition comprising a variant, fusion protein or ligand of any preceding claim and a pharmaceutically acceptable diluent, carrier, excipient or vehicle.

In a further aspect, there is provided a nucleic acid comprising a nucleotide sequence encoding a variant according to the invention or a multispecific ligand or

fusion protein in accordance with the invention. Suitably, there is provided a nucleic acid comprising the nucleotide sequence of a DOM7h-11 variant selected from the nucleotide sequence of DOM7h-11-56 (SEQ ID NO: 425), DOM7h-11-57 (SEQ ID NO: 426), DOM7h-11-65 (SEQ ID NO: 427), DOM7h-11-67 (SEQ ID NO:428), DOM7h-11-68 (SEQ ID NO:429), DOM7h-11-69 (SEQ ID NO: 430), DOM7h-11-79 (SEQ ID NO:431), DOM7h-11-80 (SEQ ID NO: 432), DOM 7h-11-90 (SEQ ID NO: 433), DOM 7h-11-86 (SEQ ID NO: 434), DOM 7h-11-87 (SEQ ID NO: 435), or DOM 7h-11-88 (SEQ ID NO: 436) or a nucleotide sequence that is at least 80% identical to said selected sequence.

Another aspect provides a vector comprising a nucleic acid in accordance with the invention. A further aspect provides an isolated host cell comprising a vector of the invention.

In a further aspect there is provided a method of treating or preventing a disease or disorder in a patient, comprising administering at least one dose of a variant in accordance with any aspect or embodiment of the invention to said patient.

## BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: Amino-acid sequence alignment for DOM7h-11 variant dAbs. A "." at a particular position indicates the same amino as found in DOM7h-11 at 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).

Figure 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 x $10^{-B}$ and C e D means C x $10^{D}$.

The overall kinetic ranges in various species, as supported by the 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 (e.g., 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 (e.g., chronic or acute) to be treated therapeutically.

Figure 3: Amino-acid (A) and nucleic acid (B) sequence alignment for DOM7h-11-15 variant dAbs. A "." at a particular position indicates the same amino as found in DOM7h-11-15 at that position.

## 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) 4$^{th}$ 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) 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 assay) can be inhibited with an antagonist of TNFR1.

A "patient" is any animal, e.g., a mammal, e.g., 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 , 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 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 (*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 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 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 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" 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, 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* $V_{HH}$ dAbs. *Camelid* $V_{HH}$ are immunoglobulin single variable domain polypeptides that are derived from species including camel, llama, alpaca, dromedary, and guanaco, which produce heavy chain antibodies naturally devoid of light chains. The $V_{HH}$ may be humanized.

A "domain" is a folded protein structure which has tertiary structure independent of the rest of the protein. Generally, domains are responsible for discrete functional properties of proteins, and in many cases may be added, removed or transferred to other proteins without loss of function of the remainder of the protein and/or of the 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 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 domain.

A "lineage" refers to a series of immunoglobulin single variable domains that are derived from the same "parental" clone. For example, a lineage comprising a number of variant clones may be generated from a parental or starting immunoglobulin

single variable domain by diversification, site directed mutagenesis, generation of error prone or doped libraries. Suitably binding molecules are generated in a process of affinity maturation. In the present invention, reference is made to "DOM7h-11" which is an anti-SA immunoglobulin single variable domain described in PCT/EP2010/052008 and PCT/EP2010/052007. DOM7h-11-15 is one of the DOM7h-11 lineage derived from DOM7h-11 parental clone, as described herein.

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 protective composition after disease or condition symptoms become manifest. "Suppression" or "suppressing" refers to 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 (e.g., 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, 2nd 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 (t½ alpha and t½ beta) and AUC can be determined from a curve of serum concentration of ligand against time. The WinNonlin analysis package, e.g. version 5.1 (available from Pharsight Corp., Mountain View, CA94040, 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 tα 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 tα 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 tβ 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 tβ half–life is (or is about) up to and including 21 or 25

days. In one embodiment, the upper end 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 tβ half life in the range 12 to 60 hours (or about 12 to 60 hours). In a further embodiment, it will be in the range 12 to 48 hours (or about 12 to 48 hours). In a further embodiment still, it will be in the range 12 to 26 hours (or about 12 to 26 hours).

As an alternative to using two-compartment modeling, the skilled person will be familiar with the use of non-compartmental 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, e.g. version 5.1 (available from Pharsight Corp., Mountain View, CA94040, 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 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 is about) from 8 hours to 60 hours, or 8 hours to 48 hours or 12 to 120 hours, e.g., 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) up to 600 mg.min/ml. In one embodiment, the upper end of the range is (or is about) 500, 400, 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 150 mg.min/ml, 15 to 100 mg.min/ml, 15 to 75 mg.min/ml, and 15 to 50mg.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 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 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 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 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, e.g., a scaffold selected from the group consisting of CTLA-4, lipocalin, SpA, an adnectin, affibody, an avimer, GroEl, 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 at position 22, 42 or 91(numbering according to Kabat) compared to DOM7h-11. In one embodiment, the variant comprises at least one mutation at position 22, 42 or 91(numbering according to Kabat) compared to DOM7h-11-15. Suitably a variant in accordance with the invention has 1, 2, 3 or up to 8 changes compared to the amino acid sequence of DOM7h-11 or DOM7h-11-15.

In another 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 framework region 3 (FW3) (amino acids 57-88) or complementarity determining region 3 (CDR3) (amino acids 89-97) compared to DOM7h-11, and wherein the variant has 1, 2, 3 or up to 8 changes compared to the amino acid sequence of DOM7h-11. In one embodiment, the variant comprises at least one mutation at these positions compared to DOM7h11-15.

In one embodiment, the mutations at any of these positions are mutations to residues as exemplified in the Examples section herein. In another embodiment, mutations are to conservative amino acids substitutions of the exemplified residues.

Conservative amino acid substitutions are well know to the person skilled in the art and are exemplified by the following table:

| Amino Acid Substitution | | |
|---|---|---|
| Original Residues | Exemplary Substitutions | Preferred Substitutions |
| Ala | Val, Leu, Ile | Val |
| Arg | Lys, Gln, Asn | Lys |
| Asn | Gln | Gln |
| Asp | Glu | Glu |
| Cys | Ser, Ala | Ser |
| Gln | Asn | Asn |
| Glu | Asp | Asp |
| Gly | Pro, Ala | Ala |
| His | Asn, Gln, Lys, Arg | Arg |
| Ile | Leu, Val, Met, Ala, Phe, | Leu |

| | | |
|---|---|---|
| | Norleucine | |
| Leu | Norleucine, Ile, Val, Met, Ala, Phe | Ile |
| Lys | Arg, 1,4 Diamino-butyricAcid, Gln, Asn | Arg |
| Met | Leu, Phe, Ile | Leu |
| Phe | Leu, Val, Ile, Ala, Tyr | Leu |
| Pro | Ala | Gly |
| Ser | Thr, Ala, Cys | Thr |
| Thr | Ser | Ser |
| Trp | Tyr, Phe | Tyr |
| Tyr | Trp, Phe, Thr, Ser | Phe |
| Val | Ile, Met, Leu, Phe, Ala, Norleucine | Leu |

Conservative amino acid substitutions may also relate to non-naturally occurring amino acid residues, such as peptidomimetics and other reversed or inverted forms of amino acid moieties which may be incorporated by chemical peptide synthesis.

Thermostability, or thermodynamic stability, is the quality of a substance/protein to resist (ir-)reversible unfolding upon exposure to elevated temperatures.

A measure of thermostability/thermodynamic stability can be made using Differential scanning calorimetry (DSC). DSC is a thermoanalytical technique in which the difference in the amount of energy or heat required to increase the temperature of a sample and reference are measured as a function of temperature. It can be used to study a wide range of thermal transitions in proteins and is useful for determining the melting temperatures as well as thermodynamic parameters. Briefly, the protein is heated at a constant rate of 180 degrees C/hr (at 1mg/mL routinely in PBS) and a detectable heat capacity change associated with thermal denaturation measured. The transition midpoint ($T_m$) 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 determines the apparent transition midpoint ($_{app}T_m$) as most of the proteins examined do

not fully refold. The higher the Tm or appTm, the more stable the molecule. Software packages such as was Origin$^R$ v7.0383 (Origin Lab) can be used to generate $T_m$ values.

In one embodiment of the invention, improved thermostability means an increased or higher $T_m$ compared to the parent molecule. Suitably the parent molecule is DOM7h-11 or DOM7h-11-15. Suitably "improved" thermostability means a $T_m$ value higher than the $T_m$ value of the parent molecule. Suitably "improved thermostability" means at least 54°C or at least 55°C. In one embodiment, "improved thermostability" means at least 57°C. In another embodiment, "improved thermostability" means greater than 55°C or greater than 57°C. Suitably $T_m$ is measured using DSC as described herein.

Improved thermostability in an immunoglobulin single variable domain is desirable as it provides enhanced stability of an immunoglobulin single variable domain or protein. Importantly, enhanced thermostability gives a measure of the likelihood of a protein being developable such that a product comprising that improved immunoglobulin single variable domain will have good stability throughout the production process and/or a suitable stability/shelf-life. Improved thermostability and exemplary methods for measuring it such as circular dichroism spectroscopy are describe, for example, in van der Sloot et al. Protein Engineering, Design and Selection, 2004, vol.17, no. 9, p.673-680 and Demarest et al. J. Mol. Biol. 2004, 335, 41-48.

The molecular basis for improved or higher thermostability may be a higher specific number of intra-molecule hydrogen- and ionic interactions than found in a non- or less-thermostable variant.

An immunoglobulin single variable domain that is shown to have improved thermostability may also, as a direct consequence, give a higher initial expression yield from host cell expression systems. This is because improved thermostability may arise from their being a higher number of intra-molecule interactions which may, in turn, lead to a lower level of misfolding and/or faster kinetics of folding during translation or trans-membrane transport.

In addition, a protein such as an immunoglobulin single variable domain with improved thermostability may display better overall developability as the protein is

more likely to be more resistant to down-stream processes such as increased temperatures and pressure as well as extreme pHs and salt conditions when compared to an immunoglobulin single variable domain with a lower thermostability.

In one embodiment, immunoglobulin single variable domains in accordance with the invention may be used to generate dual or multi-specific compositions or fusion polypeptides. Accordingly, immunoglobulin single variable domains in accordance with the invention may be used in larger constructs. Suitable constructs include fusion proteins between an anti-SA immunoglobulin single variable domain (dAb) and a monoclonal antibody, NCE, protein or polypeptide and so forth. Accordingly, anti-SA immunoglobulin single variable domains in accordance with the invention may be used to construct multi-specific molecules, for example, bi-specific molecules such as dAb-dAb (i.e. two linked immunoglobulin single variable domains in which one is an anti-SA dAb), mAb-dAb or polypeptide-dAb constructs. In these constructs the anti-SA dAb (AlbudAb$^{TM}$) component provides for half-life extension through binding to serum albumin (SA). Suitable mAb-dAbs and methods for generating these constructs are described, for example, in WO2009/068649.

Choosing an anti-SA immunoglobulin single variable domain with enhanced, improved or increased thermostability may be desirable as a starting point for a molecule that is to be made into a fusion protein as single molecules may lose thermostability properties once they are linked into a bi-specific construct. Accordingly, starting with a moiety with a higher thermostability will enable any loss in thermostability to be taken into account such that after a bi (or multi) specific construct is generated, an overall useful thermostability is maintained.

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, 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 ($K_d$) from (or from about) 1.5 x $10^{-4}$ to (or to about) 0.1 $sec^{-1}$ , optionally from (or from about) 3 x $10^{-4}$ 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 x $10^6$ to (or to about) 1 x $10^4$ $M^{-1}sec^{-1}$ , optionally from (or from about) 1 x $10^6$ to (or to about) 2 x $10^4$ $M^{-1}sec^{-1}$ as determined by surface plasmon resonance;

(d) The variant comprises a binding site that specifically binds *Cynomolgus* monkey SA with a dissociation 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 variant comprises a binding site that specifically binds *Cynomolgus* monkey SA with an off-rate constant ($K_d$) from (or from about) 1.5 x $10^{-4}$ to (or to about) 0.1 $sec^{-1}$ , optionally from (or from about) 3 x $10^{-4}$ 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 x $10^6$ to (or to about) 1 x $10^4$ $M^{-1}sec^{-1}$ , optionally from (or from about) 1 x $10^6$ to (or to about) 5 x $10^3$ $M^{-1}sec^{-1}$ 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 x $10^{-3}$ to (or to about) 0.15 $sec^{-1}$ , optionally from (or from about) 9 x $10^{-3}$ 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 x $10^6$ to (or to about) 1 x $10^4$ $M^{-1}sec^{-1}$ , optionally from (or from about) 1 x $10^6$ to (or to about) 3 x $10^4$ $M^{-1}sec^{-1}$ 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 x $10^{-3}$ to (or to about) 0.15 $sec^{-1}$ as determined by surface plasmon resonance; and/or

(l) The variant comprises a binding site that specifically binds mouse SA with an on-rate constant ($K_a$) from (or from about) 2 x $10^6$ to (or to about) 1 x $10^4$ $M^{-1}sec^{-1}$ , optionally from (or from about) 2 x $10^6$ to (or to about) 1.5 x $10^4$ $M^{-1}sec^{-1}$ 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 $K_a$ 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, e.g., the moiety is an antibody, antibody fragment, scFv, Fab, dAb or a binding moiety comprising a non-immunoglobulin 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 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 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 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 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 preferably 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-β1, insulin, IFN-γ, IGF-I, IGF-II, IL-1α, IL-1β, 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 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-1α, MIP-1β, MIP-3α, MIP-3β, MIP-4, myeloid progenitor inhibitor factor-1 (MPIF-1), NAP-2, Neurturin, Nerve growth factor, β-NGF, NT-3, NT-4, Oncostatin M, PDGF-AA, PDGF-AB, PDGF-BB, PF-4, RANTES, SDF1α, SDF1β, 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, TPO, VEGF, VEGF receptor 1, VEGF receptor 2, VEGF receptor 3, GCP-2, GRO/MGSA, GRO-β, GRO-γ, 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, IFN-gamma, MMP-12, CEA, H. pylori, TB, influenza, Hepatitis E, MMP-12, internalizing receptors that are over-expressed on certain cells, such as the epidermal growth factor receptor (EGFR), ErBb2 receptor on tumor cells, an internalising cellular receptor, LDL receptor, FGF2 receptor, ErbB2 receptor, transferrin receptor, PDGF receptor, VEGF receptor, PsmAr, an extracellular matrix protein, elastin, fibronectin, laminin, α1-antitrypsin, tissue factor protease inhibitor, PDK1, GSK1, Bad, caspase-9, Forkhead, an antigen of Helicobacter pylori, an antigen of Mycobacterium 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, e.g., an anti-TNFR1 dAb. Optionally, the ligand has only one anti-TNFR1 binding moiety (e.g., dAb) to reduce the chance of receptor cross-linking.

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 anti-TNFR1 binding moiety or dAb is any such moiety or dAb disclosed in co-pending application PCT/EP2010/052005, 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 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 (e.g., 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 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 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 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-immunoglobulin 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 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 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 through linkers as described above.

An aspect of the invention provides a fusion product, e.g., 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 described above in accordance with the present invention.

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 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 herein) variant which specifically binds to serum albumin, or which specifically binds both human serum albumin and at 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-11-56, DOM7h-11-57, DOM7h-11-65, DOM7h-11-67, DOM7h-11-68, DOM7h-11-69, DOM7h-11-79 and DOM7h-11-80 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.

While the present invention is described with reference to DOM7h-11 variants, it will be appreciated that analogous mutations into other anti-SA immunoglobulin single variable domain lineages may be envisaged.

**SEQUENCES**

**Table 1: Amino Acid Sequences of DOM7h-11 Variant dAbs**

DOM7h-11-12 (SEQ ID NO: 1)
DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILFGSRLQSGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

DOM7h-11-15 (SEQ ID NO: 2)
DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQSGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

DOM7h-11-18 (SEQ ID NO: 3)
DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLIWFGSRLQSGVP

SRFSGSGSGTDFTLTISSLQPEDFATYHCAQAGTHPTTFGQGTKVEIKR

DOM7h-11-19 (SEQ ID NO: 4)
DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILFGSRLQSGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCAQTGTHPTTFGQGTKVEIKR

DOM7h-11-3 (SEQ ID NO: 5)
DIQMTQSPSSLSASVGDRVTITCRASRPIGTTLSWYQQKPGKAPKLLILWNSRLQSGVP
SRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

**Table 2: Nucleotide Sequences of DOM7h-11 Variant dAbs**

DOM7h-11-12 (SEQ ID NO: 6)
GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCG
TGTCACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGATGTTAA GTTGGT
ACCA GCAGAAACCA GGGAAAGCCC CTAAGCTCCT GATCTTGTTT GGTTCCCGG
T TGCAAAGTGG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACAGAT T
TCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG CTACGTACTA CTGT
GCGCAG GCTGGGACGC ATCCTACGAC GTTCGGCCAA GGGACCAAGG TGGAAAT
CAA ACGG

DOM7h-11-15 (SEQ ID NO: 7)
GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCG
TGTCACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGATGTTAA GTTGGT
ACCA GCAGAAACCA GGGAAAGCCC CTAAGCTCCT GATCCTTGCT TTTTCCCGT
T TGCAAAGTGG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACAGAT T
TCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG CTACGTACTA CTGC
GCGCAG GCTGGGACGC ATCCTACGAC GTTCGGCCAA GGGACCAAGG TGGAAAT
CAA ACGG

DOM7h-11-18 (SEQ ID NO: 8)
GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCG
TGTCACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGATGTTAA GTTGGT
ACCA GCAGAAACCA GGGAAAGCCC CAAAGCTCCT GATCTGGTTT GGTTCCCGG
T TGCAAAGTGG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACAGAT T
TCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG CTACGTACCA CTGT
GCGCAG GCGGGGACGC ATCCTACGAC GTTCGGCCAA GGGACCAAGG TGGAAAT
CAA ACGG

DOM7h-11-19 (SEQ ID NO: 9)
GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCG
TGTCACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGATGTTAA GTTGGT
ACCA GCAGAAACCA GGGAAAGCCC CTAAGCTCCT GATCTTGTTT GGTTCCCGG
T TGCAAAGTGG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACGGAT T
TCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG CTACGTACTA CTGT

GCGCAG ACTGGGACGC ATCCCACGAC GTTCGGCCAA GGGACCAAGG TGGAAAT CAA ACGG

DOM7h-11-3 (SEQ ID NO: 10)
GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGAGA CCG TGTCACC ATCACTTGCC GGGCAAGTCG TCCGATTGGG ACGACGTTAA GTTGGT ACCA GCAGAAACCA GGGAAAGCCC CTAAGCTCCT GATCCTTTGG AATTCCCGT T TGCAAAGTGG GGTCCCATCA CGTTTCAGTG GCAGTGGATC TGGGACAGAT T TCACTCTCA CCATCAGCAG TCTGCAACCT GAAGATTTTG CTACGTACTA CTGT GCGCAG GCTGGGACGC ATCCTACGAC GTTCGGCCAA GGGACCAAGG TGGAAAT CAA 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 YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRTERSPVFDYWGQGTLV TVSS

>DOM1h-549 (SEQ ID NO: 14)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVDYEMHWVRQAPGKGLEWVSSISESGTTT YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKRRFSASTFDYWGQGTLVT VSS

>DOM1h-574 (SEQ ID NO: 15)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGGHT YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGHWEPFDYWGQGTLVT VSS

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

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

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

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

>DOM1h-574-9 (SEQ ID NO: 20)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGGHT
YYADSVKGRFTISRDNSKNTLYMQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-10 (SEQ ID NO: 21)
EVQLLESGGGLVQPGGSLRLSCAASGFTFGKYSMGWVRQAPGKDLEWVSQISNTGGHT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-11 (SEQ ID NO: 22)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGGHT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPFDHWGQGTLVT
VSS

>DOM1h-574-12 (SEQ ID NO: 23)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDHT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKYTGRWEPFDYWGQGTLVT
VSS

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

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

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

>DOM1h-574-16 (SEQ ID NO: 27)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-17 (SEQ ID NO: 28)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISNTGDHT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

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

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

>DOM1h-574-25 (SEQ ID NO: 31)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-26 (SEQ ID NO: 32)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFEYWGQGTLVT
VSS

>DOM1h-574-27 (SEQ ID NO: 33)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGTLVT
VSS

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

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

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

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

>DOM1h-574-32 (SEQ ID NO: 38)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-33 (SEQ ID NO: 39)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNSLYLQMNSLRAEDTAVYYCAIYTGRWVPFDNWGQGTLVT
VSS

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

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

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

>DOM1h-574-38 (SEQ ID NO: 43)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-39 (SEQ ID NO: 44)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRR
YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-40 (SEQ ID NO: 45)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFKYWGQGTLVT
VSS

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

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

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

>DOM1h-574-66 (SEQ ID NO: 49)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGTLVT
VSS

>DOM1h-574-67 (SEQ ID NO: 50)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-68 (SEQ ID NO: 51)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT
VSS

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

>DOM1h-574-70 (SEQ ID NO: 53)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAVYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-71 (SEQ ID NO: 54)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGTLVT
VSS

>DOM1h-574-72 (SEQ ID NO: 55)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

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

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

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

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

>DOM1h-574-77 (SEQ ID NO: 60)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-78 (SEQ ID NO: 61)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT
VSS

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

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

>DOM1h-574-85 (SEQ ID NO: 64)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRR
YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWKPFEYWGQGTLVT
VSS

>DOM1h-574-86 (SEQ ID NO: 65)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRR
YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-87 (SEQ ID NO: 66)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRR
YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT
VSS

>DOM1h-574-88 (SEQ ID NO: 67)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTGDRR
YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

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

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

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

>DOM1h-574-93 (SEQ ID NO: 71)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-94 (SEQ ID NO: 72)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAAYYCAIYTGRWPDFDYWGQGTLVT
VSS

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

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

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

>DOM1h-574-98 (SEQ ID NO: 76)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWPDFDYWGQGTLVT
VSS

>DOM1h-574-99 (SEQ ID NO: 77)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWPDFEYWGQGTLVT
VSS

>DOM1h-574-100 (SEQ ID NO: 78)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISAWGDRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

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

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

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

>DOM1h-574-104 (SEQ ID NO: 82)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISDKGTRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

>DOM1h-574-105 (SEQ ID NO: 83)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISETGRRT
YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFDYWGQGTLVT
VSS

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

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

>DOM1h-574-108 (SEQ ID NO: 86)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGPEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-109 (SEQ ID NO: 87)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-110 (SEQ ID NO: 88)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-111 (SEQ ID NO: 89)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT
VSS

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

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

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

>DOM1h-574-115 (SEQ ID NO: 93)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-116 (SEQ ID NO: 94)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRR
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

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

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

>DOM1h-574-119 (SEQ ID NO: 97)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCALYTGRWVSFEYWGQGTLVT
VSS

>DOM1h-574-120 (SEQ ID NO: 98)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAVYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-121 (SEQ ID NO: 99)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCALYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-122 (SEQ ID NO: 100)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTADRR
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

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

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

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

>DOM1h-574-126 (SEQ ID NO: 104)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR
YYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-127 (SEQ ID NO: 105)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISNTADRR
YYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

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

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

>DOM1h-574-130 (SEQ ID NO: 108)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIANTGDRR
YYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-131 (SEQ ID NO: 109)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-132 (SEQ ID NO: 110)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWRPFEYWGQGTLVT
VSS

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

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

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

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

>DOM1h-574-138 (SEQ ID NO: 115)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-139 (SEQ ID NO: 116)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

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

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

>DOM1h-574-142 (SEQ ID NO: 119)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-143 (SEQ ID NO: 120)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDDAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-144 (SEQ ID NO: 121)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQIADTADRR
YYDDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-145 (SEQ ID NO: 122)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQIADTGDRR
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

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

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

EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWGPFVYWGQGTLVT
VSS

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

>DOM1h-574-149 (SEQ ID NO: 126)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWGPFQYWGQGTLVT
VSS

>DOM1h-574-150 (SEQ ID NO: 127)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFQYWGQGTLVT
VSS

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

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

>DOM1h-574-153 (SEQ ID NO: 130)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFQYWGQGTLVT
VSS

>DOM1h-574-154 (SEQ ID NO: 131)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-155 (SEQ ID NO: 132)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-156 (SEQ ID NO: 133)

EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

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

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

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

>DOM1h-574-160 (SEQ ID NO: 137)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTADRT
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWEPFVYWGQGTLVT
VSS

>DOM1h-574-161 (SEQ ID NO: 138)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTADRT
YYSHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

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

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

>DOM1h-574-164 (SEQ ID NO: 141)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTADRT
YYTHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-165 (SEQ ID NO: 142)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-166 (SEQ ID NO: 143)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTADRT
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-167 (SEQ ID NO: 144)
EVQLLESGGGLVQPGGSLRLSCAASGFTFLKYSMGWVRQAPGKGLEWVSQISDTGDRR
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

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

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

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

>DOM1h-574-172 (SEQ ID NO: 148)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTADRT
YYDHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWVPFEYWGQGTLVT
VSS

>DOM1h-574-173 (SEQ ID NO: 149)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTADRR
YYAHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-174 (SEQ ID NO: 150)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQISDTADRR
YYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-175 (SEQ ID NO: 151)
EVQLLESGGGLVQPGGSLRLSCAASGFTFVKYSMGWVRQAPGKGLEWVSQIADTADRR
YYAHAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
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
YYDHSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAIYTGRWAPFEYWGQGTLVT
VSS

>DOM1h-574-179 (SEQ ID NO: 155)
EVQLLESGGGLVQPGGSLRLSCAASGFTFFKYSMGWVRQAPGKGLEWVSQISDTADRR
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

**Table 4: Nucleotide sequences of anti-TNFR1 dAbs**

>DOM1h-509 (SEQ ID NO: 159)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
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GGCTCCAGGGAAGAGTCTAGAGTGGGTCTCAAGTATTGATACTAGGGGTTCGTCTACA
TACTACGCAGACCCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GAAAGCTGTGACGATGTTTTCTCCTTTTTTTGACTACTGGGGTCAGGGAACCCTGGTC
ACCGTCTCGAGC

>DOM1h-510 (SEQ ID NO: 160)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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ACCCTGGTCACCGTCTCGAGC

>DOM1h-543 (SEQ ID NO: 161)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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ACCGTCTCGAGC

>DOM1h-549 (SEQ ID NO: 162)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCATCTATTAGTGAGAGTGGTACGACGACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

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

>DOM1h-574-1 (SEQ ID NO: 164)
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>DOM1h-574-2 (SEQ ID NO: 165)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCTCGAGC

>DOM1h-574-4 (SEQ ID NO: 166)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGGTCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCTCGAGC

>DOM1h-574-180 (SEQ ID NO: 167)
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CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-7 (SEQ ID NO: 168)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCTCGAGC

>DOM1h-574-8 (SEQ ID NO: 169)
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GGCTCCAGGGAAAGGTCCAGAGTGGGTCTCACAGATTTCGAATACGGGTGGTCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-9 (SEQ ID NO: 170)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATATCCCGCGACAATTCCAAGAACA
CGCTGTATATGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-10 (SEQ ID NO: 171)
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>DOM1h-574-11 (SEQ ID NO: 172)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-12 (SEQ ID NO: 173)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-13 (SEQ ID NO: 174)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GAAATATACGGGTCGTTGGGAGCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACC
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>DOM1h-574-14 (SEQ ID NO: 175)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-15 (SEQ ID NO: 176)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCATACA
TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-16 (SEQ ID NO: 177)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCTCGAGC

>DOM1h-574-17 (SEQ ID NO: 178)
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>DOM1h-574-18 (SEQ ID NO: 179)
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>DOM1h-574-19 (SEQ ID NO: 180)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-25 (SEQ ID NO: 181)
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>DOM1h-574-26 (SEQ ID NO: 182)
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>DOM1h-574-27 (SEQ ID NO: 183)
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>DOM1h-574-28 (SEQ ID NO: 184)
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CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
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>DOM1h-574-30 (SEQ ID NO: 186)
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>DOM1h-574-31 (SEQ ID NO: 187)
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>DOM1h-574-32 (SEQ ID NO: 188)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-35 (SEQ ID NO: 190)
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>DOM1h-574-37 (SEQ ID NO: 192)
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>DOM1h-574-38 (SEQ ID NO: 193)
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>DOM1h-574-39 (SEQ ID NO: 194)
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>DOM1h-574-40 (SEQ ID NO: 195)
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CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
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>DOM1h-574-54 (SEQ ID NO: 197)
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GTCACGAGC

>DOM1h-574-65 (SEQ ID NO: 198)
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CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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>DOM1h-574-67 (SEQ ID NO: 200)
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GTCTCGAGC

>DOM1h-574-68 (SEQ ID NO: 201)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGGTGATCGTAGA
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GTCTCGAGC

>DOM1h-574-69 (SEQ ID NO: 202)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGGTGATCGTAGA
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GTCTCGAGC

>DOM1h-574-70 (SEQ ID NO: 203)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCTGATCGTACA
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GTCTCGAGC

>DOM1h-574-71 (SEQ ID NO: 204)
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GTCTCGAGC

>DOM1h-574-72 (SEQ ID NO: 205)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCTGATCGTACA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-73 (SEQ ID NO: 206)
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CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-74 (SEQ ID NO: 207)
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CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-75 (SEQ ID NO: 208)
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GTCTCGAGC

>DOM1h-574-76 (SEQ ID NO: 209)
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GTCTCGAGC

>DOM1h-574-77 (SEQ ID NO: 210)
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GTCTCGAGC

>DOM1h-574-78 (SEQ ID NO: 211)
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TACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-79 (SEQ ID NO: 212)
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GTCTCGAGC

>DOM1h-574-84 (SEQ ID NO: 213)
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TACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCTCGAGC

>DOM1h-574-85 (SEQ ID NO: 214)
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TACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-86 (SEQ ID NO: 215)
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GGCCCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACGGGTGATCGTAGA
TACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAAGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-87 (SEQ ID NO: 216)
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TACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-88 (SEQ ID NO: 217)
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CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-90 (SEQ ID NO: 218)
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CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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>DOM1h-574-91 (SEQ ID NO: 219)
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TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-92 (SEQ ID NO: 220)
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>DOM1h-574-93 (SEQ ID NO: 221)
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GTCTCGAGC

>DOM1h-574-94 (SEQ ID NO: 222)
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TACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-95 (SEQ ID NO: 223)
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TACTACGCAGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-96 (SEQ ID NO: 224)
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TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-97 (SEQ ID NO: 225)
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TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-98 (SEQ ID NO: 226)
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>DOM1h-574-99 (SEQ ID NO: 227)
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>DOM1h-574-100 (SEQ ID NO: 228)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-101 (SEQ ID NO: 229)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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>DOM1h-574-102 (SEQ ID NO: 230)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-103 (SEQ ID NO: 231)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-104 (SEQ ID NO: 232)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCTCGAGC

>DOM1h-574-105 (SEQ ID NO: 233)
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>DOM1h-574-106 (SEQ ID NO: 234)
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TACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-107 (SEQ ID NO: 235)
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>DOM1h-574-108 (SEQ ID NO: 236)
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>DOM1h-574-109 (SEQ ID NO: 237)
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>DOM1h-574-110 (SEQ ID NO: 238)
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>DOM1h-574-111 (SEQ ID NO: 239)
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>DOM1h-574-112 (SEQ ID NO: 240)
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>DOM1h-574-113 (SEQ ID NO: 241)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCTGATCGCAGA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-114 (SEQ ID NO: 242)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTTGAATACTGCTGATCGTACA
TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-115 (SEQ ID NO: 243)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGAATACTGCTGATCGTACA
TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-116 (SEQ ID NO: 244)
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GTCTCGAGC

>DOM1h-574-117 (SEQ ID NO: 245)
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GTCTCGAGC

>DOM1h-574-118 (SEQ ID NO: 246)
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>DOM1h-574-119 (SEQ ID NO: 247)
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>DOM1h-574-120 (SEQ ID NO: 248)
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GTCTCGAGC

>DOM1h-574-121 (SEQ ID NO: 249)
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>DOM1h-574-122 (SEQ ID NO: 250)
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>DOM1h-574-123 (SEQ ID NO: 251)
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GTCTCGAGC

>DOM1h-574-124 (SEQ ID NO: 252)
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GTCTCGAGC

>DOM1h-574-125 (SEQ ID NO: 253)
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GTCTCGAGC

>DOM1h-574-126 (SEQ ID NO: 254)
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GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGAATACGGGTGATCGTAGA
TACTACGCACACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCTCGAGC

>DOM1h-574-127 (SEQ ID NO: 255)
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TACTACGCACACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCTCGAGC

>DOM1h-574-128 (SEQ ID NO: 256)
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TACTACGCACACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCTCGAGC

>DOM1h-574-129 (SEQ ID NO: 257)
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TACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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GTCTCGAGC

>DOM1h-574-130 (SEQ ID NO: 258)
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TACTACGCAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-131 (SEQ ID NO: 259)
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GTCTCGAGC

>DOM1h-574-132 (SEQ ID NO: 260)
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>DOM1h-574-133 (SEQ ID NO: 261)
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>DOM1h-574-134 (SEQ ID NO: 262)
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TACTACTCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-135 (SEQ ID NO: 263)
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TACTACACACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
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GTCTCGAGC

>DOM1h-574-137 (SEQ ID NO: 264)
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TACTACACAGACGCGGTGAAGGGGCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-138 (SEQ ID NO: 265)
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TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-139 (SEQ ID NO: 266)
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TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-140 (SEQ ID NO: 267)
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TACTACGATGACTCTGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
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>DOM1h-574-141 (SEQ ID NO: 268)
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>DOM1h-574-142 (SEQ ID NO: 269)
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>DOM1h-574-143 (SEQ ID NO: 270)
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>DOM1h-574-144 (SEQ ID NO: 271)
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>DOM1h-574-145 (SEQ ID NO: 272)
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>DOM1h-574-146 (SEQ ID NO: 273)
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>DOM1h-574-147 (SEQ ID NO: 274)
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>DOM1h-574-148 (SEQ ID NO: 275)
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>DOM1h-574-149 (SEQ ID NO: 276)
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>DOM1h-574-150 (SEQ ID NO: 277)
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>DOM1h-574-151 (SEQ ID NO: 278)
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>DOM1h-574-152 (SEQ ID NO: 279)
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CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
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>DOM1h-574-153 (SEQ ID NO: 280)
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>DOM1h-574-154 (SEQ ID NO: 281)
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>DOM1h-574-155 (SEQ ID NO: 282)
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GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-156 (SEQ ID NO: 283)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-157 (SEQ ID NO: 284)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTGAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGAGGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-158 (SEQ ID NO: 285)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGAGGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-159 (SEQ ID NO: 286)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-160 (SEQ ID NO: 287)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTGAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-161 (SEQ ID NO: 288)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTGAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACTCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-162 (SEQ ID NO: 289)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACTCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-163 (SEQ ID NO: 290)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACACACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-164 (SEQ ID NO: 291)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTGAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACACACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-165 (SEQ ID NO: 292)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-166 (SEQ ID NO: 293)
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TCTCCTGTGCAGCCTCCGGATTCACCTTTTTGAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-167 (SEQ ID NO: 294)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTGAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACCGGTGATCGTAGA
TACTACGATCACTCTGTGAAGGGCCGGTTCACTATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-168 (SEQ ID NO: 295)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACCGGTGATCGTAGA
TACTACGATCACTCTGTGAAGGGCCGGTTCACTATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-169 (SEQ ID NO: 296)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCTGATCGTACA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGCGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-170 (SEQ ID NO: 297)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTACA
TACTACGCACACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-171 (SEQ ID NO: 298)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTGCAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCTGATCGTACA
TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-172 (SEQ ID NO: 299)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCTGATCGTACA
TACTACGATCACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCTGAGGACACCGCGGTATATTACTGTGC
GATATATACTGGGCGTTGGGTGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-173 (SEQ ID NO: 300)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCTGATCGTAGA
TACTACGCACACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-174 (SEQ ID NO: 301)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTAGA
TACTACGCACACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-175 (SEQ ID NO: 302)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCTGATCGTAGA
TACTACGCACACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-176 (SEQ ID NO: 303)
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTAGA
TACTACGATCACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-177 (SEQ ID NO: 304)
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TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCTGATCGTAGA
TACTACGATCACGCGGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGGACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-178 (SEQ ID NO: 305)
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TCTCCTGTGCAGCCTCCGGATTCACCTTTGTTAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTGCGGATACTGCTGATCGTAGA
TACTACGATCACTCCGTGAAGGGCCGGTTCACCATCTCCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGGTGGGCGCCTTTTGAGTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

>DOM1h-574-179 (SEQ ID NO: 306)
GAGGTGCAGCTGCTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTC
TCTCCTGTGCAGCCTCCGGATTCACCTTTTTCAAGTATTCGATGGGGTGGGTCCGCCA
GGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACAGATTTCGGATACTGCTGATCGTAGA
TACTACGATGACGCGGTGAAGGGCCGGTTCACCATCACCCGCGACAATTCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGC
GATATATACGGGTCGTTGGGAGCCTTTTGTCTACTGGGGTCAGGGAACCCTGGTCACC
GTCTCGAGC

**Table 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: 307)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRS
SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGAALPRTFGQGTKVEIK
R

Nucleotide sequence (SEQ ID NO: 308)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG

GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGT
CTCAGTTATCTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA
TCATGTGGCGTTCCTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAG
TGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGAT
TTTGCTACGTACTACTGTGCTCAGGGTGCGGCGTTGCCTAGGACGTTCGGCC
AAGGGACCAAGGTGGAAATCAAACGG

**DOM7h-14-10/Exendin-4 fusion DMS number 7139**

Amino acid sequence (SEQ ID NO: 309)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRS
SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFGQGTKVEIK
R

Nucleotide sequence (SEQ ID NO: 310)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG
GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGT
CTCAGTTATCTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA
TCATGTGGCGTTCCTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAG
TGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGAT
TTTGCTACGTACTACTGTGCTCAGGGTTTGAGGCATCCTAAGACGTTCGGCC
AAGGGACCAAGGTGGAAATCAAACGG

**DOM7h-14-18/Exendin-4 fusion DMS number 7140**

Amino acid sequence (SEQ ID NO: 311)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRS
SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLMKPMTFGQGTKVEIK
R

Nucleotide sequence (SEQ ID NO: 312)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG

GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGT
CTCAGTTATCTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA
TCATGTGGCGTTCCTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAG
TGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGAT
TTTGCTACGTACTACTGTGCTCAGGGTCTTATGAAGCCTATGACGTTCGGCC
AAGGGACCAAGGTGGAAATCAAACGG

**DOM7h-14-19/Exendin-4 fusion DMS number 7141**

Amino acid sequence (SEQ ID NO: 313)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTISCRASQWIGSQLSWYQQKPGEAPKLLIMWRS
SLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGAALPRTFGQGTKVEIK
R

Nucleotide sequence (SEQ ID NO: 314)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG
GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCTCTTGCCGGGCAAGTCAGTGGATTGGGTC
TCAGTTATCTTGGTACCAGCAGAAACCAGGGGAAGCCCCTAAGCTCCTGAT
CATGTGGCGTTCCTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGT
GGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATT
TTGCTACGTACTACTGTGCTCAGGGTGCGGCGTTGCCTAGGACGTTCGGCCA
AGGGACCAAGGTGGAAATCAAACGG

**DOM7h-11/Exendin-4 fusion DMS number 7142**

Amino acid sequence (SEQ ID NO: 315)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTITCRASRPIGTTLSWYQQKPGKAPKLLIWFGSR
LQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

Nucleotide sequence (SEQ ID NO: 316)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG

GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGA
CGACGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA
TCTGGTTTGGTTCCCGGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAG
TGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGAT
TTTGCTACGTACTACTGTGCGCAGGCTGGGACGCATCCTACGACGTTCGGCC
AAGGGACCAAGGTGGAAATCAAACGG

**DOM7h-11-12/Exendin-4 fusion DMS number 7147**

Amino acid sequence (SEQ ID NO: 317)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILFGSR
LQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

Nucleotide sequence (SEQ ID NO: 318)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG
GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC
GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGA
CGATGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA
TCTTGTTTGGTTCCCGGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAG
TGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGAT
TTTGCTACGTACTACTGTGCGCAGGCTGGGACGCATCCTACGACGTTCGGCC
AAGGGACCAAGGTGGAAATCAAACGG

**DOM7h-11-15/Exendin-4 fusion DMS number 7143**

Amino acid sequence (SEQ ID NO: 319)

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGGSGGG
GSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSR
LQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR

Nucleotide sequence (SEQ ID NO: 320)

CATGGTGAAGGAACATTTACCAGTGACTTGTCAAAACAGATGGAAGAGGAG
GCAGTGCGGTTATTTATTGAGTGGCTTAAGAACGGAGGACCAAGTAGCGGG
GCACCTCCGCCATCGGGTGGTGGAGGCGGTTCAGGCGGAGGTGGCAGCGGC

GGTGGCGGGTCGGACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCAT
CTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGA
CGATGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGA
TCCTTGCTTTTTCCCGTTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGT
GGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATT
TTGCTACGTACTACTGCGCGCAGGCTGGGACGCATCCTACGACGTTCGGCCA
AGGGACCAAGGTGGAAATCAAACGG

**DOM7h14-10/ G4SC-NCE fusion**

Amino acid sequence (SEQ ID NO: 321) encoding DOM7h14-10/G4SC

DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSL
QSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFGQGTKVEIKRG
GGGSC

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) encoding DOM7h14-10/G4SC

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACC
GTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTG
GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCATGTGGCGTTC
CTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGAC
AGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTAC
TACTGTGCTCAGGGTTTGAGGCATCCTAAGACGTTCGGCCAAGGGACCAAG
GTGGAAATCAAACGGGGTGGCGGAGGGGGTTCCTGT

**DOM7h14-10/TVAAPSC fusion**

Amino acid sequence (SEQ ID NO: 323)

DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSL
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: 324)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACC
GTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTG

GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCATGTGGCGTTC
CTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGAC
AGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTAC
TACTGTGCTCAGGGTTTGAGGCATCCTAAGACGTTCGGCCAAGGGACCAAG
GTGGAAATCAAACGGACCGTCGCTGCTCCATCTTGT

(used in mouse studies):-

**DOM7h-11/DOM1m-21-23 fusion DMS number 5515**

Amino acid sequence (SEQ ID NO: 325)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS
YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA
FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTTLS
WYQQKPGKAPKLLIWFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
AQAGTHPTTFGQGTKVEIKR

Amino acid plus nucleotide plus myc tag sequence (SEQ ID NO: 326)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS
YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA
FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTTLS
WYQQKPGKAPKLLIWFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC
AQAGTHPTTFGQGTKVEIKRAAAEQKLISEEDLN

Nucleotide sequence (SEQ ID NO: 327)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCC
CTGCGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGG
GGTGGCTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTG
ATTCTTATGGTCGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCA
GCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCC
TGCGTGCCGAGGACACCGCCGTATATTACTGTGCGAAAATTTCTCAGTTTGG
GTCAAATGCGTTTGACTACTGGGGTCAGGGAACCCAGGTCACCGTCTCGAG
CGCTAGCACCAGTGGTCCATCGGACATCCAGATGACCCAGTCTCCATCCTCC
CTGTCTGCATCTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTC
CGATTGGGACGACGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTA
AGCTCCTGATCTGGTTTGGTTCCCGGTTGCAAAGTGGGGTCCCATCACGTTT
CAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCA
ACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGGGACGCATCCTACG
ACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Nucleotide plus myc tag sequence (SEQ ID NO: 328)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCC
CTGCGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGG
GGTGGCTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTG
ATTCTTATGGTCGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCA
GCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCC
TGCGTGCCGAGGACACCGCCGTATATTACTGTGCGAAAATTTCTCAGTTTGG
GTCAAATGCGTTTGACTACTGGGGTCAGGGAACCCAGGTCACCGTCTCGAG
CGCTAGCACCAGTGGTCCATCGGACATCCAGATGACCCAGTCTCCATCCTCC
CTGTCTGCATCTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTC
CGATTGGGACGACGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTA
AGCTCCTGATCTGGTTTGGTTCCCGGTTGCAAAGTGGGGTCCCATCACGTTT
CAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCA
ACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGGGACGCATCCTACG
ACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGGGCGGCCGCAGAACA
AAAACTCATCTCAGAAGAGGATCTGAATTAA

**DOM7h-11-12/DOM1m-21-23 fusion DMS number 5516**

Amino acid sequence (SEQ ID NO: 329)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS
YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA
FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLS
WYQQKPGKAPKLLILFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCA
QAGTHPTTFGQGTKVEIKR

Amino acid plus nucleotide plus myc tag sequence (SEQ ID NO: 330)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS
YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA
FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLS
WYQQKPGKAPKLLILFGSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCA
QAGTHPTTFGQGTKVEIKRAAAEQKLISEEDLN

Nucleotide sequence (SEQ ID NO: 331)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCC
CTGCGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGG
GGTGGCTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTG
ATTCTTATGGTCGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCA
GCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCC
TGCGTGCCGAGGACACCGCCGTATATTACTGTGCGAAAATTTCTCAGTTTGG
GTCAAATGCGTTTGACTACTGGGGTCAGGGAACCCAGGTCACCGTCTCGAG
CGCTAGCACCAGTGGTCCATCGGACATCCAGATGACCCAGTCTCCATCCTCC

CTGTCTGCATCTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTC
CGATTGGGACGATGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTA
AGCTCCTGATCTTGTTTGGTTCCCGGTTGCAAAGTGGGGTCCCATCACGTTT
CAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCA
ACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGGGACGCATCCTACG
ACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Nucleotide plus myc tag sequence (SEQ ID NO: 332)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCC
CTGCGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGG
GGTGGCTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTG
ATTCTTATGGTCGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCA
GCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCC
TGCGTGCCGAGGACACCGCCGTATATTACTGTGCGAAAATTTCTCAGTTTGG
GTCAAATGCGTTTGACTACTGGGGTCAGGGAACCCAGGTCACCGTCTCGAG
CGCTAGCACCAGTGGTCCATCGGACATCCAGATGACCCAGTCTCCATCCTCC
CTGTCTGCATCTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTC
CGATTGGGACGATGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTA
AGCTCCTGATCTTGTTTGGTTCCCGGTTGCAAAGTGGGGTCCCATCACGTTT
CAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCA
ACCTGAAGATTTTGCTACGTACTACTGTGCGCAGGCTGGGACGCATCCTACG
ACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGGGCGGCCGCAGAACA
AAAACTCATCTCAGAAGAGGATCTGAATTAA

**DOM7h-11-15/DOM1m-21-23 fusion DMS number 5517**

Amino acid sequence (SEQ ID NO: 333)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS
YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA
FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLS
WYQQKPGKAPKLLILAFSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCA
QAGTHPTTFGQGTKVEIKR

Amino acid plus nucleotide plus myc tag sequence(SEQ ID NO: 334)

EVQLLESGGGLVQPGGSLRLSCAASGFTFNRYSMGWLRQAPGKGLEWVSRIDS
YGRGTYYEDPVKGRFSISRDNSKNTLYLQMNSLRAEDTAVYYCAKISQFGSNA
FDYWGQGTQVTVSSASTSGPSDIQMTQSPSSLSASVGDRVTITCRASRPIGTMLS
WYQQKPGKAPKLLILAFSRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCA
QAGTHPTTFGQGTKVEIKRAAAEQKLISEEDLN

Nucleotide sequence (SEQ ID NO: 335)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCC
CTGCGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGG
GGTGGCTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCACGGATTG
ATTCTTATGGTCGTGGTACATACTACGAAGACCCCGTGAAGGGCCGGTTCA
GCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCC
TGCGTGCCGAGGACACCGCCGTATATTACTGTGCGAAAATTTCTCAGTTTGG
GTCAAATGCGTTTGACTACTGGGGTCAGGGAACCCAGGTCACCGTCTCGAG
CGCTAGCACCAGTGGTCCATCGGACATCCAGATGACCCAGTCTCCATCCTCC
CTGTCTGCATCTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTC
CGATTGGGACGATGTTAAGTTGGTACCAGCAGAAACCAGGGAAAGCCCCTA
AGCTCCTGATCCTTGCTTTTTCCCGTTTGCAAAGTGGGGTCCCATCACGTTTC
AGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAA
CCTGAAGATTTTGCTACGTACTACTGCGCGCAGGCTGGGACGCATCCTACGA
CGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG

Nucleotide plus myc tag sequence (SEQ ID NO: 336)

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCC
CTGCGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATAGGTATAGTATGG
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.

**EXEMPLIFICATION**

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

Derivation of DOM7h-11 variants is described.

**EXAMPLE 1: Vk Affinity Maturation**

**Selections:**

HSA (Human Serum Albumin) and RSA (Rat Serum Albumin) antigens were obtained from Sigma (essentially 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 samples twice through PD10 desalting column followed by overnight dialysis against 1000x excess volume of PBS at 4°C. Resulting product was tested by mass spec and 1-2 biotins per molecule were observed.

**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 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 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 the c-myc tag 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 encoding 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 *Sal* I and *Not* I and used in a ligation reaction with cut phage vector pDOM33. 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 *Sal* I and *Not* I and used in a ligation reaction with pDOM4 for mutagenesis of multiple residues and pDOM5 for mutagenesis of single residues. The pDOM5 vector is a pUC119-based expression vector where protein expression is driven by the LacZ promoter. A GAS1 leader sequence (see WO 2005/093074) ensures secretion of isolated, soluble dAbs into the periplasm and culture supernatant of *E. coli.* dAbs are cloned SalI/NotI in this vector, which appends a myc tag at the C-terminus of the dAb. This protocol using *SalI* 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 2xTY agar containing 15 μg/ml tetracycline, yielding library sizes of $>5\times10^7$ clones.

The error-prone libraries had the following average mutation rate and size: DOM7h-11 (2.5 mutations per dAb), size:_6.1 x $10^8$ , DOM7h-14 (2.9 mutations per dAb) , size: 5.4 x $10^8$.

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 library are as follows (amino acids based on VK dummy DPK9 sequence):

| | Library size | |
|---|---|---|
| | DOM7h-11 | DOM7h-14 |
| 1 – Q27, S28, S30, S31 (CDR1) | 8.8 x $10^7$ | 5.8 x $10^7$ |
| 2 – S30, S31, Y32, N34 (CDR1) | 4.6 x $10^8$ | 4.2 x $10^8$ |

| | | |
|---|---|---|
| 3 – Y49, A50, A51, S53 (CDR2) | $3.9 \times 10^8$ | $2.4 \times 10^8$ |
| 4 – Q89, S91, Y92, S93 (CDR3) | $1.8 \times 10^8$ | $2.5 \times 10^8$ |
| 5 – Y92, Y93, T94, N96 (CDR3) | $4.0 \times 10^8$ | $3.3 \times 10^8$ |

**Example 2: Selection strategies:**

1) Three phage selection strategies were adopted for Vκ AlbudAb™ (anti-serum albumin dAb) affinity maturation: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 1mg/ml. Round 2 was performed against 100nM HSA and round 3 against 10nM (CDR selections) or 20 or 100nM (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 1mg/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 1mg/ml without trypsin; the second round against passively coated HSA at 1mg/ml with 20µg/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 µg/ml or 100 µg/ml trypsin for 1 hour at 37°C. The final round of selection was performed by soluble selection using biotinylated HSA against 100nM HSA with 100 µg/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 1mg/ml passively coated HSA or 1 μM HSA (soluble selection), followed by a further three rounds of soluble selections against biotinylated RSA at concentrations of 1 μM for round 1, 100nm for round 2 and 20nM, 10nM or 1nM 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 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 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 (*Cynomolgus* 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. 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 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 2.5L shake flasks in Onex media at 30°C for 48hrs at 250rpm. dAbs were purified from the culture media by absorption to protein L agarose followed by elution with 10mM glycine pH2.0. Binding to HSA, CSA, MSA and RSA by BIAcore was confirmed using purified protein at 3 concentrations 1μM, 500nM and 50nM. To determine the binding affinity ($K_D$) of the AlbudAbs to each serum albumin; purified dAbs were analysed by BIAcore over albumin concentration range from 5000nM to 39nM (5000nM, 2500nM, 1250nM, 625nM, 312nM, 156nM, 78nM, 39nM).

**Table 6**

| **AlbudAb** | **Affinity ($K_D$) to SA (nM)** | **Kd** | **Ka** |
|---|---|---|---|
| | **Rat** | | |
| **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 |
| **DOM 7h-14-19** | 890 | 2.870E-01 | 3.20E+05 |
| **DOM 7h-14-28** | 45 (140) | 7.0E-02 (1.141e-1) | 2.10E+06 (8.3e5) |
| **DOM 7h-14-36** | 30 (6120) | 2.9E-02 (5.54e-2) | 1.55E+06 (9e3) |
| | | | |
| **DOM 7h-11** | 2100 | 1.00E-01 | 4.80E+04 |
| **DOM 7h-11-3** | 10000 (88000) | (7.18e-1) | (8.11e3) |

| | | | |
|---|---|---|---|
| **DOM 7h-11-12** | 200 | 5.22E-01 | 2.76E+06 |
| **DOM 7h-11-15** | 20 | 2.10E-02 | 1.10E+06 |
| **DOM 7h-11-18** | 80 (29000) | 6.0E-02 (3.7e-1) | 1.64E+06 (1.3e4) |
| **DOM 7h-11-19** | 28 (17000) | 9.1e-02 (1.4e-1) | 9.80E+05 (8.1e3) |
| | | | |
| | **Cyno** | | |
| **DOM 7h-14** | 66 | 9.65E-02 | 1.50E+06 |
| **DOM 7h-14-10** | 9 | 1.15E-02 | 1.60E+06 |
| **DOM 7h-14-18** | 180 | 1.05E-01 | 6.30E+5 |
| **DOM 7h-14-19** | 225 | 1.56E-01 | 7.00E+05 |
| **DOM 7h-14-28** | 66 (136) | 1.3E-01 (1.34e-1) | 2.50E+06 (9.8e5) |
| **DOM 7h-14-36** | 35 (7830) | 1.9E-02 (1.1e-1) | 9.80E+06 (1.43e4) |
| | | | |
| **DOM 7h-11** | 1000 | 6.82E-01 | 8.00E+05 |
| **DOM 7h-11-3** | 670 (200) | 9.6E-02 (1.5e-1) | 2.90E+05 (7.26e5) |
| **DOM 7h-11-12** | ≥6000 | | |
| **DOM 7h-11-15** | 3 | 5.57E-03 | 5.80E+06 |
| **DOM 7h-11-18** | 10000 (65000) | 1.36 (4.8e-1) | 2.25E+05 (7.3e3) |
| **DOM 7h-11-19** | ≥10000 (375000) | (6.2e-1) | (1.7e3) |
| | | | |
| | **Mouse** | | |
| **DOM 7h-14** | 12 | 4.82E-02 | 4.10E+06 |

| | | | |
|---|---|---|---|
| **DOM 7h-14-10** | 30 | 3.41E-02 | 1.29E+06 |
| **DOM 7h-14-18** | 65 | 9.24E-02 | 2.28E+06 |
| **DOM 7h-14-19** | 60 | 5.76E-02 | 1.16E+06 |
| **DOM 7h-14-28** | 26 (31) | 3.4E-02 (7.15e-2) | 1.60E+06 (2.28e6) |
| **DOM 7h-14-36** | 35 (33) | 2.3E-02 (7.06e-2) | 8.70E+05 (2.11e6) |
| | | | |
| **DOM 7h-11** | 5000 | 9.00E-01 | |
| **DOM 7h-11-3** | ≥10000 (36000) | (6.12e-1) | (1.67e4) |
| **DOM 7h-11-12** | 130 | 1.89E-01 | 1.53E+06 |
| **DOM 7h-11-15** | 10 | 9.40E-03 | 1.10E+06 |
| **DOM 7h-11-18** | 150 (1600) | 2.4E-02 (6.23e-2) | 4.40E+05 (4e4) |
| **DOM 7h-11-19** | 100 (18000) | 3.7E-02 (8.8e-2) | 1.40E+06 (4.9e3) |
| | | | |
| | **Human** | | |
| **DOM 7h-14** | 33 | 4.17E-02 | 1.43E+06 |
| **DOM 7h-14-10** | 12 | 1.39E-02 | 1.50E+06 |
| **DOM 7h-14-18** | 280 | 3.39E-02 | 1.89E+05 |
| **DOM 7h-14-19** | 70 | 5.25E-02 | 8.26E+05 |
| **DOM 7h-14-28** | 30 (8260) | 3.3E-02 (5.6e-2) | 1.24E+06 (6.78e3) |
| **DOM 7h-14-36** | 28 (1260) | 2.4E-02 (6.7e-2) | 1.23E+06 (5.4e4) |
| | | | |
| **DOM 7h-11** | 2800 | 6.41E-01 | 7.00E+05 |

| | | | |
|---|---|---|---|
| **DOM 7h-11-3** | 32 (130) | 1.6E-02 (2.35e-2) | 6.50E+05 (1.86e5) |
| **DOM 7h-11-12** | 350 | 4.13E-01 | 1.26E+06 |
| **DOM 7h-11-15** | 1 | 1.84E-03 | 2.00E+06 |
| **DOM 7h-11-18** | 36 (32000) | 5.1E-02 (2.7e-1) | 3.40E+06 (8.39e3) |
| **DOM 7h-11-19** | 65 (38000) | 1.1E-01 (2.09e-1) | 1.80E+06 (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. 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.

**<u>Example 3: Origins of key DOM7h-11 lineage clones:</u>**

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

DOM7h-11-12: From affinity maturation performed against HSA using the error prone library, round 3 outputs (100nM, HSA) with 100ug/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 1nM 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 20nM 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 5nM of RSA

**Table 7: CDR sequences (according to Kabat; ref. as above)**

| AlbudAb | CDR | | |
|---|---|---|---|
| | CDR1 | CDR2 | CDR3 |
| **DPK9 Vk dummy** | SQSISSYLN (SEQ ID NO: 337) | YAASSLQS (SEQ ID NO: 338) | QQSYSTPNT (SEQ ID NO: 339) |
| **DOM7h-11** | SRPIGTTLS (SEQ ID NO: 340) | WFGSRLQS (SEQ ID NO: 341) | AQAGTHPTT (SEQ ID NO: 342) |
| **DOM7h-11-12** | SRPIGTMLS (SEQ ID NO: 343) | LFGSRLQS (SEQ ID NO: 344) | AQAGTHPTT (SEQ ID NO: 345) |
| **DOM 7h-11-15** | SRPIGTMLS (SEQ ID NO: 346) | LAFSRLQS (SEQ ID NO: 347) | AQAGTHPTT (SEQ ID NO: 348) |
| **DOM 7h-11-18** | SRPIGTMLS (SEQ ID NO: 349) | WFGSRLQS (SEQ ID NO: 350) | AQAGTHPTT (SEQ ID NO: 351) |
| **DOM 7h-11-19** | SRPIGTMLS (SEQ ID NO: 352) | LFGSRLQS (SEQ ID NO: 353) | AQTGTHPTT (SEQ ID NO: 354) |
| **DOM 7h-11-3** | SRPIGTTLS (SEQ ID NO: 355) | LWFSRLQS (SEQ ID NO: 356) | AQAGTHPTT (SEQ ID NO: 357) |

**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 (100nM, HSA) with 100ug/ml trypsin.

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

**Table 8: CDR sequences (according to Kabat; ref. as above)**

| AlbudAb | CDR | | |
|---|---|---|---|
| | CDR1 | CDR2 | CDR3 |
| **DPK9 Vk dummy** | SQSISSYLN (SEQ ID NO: 337) | YAASSLQS (SEQ ID NO: 338) | QQSYSTPNT (SEQ ID NO: 339) |
| **DOM 7h-14** | SQWIGSQLS (SEQ ID NO: 358) | MWRSSLQS (SEQ ID NO: 359) | AQGAALPRT (SEQ ID NO: 360) |
| **DOM 7h-14-10** | SQWIGSQLS (SEQ ID NO: 361) | MWRSSLQS (SEQ ID NO: 362) | AQGLRHPKT (SEQ ID NO: 363) |
| **DOM 7h-14-18** | SQWIGSQLS (SEQ ID NO: 364) | MWRSSLQS (SEQ ID NO: 365) | AQGLMKPMT (SEQ ID NO: 366) |
| **DOM 7h-14-19** | SQWIGSQLS (SEQ ID NO: 367) | MWRSSLQS (SEQ ID NO: 368) | AQGAALPRT (SEQ ID NO: 369) |
| **DOM 7h-14-28** | SQWIGSQLS (SEQ ID NO: 370) | MWRSSLQS (SEQ ID NO: 371) | AQGAALPKT (SEQ ID NO: 372) |
| **DOM 7h-14-36** | SQWIGSQLS (SEQ ID NO: 373) | MWRSSLQS (SEQ ID NO: 374) | AQGFKKPRT (SEQ ID NO: 375) |

**Example 5: Expression and Biophysical Characterisation:**

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

SEC MALLS (size exclusion chromatography with multi-angle-LASER-light-scattering) is a non-invasive technique for the characterizing of macromolecules in solution. Briefly, proteins (at concentration of 1mg/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 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 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 1mg/mL in PBS) and a detectable heat 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 (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 Origin$^R$ v7.0383.

**Table 9**

| AlbudAb | Biophysical parameters | |
|---|---|---|
| | SEC MALLS | DSC Tm(°C) |
| **DOM7h-14** | M | 60 |
| **DOM 7h-14-10** | M | 59 |
| **DOM 7h-14-18** | M | 58 |
| **DOM 7h-14-19** | M | 59 |
| **DOM 7h-14-28** | M | 58.3/60.2 |
| **DOM 7h-14-36** | M | 59.2 |
| | | |
| **DOM 7h-11** | M | 66.9-72.2 |
| **DOM 7h-11-3** | M (95%)* | 66.6/70.5 |
| **DOM 7h-11-12** | M (<2%D) | 71.7 |

| | | |
|---|---|---|
| **DOM 7h-11-15** | M (<5%D) | 58.5-60.5 |
| **DOM 7h-11-18** | M (98%) | 58.9/65.8 |
| **DOM 7h-11-19** | M | 71.8/76.6 |

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

Expression levels for all clones in Table 9 were observed in the range from 15 to 119mg/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°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™, 20-50mg quantities were expressed in E. coli and purified from bacterial culture supernatant using protein L affinity resin and eluted with 100mM glycine pH2. The proteins were concentrated to greater than 1mg/ml, buffer exchanged into PBS and endotoxin depleted using Q spin columns (Vivascience). For Rat pharmacokinetic (PK) analysis, AlbudAbs were dosed as single i.v injections at 2.5mg/kg using 3 rats per compound. Serum samples were taken at 0.16, 1, 4, 12, 24, 48, 72, 120, 168hrs. 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 2.5mg/kg per dose group of 3 subjects and serum samples taken at 10mins;

1h; 8h; 24h; 48h; 72h; 96h. 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 2.5mg/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, 504hrs. 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 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 x PBS+0.1% Tween20 followed by 3 x PBS. TMB (SureBlue TMB 1-Component Microwell Peroxidase Substrate, KPL, catalogue number 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 450nm.

From the raw ELISA data, the concentration of unknown samples was established by interpolation against the standard 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, CA94040, USA). The data was fitted 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: Single AlbudAb™ PK**

| Species | AlbudAb | Albumin $K_D$ (nM) | PK parameters | | | |
|---|---|---|---|---|---|---|
| | | | AUC h x µg/ml | CL ml/h/kg | t1/2 h | Vz ml/kg |
| | | | | | | |
| 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 |
| | **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 |
| | **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 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 compared to parent. This improvement in AUC/t1/2 correlates with an improved in vitro KD to serum albumin.

## Example 7: AlbudAb™ IFN fusions

Cloning and expression

As well as single AlbudAbs, the affinity matured Vk AlbudAbs were linked to Interferon alpha 2b (IFNα2b) to determine whether a useful PK of the AlbudAb was maintained as a fusion protein.

Interferon alpha 2b amino acid sequence:

CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKDRHDFGFPQEEFGNQFQKAETIP VLHEMIQQIFNLFSTKDSSAAWDETLLDKFYTELYQQLNDLEACVIQGVGVTET PLMKEDSILAVRKYFQRITLYLKEKKYSPCAWEVVRAEIMRSFSLSTNLQESLRS KE (SEQ ID NO:376)

Interferon alpha 2b nucleotide sequence:

TGTGATCTGCCTCAAACCCACAGCCTGGGTAGCAGGAGGACCTTGATGCTC CTGGCACAGATGAGGAGAATCTCTCTTTTCTCCTGCTTGAAGGACAGACATG ACTTTGGATTTCCCCAGGAGGAGTTTGGCAACCAGTTCCAAAAGGCTGAAA CCATCCCTGTCCTCCATGAGATGATCCAGCAGATCTTCAATCTCTTCAGCAC

AAAGGACTCATCTGCTGCTTGGGATGAGACCCTCCTAGACAAATTCTACACT
GAACTCTACCAGCAGCTGAATGACCTGGAAGCCTGTGTGATACAGGGGGTG
GGGGTGACAGAGACTCCCCTGATGAAGGAGGACTCCATTCTGGCTGTGAGG
AAATACTTCCAAAGAATCACTCTCTATCTGAAAGAGAAGAAATACAGCCCT
TGTGCCTGGGAGGTTGTCAGAGCAGAAATCATGAGATCTTTTTCTTTGTCAA
CAAACTTGCAAGAAAGTTTAAGAAGTAAGGAA (SEQ ID NO:377)

IFNa2b was linked to the AlbudAb via a TVAAPS linker region (see WO2007085814). The constructs were cloned by SOE-PCR (single overlap extension according to the method of Horton *et al.* Gene, 77, p61 (1989) ). PCR amplification of the AlbudAb and IFN sequences were carried out separately using primers with a ~15 base pair overlap at the TVAAPS linker region. The primers used are as follows:-

| | |
|---|---|
| IFNα2b SOE fragment 5' | GCCCGGATCCACCGGCTGTGATCTG (SEQ ID NO:378) |
| IFNα2b SOE fragment 3' | GGAGGATGGAGACTGGGTCATCTGGATGTC (SEQ ID NO:379) |
| Vk SOE fragment 5' | GACATCCAGATGACCCAGTCTCCATCCTCC (SEQ ID NO:380) |
| Vk SOE fragment 3' to also introduce a myc tag | GCGCAAGCTTTTATTAATTCAGATCCTCTTC TGAGATGAGTTTTTGTTCTGCGGCCGCCCGT TTGATTTCCACCTTGGTCCC (SEQ ID NO:381) |

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

| | |
|---|---|
| IFNα2b SOE fragment 5' | GCCCGGATCCACCGGCTGTGATCTG (SEQ ID NO:382) |
| Vk SOE fragment 3' to also introduce a myc tag | GCGCAAGCTTTTATTAATTCAGATCCTCTTC TGAGATGAGTTTTTGTTCTGCGGCCGCCCGT TTGATTTCCACCTTGGTCCC (SEQ ID NO:383) |

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:384)

Leader sequence (nucleotide):
ATGGAGACCGACACCCTGCTGCTGTGGGTGCTGCTGCTGTGGGTGCCCGGA TCCACCGGGC (SEQ ID NO:385)

Plasmid DNA was prepared using QIAfilter megaprep (Qiagen). 1µg 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 100mM glycine pH2. The proteins were concentrated to greater than 1mg/ml, buffer exchanged into PBS and endotoxin depleted using Q spin columns (Vivascience).

**Affinity Determination and Biophysical Characterisation:**

To determine the binding affinity ($K_D$) of the AlbudAb-IFNα2b fusion proteins to each serum albumin; purified fusion proteins were analysed by BIAcore over albumin (immobilised by primary-amine coupling onto CM5 chips; BIAcore) using fusion protein concentrations from 5000nM to 39nM (5000nM, 2500nM, 1250nM, 625nM, 312nM, 156nM, 78nM, 39nM) in HBS-EP BIAcore buffer.

**Table 12: Affinity to SA**

| AlbudAb | Fusion | Affinity to | Kd | Ka |
|---|---|---|---|---|

| | | **SA (nM)** | | |
|---|---|---|---|---|
| | | **Rat** | | |
| **DOM7h-14** | IFNα2b | 350 | 4.500E-02 | 1.28E+05 |
| **DOM7h-14-10** | IFNα2b | 16 | 4.970E-03 | 5.90E+05 |
| **DOM 7h-14-18** | IFNα2b | 780 | 2.127E-01 | 5.80E+05 |
| **DOM 7h-14-19** | IFNα2b | 1900 | 1.206E-01 | 7.96E+04 |
| | | | | |
| **DOM 7h-11** | IFNα2b | 6000 | 7.500E-01 | nd |
| **DOM 7h-11-12** | IFNα2b | 1700 | 3.100E-01 | 1.30E+05 |
| **DOM 7h-11-15** | IFNα2b | 200 | 1.660E-02 | 1.50E+05 |
| | | | | |
| | | **Cyno** | | |
| **DOM 7h-14** | IFNα2b | 60 | 1.32E-02 | 5.0E+05 |
| **DOM 7h-14-10** | IFNα2b | 19 | 7.05E-03 | 4.50E+05 |
| **DOM 7h-14-18** | IFNα2b | no binding | no binding | no binding |
| **DOM 7h-14-19** | IFNα2b | 520 | 8.47E-02 | 2.73E+05 |
| | | | | |
| **DOM 7h-11** | IFNα2b | 3300 | 3.59E-01 | 1.20E+05 |
| **DOM 7h-11-12** | IFNα2b | 630 | 3.45E-01 | 7.00E+05 |
| **DOM 7h-11-15** | IFNα2b | 15 | 4.86E-03 | 3.60E+05 |
| | | | | |
| | | **Mouse** | | |
| **DOM 7h-14** | IFNα2b | 240 | 3.21E-02 | 1.50E+06 |
| **DOM 7h-14-10** | IFNα2b | 60 | 3.45E-02 | 6.86E+05 |
| **DOM 7h-14-18** | IFNα2b | 180 | 1.50E-01 | 9.84E+05 |
| **DOM 7h-14-19** | IFNα2b | 490 | 4.03E-02 | 1.19E+05 |
| | | | | |
| **DOM 7h-11** | IFNα2b | 6000 | 1.55E-01 | nd |
| **DOM 7h-11-12** | IFNα2b | 150 | 9.49E-02 | 6.30E+05 |

| | | | | |
|---|---|---|---|---|
| **DOM 7h-11-15** | IFNα2b | 28 | 6.69E-03 | 2.80E+05 |
| | | | | |
| | | **Human** | | |
| **DOM 7h-14** | IFNα2b | 244 | 2.21E-02 | 9.89E+04 |
| **DOM 7h-14-10** | IFNα2b | 32 | 6.58E-03 | 3.48E+05 |
| **DOM 7h-14-18** | IFNα2b | 470 | 2.75E-01 | 6.15E+05 |
| **DOM 7h-14-19** | IFNα2b | 350 | 4.19E-02 | 1.55E+05 |
| | | | | |
| **DOM 7h-11** | IFNα2b | 670 | 2.02E-01 | 7.00E+05 |
| **DOM 7h-11-12** | IFNα2b | 500 | 1.66E-01 | 3.90E+05 |
| **DOM 7h-11-15** | IFNα2b | 10 | 1.87E-03 | 3.50E+05 |

When IFNα2b is linked to the AlbudAb variants, in all cases the affinity of AlbudAb 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 binding affinity to serum albumin across species compared to parent.

**Table 13: Biophysical Characterisation**

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

| AlbudAb | Fusion | DMS number | Biophysical parameters | |
|---|---|---|---|---|
| | | | SEC MALLS | DSC Tm($^{o}$C) |
| **DOM 7h-14** | IFNα2b | DMS7321 | M/D | 58-65 |
| **DOM 7h-14-10** | IFNα2b | DMS7322 | M/D | 55-65 |
| **DOM 7h-14-18** | IFNα2b | DMS7323 | M/D | 55-65 |

| | | | | |
|---|---|---|---|---|
| **DOM 7h-14-19** | IFNα2b | DMS7324 | M/D | 59-66 |
| | | | | |
| **DOM 7h-11** | IFNα2b | DMS7325 | M/D | 65.8-66.2 |
| **DOM 7h-11-12** | IFNα2b | DMS7326 | M/D | 67-67.3 |
| **DOM 7h-11-15** | IFNα2b | DMS7327 | M/D | 56.3-66.2 |

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

Expression for all clones in Table 13 was observed in the range of 17.5 to 54 mg/L in HEK293.

For IFNα2b-DOM7h-14 and IFNα2b-DOM7h-11 variants, favorable biophysical parameters and expression levels were maintained during affinity maturation.

PK Determination for AlbudAb-IFNα2bfusions

AlbudAbs IFNα2b fusions DMS7321 (IFNα2b-DOM7h-14) DMS7322 (IFNα2b-DOM7h-14-10) DMS7323 (IFNα2b-DOM7h-14-18), DMS7324 (IFNα2b-DOM7h-14-19), DMS7325 (IFNα2b-DOM7h-11), DMS7326 (IFNα2b-DOM7h-11-12), DMS7327 (IFNα2b-DOM7h-11-15) were expressed with the myc tag at 20-50mg quantities in HEK293 cells and purified from culture supernatant using protein L affinity resin and eluted with 100mM glycine pH2. The proteins were concentrated to greater than 1mg/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 2.0mg/kg using 3 rats per compound. Serum samples were taken at 0.16, 1, 4, 8, 24, 48, 72, 120, 168hrs. Analysis of serum levels was by EASY ELISA according to manufacturer's instructions (GE Healthcare, catalogue number RPN5960).

For Mouse PK, DMS7322 (IFN2b-DOM7h-14-10) DMS7325 (IFN2b-DOM7h-11), DMS7326 (IFN2b-DOM7h-11-12), DMS7327 (IFN2b-DOM7h-11-15) all with myc tags were dosed as single i.v injections at 2.0mg/kg per dose group of 3 subjects and serum samples taken at 10 mins; 1h; 8h; 24h; 48h; 72h; 96h. Analysis of serum

levels was by EASY ELISA according to manufacturer's instructions (GE Healthcare, catalogue number RPN5960).

**Table 14:**

| Species | AlbudAb | Fusion | Albumin $K_D$ (nM) | PK parameters | | | |
|---|---|---|---|---|---|---|---|
| | | | | AUC h x ug/ml | CL ml/h/kg | t1/2 h | Vz ml/kg |
| Rat | **7h-14** | IFNα2b | 350 | 832.1 | 2.4 | 27 | 94.5 |
| | **7h-14-10** | IFNα2b | 16 | 1380.7 | 1.5 | 35.8 | 75.2 |
| | **7h-14-18** | IFNα2b | 780 | 691.2 | 2.9 | 22.4 | 93.7 |
| | **7h-14-19** | IFNα2b | 1900 | 969.4 | 2.2 | 25 | 78.7 |
| | | | | | | | |
| | **7h-11** | IFNα2b | 6000 | 327.9 | 6.5 | 11 | 101.9 |
| | **7h-11-12** | IFNα2b | 1700 | 747.1 | 2.8 | 25.8 | 104.7 |
| | **7h-11-15** | IFNα2b | 200 | 1118.7 | 1.8 | 39.5 | 103.6 |
| | | | | | | | |
| Mouse | **7h-14** | IFNα2b | 240 | 761.2 | 2.6 | 30.4 | 115.3 |
| | **7h-14-10** | IFNα2b | 60 | 750.5 | 2.7 | 30.9 | 118.6 |
| | | | | | | | |
| | **7h-11** | IFNα2b | 6000 | 493.9 | 4.0 | 8.8 | 51.2 |
| | **7h-11-12** | IFNα2b | 150 | 439.6 | 4.5 | 21.5 | 140.9 |
| | **7h-11-15** | IFNα2b | 28 | 971.8 | 2.1 | 33.6 | 99.6 |
| | | | | | | | |

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 IFNα2b -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 IFNα2b-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 10-fold decrease in the binding to RSA compared to the single AlbudAb. 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:**

| Species | AlbudAb | Fusion | Albumin $K_D$ (nM) | PK param-eters | | | |
|---|---|---|---|---|---|---|---|
| | | | | AUC h x ug/ml | CL ml/h/kg | t1/2 h | Vz ml/kg |
| Rat | DOM7h-14 | Exendin-4 | 2400 | 18 | 57.1 | 11 | 901.9 |
| | DOM7h-14-10 | Exendin-4 | 19 | 43.6 | 23.1 | 22.1 | 740.3 |
| | DOM7h-14-18 | Exendin-4 | 16000 | 16.9 | 75.7 | 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- | Exendin-4 | 130 | 36.3 | 27.6 | 19.3 | 765.7 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 11-15 | | | | | | |
| | | | | | | | |
| | 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, the use of genetic fusions with an albumin-binding dAb (AlbudAb) to extend the PK half-life of anti-TNFR1 dAbs in vivo was described (see, eg, WO04003019, WO2006038027, WO2008149148). Reference is made to the protocols in these PCT applications. In the table above, DOM1m-21-23 is an anti-mouse TNFR1 dAb.

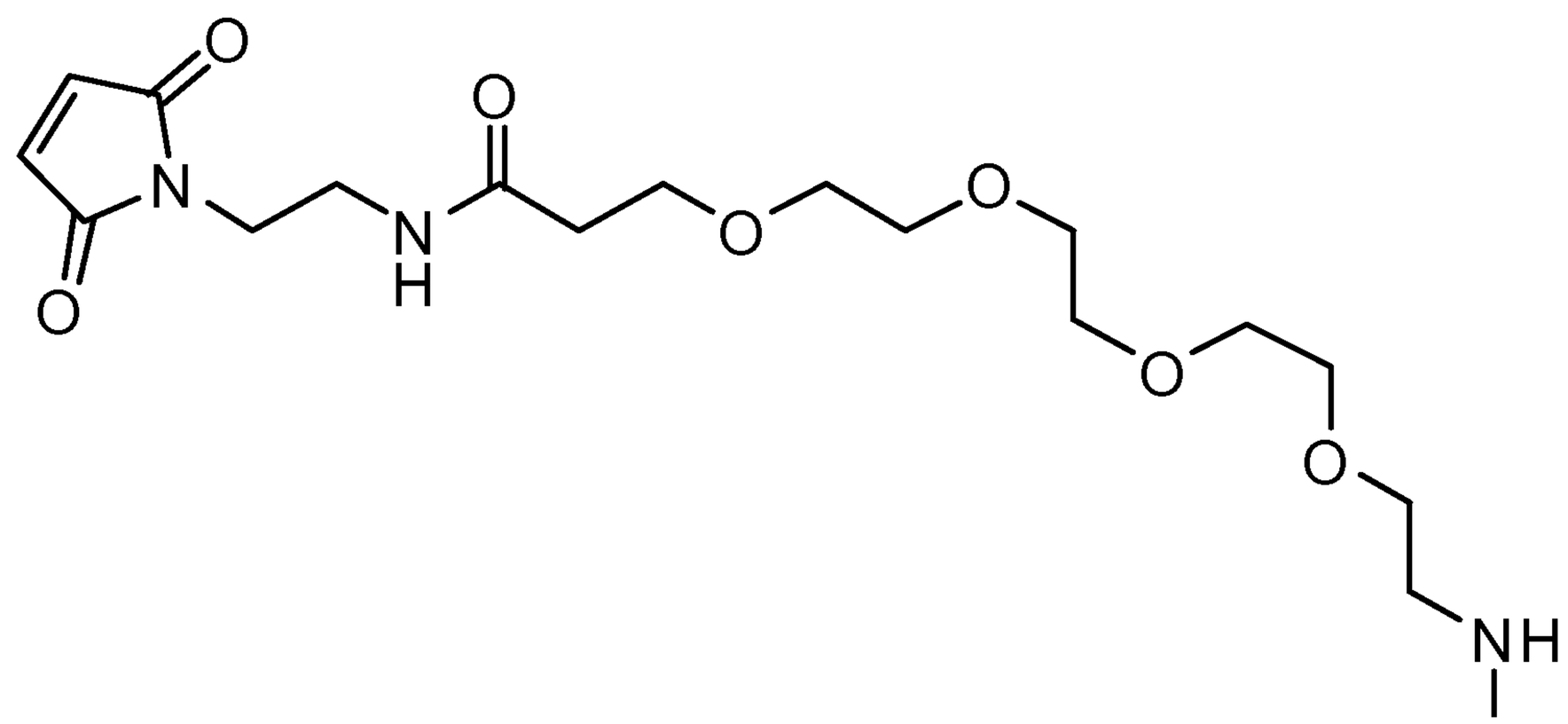
To produce genetic fusions of exendin-4 or with DOM7h-14 (or other AlbudAb) which binds serum albumin, the exendin-4-linker-AlbudAb sequence was cloned into the pTT-5 vector (obtainable from CNRC, Canada). In each case the exendin-4 was at the 5' end of the construct and the dAb at the 3' end. The linker was a $(G_4S)_3$ linker. Endotoxin-free 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 250ml/flask of HEK293E cells at $1.75x10^6$ cells/ml using 333ul of 293fectin (Invitrogen) and 250ug of DNA per flask and expression 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 50ml of 0.1M glycine pH2 and neutralised with Tris pH8.. Protein of the expected size was identified on an SDS-PAGE gel.

NCE Albudab fusions:

A new chemical entity (NCE) AlbudAb fusion was tested. The NCE, a small molecule ADAMTS-4 inhibitor 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 amino acid position R108C, or following a 5 amino acid (GGGGSC) or 6 amino acid (TVAAPSC) 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 healthcare) into 25mM Bis-Tris, 5mM 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 room temperature and dialysed extensively into 20mM Tris pH7.4

PEG linker:



Sequences:

DOM7h-14 R108C:

DIQMTQSPSSLSASVGDRVTITCRASQWIGSQLSWYQQKPGKAPKLLIMWRSSL
QSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQGLRHPKTFGQGTKVEIKC
(SEQ ID NO:386)

Nucleotide:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACC
GTGTCACCATCACTTGCCGGGCAAGTCAGTGGATTGGGTCTCAGTTATCTTG
GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCATGTGGCGTTC
CTCGTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGAC
AGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTAC
TACTGTGCTCAGGGTTTGAGGCATCCTAAGACGTTCGGCCAAGGGACCAAG
GTGGAAATCAAATGC (SEQ ID NO:387)

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

NCE-AlbudAbs DOM7h-14-10 GGGGSC and DOM7h14-10 TVAAPSC, exhibit a 5 to 10 fold decrease in *in vitro* affinity ($K_D$) to RSA as determined by BIAcore when fused to the chemical entity. PK data are not available for these molecules yet.

dAb-Albudab fusion: the 2 DOM7h-11 AlbudAbs 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 a micromolar $K_D$ when fused (2.8uM) as well as when unfused (~5uM).

Exendin 4-AlbudAb 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 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.

Generally, Albudab-therapeutics are classified as being therapeutically amenable (for treatment and/or prophylaxis of diseases, conditions or indications) when the AlbudAb-drug fusions show an affinity range ($K_D$) of from 0.1 nM to 10 mM for serum albumin binding.

The therapeutic ranges of AlbudAbs and AlbudAb fusions (Protein-AlbudAbs for example IFNa2b-DOM7h-14-10; Peptide-AlbudAbs for example Exendin-4-DOM7h-14-10; dAb-AlbudAbs for example DOM1m21-23-DOM7h11-15; NCE-AlbudAb for example ADAMTS-4-DOM7h-14-10) are described as follows: Affinity ($K_D$) ranges that are useful for therapy of chronic or acute conditions, diseases or indications are shown. Also shown are affinity ranges marked as "intermediate". AlbudAbs and fusions in this range have utility for chronic or acute diseases, conditions or indications. In this way, the affinity of the AlbudAb 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 AlbudAbs with affinities that allow for each AlbudAb 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 therapy at hand. See Figure 2.

**Example 9: DOM7h-11-15$^{S12P}$ Sequences**

Amino Acid Sequence of DOM7h-11-15$^{S12P}$

DIQMTQSPSSLPASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQ
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR
(SEQ ID NO: 388)

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):-

GACATCCAGATGACCCAGTCTCCATCCTCCCTGCCTGCATCTGTAGGAGACC
GTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTG
GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCC
CGTTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACA
GATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACT
ACTGCGCGCAGGCTGGGACGCATCCTACGACGTTCGGCCAAGGGACCAAGG
TGGAAATCAAACGG (SEQ ID NO: 389)

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:-

GCAACAGCGTCGACGGACATCCAGATGACCCAGTCTCCATCCTCCCTGCCTG
CATCTGTAGG (SEQ ID NO: 390).

An alternative aspect of the invention provides a nucleic acid comprising the nucleotide sequence of SEQ ID NO: 389 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, e.g., TVAAPS. 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.

## EXAMPLE 10: DOM 7h-11-15 variants

### i) Vk Affinity Maturation

**Selections:**

HSA (Human Serum Albumin) and RSA (Rat Serum Albumin) antigens and biotinylated products were obtained as described in Example 1.

**Affinity maturation libraries:**

Both error prone and doped libraries were created using DOM7h-11-15 parental dAb (see SEQ ID NO: 2) as a template with arginine at position 108 mutated to tryptophan (DOM7h-11-15 R108W (DOM7h-11-55)) allowing use of trypsin for phage selection. The libraries were generated in the pDOM33 vector.

For the doped CDR libraries, primary PCR reactions were performed using doped oligonucleotides containing biased degenerated codons to diversify the required positions in the dAb. Generation of doped libraries is described, for example, in Balint and Larrick, Gene, 137, 109-118 (1993). Primers were designed in order to change only the first two nucleotides from each degenerated codon so that the parental nucleotides were present in 85% of cases and in 5% of cases all other possible nucleotides were present. Six codons per CDR were targeted for being mutated simultaneously with 15% probability per nucleotide in the codon to be different than the parental nucleotide. Assembly PCR was then used to generate a full length diversified insert. The inserts were digested with *Sal* I and *Not* I and used in a ligation reaction with pDOM33. The ligation of libraries were then used to transform *E. coli* strain TB1 by electroporation and the transformed cells plated on 2xTY agar containing 15 μg/ml tetracycline.

There were three doped libraries, one per each CDR and the mutation rate and libraries sizes were as follows:

CDR1 library- 1.6 amino acid mutation per dAb with library size of $1.4x\ 10^8$

CDR2 library- 1.7 amino acid mutation per dAb with library size of $2x\ 10^8$

CDR3 library- 2 amino acid mutation per dAb with library size of $1.1x\ 10^8$

**ii) Selection strategies:**

**Selections against HSA** Two rounds of selection against HSA were carried out. Each CDR library was selected as an individual pool in all rounds. Both rounds of

selections were performed in solution against biotinylated HSA at 10nM concentration. Libraries were eluted with 0.1M glycine pH 2.0 before neutralization with 1M Tris pH 8.0 and before infection into log phase TG1 cells. The second round of each selection was subcloned into pDOM5 for screening.

**Cross over selection** Two rounds of selection against biotinylated SA in solution were carried out. The first round was performed against HSA at 10nM concentration and the second round against RSA at 100nm concentration. Each CDR library was selected as an individual pool in all rounds. Libraries were eluted with 0.1M glycine pH 2.0 before neutralization with 1M Tris pH 8.0 and before infection into log phase TG1 cells. The second round of each selection was subcloned into pDOM5 for screening.

**ii) Screening strategy and affinity determination**

In each case after selection a pool of phage DNA from the appropriate round of selection was prepared using a QIAfilter 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 transform chemically competent *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. For each selection output, 93 clones were tested for binding to HSA, and RSA by BIAcore™ (surface plasmon resonance). 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 centrifuged and analysed by BIAcore for binding to high density HSA, and RSA CM5 chips. Clones which were found to bind equally or better than parental clone to both these species of serum albumin by off-rate screening were sequenced revealing unique dAb sequences.

Unique dAbs were expressed as bacterial supernatants in 0.5L shake flasks in Onex media at 30°C for 48hrs at 250rpm. dAbs were purified from the culture media by absorption to protein L streamline followed by elution with 0.1M glycine pH2.0.

To determine the binding affinity ($K_D$) of the AlbudAbs to Human, Rat, Mouse and Cynomolgus serum albumin; purified dAbs were analysed by BIAcore over albumin concentration range from 500nM to 3.9nM (500nM, 250nM, 125nM, 31.25nM, 15.625nM, 7.8125nM, 3.90625nM).

MSA antigen was obtained from Sigma (essentially fatty acid free, ~99% (agarose gel electrophoresis), lyophilized powder Cat. No. A3559) and CSA was purified from *Cynomolgus* serum albumin using prometic blue resin (Amersham).

The affinities to all tested serum albumin species of key clones is presented in Table 16.

In these assays, myc-tagged molecules were used in PK studies.

**Table 16 A to D**

| A | RSA | | | |
|---|---|---|---|---|
| | ka (1/Ms) | kd (Ms) | KA (1/M) | KD (nM) |
| DOM7h-11-15 | | | | 21.0 |
| DOM7h-11-56 | | | | 23.4 |
| DOM7h-11-57 | 5.66E+05 | 1.93E-02 | 3.42E+07 | 29.2 |
| DOM7h-11-65 | 7.80E+05 | 2.04E-02 | 4.06E+07 | 24.6 |
| DOM7h-11-67 | 1.33E+06 | 1.46E-02 | 8.60E+07 | 11.6 |
| DOM7h-11-68 | | | | 25.3 |
| DOM7h-11-69 | | | | 27.1 |
| DOM7h-11-79 | | | | 11.1 |
| DOM7h-11-80 | | | | 24.1 |

| B | HSA | | | |
|---|---|---|---|---|
| | ka (1/Ms) | kd (Ms) | KA (1/M) | KD (nM) |
| DOM7h-11-15 | | | | 1.4 |
| DOM7h-11-56 | | | | 1.6 |
| DOM7h-11-57 | 1.22E+06 | 1.97E-03 | 5.52E+08 | 1.8 |
| DOM7h-11-65 | 1.30E+06 | 2.22E-03 | 5.52E+08 | 1.8 |
| DOM7h-11-67 | 1.75E+06 | 1.65E-03 | 1.12E+09 | 0.9 |
| DOM7h-11-68 | | | | 33.5 |
| DOM7h-11-69 | | | | 3.2 |
| DOM7h-11-79 | | | | 5.9 |
| DOM7h-11-80 | | | | 2.1 |

| C | CSA | | | |
|---|---|---|---|---|
| | ka (1/Ms) | kd (Ms) | KA (1/M) | KD (nM) |
| DOM7h-11-15 | | | | 5.3 |
| DOM7h-11-56 | | | | 5.2 |
| DOM7h-11-57 | 1.34E+06 | 7.23E-03 | 1.63E+08 | 6.1 |
| DOM7h-11-65 | 1.19E+06 | 7.96E-03 | 6.35E+07 | 15.7 |
| DOM7h-11-67 | 2.03E+06 | 5.34E-03 | 3.69E+08 | 2.7 |

| | | | | |
|---|---|---|---|---|
| DOM7h-11-68 | | | | 37.9 |
| DOM7h-11-69 | | | | 5.9 |
| DOM7h-11-79 | | | | 11.7 |
| DOM7h-11-80 | | | | 5.5 |

| D | MSA | | | |
|---|---|---|---|---|
| | ka (1/Ms) | kd (Ms) | KA (1/M) | KD (nM) |
| DOM7h-11-15 | | | | 10.3 |
| DOM7h-11-56 | | | | 7.6 |
| DOM7h-11-57 | | | | 10.9 |
| DOM7h-11-65 | | | | 9.4 |
| DOM7h-11-67 | | | | 6.7 |
| DOM7h-11-68 | | | | 15.5 |
| DOM7h-11-69 | | | | 10.0 |
| DOM7h-11-79 | | | | 6.9 |
| DOM7h-11-80 | | | | 10.9 |

All DOM7h-11-15 variants are cross-reactive to rat, human, cyno and mouse serum albumin. (dissociation constant (KD); off-rate constant ($K_d$); on-rate constant ($K_a$)).

**iv) Expression and Biophysical Characterisation:**

Bacterial expression and expression by SECMALLS and DSC was carried out as described above in Example 5.

Table 17.

| AlbudAb | Biophysical parameters | | |
|---|---|---|---|
| | DSC Tm(oC) | SEC MALLS | Average Expression level (mg/l) |
| DOM7h-11-15 (R108W) | 53.9 | T/D, Monomer | 21 |
| DOM7h-11-56 | 56.1 | Trimer, Monomer | 10 |
| DOM7h-11-57 | 58.2 | Monomer | 15 |
| DOM7h-11-65 | 61.2 | Monomer | 40 |
| DOM7h-11-67 | 57.2 | Monomer | 36 |
| DOM7h-11-68 | 55.9 | Monomer | 12 |
| DOM7h-11-69 | 57.8 | Monomer | 22 |
| DOM7h-11-79 | 55.1 | T/D, D/M, Monomer | 16 |
| DOM7h-11-80 | 56.2 | Monomer | 11 |

T/D and D/M indicates an equilibrium between trimer and dimer or dimer and monomer, respectively, as detected by SEC-MALLS.

All the DOM7h-11-15 variants presented in the Table 2 have favorable biophysical parameters (monomeric in solution as determined by SEC MALLs and appTm of >55°C as determined by DSC) and expression levels were mostly maintained during affinity maturation. Thermostability is advantageous because it may improve the shelf life of the drug fused to AlbudAb with higher melting temperature when compared to Albudab with low Tm.

**v) CDR3 and Framework 3 sequences of most thermostable clones**

The essential differences in properties of the most thermostable AlbudAbs (appTm of >57°C) are due to single amino acid mutations in CDR 3 or framework 3 (mutations due to polymerase error) of these clones when compared to parental clone DOM7h-11-15. Sequences of framework 3 or CDR 3 containing favorable mutations are presented in Tables 18 and 19. Amino acids that distinguish thermostable AlbudAbs from parent are in bold.

Full amino acid and nucleotide sequences of parent and all thermostable variants of DOM7h-11-15 (Tm of >55°C) are listed in the sequences section (sequence 1-18). Most of the clones has arginine at position 108 mutated to tryptophan which was done to enable trypsin driven selection if necessary (knocking trypsin recognition site out).. Mutation of isoleucine to asparagine at position 106 in DOM7h-11-67 was also included.

Other clones (see DOM 7h-11-87, DOM 7h-11-90, DOM 7h-11-86) were derived in which position 108 was back mutated to arginine (W108R) and, optionally, position 106 was back mutated to isoleucine. The sequences of these clones are listed below.

Binding to SA is summarized in the following tables:

| | **HSA** | | | |
|---|---|---|---|---|
| | ka (1/Ms) | kd (Ms) | KA | **KD (M)** |

| | | | (1/M) | |
|---|---|---|---|---|
| DOM7h-11-90 | 4.69E+05 | 8.70E-05 | 5.27E+07 | 2.02E-08 |
| DOM7h-11-86 | 7.90E+05 | 8.83E-05 | 9.51E+07 | 1.07E-08 |
| DOM7h-11-87 | 1.17E+06 | 1.04E-04 | 1.37E+08 | 7.39E-09 |
| DOM7h-11-88 | 1.14E+06 | 8.12E-05 | 1.51E+08 | 6.71E-09 |

| | **RSA** | | | |
|---|---|---|---|---|
| | ka (1/Ms) | kd (Ms) | KA (1/M) | **KD (M)** |
| DOM7h-11-90 | 3.76E+05 | 3.66E-04 | 1.91E+07 | 5.36E-08 |
| DOM7h-11-86 | 5.60E+05 | 3.87E-04 | 2.80E+07 | 3.78E-08 |
| DOM7h-11-87 | 8.30E+05 | 1.90E-04 | 5.77E+07 | 1.76E-08 |
| DOM7h-11-88 | 8.46E+05 | 2.03E-04 | 5.96E+07 | 1.69E-08 |

| | **CSA** | | | |
|---|---|---|---|---|
| | ka (1/Ms) | kd (Ms) | KA (1/M) | **KD (M)** |
| DOM7h-11-90 | 7.47E+05 | 1.31E-04 | 1.01E+08 | 9.99E-09 |
| DOM7h-11-86 | *8.33E+05* | 1.43E-04 | 1.08E+08 | 1.34E-08 |
| DOM7h-11-87 | 1.37E+06 | 1.23E-04 | 2.47E+08 | 4.21E-09 |
| DOM7h-11-66 | 1.49E+06 | 1.27E-04 | 2.76E+08 | 3.65E-09 |

5 Table showing biophysical properties

| AlbudAb | Average expression level mg/L | Thermal stability Tm (°C) | Solution state |
|---|---|---|---|
| DOM7h-11-90 ( DOM7h-11-57 W108R/N106I) | 4 | **60** | Monomer |
| DOM7h-11-86 ( DOM7h-11-65 W108R/N106I) | 17 | **61.5** | Monomer |
| DOM7h-11-87 ( DOM7h-11-67 W108R/N106I) | 17 | **57.2** | Monomer |
| DOM7h-11-88 (DOM7h-11-67 W108R) | 16 | 57 | Monomer |

**Table 18**

Amino acids that distinguish thermostable AlbudAbs from parent are in bold. All numbering is with reference to Kabat.

| AlbudAb | Amino acid sequences | |
|---|---|---|
| | Framework 3 (amino acid residues 57 to 88) | CDR 3 (amino acid residues 89-97) |
| DOM7h-11-15 | GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC (SEQ ID NO: 391) | AQAGTHPTT (SEQ ID NO: 392) |
| DOM7h-11-57 | GVPSRFSGSGSGTDFTLTIS**N**LQPEDFATYYC (SEQ ID NO: 393) | AQAGTHPTT (SEQ ID NO: 394) |
| DOM7h-11-65 | GVPSRFSGSGSGTDFTLTISSLQPED**V**ATYYC (SEQ ID NO: 395) | AQAGTHPTT (SEQ ID NO: 396) |
| DOM7h-11-67 | GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC (SEQ ID NO: 397) | AQAGTH**H**TT (SEQ ID NO: 398) |
| DOM7h-11-69 | GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC (SEQ ID NO: 399) | AQAG**V**HPTT (SEQ ID NO: 400) |
| | | |

**Table 19**

| AlbudAb | Nucleotide sequences | |
|---|---|---|
| | Framework 3 | CDR 3 |
| DOM7h-11-15 | GGGGTCCCATCACGTTTCAGTGGCAGTGGATC TGGGACAGATTTCACTCTCACCATCAGCAGTC TGCAACCTGAAGATTTTGCTACGTACTACTGC (SEQ ID NO: 401) | GCGCAGGCT GGGACGCAT CCTACGACG (SEQ ID NO: 402) |
| DOM7h-11-57 | GGGGTCCCATCACGTTTCAGTGGCAGTGGATC TGGGACAGATTTCACTCTCACCATCAGCAATC TGCAACCTGAAGATTTTGCTACGTACTACTGC (SEQ ID NO:403) | GCGCAGGCT GGGACGCAT CCTACGACG (SEQ ID NO: 404) |
| DOM7h-11-65 | GGGGTCCCATCACGTTTCAGTGGCAGTGGATC TGGGACAGATTTCACTCTCACCATCAGCAGTC TGCAACCTGAAGATGTTGCTACGTACTACTGT (SEQ ID NO: 405) | GCGCAGGCT GGGACGCAT CCTACGACG (SEQ ID NO: 406) |
| DOM7h-11-67 | GGGGTCCCATCACGTTTCAGTGGCAGTGGATC | GCGCAGGCT |

| | | |
|---|---|---|
| | TGGGACAGATTTCACTCTCACCATCAGCAGTC TGCAACCTGAAGATTTTGCTACGTACTACTGT (SEQ ID NO: 407) | GGGACGCAT CATACGACG (SEQ ID NO: 408) |
| DOM7h-11-69 | GGGGTCCCATCACGTTTCAGTGGCAGTGGATC TGGGACAGATTTCACTCTCACCATCAGCAGTC TGCAACCTGAAGATTTTGCTACGTACTACTGT (SEQ ID NO: 409) | GCGCAGGCT GGGGTGCATC CTACGACG (SEQ ID NO: 410) |

The mutations to DOM 7h-11-15 identified are as follows:

| **AlbudAb** | **Mutation compared to DOM 7h-11-15** |
|---|---|
| DOM7h-11-56 | T22S, R108W |
| DOM7h-11-57 | S77N, R108W |
| DOM7h-11-65 | F83V, R108W |
| DOM7h-11-67 | P95H, I106N,R108W |
| DOM7h-11-68 | K42E, A91T, R108W |
| DOM7h-11-69 | T93V |
| DOM7h-11-79 | A91T, R108W |
| DOM7h-11-80 | T22F, R108W |

## Sequences of DOM7h-11-15 variants

### Amino acid sequences

DOM7h-11-15 R108W (DOM7h-11-55)

DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQ
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKW
(SEQ ID NO: 411)

DOM7h-11-56

DIQMTQSPSSLSASVGDRVTISCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQ
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKW
(SEQ ID NO: 412)

DOM7h-11-57

DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQ
SGVPSRFSGSGSGTDFTLTISNLQPEDFATYYCAQAGTHPTTFGQGTKVEIKW
(SEQ ID NO: 413)

DOM7h-11-65

DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQ
SGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCAQAGTHPTTFGQGTKVEIKW
(SEQ ID NO: 414)

DOM7h-11-67

DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQ
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHHTTFGQGTKVENKW
(SEQ ID NO: 415)

DOM7h-11-68

DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGEAPKLLILAFSRLQ
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQTGTHPTTFGQGTKVEIKW
(SEQ ID NO: 416)

DOM7h-11-69

DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQ
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGVHPTTFGQGTKVEIKR
(SEQ ID NO: 417)

DOM7h-11-79

DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQ
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQTGTHPTTFGQGTKVEIKW
(SEQ ID NO: 418)

DOM7h-11-80

DIQMTQSPSSLSASVGDRVTIFCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQ
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHPTTFGQGTKVEIKW
(SEQ ID NO: 419)

>DOM7h-11-90

DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQ
SGVPSRFSGSGSGTDFTLTISNLQPEDFATYYCAQAGTHPTTFGQGTKVEIKR
(SEQ ID NO: 420)

>DOM7h-11-86
DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQ
SGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCAQAGTHPTTFGQGTKVEIKR
(SEQ ID NO: 421)

>DOM7h-11-87
DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQ
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHHTTFGQGTKVEIKR
(SEQ ID NO: 422)

DOM7h-11-88
DIQMTQSPSSLSASVGDRVTITCRASRPIGTMLSWYQQKPGKAPKLLILAFSRLQ
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCAQAGTHHTTFGQGTKVENKR
(SEQ ID NO: 423)

**Nucleotide sequences**

DOM7h-11-15 R108W (DOM7h-11-55)
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACC
GTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTG
GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCC
CGTTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACA
GATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACT
ACTGCGCGCAGGCTGGGACGCATCCTACGACGTTCGGCCAAGGGACCAAGG
TGGAAATCAAATGG (SEQ ID NO: 424)

DOM7h-11-56
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACC
GTGTCACCATCTCTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTG
GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCC
CGTTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACA
GATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACT
ACTGCGCGCAGGCTGGGACGCATCCTACGACGTTCGGCCAAGGGACCAAGG
TGGAAATCAAATGG (SEQ ID NO: 425)

DOM7h-11-57
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACC
GTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTG
GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCC
CGTTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACA

GATTTCACTCTCACCATCAGCAATCTGCAACCTGAAGATTTTGCTACGTACT
ACTGCGCGCAGGCTGGGACGCATCCTACGACGTTCGGCCAAGGGACCAAGG
TGGAAATCAAATGG (SEQ ID NO: 426)

DOM7h-11-65

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACC
GTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTG
GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCC
CGTTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACA
GATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATGTTGCTACGTACT
ACTGTGCGCAGGCTGGGACGCATCCTACGACGTTCGGCCAAGGGACCAAGG
TGGAAATCAAATGG (SEQ ID NO: 427)

DOM7h-11-67

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACC
GTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTG
GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCC
CGTTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACA
GATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACT
ACTGTGCGCAGGCTGGGACGCATCATACGACGTTCGGCCAAGGGACCAAGG
TGGAAAACAAATGG (SEQ ID NO: 428)

DOM7h-11-68

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACC
GTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTG
GTACCAGCAGAAACCAGGGGAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCC
CGTTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACA
GATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACT
ACTGTGCGCAGACTGGGACGCATCCTACGACGTTCGGCCAAGGGACCAAGG
TGGAAATCAAATGG (SEQ ID NO: 429)

DOM7h-11-69

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACC
GTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTG
GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCC
CGTTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACA
GATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACT
ACTGTGCGCAGGCTGGGGTGCATCCTACGACGTTCGGCCAAGGGACCAAGG
TGGAAATCAAACGG (SEQ ID NO: 430)

DOM7h-11-79

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACC
GTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTG
GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCC
CGTTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACA
GATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACT
ACTGTGCGCAGACTGGGACGCATCCTACGACGTTCGGCCAAGGGACCAAGG
TGGAAATCAAATGG (SEQ ID NO: 431)

DOM7h-11-80

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACC
GTGTCACCATCTTTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTG
GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCC
CGTTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACA
GATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACT
ACTGCGCGCAGGCTGGGACGCATCCTACGACGTTCGGCCAAGGGACCAAGG
TGGAAATCAAATGG (SEQ ID NO: 432)

>DOM7h-11-90

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACC
GTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTG
GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCC
CGTTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACA
GATTTCACTCTCACCATCAGCAATCTGCAACCTGAAGATTTTGCTACGTACT
ACTGCGCGCAGGCTGGGACGCATCCTACGACGTTCGGCCAAGGGACCAAGG
TGGAAATCAAACGG (SEQ ID NO: 433)

>DOM7h-11-86
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACC
GTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTG
GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCC
CGTTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACA
GATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATGTTGCTACGTACT
ACTGTGCGCAGGCTGGGACGCATCCTACGACGTTCGGCCAAGGGACCAAGG
TGGAAATCAAACGG (SEQ ID NO: 434)

>DOM7h-11-87
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACC
GTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTG
GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCC
CGTTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACA
GATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACT
ACTGTGCGCAGGCTGGGACGCATCATACGACGTTCGGCCAAGGGACCAAGG
TGGAAATCAAACGG (SEQ ID NO: 435)

DOM7h-11-88
GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACC
GTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTG
GTACCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCC

CGTTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACA
GATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACT
ACTGTGCGCAGGCTGGGACGCATCATACGACGTTCGGCCAAGGGACCAAGG
TGGAAAACAAACGG (SEQ ID NO: 436)

5

## TABLE OF SEQUENCES

| Description | SEQ ID No | |
|---|---|---|
| | Amino acids | Nucleotide |
| DOM7h-11-12 amino acid | 1 | 6 |
| DOM7h-11-15 amino acid | 2 | 7 |
| DOM7h-11-18 amino acid | 3 | 8 |
| DOM7h-11-19 amino acid | 4 | 9 |
| DOM7h-11-3 nucleotide | 5 | 10 |
| Sequences of anti-TNFR1 dAbs | 11 to 158 | 159 to 306 |
| DOM7h-14/Exendin-4 fusion DMS number 7138 | 307 | 308 |
| DOM7h-14-10/Exendin-4 fusion DMS number 7139 | 309 | 310 |
| DOM7h-14-18/Exendin-4 fusion DMS number 7140 | 311 | 312 |
| DOM7h-14-19/Exendin-4 fusion DMS number 7141 | 313 | 314 |
| DOM7h-11/Exendin-4 fusion DMS number 7142 | 315 | 316 |
| DOM7h-11-12/Exendin-4 fusion DMS number 7147 | 317 | 318 |
| DOM7h-11-15/Exendin-4 fusion DMS number 7143 | 319 | 320 |
| DOM7h14-10/ G4SC-NCE fusion | 321 | 322 |
| DOM7h14-10/TVAAPSC fusion | 323 | 324 |
| DOM7h-11/DOM1m-21-23 fusion DMS number 5515 | 325 | 327 |
| DOM7h-11/DOM1m-21-23 fusion DMS number 5515 plus myc tag | 326 | 328 |
| DOM7h-11-12/DOM1m-21-23 fusion | 329 | 331 |

| | | |
|---|---|---|
| DMS number 5516 | | |
| DOM7h-11-12/DOM1m-21-23 fusion DMS number 5516 plus myc tag | 330 | 332 |
| DOM7h-11-15/DOM1m-21-23 fusion DMS number 5517 | 333 | 335 |
| DOM7h-11-15/DOM1m-21-23 fusion DMS number 5517 plus myc tag | 334 | 336 |
| DPK9 Vk dummy CDRs | 337-339 | |
| DOM7h-11 CDRs | 340-342 | |
| DOM7h-11-12 CDRs | 343-345 | |
| DOM 7h-11-15 CDRs | 346-348 | |
| DOM 7h-11-18 CDRs | 349-351 | |
| DOM 7h-11-19 CDRs | 352-354 | |
| DOM 7h-11-3 CDRs | 355-357 | |
| DOM 7h-14 CDRs | 358-360 | |
| DOM 7h-14-10 CDRs | 361-363 | |
| DOM 7h-14-18 CDRs | 364-366 | |
| DOM 7h-14-19 CDRs | 367-369 | |
| DOM 7h-14-28 CDRs | 370-372 | |
| DOM 7h-14-36 CDRs | 373-375 | |
| Interferon alpha 2b | 376 | 377 |
| IFNα2b SOE fragment 5' | | 378 |
| IFNα2b SOE fragment 3' | | 379 |
| Vk SOE fragment 5' | | 380 |
| Vk SOE fragment 3' to also introduce a myc tag | | 381 |
| IFNα2b SOE fragment 5' | | 382 |

| | | |
|---|---|---|
| Vk SOE fragment 3' to also introduce a myc tag | | 383 |
| Leader sequence | 384 | 385 |
| DOM7h-14 R108C | 386 | 387 |
| DOM7h-11-15$^{S12P}$ | 388 | 389 |
| primer sequence | | 390 |
| FR3 and CDR3 sequences for thermostable variants | 391 to 400 | 401 to 410 |
| DOM7h-11-15 R108W | 411 | 424 |
| DOM7h-11-56 | 412 | 425 |
| DOM7h-11-57 | 413 | 426 |
| DOM7h-11-65 | 414 | 427 |
| DOM7h-11-67 | 415 | 428 |
| DOM7h-11-68 | 416 | 429 |
| DOM7h-11-69 | 417 | 430 |
| DOM7h-11-79 | 418 | 431 |
| DOM7h-11-80 | 419 | 432 |
| DOM7h-11-90 | 420 | 433 |
| DOM7h-11-86 | 421 | 434 |
| DOM7h-11-87 | 422 | 435 |
| DOM7h-11-88 | 423 | 436 |
| Linker sequence | 437 | |
| DOM7h-11 | 438 | |

CLAIMS:

1. An anti-serum albumin (SA) immunoglobulin single variable domain variant of DOM7h-11 (DOM7h-11 as shown in Figure 1 (SEQ ID NO: 438), said variant having a Tm of at least 54°C.

2. An anti-SA immunoglobulin as claimed in claim 1 wherein said variant comprises at least one mutation in any of positions 22, 42 or 91 (numbering according to Kabat) compared to DOM7h-11.

3. An anti-SA immunoglobulin single variable domain variant as claimed in claim 2 wherein said variant is a variant of DOM7h-11-15 (DOM7h-11-15 as shown in Figure 1 (SEQ ID NO: 2)) and comprises at least one mutation in any of positions 22, 42, or 91 (numbering according to Kabat) compared to DOM7h-11-15.

4. The variant of any of claims 1 to 3, wherein the variant comprises at least one mutation selected from the following:

Position 22 = Ser, Phe, Thr, Ala or Cys;
Position 42 = Glu or Asp;
Position 91 = Thr or Ser..

5. An anti-SA immunoglobulin single variable domain variant as claimed in claim 4 wherein position 22 is Ser or Phe.

6. An anti-SA immunoglobulin single variable domain variant as claimed in claim 4 wherein position 42 is Glu and position 91 is Thr.

7. An anti-SA immunoglobulin single variable domain variant as claimed in claim 4 wherein position 91 is Thr.

8. An anti-SA immunoglobulin single variable domain variant as claimed in claim 4 wherein position 22 is Phe.

9. The variant of claim 1 or claim 2, wherein the variant comprises an amino acid sequence that is identical to the amino acid sequence of a single variable domain selected from DOM7h-11-56 (SEQ ID NO: 412), DOM7h-11-68 (SEQ ID NO: 416), DOM7h-11-79 (SEQ ID NO:418) and DOM7h-11-80 (SEQ ID NO: 419) or has up to 4 changes compared to the selected amino acid sequence.

10. An anti-SA immunoglobulin single variable domain variant as claimed in claim 1 wherein the variant comprises at least one mutation in the FW3 region (positions 57 to 88, numbering according to Kabat) or in the CDR3 region (positions 89 to 97, numbering according to Kabat) compared to DOM7h-11.

11. An anti-SA immunoglobulin single variable domain variant as claimed in claim 7 wherein said variant is a variant of DOM7h-11-15 (DOM7h-11-15 as shown in Figure 1) and comprises at least one mutation in the FW3 region (positions 57 to 88, numbering according to Kabat) or in the CDR3 region (positions 89 to 97, numbering according to Kabat) compared to DOM7h-11-15.

12. An anti-SA immunoglobulin single variable domain variant as claimed in claim 7 or 8 wherein said variant comprises at least one mutation at any of positions 77, 83, 93 or 95 (numbering according to Kabat).

13. The variant of any of claims 7 to 9, wherein the variant comprises at least one mutation selected from the following:

Position 77 = Asn, Gln

Position 83 = Val, Ile, Met, Leu, Phe, Ala or Norleucine.
Position 93 = Val, Ile, Met, Leu, Phe, Ala or Norleucine.
Position 95 = His, Asn, Gln, Lys or Arg.

14. An anti-SA immunoglobulin single variable domain as claimed in any preceding claim further comprising a mutation at position 106 or 108 (numbering according to Kabat).

15. An anti-SA immunoglobulin single variable domain variant as claimed in claim 14 wherein position 106 is Asn or Gln.

16. An anti-SA immunoglobulin single variable domain variant as claimed in claim 14 wherein position 108 is Trp, Tyr or Phe.

17. An anti-SA immunoglobulin single variable domain variant as claimed in any preceding claim wherein position 77 is Asn.

18. An anti-SA single variable domain as claimed in any preceding claim wherein position 83 is Val.

19. An anti-SA single variable domain as claimed in any preceding claim wherein position 95 is His.

20. An anti-SA single variable domain as claimed in any preceding claim wherein position 95 is His.

21. An anti-SA single variable domain as claimed in any preceding claim wherein position 93 is Val.

22. The variant of claim 1, wherein the variant comprises an amino acid sequence that is identical to the amino acid sequence of a single variable domain selected from DOM7h-11-57 (SEQ ID NO: 413), DOM7h-11-65 (SEQ ID NO: 414),

DOM7h-11-67 (SEQ ID NO:415) and DOM7h-11-69 (SEQ ID NO: 417) 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 FW3 or CDR3 region as defined in any one of claims 1 to 12.

23. A variant as claimed in any of claims 10 to 21 said variant having a Tm of at least 57°C.

24. A variant as claimed in any preceding claim, wherein said variant has an increased Tm value compared to DOM7h-11.

25. A variant as claimed in any preceding claim wherein said variant has an increased Tm value compared to DOM7h-11-15.

26. A variant as claimed in any preceding claim comprising any combination of any of the mutations listed in claims 4 and 13.

27. The variant of any preceding claim, 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 nM, optionally from about 1 to about 6000 nM, as determined by surface plasmon resonance.

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

29. The variant of any preceding claim, wherein the variant comprises a binding site that specifically binds human SA with an on-rate constant ($K_a$) of from about $2 \times 10^6$ to about $1 \times 10^4$ $M^{-1}sec^{-1}$ , optionally from about $1 \times 10^6$ to about $2 \times 10^4$ $M^{-1}sec^{-1}$ as determined by surface plasmon resonance.

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

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

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

33. A multispecific ligand comprising an anti-SA variant of any preceding claim and a binding moiety that specifically binds a target antigen other than SA.

34. An anti-SA variant single variable domain of any one of claims 1 to 17, wherein the variable domain is conjugated to a drug (optionally an NCE drug), optionally wherein the selected variant is DOM7h-11-56 (SEQ ID NO: 412), DOM7h-11-57 (SEQ ID NO: 413), DOM7h-11-65 (SEQ ID NO: 414), DOM7h-11-67 (SEQ ID NO:415), DOM7h-11-68 (SEQ ID NO:416), DOM7h-11-69 (SEQ ID NO: 417), DOM7h-11-79 (SEQ ID NO:418), DOM7h-11-80 (SEQ ID NO:419), DOM7h-11-90 (SEQ ID NO:420), DOM7h-11-86 (SEQ ID NO:421), DOM7h-11-87 (SEQ ID NO:422) or DOM7h-11-88 (SEQ ID NO:423).

35. A fusion protein comprising a polypeptide or peptide drug fused to a variant according to any one of claims 1 to 17, optionally wherein the selected variant is

DOM7h-11-56 (SEQ ID NO: 412), DOM7h-11-57 (SEQ ID NO: 413), DOM7h-11-65 (SEQ ID NO: 414), DOM7h-11-67 (SEQ ID NO:415), DOM7h-11-68 (SEQ ID NO:416), DOM7h-11-69 (SEQ ID NO: 417), DOM7h-11-79 (SEQ ID NO:418), DOM7h-11-80 (SEQ ID NO:419), DOM7h-11-90 (SEQ ID NO:420), DOM7h-11-86 (SEQ ID NO:421), DOM7h-11-87 (SEQ ID NO:422) or DOM7h-11-88 (SEQ ID NO:423).

36. A fusion protein according to claim 20, wherein the fusion protein comprises a linker (e.g., a linker comprising the amino acid sequence TVA, optionally TVAAPS) between the variant and the drug.

37. A composition comprising a variant, fusion protein or ligand of any preceding claim and a pharmaceutically acceptable diluent, carrier, excipient or vehicle.

38. A nucleic acid comprising a nucleotide sequence encoding a variant according to any one of claims 1 to 17 or a multispecific ligand of claim 18 or fusion protein of claim 20 or 21.

39. A nucleic acid comprising the nucleotide sequence of a DOM7h-11 variant selected from the nucleotide sequence of DOM7h-11-56 (SEQ ID NO: 425), DOM7h-11-57 (SEQ ID NO: 426), DOM7h-11-65 (SEQ ID NO: 427), DOM7h-11-67 (SEQ ID NO:428), DOM7h-11-68 (SEQ ID NO:429), DOM7h-11-69 (SEQ ID NO: 430), DOM7h-11-79 (SEQ ID NO:431), DOM7h-11-80 (SEQ ID NO:432), DOM7h-11-90 (SEQ ID NO:433), DOM7h-11-86 (SEQ ID NO:434), DOM7h-11-87 (SEQ ID NO:435) or DOM7h-11-88 (SEQ ID NO:436).or a nucleotide sequence that is at least 80% identical to said selected sequence.

40. A vector comprising the nucleic acid of claim 23, 24 or 25.

41. An isolated host cell comprising the vector of claim 26.

42. A method of treating or preventing a disease or disorder in a patient, comprising administering at least one dose of a variant according to any one of claims 1 to 22 to said patient.

| Kabat Residue | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DOM7h-11 | D | I | Q | M | T | Q | S | P | S | S | L | S | A | S | V | G | D | R | V | T |
| DOM7h-11-12 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| DOM7h-11-15 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| DOM7h-11-18 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| DOM7h-11-19 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| DOM7h-11-3 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |

| Kabat Residue | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DOM7h-11 | I | T | C | **R** | **A** | **S** | **R** | **P** | **I** | **G** | **T** | **T** | **L** | **S** | W | Y | Q | Q | K | P |
| DOM7h-11-12 | . | . | . | **.** | **.** | **.** | **.** | **.** | **.** | **.** | **.** | **M** | **.** | **.** | . | . | . | . | . | . |
| DOM7h-11-15 | . | . | . | **.** | **.** | **.** | **.** | **.** | **.** | **.** | **.** | **M** | **.** | **.** | . | . | . | . | . | . |
| DOM7h-11-18 | . | . | . | **.** | **.** | **.** | **.** | **.** | **.** | **.** | **.** | **M** | **.** | **.** | . | . | . | . | . | . |
| DOM7h-11-19 | . | . | . | **.** | **.** | **.** | **.** | **.** | **.** | **.** | **.** | **M** | **.** | **.** | . | . | . | . | . | . |
| DOM7h-11-3 | . | . | . | **.** | **.** | **.** | **.** | **.** | **.** | **.** | **.** | . | **.** | **.** | . | . | . | . | . | . |

| Kabat Residue | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DOM7h-11 | G | K | A | P | K | L | L | I | W | **F** | **G** | **S** | **R** | **L** | **Q** | **S** | G | V | P | S |
| DOM7h-11-12 | . | . | . | . | . | . | . | . | L | **.** | **.** | **.** | **.** | **.** | **.** | **.** | . | . | . | . |
| DOM7h-11-15 | . | . | . | . | . | . | . | . | L | **A** | **F** | **.** | **.** | **.** | **.** | **.** | . | . | . | . |
| DOM7h-11-18 | . | . | . | . | . | . | . | . | . | **.** | **.** | **.** | **.** | **.** | **.** | **.** | . | . | . | . |
| DOM7h-11-19 | . | . | . | . | . | . | . | . | L | **.** | **.** | **.** | **.** | **.** | **.** | **.** | . | . | . | . |
| DOM7h-11-3 | . | . | . | . | . | . | . | . | L | **W** | **N** | **.** | **.** | **.** | **.** | **.** | . | . | . | . |

| Kabat Residue | 61 | 62 | 63 | 64 | 65 | 66 | 67 | 68 | 69 | 70 | 71 | 72 | 73 | 74 | 75 | 76 | 77 | 78 | 79 | 80 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DOM7h-11 | R | F | S | G | S | G | S | G | T | D | F | T | L | T | I | S | S | L | Q | P |
| DOM7h-11-12 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |

Figure 1A

| | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DOM7h-11-15 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| DOM7h-11-18 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| DOM7h-11-19 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| DOM7h-11-3 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| | | | | | | | | | | | | | | | | | | | | |
| Kabat Residue | ' | ' | ' | ' | 85 | ' | ' | ' | ' | 90 | ' | ' | ' | ' | 95 | ' | ' | ' | ' | 100 |
| DOM7h-11 | E | D | F | A | T | Y | Y | C | **A** | **Q** | **A** | **G** | **T** | **H** | **P** | **T** | **T** | F | G | Q |
| DOM7h-11-12 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| DOM7h-11-15 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| DOM7h-11-18 | . | . | . | . | . | . | H | . | . | . | . | . | . | . | . | . | . | . | . | . |
| DOM7h-11-19 | . | . | . | . | . | . | . | . | . | . | **T** | . | . | . | . | . | . | . | . | . |
| DOM7h-11-3 | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Kabat Residue | ' | ' | ' | ' | 105 | ' | ' | ' |
| DOM7h-11 | G | T | K | V | E | I | K | R |
| DOM7h-11-12 | . | . | . | . | . | . | . | . |
| DOM7h-11-15 | . | . | . | . | . | . | . | . |
| DOM7h-11-18 | . | . | . | . | . | . | . | . |
| DOM7h-11-19 | . | . | . | . | . | . | . | . |
| DOM7h-11-3 | . | . | . | . | . | . | . | . |

Figure 1B

| | | | |
|---|---|---|---|
| **human** | kinetics based on DOM7h-11 lineage (ranges supported by data) | | |
| | | | |
| | **overall range** | | |
| | KD: 1 to 10000 | | |
| | Kd:1.5e-4 to 0.1 ; Ka:2e6 to 1e4 | | |
| **therapeutic ranges** | chronic | intermediate | acute |
| | high affinity | medium affinity | low affinity |
| | KD: 0.1-400 | KD: 400-2000 | KD: 2000-10000 |
| | Kd:1.5e-4 to 8e-3 ; Ka:1e6 to 5e4 | Kd: 8e-3 to 0.08 ; Ka: 2e4 to 5e4 | Kd:0.08 to 0.1 ; Ka: 5e4 to 1e4 |
| optional ranges | KD: 1-200 | KD: 400-1500 | KD: 2000-6000 |
| | Kd:3e-4 to 2e-3; Ka: 1e6 to 5e4 | Kd:8e-3 to 0.08; Ka: 2e4 to 6e4 | Kd:0.08 to 0.1 ; Ka: 5e4 to 2e4 |
| Examples | DOM7h-11-15, DOM7h-14, DOM7h-14-10, DMS7322; DMS7327 | DMS7326; DMS7323 | DOM7h-11 |

Figure 2A

| | | | |
|---|---|---|---|
| **Cyno** | | | |
| | | | |
| | **overall range** | | |
| | KD: 1 to 10000 | | |
| | Kd:1.5e-4 to 0.1 ; Ka:2e6 to 1e4 | | |
| **therapeutic ranges** | chronic | intermediate | acute |
| | high affinity | medium affinity | low affinity |
| | KD: 0.1-400 | KD: 400-2000 | KD: 2000-10000 |
| | Kd:1.5e-4 to 8e-3 ; Ka:2e6 to 2e4 | Kd: 8e-3 to 0.08 ; Ka: 2e4 to 5e4 | Kd:0.08 to 0.1 ; Ka: 5e4 to 1e4 |
| optional ranges | KD: 1-200 | KD: 400-1500 | KD: 2000-6000 |
| | Kd:3e-4 to 2e-3; Ka: 1e6 to 1e4 | Kd:2e-3 to 0.05; Ka: 2e4 to 1e4 | Kd:0.08 to 0.1 ; Ka: 5e4 to 2e4 |
| Examples | DMS7327; DOM7h-11-15; DOM7h-14; DOM7h-14-10; DOM7h-14-18; DMS7321; DMS7322 | DOM7h-11; DMS7326; DMS7324; | DMS7325 |

Figure 2B

| 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; DMS7327; DOM7h-14; DMS7322 | DMS7326; DOM7h-14-18; DOM7h-14-19; DMS7321; DMS7323 | DMS7325; DOM7h-11; |

Figure 2C

| **Mouse** | | | |
|---|---|---|---|
| | | | |
| | **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: 1-100 | 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; DMS7327; DOM7h-14; DOM7h-14-10; DOM7h-14-18; DOM7h-14-19; DMS7322 | DMS7321; DMS7323; DMS7324; DOM7h-11-12; DMS7326 | DMS7325; DOM7h-11 |

Figure 2D

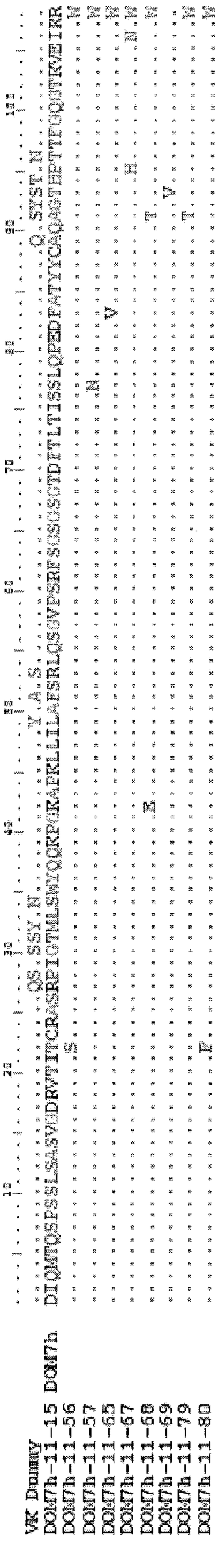

VK Dummy
DOMh-11-15 DOMh
DOMh-11-56
DOMh-11-57
DOMh-11-65
DOMh-11-67
DOMh-11-68
DOMh-11-69
DOMh-11-79
DOMh-11-80

Figure 3A

```
                                10        20        30        40        50        60        70        80        90        100       110
                                ....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|
VK Dummy                        ..........................................................................AGAGC...A.C.GCTAT....A.........
DOM7h-11-15 DOM7h               GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACCGTGTCACCATCACTTGCCGGGCAAGTCGTCCGATTGGGACGATGTTAAGTTGGTACCA
DOM7h-11-56                     ..........................................................T.......................................
DOM7h-11-57                     ..........................................................T.......................................
DOM7h-11-65                     ..........................................................T.......................................
DOM7h-11-67                     ..........................................................T.......................................
DOM7h-11-68                     ..........................................................T.......................................
DOM7h-11-69                     ..........................................................T.......................................
DOM7h-11-79                     ..........................................................T.......................................
DOM7h-11-80                     ..........................................................TT......................................

                                120       130       140       150       160       170       180       190       200       210       220
                                ....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|
VK Dummy                        ..................................TA...GCA..A.....................................................
DOM7h-11-15 DOM7h               GCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCCTTGCTTTTTCCCGTTTGCAAAGTGGGGTCCCATCACGTTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCA
DOM7h-11-56                     .....................................................................................................
DOM7h-11-57                     .....................................................................................................
DOM7h-11-65                     .....................................................................................................
DOM7h-11-67                     .....................................................................................................
DOM7h-11-68                     ............G........................................................................................
DOM7h-11-69                     .....................................................................................................
DOM7h-11-79                     .....................................................................................................
DOM7h-11-80                     .....................................................................................................

                                230       240       250       260       270       280       290       300       310       320
                                ....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|
VK Dummy                        ..........................................TCAA...AG.TAC.GTACC....AT.....................................G
DOM7h-11-15 DOM7h               CCATCAGCAGTCTGCAACCTGAAGATTTTGCTACGTACTACTGCGCGCAGGCTGGGACGCATCCTACGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGG
DOM7h-11-56                     ..........................................................................................T..
DOM7h-11-57                     .........A................................................................................T..
DOM7h-11-65                     ........................G..................T.....................................................T..
DOM7h-11-67                     ..........................................T.....................A.....................A....T..
DOM7h-11-68                     ..........................................T......A..............................................T..
DOM7h-11-69                     ..........................................T.............GT.....................................
DOM7h-11-79                     ..........................................T......A..............................................T..
DOM7h-11-80                     ..........................................................................................T..
```

Figure 3B