IMPROVED ANTI-SERUM ALBUMIN BINDING SINGLE VARIABLE DOMAINS

The invention relates to improved anti-serum albumin immunoglobulin single variable domains, as well as ligands and drug conjugates comprising such domains, compositions, nucleic acids, vectors and hosts.

BACKGROUND OF THE INVENTION

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

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

Reference is also made to Holt *et al*, "Anti-Serum albumin domain antibodies for extending the half-lives of short lived drugs", Protein Engineering, Design & Selection, vol 21, no 5, pp283-288, 2008.

It would be desirable to provide improved heavy chain variable domain dAbs 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, eg, 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 (eg, TNFR1) on the cell surface, thus increasing the likelihood of receptor agonism and detrimental receptor signaling. It would also be desirable to provide anti-SA dAbs that have relatively high melting temperatures. This is useful for providing stable formulations, eg, storage-stable formulations and variable domains that have a good shelf-life.

SUMMARY OF THE INVENTION

Aspects of the present invention solve these problems.

In one aspect the invention, therefore, there is provided an anti-serum albumin (SA) immunoglobulin single variable domain comprising an amino acid sequence that is at least 80% identical to an amino acid sequence selected from SEQ ID NOs: 97 to 191 and 198 to 203.

An aspect of the invention provides an anti-serum albumin (SA) immunoglobulin single variable domain comprising an amino acid sequence having up to 4 amino acid changes compared to an amino acid sequence selected from SEQ ID NOs: 97 to 191 and 198 to 203.

An aspect of the invention provides an anti-serum albumin (SA) immunoglobulin single variable domain comprising an amino acid sequence that is

encoded by a nucleotide sequence which is at least 80% identical to a sequence selected from SEQ ID NOs 1 to 96 and 192-197.

An aspect of the invention provides a multispecific ligand comprising an anti-SA variable domain of the invention and a binding moiety that specifically binds a target antigen other than SA.

An aspect of the invention provides an anti-SA single variable domain of the invention, wherein the variable domain is conjugated to a drug (optionally an NCE drug).

An aspect of the invention provides a fusion product, eg, a fusion protein or fusion with a peptide or NCE (new chemical entity) drug, comprising a polypeptide, protein, peptide or NCE drug fused or conjugated (for an NCE) to any anti-SA variable domain of the invention. For example, the variable domain comprises or consists of the amino acid sequence of any one of SEQ ID NOs: 97 to 103 and 198 to 203 (or an amino acid sequence that is at least 95, 96, 97, 98 or 99% identical to the amino acid sequence of any one of SEQ ID NOs: 97 to 103 and 198 to 203).

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

An aspect of the invention provides a nucleic acid comprising a nucleotide sequence encoding a variable domain, or a multispecific ligand or fusion protein of the invention.

An aspect of the invention provides a nucleic acid comprising a nucleotide sequence that is at least 80% identical to a sequence selected from SEQ ID NOs 1 to 96 and 192-197.

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 of the invention.

An aspect of the invention provides a method of treating or preventing a disease or disorder in a patient, comprising administering at least one dose of a variable domain, or a multispecific ligand or fusion protein of the invention to said patient.

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

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

A variable domain with moderate affinity, (but specificity to SA) would only stay in serum circulation for a short time (eg, for a few hours or a few days) allowing

for the specific targeting of therapeutic targets involved in acute diseases by the fused therapeutic agent.

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

DETAILED DESCRIPTION OF THE INVENTION

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

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

As used herein, the term "antagonist of Tumor Necrosis Factor Receptor 1 (TNFR1)" or "anti-TNFR1 antagonist" or the like refers to an agent (e.g., a molecule, a compound) which binds TNFR1 and can inhibit a (i.e., one or more) 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, eg, a mammal, eg, a non-human primate (such as a baboon, rhesus monkey or Cynomolgus monkey), mouse, human, rabbit, rat, dog, cat or pig. In one embodiment, the patient is a human.

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

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

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

As used herein, "antibody format" refers to any suitable polypeptide structure in which one or more antibody variable domains can be incorporated so as to confer binding specificity for antigen on the structure. A variety of suitable antibody formats are known in the art, such as, chimeric 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.

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 (eg, single variable domain, fusion protein or multi-specific ligand) half-life will be familiar to those skilled in the art. Details may be found in *Kenneth, A et al:* Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists and in *Peters et al,* Pharmacokinetc analysis: A Practical Approach (1996). Reference is also made to "Pharmacokinetics", M Gibaldi & D Perron, published by Marcel Dekker, 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, eg 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, eg 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, eg, in man.

In addition, or alternatively to the above criteria, the variable domain, fusion protein or ligand according to the invention has an AUC value (area under the curve) in the range of (or of about) 1 mg.min/ml or more. In one embodiment, the lower end of the range is (or is about) 5, 10, 15, 20, 30, 100, 200 or 300 mg.min/ml. In addition, or alternatively, the variable domain, fusion protein or ligand according to the invention has an AUC in the range of (or of about) 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 that is structurally and/or functionally similar to a cognate partner or target.

The term "binding moiety" refers to a domain that specifically binds an antigen or epitope independently of a different epitope or antigen binding domain. A binding moiety may be a domain antibody (dAb) or may be a domain which is a derivative of a non-immunoglobulin protein scaffold, eg, a scaffold selected from the group consisting of CTLA-4, lipocalin, SpA, an adnectin, affibody, an avimer, 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 embodiment, a variable domain of the invention comprises one or more of the following kinetic characteristics:-

(a) The variable domain 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 variable domain 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 variable domain 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 variable domain 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 abou)t 1 to (or to about) 6000 nM, as determined by surface plasmon resonance;

(e) The variable domain of any preceding claim, wherein the variable domain 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 variable domain of any preceding claim, wherein the variable domain 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 variable domain 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 variable domain 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 variable domain 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 variable domain 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 variable domain 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 variable domain 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 variable domain 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 variable domain 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 variable domain of any preceding aspect or embodiment of the invention and a binding moiety that specifically binds a target antigen other than SA. The binding moiety can be any binding moiety that specifically binds a target, eg, the moiety is an antibody, antibody fragment, scFv, Fab, dAb or a binding moiety comprising a 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 variable domain, 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 variable domain of the invention and an anti-TNFR1 binding moiety, eg, an anti-TNFR1 dAb. Optionally, the ligand has only one anti-TNFR1 binding moiety (eg, dAb) to reduce the chance of receptor cross-linking. In one embodiment, the anti-SA dAb comprises or consists of the amino acid sequence of any one of SEQ ID NOs: 97 to 103 and 198 to 203 (or an amino acid sequence that is at least 95, 96, 97, 98 or 99% identical to the amino acid sequence of any one of SEQ ID NOs: 97 to 103 and 198 to 203).

In one embodiment, the anti-TNFR1 binding moiety is DOM1h-131-206 disclosed in WO2008149148 (the amino acid sequence of which and the nucleotide sequence of which, as disclosed in that PCT application, are expressly incorporated herein by reference as though explicitly written herein and for use with the present invention, and it is contemplated that any part of such disclosure can be incorporated into one or more claims herein). In one embodiment, the multispecific ligand comprises or consists of the amino acid sequence of DOM1h-131-206 and the amino acid sequence of any one of SEQ ID NOs: 97 to 103 and 198 to 203 (or an amino acid sequence that is at least 95, 96, 97, 98 or 99% identical to the amino acid sequence of any one of SEQ ID NOs: 97 to 103 and 198 to 203).

In one embodiment, the anti-TNFR1 binding moiety or dAb is any such moiety or dAb disclosed in co-pending application USSN 61/153,746, the disclosure of which is incorporated herein by reference. In one embodiment, the anti-TNFR1 binding moiety comprises an amino acid sequence that is at least 95% identical to the amino acid sequence of DOM1h-574-156, DOM1h-574-72, DOM1h-574-109, DOM1h-574-138, DOM1h-574-162 or DOM1h-574-180 or the amino acid sequence of any anti-TNFR1 dAb disclosed herein. In one embodiment, the multispecific ligand comprises or consists of the amino acid sequence of DOM1h-574-156 and the amino acid sequence of any one of SEQ ID NOs: 97 to 103 and 198 to 203 (or an amino acid sequence that is at least 95, 96, 97, 98 or 99% identical to the amino acid sequence of any one of SEQ ID NOs: 97 to 103 and 198 to 203).

In one embodiment, the ligand of the invention is a fusion protein comprising a variable domain 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 variable domain 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 domain 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 variable domain of the invention. In one example, the drug is covalently linked to the variable domain (eg, the variable domain 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 variable domain. The drug can be covalently or noncovalently bonded to the variable domain 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 variable domain 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 (eg, monomer) 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, and 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, eg, a fusion protein or fusion with a peptide or conjugate with an NCE (new chemical entity) drug, comprising a polypeptide drug fused or conjugated (for an NCE) to any variable domain as described above, optionally wherein the variable domain comprises or consists of the amino acid sequence of any one of SEQ ID NOs: 97 to 103 and 198 to 203 (or an amino acid sequence that is at least 95, 96, 97, 98 or 99% identical to the amino acid sequence of any one of SEQ ID NOs: 97 to 103 and 198 to 203).

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

Also encompassed herein is an isolated nucleic acid encoding any of the variable domain, fusion proteins, conjugates or ligands described herein, e.g., a ligand which contains one single variable domain (eg, monomer) of the invention 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, 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 (eg, a non-human host cell or a host cell that is not isolated from a human or human embryo) 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 variable domains, fusion proteins or ligands which contains one single variable domain (monomer) or more than one single variable domains (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 variable domains, 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 variable domains, 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 domains, 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 domain, 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 variable domain 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 selected from any one of SEQ ID NOs: 1 to 96 and 192-197, 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 domains, ligands, fusion proteins, conjugates, nucleic acids, vectors, hosts and compositions of the present invention.

SEQUENCES OF ANTI-SERUM ALBUMIN VH SINGLE VARIABLE DOMAINS

All variable domains bind at least one species of serum albumin as determined by SPR..

Nucleotide sequences:

DOM7h-112 SEQ ID NO: 1
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGGGGGGTATGTGATGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGCTATTAATAGGTTTGGTTCGTCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGTAGTTTGCGGCATTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

DOM7h-98 SEQ ID NO: 2
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGGTAATTATGCGATGGCGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCGATTGATATGGTTGGTATTAAGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGTTTTCGTATTTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

DOM7r-29 SEQ ID NO: 3
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTAAGGATTATGATATGACTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAATGATTTCTTCGTCGGGTCTTTGGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGTTTTAGGCTGTTTCCTCGGACTTTTGACTACTGGGGTCAGGGAACCCTGGTCAC
CGTCTCGAGCG

DOM7r-35 SEQ ID NO: 4
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTTCGCTGTATAGGATGGTGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG

GGTCTCAATGATTTCTCAGTTTGGTAATCAGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGTTAGGTCTTGGGATCAGACTGGTGGTCGTCGTACTTTTGACTACTGGGGTCAGGG
AACCCTGGTCACCGTCTCGAGC

DOM7r-36 SEQ ID NO: 5
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTAATCATTATACGATGGGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATTGATTCATCCGAGTGGTACGGTGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATGGAGTTCGAGGGCGTTTGACTACTG
GGGTCAGGGAACCCTGGTCACCGTCTCGAGC

DOM7r-38 SEQ ID NO: 6
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGATAATAATGCGATGGGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTAGTGCGAATGGTAATGCGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGGACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGGTTTCGTCGGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

DOM7r31 SEQ ID NO: 7
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTACAG
CCTCCGGATTCACCTTTAGGCATTATCGTATGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATGGATTCGTCCGGATGGTACGTTTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATCTTATATGGGTGATAGGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTC
GAGCG

DOM7h-32 SEQ ID NO: 8
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGCGCAG
CCTCCGGATTCACCTTTGGTAATTATCCGATGACGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTGGAGTG
GGTCTCAACTATTAGTTATGGTGGTCTTGCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAATGGCGATTAATGGTGTTAGGCCTAGGCGGTTTGACTACTGGGGTCAGGGAACCCT
GGTCACCGTCTCGAGC

DOM7h-33 SEQ ID NO: 9
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTATGGCGTATCAGATGGCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTCATCAGACGGGTTTTTCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTAT
ATTACTGTGCGAAAGTGCGTTCTATGCGTCCTTATAAGTTTGACTACTGGGGTCAGGGAACCCTGGTCAC
CGTCTCGAGC

DOM7h-34 SEQ ID NO: 10
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGGTGATAAGGCAATGGGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACGATTAGTGCTCCTGGTAACCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGTTTTCGGAATTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

DOM7h-83 SEQ ID NO: 11
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGATGGGATGCGTATGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG

GGTCTCAGCTATTGAGGTGAATGGTCAGCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAATGGCTCATCCTCAGTCGGGGGTGGCTTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7h-84 SEQ ID NO: 12
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTACGCCTGATGCTATGGCGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCGATTGGTGTGAATGGTTCTCCGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAGGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAATGGCTCATCCTCAGTCGGGGGTGGCTTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7h-85 SEQ ID NO: 13
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTTATCAGTCGGATATGTCTTGGGTCCGCCAGGCTCCAGGGAAAGGTCTAGAGTG
GGTCTCATCTATTTCTTCTCAGGGTCGTTCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAATGGCTCATCCTCAGTCGGGGGTGGCTTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7h-86 SEQ ID NO: 14
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTACAG
CCTCCGGATTCACCTTTGCGGCGAGGGATATGAGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTGGAGTG
GGTCTCAAGTATTTCTGCTCAGGGTGCTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACGATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTAT
ATTACTGTGCGAAACCTCGGCATCCTCAGGGGGGGGTTACTTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7h-87 SEQ ID NO: 15
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGATAATGGGGATATGGTTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGGGATTGCGCATAATGGTCGTAATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAAATTTGGGTCAGGGTTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

DOM7h-88 SEQ ID NO: 16
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCACCTGTGCAG
CCTCCGGATTCACCTTGAATGGTACGTCGATGGGGTGGGTCCGCCAGGCTCCAGGGAAGGATCTAGAGTG
GGTCTCATCTATTATGCCTGTGGGTTCTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAATGGCTCATCCTCAGTCGGGGGTGGCTTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7h-89 SEQ ID NO: 17
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGATCATGCGCCTATGAAGTGGGCCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATATATTGGGTCGGCGGGTAATATGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGATGAGGGGCCGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

DOM7h-90 SEQ ID NO: 18

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTACAG
CCTCCGGATTCACCTTTGATGGGATGGATATGAGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAAGTATTTCTACGACTGGTGGGACTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACCTCGGCATCCTCAGGGGGGGGTTACTTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7h-91 SEQ ID NO: 19
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
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GGTCTCAACTATTCATTCGGAGGGTTCTCGGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACCTCGGCATCCTCAGGGGGGGGTTACTTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7h-92 SEQ ID NO: 20
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTAGTACTGGGGAGATGGCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
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TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
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CACCGTCTCGAGC

DOM7h-93 SEQ ID NO: 21
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTCCTAGTGCTGATATGGTTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCACGTATTTCGCCTGAGGGTAATCATACATACTACGCAGACTCCGTGAAGGGTCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTAT
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CGTCTCGAGC

DOM7h-94 SEQ ID NO: 22
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGCGAATGCGACTATGTCGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
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TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATATTCGTGGCATCCGGATCTGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGT
CTCGAGC

DOM7h-95 SEQ ID NO: 23
GAGGTGCGGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTAAGGATTATGGGATGAATTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
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TCCCGCGACAACTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATTGGCTGCTCCGGTTCGTCAGAAGGGGATGGATTTTGACTACTGGGGTCAGGGAAC
CCTGGTCACCGTCTCGAGC

DOM7h-96 SEQ ID NO: 24
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGAGTGGTATAATATGTCGTGGGTCCGCCAGGCTCCAGGGAAGGATCTGGAGTG
GGTCTCATCGATTTCTCATGATGGTTGGAATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGGATGATTGGTTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

DOM7h-97 SEQ ID NO: 25
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGATATTTATACGATGCATTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
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TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATCTAAGCGTAGGTTTCTTAAGAGGTTTGACTACTGGGGTCAGGGAACCCTGGTCAC
CGTCTCGAGC

DOM7h-99 SEQ ID NO: 26
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ATTACTGTGCGAAAGCTAGTATGTGGACGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAA
C

DOM7h-100 SEQ ID NO: 27
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTATGTTGTATCATATGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
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TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACTGGGGCTTCGGGGTGTGCTGTGGCGGAGGAGGTTTGACTACTGGGGTCAGGGAAC
CCTGGTCACCGTCTCGAGC

DOM7h-101 SEQ ID NO: 28
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
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TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
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GGTCACCGTCTCGAGC

DOM7h-102 SEQ ID NO: 29
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGGTCCGTATTGGATGGCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
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TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTAT
ATTACTGTGCGAAAGGGCGTCCTCGTGTTGGTTTGTGGAGGTCGGGGTTTGACTACTGGGGTCAGGGAAC
CCTGGTCACCGTCTCGAGC

DOM7h-103 SEQ ID NO: 30
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
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GGTCTCATCTATTAATATTACTGGTTCTACTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAGATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGTTTTAGGTCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

DOM7h-106 SEQ ID NO: 31
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGCTGGTTATACGATGTCGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACGATTTCGGGTTTTGGTTGGACTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTAT
ATTACTGTGCGAAAAGGCTGGGGATGCGTTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

DOM7h-109 SEQ ID NO: 33
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGGTCCGTATTCGATGGGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATTTATTCATTCTGATGGTCGTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAAAGACGCCTTATAGGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

DOM7h-111 SEQ ID NO: 34
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGGGCAGTATGCTATGCAGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCTATTAATATTACTGGTTCTACTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAGATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGTTTTAGGTCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

DOM7h-114 SEQ ID NO: 35
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTAGGCGGTATGCGATGTCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACGATTTCGCCTTATGGTCCTGTTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAATAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGCTTATTATGGTGGGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

DOM7r-34 SEQ ID NO: 36
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGATGCTTATGCTATGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAAAGATTGATTCTCCTGGTTGGAGGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATCGGCTCGGATGCGTTCTCGGCATTTTGACTACTGGGGTCAGGGAACCCTGGTCAC
CGTCTCGAGC

DOM7r-37 SEQ ID NO: 37
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTAAGGATTATGGGATGAATTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCACGGATTAGTAGGAATGGTACTGTTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAATTAGGTGGAATACTGCTCAGGTGCCTGTGTTTGACTACTGGGGTCAGGGAACTCT
GGTCACCGTCTCGAGC

DOM7r-39 SEQ ID NO: 38
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAA
CCTCCGGATTCACCTTTCCGTCTTATACGATGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCACGTATTTCTCGTACTGGGAATTATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTAT
ATTACTGTGCGAAACCTATGTATAATAGGGGGTCTTCGTATTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7r-40 SEQ ID NO: 39
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTTCGCAGTATCAGATGTCGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCGATTTCGCCTACGGGTATTCAGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC

TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAAGGCTTATTGGGATGCCGTATGTTGAGGATACTTTTGACTACTGGGGTCAGGGAAC
CCTGGTCACCGTCTCGAGC

DOM7r-41 SEQ ID NO: 40
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTATGGAGTATGAGATGGAGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGGTATTACTAATTCTGGTTCTGGGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAACTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGATAATGCAGCATCCTCAGGCGACTGGGGGGAGGGTTGGGTTTGACTACTGGGGTCAGGG
AACCCTGGTCACCGTCTCGAGC

DOM7r-42 SEQ ID NO: 41
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTCCGAGGTATACTATGAAGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCGATTGATAGGACGGGTCGTAAGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTAT
ATTACTGTGCGAAAGAGTCGTTGGTTTCGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

DOM7r-43 SEQ ID NO: 42
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGGTGGTTATACGATGCCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTTCTCGTGATGGTAATTATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGATATTGGTATGGGTTTTGACTACGGGGGGCGGGGAACCCTGGTCACCGTCTCGAG
C

DOM7r-44 SEQ ID NO: 43
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGAGATTTATGCGATGCATTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACGATTAGTTCGGGTGGTAAGGGGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATCGCGTACTATGTATTTTCGTGTTAGGGAGGCTTTTGACTACTGGGGTCAGGGAAC
CCTGGTCACCGTCTCGAGC

DOM7r-45 SEQ ID NO: 44
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTCGTGCTTATAGGATGATGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTGGAGTG
GGTCTCATCTATTGATCCTGATGGTGCGGTTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGGAACATTTTGATCTTGCGATGCCGAATCCGAATGCGAAGTTTGACTACTGGGGTCAGGG
AACCCTGGTCACCGTCTCGAGC

DOM7r-46 SEQ ID NO: 45
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGCCTCTCCTGTGCAG
CCTCCGGATTCACCTTTTCTCGTTATCAGATGTCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTGGAGTG
GGTCTCATCTATTAAGTCGAATGGTTCTTCGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACCTAGTCGGCAGAGTTTTCAGTATCCGAGTTTTGACTACTGGGGTCAGGGAACCCT
GGTCACCGTCTCGAGC

DOM7r-47 SEQ ID NO: 46

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGGGCGTTATAAGATGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCTATTTCGCCTACGGGTTCGTCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAACTGGGTATGTTATGGTTGAGCATTTTGACTACTGGGGTCAGGGAACCCTGGTCAC
CGTCTCGAGC

DOM7r-48 SEQ ID NO: 47
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTAGTGATTATCCGATGAAGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTGGAGTG
GGTCTCAACTATTAATTCTTCGGGTACGATTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACCGTTGTTGCCGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

DOM7r-49 SEQ ID NO: 48
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
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GGTCTCATGTATTCGGGATCCGGGTTTTCCGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATGTTCGCCGTCTTCTACGCAGTGTACGGGGCTTTTTGACTACTGGGGTCAGGGAAC
CCTGGTCACCGTCTCGAGC

DOM7r-50 SEQ ID NO: 49
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTAGGTTTTATGGGATGGCGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCACTTATTGATCCTCCTGGTGGGGCGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAATGGAGAGGCGGCATCTTAAGAGTGGTCATAAGGGGTTTGACTACTGGGGTCAGGG
AACCCTGGTCACCGTCTCGAGC

DOM7r-51 SEQ ID NO: 50
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTACGGAGTATGATATGATGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCTATTAGTCATAGGGGTGAGAAGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGATAAGCGTTATCGGGGGTCTCAGCATTATTTTGACTACTGGGGTCAGGGAACCCT
GGTCACCGTCTCGAGC

DOM7r-52 SEQ ID NO: 51
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTCGGAGTTATGATATGGGTTGGGCCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTGGGTCGAATGGTGCTAATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACTTATGGGTATGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

DOM7r-53 SEQ ID NO: 52
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGAGCGTTATTCTATGAGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACGATTGGTTCGACGGGTAAGTGGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGGCGTGGGTTGGTTTCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTC
GAGC

DOM7r-54 SEQ ID NO: 53

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTAGGCGTTATTCGATGTCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCTATTGATCGGTCTGGTAGGATGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATCTCGGCTGTCTTCGACGGGTTCTGAGGGTCATAATTTTGACTACTGGGGTCAGGG
AACCCTGGTCACCGTCTCGAGC

DOM7r-55 SEQ ID NO: 54
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTAAGTGGTATCCGATGAAGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTGCTTATGATGGTGTTCAGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATTGGGTCCGACTAGTCGTGTGTTTGCTGCTACTGATTTTGACTACTGGGGTCAGGG
AACCCTGGTCACCGTCTCGAGC

DOM7r-56 SEQ ID NO: 55
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTCCGAATTATGCGATGAAGTGGGGCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTGATACGAGTGGTAGTACTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACTTACTCATCCTATGGCGCCGCGTCCGGCTTTTGACTACTGGGGTCAGGGAACCCT
GGTCACCGTCTCGAGC

DOM7r-57 SEQ ID NO: 56
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
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GGTCTCATCGATTGGGCCTTGGGGTACTCCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAATTTCGCATCCTCAGGCGATGTATCATACGTTTGACTACTGGGGTCAGGGAACCCT
GGTCACCGTCTCGAGC

DOM7r-58 SEQ ID NO: 57
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
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GGTCTCAGATATTGATCATTCGGGTTCGTATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATGGTGGCATCCGCAGGGGGGGACTTTTGACTACTGGGGTCAGGGAACCCTGGTCAC
CGTCTCGAGC

DOM7r-59 SEQ ID NO: 58
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
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GGTCTCAACGATTGGGGCGAATGGTAAGGCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGGAAGCGGGTCATCCTCAGGCGCCGTCTTTTAAGAGTTTTGACTACTGGGGTCAGGGAAC
CCTGGTCACCGTCTCGAGC

DOM7r-60 SEQ ID NO: 59
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
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GGTCTCAACTATTGATCGGGATGGTGCTAATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACTTCCTCCGCCGATGTCGCCGAAGAAGTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7r-61 SEQ ID NO: 60
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
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GGTTTCAACTATTGATCGTATGGGTAGGTATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAAGGGATTCGCATCCTATGGGGTTTGACTACCGGGGTCAGGGAACCCTGGTCACCGT
CTCGAGC

DOM7r-62 SEQ ID NO: 61
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
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GGTCTCATCGATTGGTCCTACGGGTAGTGGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAACTCCTCATCCGCAGGTTTCTAGTTTTGACTACTGGGGTCAGGGAACCCTGGTCAC
CGTCTCGAGC

DOM7r-63 SEQ ID NO: 62
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
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GGTCTCAGAGATTGCGCCTTCGGGTGATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTAT
ATTACTGTGCGAAAGTGATTTGTCAGAATCAGTGTCTGTTTGACTACTGGGGTCAGGGAACCCTGGTCAC
CGTCTCGAGC

DOM7r-64 SEQ ID NO: 63
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
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GGTCTCATTTATTACTTCTGATGGTCGGGATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACCTAGTCTGCCTCATGTTACGGCTTTTGACTACTGGGGTCAGGGAACCCTGGTCAC
CGTCTCGAGC

DOM7r-65 SEQ ID NO: 64
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGAGGATGAGACGATGAGTTGGGCCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCGATTGGGGATGCTGGTATGCCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGGGAGCCGATTTATGTTCATACGACTCATTTTGACTACTGGGGTCAGGGAACCCT
GGTCACCGTCTCGAGC

DOM7r-66 SEQ ID NO: 65
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTCCGCATGGTAAGATGGGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATGGATTGCTGGGTCTGGTGATATGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATTGGGTCATCCTCAGCGGGGTTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGT
CTCGAGC

DOM7r-67 SEQ ID NO: 66
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGGGACTTCTGATATGTCGTGGGTCCGCCAGGCCCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTGATTCTGGGGGTAGTTTTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC

TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACCTCGGCATCCTCAGGGGGGGGTTACTTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7r-68 SEQ ID NO: 68
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGAGCATGTTCCTATGGCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCACGGATTAGTGAGCAGGGTAGTAATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGTGCAGCATCCTATGTCTCCGCATGAGTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7r-69 SEQ ID NO: 69
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGAGCAGGGTATGATGTCGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCGATTAATCCTGGTGGTCAGTTTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAGGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGGAAGATCTGGGGCCGGGTTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

DOM7r-70 SEQ ID NO: 70
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
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GGTCTCAACTATTGATAGGTCTGGTAATACTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTAT
ATTACTGTGCGAAAGTTTTGCATCCTCAGGCGGGGTCTGCTTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7r-71 SEQ ID NO: 71
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTCGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
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GGTCTCATATATTGATAATCAGGGTTATAATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATATAAGCTTCTGGGTCCGTCTACTGAGTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7r-72 SEQ ID NO: 72
GAGGTGCAGCTGTTGGAGTCAGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTAGTAGTGATGTTATGTCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAAGTATTACGAGGTCGGGTATGCAGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATATGCGCATCCTCAGTCGGCTGTTGAGTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7r-73 SEQ ID NO: 73
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTCGTAATGAGCCGATGAGTTGGGTGCGCCAGGCTCCAGTGAAGGGTCTAGAGTG
GGTCTCAACTATTTCGCCTGATGGTAGTGGGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACATGGTCATCCTCAGGGGGCTCGTTTTGACTACTGGGGTCAGGGAACCCTGGTCAC
CGTCTCGAGC

DOM7r-74 SEQ ID NO: 74

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTTTGAATAGTGAGATGTCGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTGGAGTG
GGTCTCAACTATTGGGTATGCGGGTACTCCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACCTCGGCATCCTCAGGGGGGGGTTACTTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7r-75 SEQ ID NO: 75
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGCTCGGGGGCCTATGTCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTACGAATGATGGTACGTCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGGAACCGCCTCATAGTGGTAGGCCTATGTTTGACTACTGGGGTCAGGGAACCCTGGTCAC
CGTCTCGAGC

DOM7r-76 SEQ ID NO: 76
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTCAGCGGACTGCTATGTCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTTGAGTG
GGTCTCATCTATTGAGGCTTCGGGTCGGTATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACAGTCGCATCCTCAGAATGGTCGTTTTGACTACTGGGGTCAGGGAACCCTGGTCAC
CGTCTCGAGC

DOM7r-77 SEQ ID NO: 77
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGATGCGTCGGAGATGGCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAAGTATTACGGTTTATGGTGATAGGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACCTCGGCATCCTCAGGGGGGGGTTACTTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7r-78 SEQ ID NO: 78
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGATGATTCGCATATGGCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAAGGATTTCGAGGGAGGGTAAGGCGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGGCACCGAATGATCAGTCGGCGGCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGT
CTCGAGC

DOM7r-79 SEQ ID NO: 79
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGATATGAGTGAGATGTCGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGCTATTACTTCGGATGGTAGTTCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACCTAGTCTGCCTCATGTTACGGCTTTTGACTACTGGGGTCAGGGAACCCTGGTCAC
CGTCTCGAGC

DOM7r-80 SEQ ID NO: 80
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGAGAGGTCTACTATGCATTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGAGATTGATGCTCTGGGTACGGATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATCGTCTGATCATCCTCAGAATAGTTTTGACTACTGGGGTCAGGGAACCCTGGTCAC
CGTCTCGAGC

DOM7r-81 SEQ ID NO: 81
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGAGCCTCGTGAGATGTATTGGGCCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCGCACGGATTGGTTGGGATGGTCATACGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACAGCTGGGTCAGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

DOM7r-82 SEQ ID NO: 82
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGATGCTTATAGTATGATGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTGGTAGGTGGGGTGAGATTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTAT
ATTACTGTGCGAAACGTCGTTATATTGGGCCTTATATGCTTTCGGGTCGTTTTGACTACTGGGGTCAGGG
AACCCTGGTCACCGTCTCGAGC

DOM7r-83 SEQ ID NO: 83
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTATGCGGTATCCTATGGTGTGGGTCCGCCAGGCTCCAGGGAGGGGTCTAGAGTG
GGTCTCATCTATTTCTCCTGCTGGTTATGGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGTCATGAGATTAGTCGGTTTTCTCGTTGGTCTTCTTTTGACTACTGGGGTCAGGG
AACCCTGGTCACCGTCTCGAGC

DOM7r-84 SEQ ID NO: 84
GAGGTGCAGCTGTTGGAGTCTGGGGGGGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTCGGAAGTATAGGATGTCGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCTATTGCGAGGAATGGTCGTTCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAACTACGTCTGGGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

DOM7r-85 SEQ ID NO: 85
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTAATAAGAAGGAGATGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCTATTGATGTGAGTGGTAATGTTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAATGGCTCATCCTCAGTCGGGGGTGGCTTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7r-88 SEQ ID NO: 86
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTCGGATGTATGATATGGCGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAAAGTG
GGTCTCAACTATTCTGTCTTCTGGTAAGGGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATTGGCTCATCCTCAGAAGGGTAGTATTTTTGACTACCGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7r-89 SEQ ID NO: 87
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTCATCAGGGTCCTATGGGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATGGATTCAGGCTACGGGTGGTGCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGGATGCATCCTCAGAGTGGTACTCTTTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7r-90 SEQ ID NO: 88
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGATGTTGCGGATATGGATTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGGGATTTCGTCGTCGGGTGGTTATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTAT
ATTACTGTGCGAAAAATTTGGGTCAGGGTTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

DOM7r-92 SEQ ID NO: 89
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGATACGAGTAGTATGTTGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGTTATTCATCAGAGTGGTACGCCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATTTCCGTTTACTCATGGTAAGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGT
CTCGAGC

DOM7r-93 SEQ ID NO: 90
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTAATAATTATACGATGGGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATTGATTCATACGAGTGGTACGGTGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATGGAGTTCGAGGGCGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

DOM7r-94 SEQ ID NO: 91
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGGGAATTATAGGATGACTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTTCTCCTTTGGGTACGTATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGGCGTTGGTCGATTTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

DOM7r-95 SEQ ID NO: 92
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGGTAGTTATCCTATGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTGGAGTG
GGTCTCATGGATTCGTGGGAGGGGTCTTGCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATATTTTCATGGTAAGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

DOM7r-96 SEQ ID NO: 93
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTAGTGCTTATGTGATGGGTTGGGTACGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCGATTCGGATGCCGGGTTATCTGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACGTACTCCTTTTTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

DOM7r-97 SEQ ID NO: 94
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTGAGCATTATTCGATGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGAGATTGATCCGGATGGTATTATGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT

ATTACTGTGCGAAAGCGCCGGGGGTTCTTGAGATGTGGATTACGCATTTTGACTACTGGGGTCAGGGAAC
CCTGGTCACCGTCTCGAGC

DOM7r-98 SEQ ID NO: 95
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTCGTCATTATGTGATGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGCTATTTCTGCGCATGGTAATCGGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATCTTATAGCCTTGCTCTGACTCCTTTTGACTACTGGGGTCAGGGAACCCTGGTCAC
CGTCTCGAGC

DOM7r-99 SEQ ID NO: 96
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTCACCTTTACTGTGTATGAGATGAAGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGCGATTTCTGCTGGGGGTAAGTATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGAGATTCGGCATCTTGATAATGCGGTTGAGTTTGACTACTGGGGTCAGGGAACCCT
GGTCACCGTCTCGAGC

Amino acid sequences:

DOM7h-112 SEQ ID NO: 97
EVQLLESGGGLVQPGGSLRLSCAASGFTFGGYVMGWVRQAPGKGLEWVSAINRFGSSTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKGSLRHFDYWGQGTLVTVSS

DOM7h-98 SEQ ID NO: 98
EVQLLESGGGLVQPGGSLRLSCAASGFTFGNYAMAWVRQAPGKGLEWVSSIDMVGIKTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKGFRIFDYWGQGTLVTVSS

DOM7r-29 SEQ ID NO: 99
EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYDMTWVRQAPGKGLEWVSMISSSGLWTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKGFRLFPRTFDYWGQGTLVTVSS

DOM7r-35 SEQ ID NO: 100
EVQLLESGGGLVQPGGSLRLSCAASGFTFSLYRMVWVRQAPGKGLEWVSMISQFGNQTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKVRSWDQTGGRRTFDYWGQGTLVTVSS

DOM7r-36 SEQ ID NO: 101
EVQLLESGGGLVQPGGSLRLSCAASGFTFNHYTMGWVRQAPGKGLEWVSLIHPSGTVTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKWSSRAFDYWGQGTLVTVSS

DOM7r-38 SEQ ID NO: 102
EVQLLESGGGLVQPGGSLRLSCAASGFTFDNNAMGWVRQAPGKGLEWVSTISANGNATYYADSVKGRFTI
SRDNSKDTLYLQMNSLRAEDTAVYYCAKGFRRFDYWGQGTLVTVSS

DOM7r31 SEQ ID NO: 103
EVQLLESGGGLVQPGGSLRLSCTASGFTFRHYRMGWVRQAPGKGLEWVSWIRPDGTFTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKSYMGDRFDYWGQGTLVTVSS

DOM7h-32 SEQ ID NO: 104
EVQLLESGGGLVQPGGSLRLSCAASGFTFGNYPMTWVRQAPGKGLEWVSTISYGGLATYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKMAINGVRPRRFDYWGQGTLVTVSS

DOM7h-33 SEQ ID NO: 105

EVQLLESGGGLVQPGGSLRLSCAASGFTFMAYQMAWVRQAPGKGLEWVSTIHQTGFSTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKVRSMRPYKFDYWGQGTLVTVSS

DOM7h-34 SEQ ID NO: 106
EVQLLESGGGLVQPGGSLRLSCAASGFTFGDKAMGWVRQAPGKGLEWVSTISAPGNRTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKGFRNFDYWGQGTLVTVSS

DOM7h-83 SEQ ID NO: 107
EVQLLESGGGLVQPGGSLRLSCAASGFTFDGMRMGWVRQAPGKGLEWVSAIEVNGQHTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKMAHPQSGVAFDYWGQGTLVTVSS

DOM7h-84 SEQ ID NO: 108
EVQLLESGGGLVQPGGSLRLSCAASGFTFTPDAMAWVRQAPGKGLEWVSSIGVNGSPTYYADSVKGRFTI
SRDNSRNTLYLQMNSLRAEDTAVYYCAKMAHPQSGVAFDYWGQGTLVTVSS

DOM7h-85 SEQ ID NO: 109
EVQLLESGGGLVQPGGSLRLSCAASGFTFYQSDMSWVRQAPGKGLEWVSSISSQGRSTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKMAHPQSGVAFDYWGQGTLVTVSS

DOM7h-86 SEQ ID NO: 110
EVQLLESGGGLVQPGGSLRLSCTASGFTFAARDMSWVRQAPGKGLEWVSSISAQGAHTYYADSVKGRFTI
SRDDSKNTLYLQMNSLRAEDTAVYYCAKPRHPQGGVTFDYWGQGTLVTVSS

DOM7h-87 SEQ ID NO: 111
EVQLLESGGGLVQPGGSLRLSCAASGFTFDNGDMVWVRQAPGKGLEWVSGIAHNGRNTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKNLGQGFDYWGQGTLVTVSS

DOM7h-88 SEQ ID NO: 112
EVQLLESGGGLVQPGGSLRLTCAASGFTLNGTSMGWVRQAPGKDLEWVSSIMPVGSHTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKMAHPQSGVAFDYWGQGTLVTVSS

DOM7h-89 SEQ ID NO: 113
EVQLLESGGGLVQPGGSLRLSCAASGFTFDHAPMKWARQAPGKGLEWVSYIGSAGNMTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKDEGPFDYWGQGTLVTVSS

DOM7h-90 SEQ ID NO: 114
EVQLLESGGGLVQPGGSLRLSCTASGFTFDGMDMSWVRQAPGKGLEWVSSISTTGGTTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKPRHPQGGVTFDYWGQGTLVTVSS

DOM7h-91 SEQ ID NO: 115
EVQLLESGGGLVQPGGSLRLSCAASGFTFEAETMAWVRQAPGKGLEWVSTIHSEGSRTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKPRHPQGGVTFDYWGQGTLVTVSS

DOM7h-92 SEQ ID NO: 116
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTGEMAWVRQAPGKGLEWVSSISSSGATTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKPRHPQGGVTFDYWGQGTLVTVSS

DOM7h-93 SEQ ID NO: 117
EVQLLESGGGLVQPGGSLRLSCAASGFTFPSADMVWVRQAPGKGLEWVSRISPEGNHTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAERPPSDYVSFDYWGQGTLVTVSS

DOM7h-94 SEQ ID NO: 118
EVQLLESGGGLVQPGGSLRLSCAASGFTFANATMSWVRQAPGKGLEWVSDIDQVGHATYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKYSWHPDLFDYWGQGTLVTVSS

DOM7h-95 SEQ ID NO: 119
EVRLLESGGGLVQPGGSLRLSCAASGFTFKDYGMNWVRQAPGKGLEWVSRISRNGTVTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKLAAPVRQKGMDFDYWGQGTLVTVSS

DOM7h-96 SEQ ID NO: 120
EVQLLESGGGLVQPGGSLRLSCAASGFTFEWYNMSWVRQAPGKDLEWVSSISHDGWNTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKGMIGFDYWGQGTLVTVSS

DOM7h-97 SEQ ID NO: 121
VQLLESGGGLVQPGGSLRLSCAASGFTFDIYTMHWVRQAPGKGLEWVSTIVPQGTPTYYADSVKGRFTIS
RDNSKNTLYLQMNSLRAEDTAVYYCAKSKRRFLKRFDYWGQGTLVTVSS

DOM7h-99 SEQ ID NO: 122
EVQLLESGGGLVQPGGSLRLSCAASGFTFARYDMQWVRQAPGKGLEWVSSIKSNGMKTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKASMWTFDYWGQGTLVTVSN

DOM7h-100 SEQ ID NO: 123
EVQLLESGGGLVQPGGSLRLSCAASGFTFMLYHMGWVRQAPGKGLEWVSAITGGGYPTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKLGLRGVLWRRRFDYWGQGTLVTVSS

DOM7h-101 SEQ ID NO: 124
EVQLLESGGGLVQPGGSLRLSCAASGFTFGAYSMMWVRQAPGKGLEWVSRISRNGTVTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKIRWNTAQVPVFDYWGQGTLVTVSS

DOM7h-102 SEQ ID NO: 125
EVQLLESGGGLVQPGGSLRLSCAASGFTFGPYWMAWVRQAPGKGLEWVSTITPSGRGTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKGRPRVGLWRSGFDYWGQGTLVTVSS

DOM7h-103 SEQ ID NO: 126
EVQLLESGGGLVQPGGSLRLSCAASGFTFGQYAMQWVRQAPGKGLEWVSSINITGSTTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKGFRSFDYWGQGTLVTVSS

DOM7h-106 SEQ ID NO: 127
VQLLESGGGLVQPGGSLRLSCAASGFTFAGYTMSWVRQAPGKGLEWVSTISGFGWTTYYADSVKGRFTIS
RDNSKNTLYLQMNSLRAEDTAVYYCAKRLGMRFDYWGQGTLVTVSS

DOM7h-109 SEQ ID NO: 129
EVQLLESGGGLVQPGGSLRLSCAASGFTFGPYSMGWVRQAPGKGLEWVSFIHSDGRHTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKKTPYRFDYWGQGTLVTVSS

DOM7h-111 SEQ ID NO: 130
EVQLLESGGGLVQPGGSLRLSCAASGFTFGQYAMQWVRQAPGKGLEWVSSINITGSTTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKGFRSFDYWGQGTLVTVSS

DOM7h-114 SEQ ID NO: 131
EVQLLESGGGLVQPGGSLRLSCAASGFTFRRYAMSWVRQAPGKGLEWVSTISPYGPVTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKAYYGGFDYWGQGTLVTVSS

DOM7r-34 SEQ ID NO: 132
EVQLLESGGGLVQPGGSLRLSCAASGFTFDAYAMGWVRQAPGKGLEWVSKIDSPGWRTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKSARMRSRHFDYWGQGTLVTVSS

DOM7r-37 SEQ ID NO: 133
EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYGMNWVRQAPGKGLEWVSRISRNGTVTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKIRWNTAQVPVFDYWGQGTLVTVSS

DOM7r-39 SEQ ID NO: 134
EVQLLESGGGLVQPGGSLRLSCATSGFTFPSYTMGWVRQAPGKGLEWVSRISRTGNYTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKPMYNRGSSYFDYWGQGTLVTVSS

DOM7r-40 SEQ ID NO: 135
EVQLLESGGGLVQPGGSLRLSCAASGFTFSQYQMSWVRQAPGKGLEWVSSISPTGIQTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKRLIGMPYVEDTFDYWGQGTLVTVSS

DOM7r-41 SEQ ID NO: 136
EVQLLESGGGLVQPGGSLRLSCAASGFTFMEYEMEWVRQAPGKGLEWVSGITNSGSGTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAIMQHPQATGGRVGFDYWGQGTLVTVSS

DOM7r-42 SEQ ID NO: 137
EVQLLESGGGLVQPGGSLRLSCAASGFTFPRYTMKWVRQAPGKGLEWVSSIDRTGRKTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKESLVSFDYWGQGTLVTVSS

DOM7r-43 SEQ ID NO: 138
EVQLLESGGGLVQPGGSLRLSCAASGFTFGGYTMPWVRQAPGKGLEWVSTISRDGNYTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKDIGMGFDYGGRGTLVTVSS

DOM7r-44 SEQ ID NO: 139
EVQLLESGGGLVQPGGSLRLSCAASGFTFEIYAMHWVRQAPGKGLEWVSTISSGGKGTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKSRTMYFRVREAFDYWGQGTLVTVSS

DOM7r-45 SEQ ID NO: 140
EVQLLESGGGLVQPGGSLRLSCAASGFTFRAYRMMWVRQAPGKGLEWVSSIDPDGAVTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAEHFDLAMPNPNAKFDYWGQGTLVTVSS

DOM7r-46 SEQ ID NO: 141
EVQLLESGGGLVQPGGSLRLSCAASGFTFSRYQMSWVRQAPGKGLEWVSSIKSNGSSTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKPSRQSFQYPSFDYWGQGTLVTVSS

DOM7r-47 SEQ ID NO: 142
EVQLLESGGGLVQPGGSLRLSCAASGFTFGRYKMGWVRQAPGKGLEWVSSISPTGSSTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKTGYVMVEHFDYWGQGTLVTVSS

DOM7r-48 SEQ ID NO: 143
EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYPMKWVRQAPGKGLEWVSTINSSGTITYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKPLLPFDYWGQGTLVTVSS

DOM7r-49 SEQ ID NO: 144
EVQLLESGGGLVQPGGSLRLSCAASGFTFARYRMCWVRQAPGKGLEWVSCIRDPGFPTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKCSPSSTQCTGLFDYWGQGTLVTVSS

DOM7r-50 SEQ ID NO: 145
VQLLESGGGLVQPGGSLRLSCAASGFTFRFYGMAWVRQAPGKGLEWVSLIDPPGGATYYADSVKGRFTIS
RDNSKNTLYLQMNSLRAEDTAVYYCAKMERRHLKSGHKGFDYWGQGTLVTVSS

DOM7r-51 SEQ ID NO: 146

EVQLLESGGGLVQPGGSLRLSCAASGFTFTEYDMMWVRQAPGKGLEWVSSISHRGEKTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKDKRYRGSQHYFDYWGQGTLVTVSS

DOM7r-52 SEQ ID NO: 147
VQLLESGGGLVQPGGSLRLSCAASGFTFRSYDMGWARQAPGKGLEWVSTIGSNGANTYYADSVKGRFTIS
RDNSKNTLYLQMNSLRAEDTAVYYCAKLMGMFDYWGQGTLVTVSS

DOM7r-53 SEQ ID NO: 148
EVQLLESGGGLVQPGGSLRLSCAASGFTFERYSMRWVRQAPGKGLEWVSTIGSTGKWTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKGRGLVSFDYWGQGTLVTVSS

DOM7r-54 SEQ ID NO: 149
EVQLLESGGGLVQPGGSLRLSCAASGFTFRRYSMSWVRQAPGKGLEWVSSIDRSGRMTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKSRLSSTGSEGHNFDYWGQGTLVTVSS

DOM7r-55 SEQ ID NO: 150
VQLLESGGGLVQPGGSLRLSCAASGFTFKWYPMKWVRQAPGKGLEWVSTIAYDGVQTYYADSVKGRFTIS
RDNSKNTLYLQMNSLRAEDTAVYYCAKLGPTSRVFAATDFDYWGQGTLVTVSS

DOM7r-56 SEQ ID NO: 151
EVQLLESGGGLVQPGGSLRLSCAASGFTFPNYAMKWGRQAPGKGLEWVSTIDTSGSTTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKLTHPMAPRPAFDYWGQGTLVTVSS

DOM7r-57 SEQ ID NO: 152
EVQLLESGGGLVQPGGSLRLSCAASGFTFDLTEMEWVRQAPGKGLEWVSSIGPWGTPTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKISHPQAMYHTFDYWGQGTLVTVSS

DOM7r-58 SEQ ID NO: 153
EVQLLESGGGLVQPGGSLRLSCAASGFTFAHQDMTWVRQAPGKGLEWVSDIDHSGSYTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKWWHPQGGTFDYWGQGTLVTVSS

DOM7r-59 SEQ ID NO: 154
EVQLLESGGGLVQPGGSLRLSCAASGFTFGSKDMSWVRQAPGKGLEWVSTIGANGKATYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAEAGHPQAPSFKSFDYWGQGTLVTVSS

DOM7r-60 SEQ ID NO: 155
EVQLLESGGGLVQPGGSLRLSCAASGFTFLNAEMSWVRQAPGKGLEWVSTIDRDGANTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKLPPPMSPKKFDYWGQGTLVTVSS

DOM7r-61 SEQ ID NO: 156
EVQLLESGGGLVQPGGSLRLSCAASGFTFEREGMMWVRQAPGKGLEWVSTIDRMGRYTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKRDSHPMGFDYRGQGTLVTVSS

DOM7r-62 SEQ ID NO: 157
EVQLLESGGGLVQPGGSLRLSCAASGFTFENEKMSWVRQAPGKGLEWVSSIGPTGSGTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKTPHPQVSSFDYWGQGTLVTVSS

DOM7r-63 SEQ ID NO: 158
EVQLLESGGGLVQPGGSLRLSCAASGFTFEIDHMGWVRQAPGKGLEWVSEIAPSGDRTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKVICQNQCLFDYWGQGTLVTVSS

DOM7r-64 SEQ ID NO: 159
EVQLLESGGGLVQPGGSLRLSCAASGFTFRDSEMSWVRQAPGKGLEWVSFITSDGRDTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKPSLPHVTAFDYWGQGTLVTVSS

DOM7r-65 SEQ ID NO: 160
EVQLLESGGGLVQPGGSLRLSCAASGFTFEDETMSWARQAPGKGLEWVSSIGDAGMPTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKGEPIYVHTTHFDYWGQGTLVTVSS

DOM7r-66 SEQ ID NO: 161
EVQLLESGGGLVQPGGSLRLSCAASGFTFPHGKMGWVRQAPGKGLEWVSWIAGSGDMTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKLGHPQRGFDYWGQGTLVTVSS

DOM7r-67 SEQ ID NO: 162
EVQLLESGGGLVQPGGSLRLSCAASGFTFGTSDMSWVRQAPGKGLEWVSTIDSGGSFTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKPRHPQGGVTFDYWGQGTLVTVSS

DOM7r-68 SEQ ID NO: 163
EVQLLESGGGLVQPGGSLRLSCAASGFTFEHVPMAWVRQAPGKGLEWVSRISEQGSNTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKVQHPMSPHEFDYWGQGTLVTVSS

DOM7r-69 SEQ ID NO: 164
EVQLLESGGGLVQPGGSLRLSCAASGFTFEQGMMSWVRQAPGKGLEWVSSINPGGQFTYYADSVKGRFTI
SRDNSRNTLYLQMNSLRAEDTAVYYCAEDLGPGFDYWGQGTLVTVSS

DOM7r-70 SEQ ID NO: 165
EVQLLESGGGLVQPGGSLRLSCAASGFTFERWPMSWVRQAPGKGLEWVSTIDRSGNTTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKVLHPQAGSAFDYWGQGTLVTVSS

DOM7r-71 SEQ ID NO: 166
EVQLLESGGGSVQPGGSLRLSCAASGFTFGGSDMGWVRQAPGKGLEWVSYIDNQGYNTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKYKLLGPSTEFDYWGQGTLVTVSS

DOM7r-72 SEQ ID NO: 167
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSDVMSWVRQAPGKGLEWVSSITRSGMQTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKYAHPQSAVEFDYWGQGTLVTVSS

DOM7r-73 SEQ ID NO: 168
EVQLLESGGGLVQPGGSLRLSCAASGFTFRNEPMSWVRQAPVKGLEWVSTISPDGSGTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKHGHPQGARFDYWGQGTLVTVSS

DOM7r-74 SEQ ID NO: 169
EVQLLESGGGLVQPGGSLRLSCAASGFTFLNSEMSWVRQAPGKGLEWVSTIGYAGTPTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKPRHPQGGVTFDYWGQGTLVTVSS

DOM7r-75 SEQ ID NO: 170
EVQLLESGGGLVQPGGSLRLSCAASGFTFARGPMSWVRQAPGKGLEWVSTITNDGTSTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAEPPHSGRPMFDYWGQGTLVTVSS

DOM7r-76 SEQ ID NO: 171
EVQLLESGGGLVQPGGSLRLSCAASGFTFQRTAMSWVRQAPGKGLEWVSSIEASGRYTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKQSHPQNGRFDYWGQGTLVTVSS

DOM7r-77 SEQ ID NO: 172
EVQLLESGGGLVQPGGSLRLSCAASGFTFDASEMAWVRQAPGKGLEWVSSITVYGDRTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKPRHPQGGVTFDYWGQGTLVTVSS

DOM7r-78 SEQ ID NO: 173

EVQLLESGGGLVQPGGSLRLSCAASGFTFDDSHMAWVRQAPGKGLEWVSRISREGKATYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAAPNDQSAAFDYWGQGTLVTVSS

DOM7r-79 SEQ ID NO: 174
EVQLLESGGGLVQPGGSLRLSCAASGFTFDMSEMSWVRQAPGKGLEWVSAITSDGSSTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKPSLPHVTAFDYWGQGTLVTVSS

DOM7r-80 SEQ ID NO: 175
EVQLLESGGGLVQPGGSLRLSCAASGFTFERSTMHWVRQAPGKGLEWVSEIDALGTDTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKSSDHPQNSFDYWGQGTLVTVSS

DOM7r-81 SEQ ID NO: 176
EVQLLESGGGLVQPGGSLRLSCAASGFTFEPREMYWARQAPGKGLEWVARIGWDGHTTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKQLGQFDYWGQGTLVTVSS

DOM7r-82 SEQ ID NO: 177
EVQLLESGGGLVQPGGSLRLSCAASGFTFDAYSMMWVRQAPGKGLEWVSTIGRWGEITYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKRRYIGPYMLSGRFDYWGQGTLVTVSS

DOM7r-83 SEQ ID NO: 178
EVQLLESGGGLVQPGGSLRLSCAASGFTFMRYPMVWVRQAPGRGLEWVSSISPAGYGTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKGHEISRFSRWSSFDYWGQGTLVTVSS

DOM7r-84 SEQ ID NO: 179
EVQLLESGGGLVQPGGSLRLSCAASGFTFRKYRMSWVRQAPGKGLEWVSSIARNGRSTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKTTSGFDYWGQGTLVTVSS

DOM7r-85 SEQ ID NO: 180
EVQLLESGGGLVQPGGSLRLSCAASGFTFNKKEMGWVRQAPGKGLEWVSSIDVSGNVTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKMAHPQSGVAFDYWGQGTLVTVSS

DOM7r-88 SEQ ID NO: 181
EVQLLESGGGLVQPGGSLRLSCAASGFTFRMYDMAWVRQAPGKGLKWVSTILSSGKGTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKLAHPQKGSIFDYRGQGTLVTVSS

DOM7r-89 SEQ ID NO: 182
EVQLLESGGGLVQPGGSLRLSCAASGFTFHQGPMGWVRQAPGKGLEWVSWIQATGGATYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKGMHPQSGTLFDYWGQGTLVTVSS

DOM7r-90 SEQ ID NO: 183
EVQLLESGGGLVQPGGSLRLSCAASGFTFDVADMDWVRQAPGKGLEWVSGISSSGGYTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKNLGQGFDYWGQGTLVTVSS

DOM7r-92 SEQ ID NO: 184
EVQLLESGGGLVQPGGSLRLSCAASGFTFDTSSMLWVRQAPGKGLEWVSVIHQSGTPTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKFPFTHGKFDYWGQGTLVTVSS

DOM7r-93 SEQ ID NO: 185
EVQLLESGGGLVQPGGSLRLSCAASGFTFNNYTMGWVRQAPGKGLEWVSLIHTSGTVTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKWSSRAFDYWGQGTLVTVSS

DOM7r-94 SEQ ID NO: 186
EVQLLESGGGLVQPGGSLRLSCAASGFTFGNYRMTWVRQAPGKGLEWVSTISPLGTYTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKGRWSIFDYWGQGTLVTVSS

DOM7r-95 SEQ ID NO: 187
EVQLLESGGGLVQPGGSLRLSCAASGFTFGSYPMGWVRQAPGKGLEWVSWIRGRGLATYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKYFHGKFDYWGQGTLVTVSS

DOM7r-96 SEQ ID NO: 188
EVQLLESGGGLVQPGGSLRLSCAASGFTFSAYVMGWVRQAPGKGLEWVSSIRMPGYLTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKRTPFFDYWGQGTLVTVSS

DOM7r-97 SEQ ID NO: 189
EVQLLESGGGLVQPGGSLRLSCAASGFTFEHYSMGWVRQAPGKGLEWVSEIDPDGIMTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKAPGVLEMWITHFDYWGQGTLVTVSS

DOM7r-98 SEQ ID NO: 190
EVQLLESGGGLVQPGGSLRLSCAASGFTFRHYVMGWVRQAPGKGLEWVSAISAHGNRTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKSYSLALTPFDYWGQGTLVTVSS

DOM7r-99 SEQ ID NO: 191
EVQLLESGGGLVQPGGSLRLSCAASGFTFTVYEMKWVRQAPGKGLEWVSAISAGGKYTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKEIRHLDNAVEFDYWGQGTLVTVSS

EXEMPLIFICATION

Example 1

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) are separated according to their hydrodynamic properties by size exclusion chromatography (column: TSK3000; S200). 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). The highest concentration at the mid-point of the eluting peak is about 8-10uM and this consequently is the concentration at which MALLS determines the in-solution state of the protein.

DSC (Differential Scanning Calorimetry): briefly, the protein is heated at a constant rate of 180 degrees 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. The software package used was Origin^R v7.0383.

Characteristics of the VH dAbs are summarised in Table 1 below. Cross-reactivity of the AlbudAbs™ (ie, anti-serum albumin dAbs) was determined against human, *Cynomolgus* monkey (cyno), rat and mouse serum albumin ("4AGs" in the table) using surface plasmon resonance (SPR). In this case, Biacore™ was used. The epitope mapping to domain 1, 2 and/or 3 (D1,2,3) of human serum albumin (HSA) was performed using SPR and purified individual domains of HSA (in-house) covalently coupled to a CM5 chip (amine coupling). The expression was in 2.5L baffled glass flasks in a volume of 500mL in OverNight ExpressTM at 30C, 250rpm.

MALLS results: A single VH AlbudAb is 14kDa in size. Any value between 14 and 28kDa as determined by MALLS is indicative of varying degrees of self-association or dimer formation (i.e 16kDa predominately monomeric under the conditions tested whereas 22kDa indicates a strong propensity to dimerise under MALLS conditions).

DSC results: The concentration of protein in a DSC experiment is much higher at 1mg/mL in the actual reaction cell compared to MALLS. This higher concentration could explain in part the presence of two appTms for some AlbudAbs as seen in table1;

the first Tm constitutes the dissociation of the dimeric complex, whereas the second Tm represents the unfolding of the actual AlbudAb protein.

Table 1

*	x-reactivity	MALLS	DSC [°C]		Expression	Binding to D1/2/3 of HSA
Clone Name	(4AGs)	[kDa]	appTm1	appTm2	(*E.coli*) mg/L in shake flasks	SPR
DOM7h-112	no human; yes other 3 antigens	16	62	66	46.6	No binding
DOM7h-98	yes	14.7	65		28.3	D2
DOM7r-29	yes	16.9	62.5		21	D2
DOM7r-35	yes	21.8	58.7	61.8	33.5	D2
DOM7r-36	yes	98 / 45 / 16	67.4	69.9	31.5	D2
DOM7r-38	yes	14.8	61.3	64.5	61.5	D2
DOM7r-31	yes	15	67.9	74.5	25	D2

*: precise in-solution affinities of the leads will be determine by ITC, equilibrium dialysis or fluorescence polarisation

Apart from DOM7h-112, all above AlbudAbs leads are fully cross-reactive between the four species of serum albumin. All identified AlbudAbs bind Domain2 of HSA and express reasonably well in shake flasks under non-optimised conditions. 5 out of 7 AlbudAbs are monomeric as determined by MALLS, whereas DOM7r-35 shows a significant propensity to dimerise under the MALLS conditions. Monomeric state is advantageous because it avoids dimerisation and the risk of products that may cross-link targets such as cell-surface receptors.

DOM7r-36 shows some degree of aggregate formation (less than 10% when quantified on MALLS). For 5 out of 7 AlbudAbs, 2 appTms can be determined. This is due to the higher experimental concentration in DSC experiments and slightly different in-solution state of the dAb at this elevated concentration (for details, see explanation also above).

Example 2

Determination of serum half life in rat

AlbudAbs were cloned into the pDOM5 vector. 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. For each AlbudAb, 20-50mg quantities were expressed in E. coli and purified from bacterial culture supernatant using protein A 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 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, 96, 120, 168hrs. Analysis of serum levels was by anti-myc capture followed by anti-VH detection ELISA as per the method described below.

Results are shown in table 2. All tested AlbudAbs show a serum-half life extending ability (negative control HEL4 dAb with T1/2 of 20mins in rat) to varying degrees; this trend can also be seen in the calculated AUC being the highest value for the longest t1/2. The longest serum half-life with 34.5hrs approximates the serum half-life of rat serm albumin.

The specific affinities of the AlbudAbs to RSA will need to be determined.

Table 2

VH dAb	T ½*	AUC 0-inf
	[hr]	[hr*ug/mL]
DOM7h-98	13.5	577.5
DOM7r-29	21.9	697.6

DOM7r-35	34.4	1249.6
DOM7r-36	26.5	910.8
DOM7r-38	8.8	203.4
DOM7r-31	11	239

*The serum half-life of rat serum albumin is 35hrs.
T ½ is a measure of the circulation time of the molecule in the subjects.
AUC=area under the curve, which is a PK profile parameter

Anti-myc ELISA method using MSD

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-VH directly labelled with the MSD sulfo-tag. Each dAb was diluted in assay buffer containing 10% control rat serum (1:1000; in-house reagent,) (method DM222). MSD (MesoScaleDiscovery; MesoScale.com) utilizes electrochemiluminescence detection of the sulfo-tag after electrochemical stimulus.

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.

Example 3: Affinity maturation of naïve VH AlbudAbs™

12 VH AlbudAb leads isolated from naïve selection were taken forward for affinity maturation. Individual error prone libraries (EP) of DOM7r-36, DOM7r-35, DOM7r-31, DOM7h-98, DOM7h-112, DOM7r-38 and DOM7r-29 were made, whereas the following parental clones were pooled and combined in a single EP library and screened together: DOM7r-83, DOM7r-85, DOM7r-92, DOM7r-94 and DOM7r-95. All libraries were greater than $2x10^9$CFU/mL.

Selections were performed in 4 rounds on soluble antigen (biotin-HSA; biotin-RSA; blocking with 2% Marvel) by cross over-selection with decreasing concentration of antigen: Round1 at 1 μM (HSA or RSA), Round 2 at 1μM (RSA or HSA), followed by 2 further rounds of selection at 100nM and 10nM, respectively, with the same antigen as in Round2. Ca. 3000 samples from both, R3 and R4 outputs were screened by supernatant BIAcore and clones ranked according to their off –rate only. Eight-point dilution kinetic affinity measurements were performed on improved clones (data below).

Table 3

Improved clone	**From round**
DOM7r-31-14	R4
DOM7r-201	R3
DOM7r-36-2	R4
DOM7r-36-8	R4
DOM7r-92-4	R4
DOM7h-98-4	R3

Table 4 - Kinetic data:

	RSA KD (M)	HSA KD (M)	CSA KD (M)	MSA KD (M)
DOM7r-201	2.4E-07	6.0E-08	5.8E-08	2.8E-07
DOM7r-36-2	1.9E-07	1.5E-07	1.8E-07	5.2E-07
DOM7r-36-8	2.1E-07	6.7E-08	9.2E-08	5.2E-07
DOM7r-92-4	2.6E-07	1.3E-07	9.8E-08	1.1E-07

DOM7h-98-4	5.8E-07	2.0E-06	3.6E-06	8.1E-07
DOM7r-31-14	4.6E-08	5.8E-08	3.1E-05	6.0E-09

Table 5 - Sequence alignment:

```
          5         15         25         35         45         55
A     EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVSA ISGSGGSTYY
B     EVQLLESGGG LVQPGGSLRL SCAASGFTFN HYTMGWVRQA PGKGLEWVSL IHPSGTVIYY
C     EVQLLESGGG LVQPGGSLRL SCAASGFTFN HYTMGWVRQA PGKGREWVSL IHPSGTVTYY
D     EVQLLESGGG LVQPGGSLRL SCAASGFTFN HYTMGWVRQA PGKGLEWVSL IHPSGTVIYY
E     EVQLLESGGG LVQPGGSLRL SCAASGFTFD TSSMLWVRQA PGKGLEWVSV IHQSGTPTYY
F     EVQLLESGGG LVQPGGSLRL SCAASGFTFG NYAMAWVRQA PGKGLEWVSS IDMVGIKTYY
G     EVQLLESGGG LVQPGGSLRL SCTASGFTFR HYRMGWVRQA PGKGLEWVSW IRPDGTFTYY

          65         75         85         95        105        115
A     ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAKSY GA~~~FDYWG QGTLVTVSS
B     ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAKWS SRA~~FDYWG QGTLVTVSS
C     ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAKWS SRA~~FDYWG QGTLVTVSS
D     ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARWS SRA~~FDYWG QGTLVTVSS
E     ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAKFP STHGKFDYWG QGTLVTVSS
F     ADSVKGRFTN SRDNSKNTLY LQMNSLRAED TAVYYCARGF RI~~~FDYWG QGTLVTVSS
G     ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAKSY MADR~FDYWG QGTLVTVSS
```

A= VH dummy
B= DOM7r-201
C= DOM7r-36-2
D= DOM7r-36-8
E= DOM7r-92-4
F= DOM7h-98-4
G= DOM7r-31-1

The CDRs are underlined; sequences are shown N- to C-terminus;"~" denote gaps introduced for alignment

Nucleotide sequences

DOM7r-201 SEQ ID NO: 192

```
GAGGTGCAACTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTC
CCTGCGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATCATTATACGA
TGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCATTG
ATTCATCCGAGTGGTACGGTGATATACTACGCAGACTCCGTGAAGGGCCG
GTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGA
ACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAATGGAGT
TCGAGGGCATTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCTAG
C
```

DOM7r-36-2 SEQ ID NO: 193

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTC
CCTGCGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATCATTATACGA
TGGGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCGAGAGTGGGTCTCATTG
ATTCATCCGAGTGGTACGGTGACATACTACGCAGACTCCGTGAAGGGCCG
GTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGA
ACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAATGGAGT
TCGAGGGCGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

DOM7r-36-8 SEQ ID NO: 194
GAGGTGCAACTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTC
CCTGCGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTAATCATTATACGA
TGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCATTG
ATTCATCCGAGTGGTACGGTGATATACTACGCAGACTCCGTGAAGGGCCG
GTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGA
ACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAGATGGAGT
TCGAGGGCGTTTGACTACTGGGGTCAGGGGACCCTGGTCACCGTCTCGAG
C

DOM7r-92-4 SEQ ID NO: 195
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTC
CCTGCGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGATACGAGTAGTA
TGTTGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCAGTT
ATTCATCAGAGTGGTACGCCTACATACTACGCAGACTCCGTGAAGGGCCG
GTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGA
ACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAATTTCCG
TCTACTCATGGTAAGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGT
CTCGAGC

DOM7h-98-4 SEQ ID NO: 196
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTC
CCTGCGTCTCTCCTGTGCAGCCTCCGGATTCACCTTTGGTAATTATGCGA
TGGCGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCATCG
ATTGATATGGTTGGTATTAAGACATACTACGCAGACTCCGTGAAGGGCCG
GTTCACCAATTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGA
ACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAGAGGTTTT
CGTATTTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

DOM7r-31-14 SEQ ID NO: 197
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTC
CCTGCGTCTCTCCTGTACAGCCTCCGGATTCACCTTTAGGCATTATCGTA
TGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCATGG
ATTCGTCCGGATGGTACGTTTACATACTACGCAGACTCCGTGAAGGGCCG
GTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGA
ACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAATCTTAT
ATGGCTGATAGGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTC
GAGC

Amino Acid Sequences

DOM7r-201 SEQ ID NO: 198
EVQLLESGGGLVQPGGSLRLSCAASGFTFNHYTMGWVRQAPGKGLEWVSL
IHPSGTVIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWS

SRAFDYWGQGTLVTVSS

DOM7r-36-2 SEQ ID NO: 199
EVQLLESGGGLVQPGGSLRLSCAASGFTFNHYTMGWVRQAPGKGREWVSL
IHPSGTVTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKWS
SRAFDYWGQGTLVTVSS

DOM7r-36-8 SEQ ID NO: 200
EVQLLESGGGLVQPGGSLRLSCAASGFTFNHYTMGWVRQAPGKGLEWVSL
IHPSGTVIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARWS
SRAFDYWGQGTLVTVSS

DOM7r-92-4 SEQ ID NO: 201
EVQLLESGGGLVQPGGSLRLSCAASGFTFDTSSMLWVRQAPGKGLEWVSV
IHQSGTPTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKFP
STHGKFDYWGQGTLVTVSS

DOM7h-98-4 SEQ ID NO: 202
EVQLLESGGGLVQPGGSLRLSCAASGFTFGNYAMAWVRQAPGKGLEWVSS
IDMVGIKTYYADSVKGRFTNSRDNSKNTLYLQMNSLRAEDTAVYYCARGF
RIFDYWGQGTLVTVSS

DOM7r-31-14 SEQ ID NO: 203
EVQLLESGGGLVQPGGSLRLSCTASGFTFRHYRMGWVRQAPGKGLEWVSW
IRPDGTFTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSY
MADRFDYWGQGTLVTVSS

CLAIMS:

1. An anti-serum albumin (SA) immunoglobulin single variable domain comprising an amino acid sequence that is at least 80% identical to an amino acid sequence selected from SEQ ID NOs: 97 to 191 and 198 to 203.

2. An anti-serum albumin (SA) immunoglobulin single variable domain comprising an amino acid sequence having up to 4 amino acid changes compared to an amino acid sequence selected from SEQ ID NOs: 97 to 191 and 198 to 203.

3. An anti-serum albumin (SA) immunoglobulin single variable domain comprising an amino acid sequence that is encoded by a nucleotide sequence which is at least 80% identical to a sequence selected from SEQ ID NOs 1 to 96 and 192 to 197.

4. The variable domain of any preceding claim, wherein the variable domain comprises the amino acid sequence of any one of SEQ ID NOs: 97 to 103 and 198 to 203.

5. The variable domain of any preceding claim, comprising 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.

6. The variable domain of any preceding claim, comprising a binding site that specifically binds human 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.

7. The variable domain of any preceding claim, comprising 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.

8. The variable domain of any preceding claim, comprising 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.

9. The variable domain of any preceding claim, comprising 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.

10. The variable domain of any preceding claim, comprising 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.

11. The variable domain of any preceding claim, wherein the variable domain has a melting temperature (Tm) of at least 55 degrees centigrade, optionally 55 $\leq$ Tm $\leq$ 75 degrees centigrade, as determined by DSC (differential scanning calorimetry).

12. The variable domain of any preceding claim, wherein the variable domain is substantially monomeric as determined by SEC-MALLS (size exclusion chromatography with multi-angle-LASER-light-scattering).

13. A multispecific ligand comprising an anti-SA variable domain of any preceding claim and a binding moiety that specifically binds a target antigen other than SA, optionally wherein the binding moiety is an TNFR1 antagonist.

14. An anti-SA single variable domain of any one of claims 1 to 12, wherein the variable domain is conjugated to a drug (optionally an NCE drug), optionally wherein the selected variable domain is according to claim 4.

15. A fusion protein comprising a polypeptide or peptide drug fused to a variable domain according to any one of claims 1 to 12, optionally wherein the selected variable domain is according to claim 4.

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

17. A nucleic acid comprising a nucleotide sequence encoding a variable domain according to any one of claims 1 to 12 and 14, or a multispecific ligand of claim 13 or fusion protein of claim 15.

18. A nucleic acid comprising a nucleotide sequence that is at least 80% identical to a sequence selected from SEQ ID NOs 1 to 96 and 192-197.

19. A vector comprising the nucleic acid of claim 17 or 18.

20. An isolated host cell comprising the vector of claim 19.

21. A method of treating or preventing a disease or disorder in a patient, comprising administering at least one dose of a variable domain according to any one of

claims 1 to 12 and 14, or a multispecific ligand of claim 13 or fusion protein of claim 15 to said patient.