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(71) Applicant:

**GLAXO GROUP LIMITED GLAXO
WELLCOME HOUSE, BERKELEY
AVENUE, GREENFORD MIDDLESEX
UB6 0NN GB**

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(72) Inventor:

**COULSTOCK, EDWARD DOMANTIS
LIMITED 315 CAMBRIDGE SCIENCE
PARK CAMBRIDGE CAMBRIDGESHIRE
CB4 0WG GB
DE ANGELIS, ELENA DOMANTIS
LIMITED 315 CAMBRIDGE SCIENCE
PARK CAMBRIDGE CAMBRIDGESHIRE
CB4 0WG GB
LIU, HAIQUN DOMANTIS LIMITED
315 CAMBRIDGE SCIENCE PARK
CAMBRIDGE CAMBRIDGESHIRE CB4
0WG GB
SCHON, OLIVER DOMANTIS LIMITED
315 CAMBRIDGE SCIENCE PARK
CAMBRIDGE CAMBRIDGESHIRE CB4
0WG GB**

(54) Title:

**IMPROVED ANTI-SERUM ALBUMIN BINDING SINGLE
VARIABLE DOMAINS**

(57) Abstract:

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

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(71) Applicant (for all designated States except US): **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **COULSTOCK, Edward** [GB/GB]; Domantis Limited, 315 Cambridge Science Park, Cambridge Cambridgeshire CB4 0WG (GB). **DE ANGELIS, Elena** [GB/GB]; Domantis Limited, 315 Cambridge Science Park, Cambridge Cambridgeshire CB4 0WG (GB). **LIU, Haiqun** [CN/GB]; Domantis Limited, 315 Cambridge Science Park, Cambridge Cambridgeshire CB4 0WG (GB). **SCHON, Oliver** [DE/GB]; Domantis Limited, 315 Cambridge Science Park, Cambridge Cambridgeshire CB4 0WG (GB).

(74) Agents: **CLUBE, Jasper Rupert** et al.; GlaxoSmithKline, Global Patents CN925.1, 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

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(54) Title: IMPROVED ANTI-SERUM ALBUMIN BINDING SINGLE VARIABLE DOMAINS

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



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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,
5 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
10 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.

15 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,
20 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
25 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

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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

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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.

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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
5 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
10 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
15 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
20 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
25 therapeutic effect. This would allow for targeting chronic or persistent 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

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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
5 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
10 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
15 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.

20 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 TNF α to TNFR1 and/or inhibit signal transduction mediated through TNFR1. Accordingly,
25 TNFR1-mediated processes and cellular responses (e.g., TNF α -induced cell death in a standard L929 cytotoxicity assay) can be inhibited with an antagonist of TNFR1.

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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
5 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
10 (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
15 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
20 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}).

25 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

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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

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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*, Pharmacokinetic 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_{α} and t_{β} 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.

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Half lives ($t_{1/2}$ alpha and $t_{1/2}$ beta) and AUC can be determined from a curve of serum concentration of ligand against time. The WinNonlin analysis package, eg version 5.1 (available from Pharsight Corp., Mountain View, 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 $t\alpha$ 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 $t\alpha$ half life in the range of up to and including 12 hours (or about 12 hours). In one embodiment, the upper end of the range is (or is about) 11, 10, 9, 8, 7, 6 or 5 hours. An example of a suitable range is (or is about) 1 to 6 hours, 2 to 5 hours or 3 to 4 hours.

In one embodiment, the present invention provides the variable domain, fusion protein or ligand according to the invention has a $t\beta$ half-life in the range of (or of about) 2.5 hours or more. In one embodiment, the lower end of the range is (or is about) 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 10 hours, 11 hours, or 12 hours. In addition, or alternatively, the $t\beta$ 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 $t\beta$ 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).

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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
5 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
10 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
15 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
20 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
25 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

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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
5 significant extent with the specific binding interaction between two or more molecules. The specific binding interaction between two or more molecules preferably includes the specific binding interaction between a single variable domain and its cognate partner or target. The interfering or competing molecule can be another single variable domain or it can be a molecule that is structurally and/or functionally similar to a cognate
10 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
15 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
20 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
25 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;

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- (b) The variable domain comprises a binding site that specifically binds human SA with an off-rate constant (K_d) from (or from about) 1.5×10^{-4} to (or to about) 0.1 sec^{-1} , optionally from (or from about) 3×10^{-4} to (or to about) 0.1 sec^{-1} as determined by surface plasmon resonance;
- 5 (c) The variable domain comprises a binding site that specifically binds human SA with an on-rate constant (K_a) from (or from about) 2×10^6 to (or to about) $1 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$, optionally from (or from about) 1×10^6 to (or to about) $2 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$ as determined by surface plasmon resonance;
- (d) The variable domain comprises a binding site that specifically binds
10 *Cynomolgus* monkey SA with a dissociation constant (K_D) from (or from about) 0.1 to (or to about) 10000 nM, optionally from (or from about) 1 to (or to about) 6000 nM, as determined by surface plasmon resonance;
- (e) The variable domain of any preceding claim, wherein the variable domain comprises a binding site that specifically binds *Cynomolgus* monkey SA with an
15 off-rate constant (K_d) from (or from about) 1.5×10^{-4} to (or to about) 0.1 sec^{-1} , optionally from (or from about) 3×10^{-4} to (or to about) 0.1 sec^{-1} as determined by surface plasmon resonance;
- (f) The variable domain of any preceding claim, wherein the variable domain comprises a binding site that specifically binds *Cynomolgus* monkey SA with an
20 on-rate constant (K_a) from (or from about) 2×10^6 to (or to about) $1 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$, optionally from (or from about) 1×10^6 to (or to about) $5 \times 10^3 \text{ M}^{-1} \text{ sec}^{-1}$ as determined by surface plasmon resonance;
- (g) The variable domain comprises a binding site that specifically binds rat SA with
25 a dissociation constant (K_D) 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;

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- (h) The variable domain comprises a binding site that specifically binds rat SA with an off-rate constant (K_d) from (or from about) 2×10^{-3} to (or to about) 0.15 sec^{-1} , optionally from (or from about) 9×10^{-3} to (or to about) 0.14 sec^{-1} as determined by surface plasmon resonance;
- 5 (i) The variable domain comprises a binding site that specifically binds rat SA with an on-rate constant (K_a) from (or from about) 2×10^6 to (or to about) $1 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$, optionally from (or from about) 1×10^6 to (or to about) $3 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$ as determined by surface plasmon resonance;
- 10 (j) The variable domain comprises a binding site that specifically binds mouse SA with a dissociation constant (K_D) 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) 2×10^{-3} to (or to about) 0.15 sec^{-1} as determined by surface plasmon resonance; and/or
- 15 (l) The variable domain comprises a binding site that specifically binds mouse SA with an on-rate constant (K_a) from (or from about) 2×10^6 to (or to about) $1 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$, optionally from (or from about) 2×10^6 to (or to about) $1.5 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$ as determined by surface plasmon resonance.

Optionally, the variable domain has

- 20 I: a K_D 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 K_D according to (a) and (g), a K_d according to (b) and (h), and a K_a according to (c) and (i); or
- 25 III: a K_D according to (a) and (j), a K_d according to (b) and (k), and a K_a according to (c) and (l); or

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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

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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- β 1, insulin, IFN- γ , IGF-I, IGF-II, IL-1 α , IL-1 β , 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, Lymphotoctin, 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-1 α , MIP-1 β , MIP-3 α , MIP-3 β , 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, SDF1 α , SDF1 β , SCF, SCGF, stem cell factor (SCF), TARC, TGF- α , TGF- β , TGF- β 2, TGF- β 3, 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, α 1-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.

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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
5 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
10 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
15 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
20 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
25 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).

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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),
5 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
10 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
15 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
20 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
25 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

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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.

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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, excipient 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

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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
5 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),
10 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
15 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.

20 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
25 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.

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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
CCTCCGGATTACCTTTGGGGGTATGTGATGGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGCTATTAATAGGTTTGGTTCGTCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGTAGTTTGCGGCATTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

DOM7h-98 SEQ ID NO: 2

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGGTAATTATGCGATGGCGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCGATTGATATGGTTGGTATTAAGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGTTTTCGTATTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

DOM7r-29 SEQ ID NO: 3

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTAAGGATTATGATATGACTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAATGATTTCTTCGTCGGGTCTTTGGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGTTTTAGGCTGTTTCCTCGGACTTTTGACTACTGGGGTCAGGGAACCCTGGTCAC
CGTCTCGAGCG

DOM7r-35 SEQ ID NO: 4

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTTCGCTGTATAGGATGGTGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG

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GGTCTCAATGATTTCTCAGTTTGGTAATCAGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGTTAGGTCTTGGGATCAGACTGGTGGTCGTCTACTTTTGACTACTGGGGTCAGGG
AACCCTGGTCACCGTCTCGAGC

5

DOM7r-36 SEQ ID NO: 5

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTAATCATTATACGATGGGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATTGATTATCCGAGTGGTACGGTGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATGGAGTTCGAGGGCGTTTGACTACTG
GGGTCAGGGAACCCCTGGTCACCGTCTCGAGC

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DOM7r-38 SEQ ID NO: 6

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTGATAATAATGCGATGGGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTAGTGCGAATGGTAATGCGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGGACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGGTTTCGTCTGGTTTGACTACTGGGGTCAGGGAACCCCTGGTCACCGTCTCGAGC

20

DOM7r31 SEQ ID NO: 7

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTACAG
CCTCCGGATTACACCTTTAGGCATTATCGTATGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATGGATTCTGTCGGATGGTACGTTTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATCTTATATGGGTGATAGGTTTGACTACTGGGGTCAGGGAACCCCTGGTCACCGTCTC
GAGCG

25

DOM7h-32 SEQ ID NO: 8

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGCGCAG
CCTCCGGATTACACCTTTGGTAATTATCCGATGACGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTGGAGTG
GGTCTCAACTATTAGTTATGGTGGTCTTGCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAATGGCGATTAATGGTGTTAGGCCTAGGCGGTTTGACTACTGGGGTCAGGGAACCCCT
GGTCACCGTCTCGAGC

35

DOM7h-33 SEQ ID NO: 9

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTATGGCGTATCAGATGGCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTATCAGACGGGTTTTTCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTAT
ATTACTGTGCGAAAGTGCGTTCTATGCGTCCTTATAAGTTTGACTACTGGGGTCAGGGAACCCCTGGTCAC
CGTCTCGAGC

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DOM7h-34 SEQ ID NO: 10

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTGGTGATAAGGCAATGGGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACGATTAGTGCTCCTGGTAACCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGTTTTCGGAATTTTGACTACTGGGGTCAGGGAACCCCTGGTCACCGTCTCGAGC

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DOM7h-83 SEQ ID NO: 11

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTGATGGGATGCGTATGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG

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GGTCTCAGCTATTGAGGTGAATGGTCAGCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAATGGCTCATCCTCAGTCGGGGGTGGCTTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

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DOM7h-84 SEQ ID NO: 12

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTTACGCCGTGATGCTATGGCGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCGATTGGTGTGAATGGTTCTCCGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAATGGCTCATCCTCAGTCGGGGGTGGCTTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

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DOM7h-85 SEQ ID NO: 13

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTTATCAGTCGGATATGTCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCTATTTCTTCTCAGGGTCGTTCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAATGGCTCATCCTCAGTCGGGGGTGGCTTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

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DOM7h-86 SEQ ID NO: 14

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTACAG
CCTCCGGATTACCTTTTGC GCGAGGGATATGAGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTGGAGTG
GGTCTCAAGTATTTCTGCTCAGGGTGCTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACGATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTAT
ATTACTGTGCGAAACCTCGGCATCCTCAGGGGGGGGTACTTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

25

DOM7h-87 SEQ ID NO: 15

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTTGATAATGGGGATATGGTTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGGGATTGCGCATAATGGTCGTAATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAAATTTGGGTCAGGGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

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DOM7h-88 SEQ ID NO: 16

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCACCTGTGCAG
CCTCCGGATTACCTTTGAATGGTACGTCGATGGGGTGGGTCCGCCAGGCTCCAGGGAAGGATCTAGAGTG
GGTCTCATCTATTATGCCTGTGGGTCTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAATGGCTCATCCTCAGTCGGGGGTGGCTTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

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DOM7h-89 SEQ ID NO: 17

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGATCATGCGCCTATGAAGTGGGCCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATATATTGGGTCGGCGGGTAATATGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGATGAGGGGCCGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

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DOM7h-90 SEQ ID NO: 18

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5 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTACAG
CCTCCGGATTACACCTTTGATGGGATGGATATGAGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAAGTATTTCTACGACTGGTGGGACTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACCTCGGCATCCTCAGGGGGGGGTTACTTTTGACTACTGGGGTCAGGGAACCCCTGGT
CACCGTCTCGAGC

10 DOM7h-91 SEQ ID NO: 19
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTGAGGCGGAGACGATGGCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTCATTCGGAGGGTCTCGGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACCTCGGCATCCTCAGGGGGGGGTTACTTTTGACTACTGGGGTCAGGGAACCCCTGGT
CACCGTCTCGAGC

15 DOM7h-92 SEQ ID NO: 20
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTAGTACTGGGGGAGATGGCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCTATTAGTTCGAGTGGTGCTACGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
20 TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACCTCGGCATCCTCAGGGGGGGGTTACTTTTGACTACTGGGGTCAGGGAACCCCTGGT
CACCGTCTCGAGC

25 DOM7h-93 SEQ ID NO: 21
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTCCCTAGTGCTGATATGGTTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCACGTATTTCCCTGAGGGTAATCATACATACTACGCAGACTCCGTGAAGGGTCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTAT
ATTACTGTGCGGAACCGCCTCCTTCGGATTATGTTTCTTTTGACTACTGGGGTCAGGGAACCCCTGGTCAC
30 CGTCTCGAGC

35 DOM7h-94 SEQ ID NO: 22
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTGCGAATGCGACTATGTGCTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGATATTGATCAGGTGGGTTCATGCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATATTCGTGGCATCCGGATCTGTTTGACTACTGGGGTCAGGGAACCCCTGGTCACCGT
CTCGAGC

40 DOM7h-95 SEQ ID NO: 23
GAGGTGCGGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTAAGGATTATGGGATGAATTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCACGGATTAGTAGGAATGGTACTGTTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
45 ATTACTGTGCGAAATTGGCTGCTCCGGTTCGTGAGAAGGGGATGGATTTTGACTACTGGGGTCAGGGAAC
CCTGGTCACCGTCTCGAGC

50 DOM7h-96 SEQ ID NO: 24
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTGAGTGGTATAATATGTGCTGGGTCCGCCAGGCTCCAGGGAAGGATCTGGAGTG
GGTCTCATCGATTTCTCATGATGGTTGGAATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGATGATTGGTTTGGACTACTGGGGTCAGGGAACCCCTGGTCACCGTCTCGAGC

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DOM7h-97 SEQ ID NO: 25

5 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGATATTTATACGATGCATTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTGTTCCGCAGGGTACTCCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATCTAAGCGTAGGTTTCTTAAGAGGTTTACTACTGGGGTCAGGGAACCCTGGTCAC
CGTCTCGAGC

DOM7h-99 SEQ ID NO: 26

10 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGCTAGGTATGATATGCAGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCGATTAAAGAGTAATGGTATGAAGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGCTAGTATGTGGACGTTTACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAA
15 C

DOM7h-100 SEQ ID NO: 27

20 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTTATGTTGTATCATATGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGCTATTACCGGGGGGGTTATCCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACTGGGGCTTCGGGGTGTGCTGTGGCGGAGGAGTTTACTACTGGGGTCAGGGAAC
CCTGGTCACCGTCTCGAGC

DOM7h-101 SEQ ID NO: 28

25 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGGTGCTTATTCTATGATGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCACGGATTAGTAGGAATGGTACTGTTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
30 ATTACTGTGCGAAAATTAGGTGGAATACTGCTCAGGTGCCTGTGTTTACTACTGGGGTCAGGGAACCTCT
GGTCACCGTCTCGAGC

DOM7h-102 SEQ ID NO: 29

35 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGGTCCGTATTGGATGGCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACGATTACGCCTTCGGGTGCTGGGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTAT
ATTACTGTGCGAAAGGGCGTCTCGTGTGGTTTGTGGAGGTCGGGGTTTACTACTGGGGTCAGGGAAC
40 CCTGGTCACCGTCTCGAGC

DOM7h-103 SEQ ID NO: 30

45 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGGGCAGTATGCTATGCAGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCTATTAATATTACTGGTTCTACTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAGATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGTTTTAGGTCTTTTACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

DOM7h-106 SEQ ID NO: 31

50 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGCTGGTTATACGATGTGCTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACGATTTCCGGTTTGGTTGGACTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTAT
ATTACTGTGCGAAAAGGCTGGGGATGCGTTTACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

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DOM7h-109 SEQ ID NO: 33

5 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGTTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGGTCCGTATTCGATGGGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATTTATTCATTCTGATGGTCGTCATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAAAGACGCCTTATAGGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

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DOM7h-111 SEQ ID NO: 34

15 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGTTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGGGCAGTATGCTATGCAGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCTATTAATATTACTGGTTCTACTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAGATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGTTTTAGGTCTTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

DOM7h-114 SEQ ID NO: 35

20 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGTTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTAGGCGGTATGCGATGTCTTGCGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACGATTTCCGCTTATGGTCCTGTTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAATAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGCTTATTATGGTGGGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

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DOM7r-34 SEQ ID NO: 36

30 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGTTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGATGCTTATGCTATGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAAAGATTGATTCTCCTGGTTGGAGGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATCGGCTCGGATGCGTTCTCGGCATTTTGACTACTGGGGTCAGGGAACCCTGGTCAC
CGTCTCGAGC

DOM7r-37 SEQ ID NO: 37

35 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGTTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTAAGGATTATGGGATGAATTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCACGGATTAGTAGGAATGGTACTGTTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAATTAGGTGGAATACTGCTCAGGTGCCTGTGTTTGACTACTGGGGTCAGGGAACCTCT
40 GGTACCGTCTCGAGC

DOM7r-39 SEQ ID NO: 38

45 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGTTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAA
CCTCCGGATTACCTTTCCGTCTTATACGATGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCACGTATTTCTCGTACTGGGAATTATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTAT
ATTACTGTGCGAAACCTATGTATAATAGGGGGTCTTCGTATTTTGACTACTGGGGTCAGGGAACCCTGGT
50 CACCGTCTCGAGC

DOM7r-40 SEQ ID NO: 39

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGTTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTTCGAGTATCAGATGTCGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCGATTTCCGCTACGGGTATTTCAGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC

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TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAAGGCTTATTGGGATGCCGTATGTTGAGGATACTTTTGACTACTGGGGTCAGGGAAC
CCTGGTCACCGTCTCGAGC

5 DOM7r-41 SEQ ID NO: 40

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTTATGGAGTATGAGATGGAGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGGTATTACTAATTCTGGTTCTGGGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
10 ATTACTGTGCGATAATGCAGCATCCTCAGGCGACTGGGGGAGGGTTGGGTTTGACTACTGGGGTCAGGG
AACCCTGGTCACCGTCTCGAGC

DOM7r-42 SEQ ID NO: 41

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
15 CCTCCGGATTACCTTTCCGAGGTATACTATGAAGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCGATTGATAGGACGGGTCTGAAGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTAT
ATTACTGTGCGAAAGAGTCGTTGGTTTCGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

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DOM7r-43 SEQ ID NO: 42

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGGTGGTTATACGATGCCCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTTCTCGTGATGGTAATTATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
25 TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGATATTGGTATGGGTTTTGACTACGGGGGCGGGGAACCCTGGTCACCGTCTCGAG
C

DOM7r-44 SEQ ID NO: 43

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
30 CCTCCGGATTACCTTTGAGATTTATGCGATGCATTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACGATTAGTTCGGGTGGTAAGGGGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATCGCGTACTATGTATTTTCGTGTTAGGGAGGCTTTTGACTACTGGGGTCAGGGAAC
35 CCTGGTCACCGTCTCGAGC

DOM7r-45 SEQ ID NO: 44

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTTCGTGCTTATAGGATGATGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTGGAGTG
40 GGTCTCATCTATTGATCCTGATGGTGCGGTTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGGAACATTTTGATCTTGCGATGCCGAATCCGAATGCGAAGTTTGACTACTGGGGTCAGGG
AACCCTGGTCACCGTCTCGAGC

45 DOM7r-46 SEQ ID NO: 45

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGCCTCTCCTGTGCAG
CCTCCGGATTACCTTTTCTCGTTATCAGATGTCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTGGAGTG
GGTCTCATCTATTAAAGTCGAATGGTTCTTCGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
50 ATTACTGTGCGAAACCTAGTCGGCAGAGTTTTTCAGTATCCGAGTTTTGACTACTGGGGTCAGGGAACCT
GGTCACCGTCTCGAGC

DOM7r-47 SEQ ID NO: 46

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5 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTGGGCGTTATAAGATGGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCTATTTCCCTACGGGTTCGTCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAACCTGGGTATGTTATGGTTGAGCATTTTGACTACTGGGGTCAGGGAACCCCTGGTCAC
CGTCTCGAGC

10 DOM7r-48 SEQ ID NO: 47
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTAGTGATTATCCGATGAAGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTGGAGTG
GGTCTCAACTATTAATTCTTCGGGTACGATTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAACCGTTGTTGCCGTTTGACTACTGGGGTCAGGGAACCCCTGGTCACCGTCTCGAGC

15 DOM7r-49 SEQ ID NO: 48
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTGCTAGGTATAGGATGTGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATGTATTCCGGGATCCGGGTTTTCCGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
20 ATTACTGTGCGAAAATGTTCCGCGTCTTCTACGCAGTGTACGGGGCTTTTTGACTACTGGGGTCAGGGAAC
CCTGGTCACCGTCTCGAGC

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

30 DOM7r-51 SEQ ID NO: 50
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTACGGAGTATGATATGATGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCTATTAGTCATAGGGGTGAGAAGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
35 TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAAGATAAGCGTTATCGGGGGTCTCAGCATATTTTTGACTACTGGGGTCAGGGAACCCCT
GGTCACCGTCTCGAGC

40 DOM7r-52 SEQ ID NO: 51
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTCCGAGTTATGATATGGGTGGGCCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTGGGTGCAATGGTGCTAATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACTTATGGGTATGTTTGACTACTGGGGTCAGGGAACCCCTGGTCACCGTCTCGAGC

45 DOM7r-53 SEQ ID NO: 52
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTGAGCGTTATTCTATGAGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACGATTGGTTCGACGGGTAAAGTGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
50 TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAAGGGCGTGGGTGTTTCTTTTGACTACTGGGGTCAGGGAACCCCTGGTCACCGTCTC
GAGC

DOM7r-54 SEQ ID NO: 53

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5 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTAGGCGTTATTCGATGTCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCTATTGATCGGTCTGGTAGGATGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAATCTCGGCTGTCTTCGACGGGTCTGAGGGTCATAATTTTGACTACTGGGGTCAGGG
AACCCTGGTCACCGTCTCGAGC

10 DOM7r-55 SEQ ID NO: 54
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTAAGTGGTATCCGATGAAGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTGCTTATGATGGTGTTCAGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAATTGGGTCCGACTAGTCGTGTGTTTGTCTACTGATTTTGACTACTGGGGTCAGGG
AACCCTGGTCACCGTCTCGAGC

15 DOM7r-56 SEQ ID NO: 55
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTCCGAATTATGCGATGAAGTGGGGCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTGATACGAGTGGTAGTACTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
20 TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACTTACTCATCCTATGGCGCCGCGTCCGGCTTTTGACTACTGGGGTCAGGGAACCCCT
GGTCACCGTCTCGAGC

25 DOM7r-57 SEQ ID NO: 56
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTGATCTTACGGAGATGGAGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTGGAGTG
GGTCTCATCGATTGGGCCCTGGGGTACTCCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAATTTGCGATCCTCAGGCGATGTATCATACGTTTGACTACTGGGGTCAGGGAACCCCT
30 GGTCACCGTCTCGAGC

35 DOM7r-58 SEQ ID NO: 57
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTGCGCATCAGGATATGACGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGATATTGATCATTCGGGTTCGTATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATGGTGGCATCCGAGGGGGGGACTTTTGACTACTGGGGTCAGGGAACCCCTGGTCAC
CGTCTCGAGC

40 DOM7r-59 SEQ ID NO: 58
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTGGTTCTAAGGATATGTCGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACGATTGGGGCGAATGGTAAGGCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
45 ATTACTGTGCGGAAGCGGGTCATCCTCAGGCGCCGTCTTTTAAGAGTTTGTACTACTGGGGTCAGGGAAC
CCTGGTCACCGTCTCGAGC

50 DOM7r-60 SEQ ID NO: 59
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTCTGAATGCGGAGATGAGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTGATCGGGATGGTGCTAATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACTTCCTCCGCGATGTCGCCGAAGAAGTTTGACTACTGGGGTCAGGGAACCCCTGGT
CACCGTCTCGAGC

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DOM7r-61 SEQ ID NO: 60

5 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGAGAGGGAGGGTATGATGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTTTCAACTATTGATCGTATGGGTAGGTATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAAGGGATTTCGCATCCTATGGGGTTTGACTACCGGGGTGAGGGAACCCCTGGTCACCGT
CTCGAGC

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DOM7r-62 SEQ ID NO: 61

15 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGGTTACCTTTGAGAATGAGAAGATGAGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCGATTGGTCCACGGGTAGTGGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAACCTCCTCATCCGAGGTTTCTAGTTTGGACTACTGGGGTCAGGGAACCCCTGGTCAC
CGTCTCGAGC

DOM7r-63 SEQ ID NO: 62

20 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGAGATTGATCATATGGGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGAGATTGCGCCTTCGGGTGATCGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTAT
ATTACTGTGCGAAAGTGATTGTGAGAATCAGTGTCTGTTTGGACTACTGGGGTCAGGGAACCCCTGGTCAC
25 CGTCTCGAGC

DOM7r-64 SEQ ID NO: 63

30 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTAGGGATTCTGAGATGTGCTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATTTATTACTTCTGATGGTTCGGGATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACCTAGTCTGCCTCATGTTACGGCTTTTGGACTACTGGGGTCAGGGAACCCCTGGTCAC
CGTCTCGAGC

DOM7r-65 SEQ ID NO: 64

35 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGAGGATGAGACGATGAGTTGGGCCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCGATTGGGGATGCTGGTATGCCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
40 ATTACTGTGCGAAAGGGGAGCCGATTATGTTACATACGACTCATTTTGGACTACTGGGGTCAGGGAACCCCT
GGTCACCGTCTCGAGC

DOM7r-66 SEQ ID NO: 65

45 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTCCGCATGGTAAGATGGGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATGGATTGCTGGGTCTGGTGATATGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATTGGGTCTCCTCAGCGGGGTTTGGACTACTGGGGTCAGGGAACCCCTGGTCACCGT
50 CTCGAGC

DOM7r-67 SEQ ID NO: 66

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGGGACTTCTGATATGTGCTGGGTCCGCCAGGCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTGATTCTGGGGTAGTTTTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC

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TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACCTCGGCATCCTCAGGGGGGGGTTACTTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

5 DOM7r-68 SEQ ID NO: 68

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGAGCATGTTCTATGGCTTGCGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCACGGATTAGTGAGCAGGGTAGTAATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
10 ATTACTGTGCGAAAGTGCAGCATCCTATGTCTCCGCATGAGTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7r-69 SEQ ID NO: 69

15 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGAGCAGGGTATGATGTGCTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCGATTAATCCTGGTGGTCAGTTTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAGGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGGAAGATCTGGGGCCGGGTTTGGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

20

DOM7r-70 SEQ ID NO: 70

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGAGCGTTGGCCTATGTCTTGCGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTGATAGGTCTGGTAATACTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
25 TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTAT
ATTACTGTGCGAAAGTTTGCATCCTCAGGCGGGGTCTGCTTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7r-71 SEQ ID NO: 71

30 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTCGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGGGGGTAGTGATATGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATATATTGATAATCAGGGTTATAATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATATAAGCTTCTGGGTCCGTCTACTGAGTTTGACTACTGGGGTCAGGGAACCCTGGT
35 CACCGTCTCGAGC

DOM7r-72 SEQ ID NO: 72

GAGGTGCAGCTGTTGGAGTCTAGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTAGTAGTGATGTTATGTCTTGCGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
40 GGTCTCAAGTATTACGAGGTCGGGTATGCAGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATATGCGCATCCTCAGTCGGCTGTTGAGTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

45 DOM7r-73 SEQ ID NO: 73

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTTCGTAATGAGCCGATGAGTTGGGTGCGCCAGGCTCCAGTGAAGGGTCTAGAGTG
GGTCTCAACTATTTTCGCTGATGGTAGTGGGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
50 ATTACTGTGCGAAACATGGTCATCCTCAGGGGGCTCGTTTTGACTACTGGGGTCAGGGAACCCTGGTCAC
CGTCTCGAGC

DOM7r-74 SEQ ID NO: 74

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5 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTTGAATAGTGAGATGTCGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTGGAGTG
GGTCTCAACTATTGGGTATGCGGGTACTCCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACCTCGGCATCCTCAGGGGGGGGTTACTTTTGACTACTGGGGTCAGGGAACCCCTGGT
CACCGTCTCGAGC

10 DOM7r-75 SEQ ID NO: 75
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTGCTCGGGGGCCTATGTCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTACGAATGATGGTACGTCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGGAACCGCCTCATAGTGGTAGGCCTATGTTTGACTACTGGGGTCAGGGAACCCCTGGTCAC
CGTCTCGAGC

15 DOM7r-76 SEQ ID NO: 76
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTTACGCGGACTGCTATGTCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTTGAGTG
GGTCTCATCTATTGAGGCTTCGGGTGCGGTATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
20 TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACAGTCGCATCCTCAGAATGGTCGTTTTGACTACTGGGGTCAGGGAACCCCTGGTCAC
CGTCTCGAGC

25 DOM7r-77 SEQ ID NO: 77
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTGATGCGTCGGAGATGGCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAAGTATTACGGTTTATGGTGATAGGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
30 ATTACTGTGCGAAACCTCGGCATCCTCAGGGGGGGGTTACTTTTGACTACTGGGGTCAGGGAACCCCTGGT
CACCGTCTCGAGC

35 DOM7r-78 SEQ ID NO: 78
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTGATGATTGCGATATGGCTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAAGGATTTTCGAGGGAGGTAAGGCGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGGCACCGAATGATCAGTCGGCGGCTTTTGACTACTGGGGTCAGGGAACCCCTGGTCACCGT
CTCGAGC

40 DOM7r-79 SEQ ID NO: 79
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTGATATGAGTGAGATGTCGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGCTATTACTTCGGATGGTAGTTCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
45 ATTACTGTGCGAAACCTAGTCTGCCTCATGTTACGGCTTTTGACTACTGGGGTCAGGGAACCCCTGGTCAC
CGTCTCGAGC

50 DOM7r-80 SEQ ID NO: 80
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACACCTTTGAGAGGTCTACTATGCATTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGAGATTGATGCTCTGGGTACGGATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATCGTCTGATCATCCTCAGAATAGTTTTGACTACTGGGGTCAGGGAACCCCTGGTCAC
CGTCTCGAGC

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DOM7r-81 SEQ ID NO: 81

5 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGAGCCTCGTGAGATGTATTGGGCCCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCGCACGGATTGGTTGGGATGGTCATACGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACAGCTGGGTCAGTTTGACTACTGGGGTCAGGGAACCCTGGTCAACCGTCTCGAGC

DOM7r-82 SEQ ID NO: 82

10 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGATGCTTATAGTATGATGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTGGTAGGTGGGGTGAGATTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTAT
ATTACTGTGCGAAACGTCGTTATATTGGGCCTTATATGCTTTTCGGGTGCTTTTGACTACTGGGGTCAGGG
15 AACCCTGGTCAACCGTCTCGAGC

DOM7r-83 SEQ ID NO: 83

20 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTTATGCGGTATCCTATGGTGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCTATTTCTCCTGCTGGTTATGGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGTCATGAGATTAGTCGGTTTTCTCGTTGGTCTTCTTTTGACTACTGGGGTCAGGG
AACCCTGGTCAACCGTCTCGAGC

DOM7r-84 SEQ ID NO: 84

25 GAGGTGCAGCTGTTGGAGTCTGGGGGGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTTCGGAAGTATAGGATGTGCTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCTATTGCGAGGAATGGTCGTCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
30 ATTACTGTGCGAAAACACTACGTCCTGGGTTTGACTACTGGGGTCAGGGAACCCTGGTCAACCGTCTCGAGC

DOM7r-85 SEQ ID NO: 85

35 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTAATAAGAAGGAGATGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCTATTGATGTGAGTGGAATGTTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAATGGCTCATCCTCAGTCGGGGGTGGCTTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7r-88 SEQ ID NO: 86

40 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTTCGGATGTATGATATGGCGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAAAGTG
GGTCTCAACTATTCTGTCTTCTGGTAAGGGTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
45 ATTACTGTGCGAAATTGGCTCATCCTCAGAAGGGTAGTATTTTGACTACCGGGGTAGGGAACCCTGGT
CACCGTCTCGAGC

DOM7r-89 SEQ ID NO: 87

50 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTTCATCAGGGTCTTATGGGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATGGATTACGGTACGGGTGGTGCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGGATGCATCCTCAGAGTGGTACTCTTTTGACTACTGGGGTCAGGGAACCCTGGT
CACCGTCTCGAGC

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DOM7r-90 SEQ ID NO: 88

5 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGATGTTGCGGATATGGATTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGGGATTTTCGTCGTCGGGTGGTTATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGATACCGCGGTAT
ATTACTGTGCGAAAAATTTGGGTCAGGGTTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

10 DOM7r-92 SEQ ID NO: 89

10 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGATACGAGTAGTATGTTGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGTTATTCATCAGAGTGGTACGCCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
15 ATTACTGTGCGAAATTTCCGTTTACTCATGGTAAGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGT
CTCGAGC

DOM7r-93 SEQ ID NO: 90

20 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTAATAATTATACGATGGGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATTTGATTACATACGAGTGGTACGGTGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAATGGAGTTCGAGGGCGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

25 DOM7r-94 SEQ ID NO: 91

25 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGGGAATTATAGGATGACTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAACTATTTCTCCTTTGGGTACGTATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
30 TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGGGCGTTGGTCGATTTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

DOM7r-95 SEQ ID NO: 92

35 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGGTAGTTATCCTATGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTGGAGTG
GGTCTCATGGATTCTGTTGGGAGGGGTCTTGCTACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
40 ATTACTGTGCGAAATATTTTCATGGTAAGTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

DOM7r-96 SEQ ID NO: 93

45 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTAGTGCTTATGTGATGGGTTGGGTACGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCATCGATTCCGATGCCGGGTATCTGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAACGTACTCCTTTTTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

DOM7r-97 SEQ ID NO: 94

50 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTGAGCATTATTCGATGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGAGATTGATCCGGATGGTATTATGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT

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ATTACTGTGCGAAAGCGCCGGGGTTCTTGAGATGTGGATTACGCATTTTACTACTGGGGTCAGGGAAC
CCTGGTCACCGTCTCGAGC

DOM7r-98 SEQ ID NO: 95

5 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTTCGTCAATTATGTGATGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
GGTCTCAGCTATTTCTGCGCATGGTAATCGGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
10 ATTACTGTGCGAAATCTTATAGCCTTGCTCTGACTCCTTTTACTACTGGGGTCAGGGAACCTGGTCAC
CGTCTCGAGC

DOM7r-99 SEQ ID NO: 96

GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGCGTCTCTCCTGTGCAG
CCTCCGGATTACCTTTTACTGTGTATGAGATGAAGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTG
15 GGTCTCAGCGATTTCTGCTGGGGGTAAGTATACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC
TCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGCGTGCCGAGGACACCGCGGTAT
ATTACTGTGCGAAAGAGATTCTGCATCTTGATAATGCGGTTGAGTTTACTACTGGGGTCAGGGAACCT
GGTCACCGTCTCGAGC

20 Amino acid sequences:

DOM7h-112 SEQ ID NO: 97

EVQLLESGGGLVQPGGSLRLSCAASGFTFGGYVMGWVRQAPGKGLEWVSAINRFGSSTYYADSVKGRFTI
25 SRDNSKNTLYLQMNSLRAEDTAVYYCAKGSRLRHFDFYWGQGTLLVTVSS

DOM7h-98 SEQ ID NO: 98

EVQLLESGGGLVQPGGSLRLSCAASGFTFGNYAMAWVRQAPGKGLEWVSSIDMVGIKTYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKGFRIFDYWGQGTLLVTVSS

30 DOM7r-29 SEQ ID NO: 99

EVQLLESGGGLVQPGGSLRLSCAASGFTFKDYDMTWVRQAPGKGLEWVSMISSSGLWYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKGFRLFPRTFDYWGQGTLLVTVSS

DOM7r-35 SEQ ID NO: 100

35 EVQLLESGGGLVQPGGSLRLSCAASGFTFSLYRMVWVRQAPGKGLEWVSMISQFGNQTYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKVRSDQTGGRRTFDYWGQGTLLVTVSS

DOM7r-36 SEQ ID NO: 101

40 EVQLLESGGGLVQPGGSLRLSCAASGFTFNHYTMGWVRQAPGKGLEWVSLIHPSGTVTYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKWSSRAFDYWGQGTLLVTVSS

DOM7r-38 SEQ ID NO: 102

45 EVQLLESGGGLVQPGGSLRLSCAASGFTFDNNAMGWVRQAPGKGLEWVSTISANGNATYYADSVKGRFTI
SRDNSKDTLYLQMNSLRAEDTAVYYCAKGFRRFDYWGQGTLLVTVSS

DOM7r31 SEQ ID NO: 103

EVQLLESGGGLVQPGGSLRLSCTASGFTFRHYRMGWVRQAPGKGLEWVSWIRPDGTFITYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKSYMGRDFDYWGQGTLLVTVSS

50 DOM7h-32 SEQ ID NO: 104

EVQLLESGGGLVQPGGSLRLSCAASGFTFGNYPMTWVRQAPGKGLEWVSTISYGLLATYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKMAINGVRPRRFDYWGQGTLLVTVSS

DOM7h-33 SEQ ID NO: 105

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EVQLLES GGGGLVQPGGSLRLSCAASGFTFMAYQMAWVRQAPGKGLEWVSTIHQTGFSTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKVRSMRPYKFDYWGQGTLLTVSS

5 DOM7h-34 SEQ ID NO: 106
EVQLLES GGGGLVQPGGSLRLSCAASGFTFDGDKAMGWVRQAPGKGLEWVSTISAPGNRTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKGFRNFDYWGQGTLLTVSS

10 DOM7h-83 SEQ ID NO: 107
EVQLLES GGGGLVQPGGSLRLSCAASGFTFDGMRMGWVRQAPGKGLEWVSAIEVNGQHTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKMAHPQSGVAFDYWGQGTLLTVSS

15 DOM7h-84 SEQ ID NO: 108
EVQLLES GGGGLVQPGGSLRLSCAASGFTFTPDAMAWVRQAPGKGLEWVSSIGVNGSPTYYADSVKGRFTI
SRDNSRNTLYLQMNSLRAEDTAVYYCAKMAHPQSGVAFDYWGQGTLLTVSS

DOM7h-85 SEQ ID NO: 109
EVQLLES GGGGLVQPGGSLRLSCAASGFTFYQSDMSWVRQAPGKGLEWVSSISSQGRSTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKMAHPQSGVAFDYWGQGTLLTVSS

20 DOM7h-86 SEQ ID NO: 110
EVQLLES GGGGLVQPGGSLRLSCTASGFTFAARDMSWVRQAPGKGLEWVSSISAQGAHTYYADSVKGRFTI
SRDDSKNTLYLQMNSLRAEDTAVYYCAKPRHPQGGVTFDYWGQGTLLTVSS

25 DOM7h-87 SEQ ID NO: 111
EVQLLES GGGGLVQPGGSLRLSCAASGFTFDNGDMVWVRQAPGKGLEWVSGIAHNGRNTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKNLGQGFYWGQGTLLTVSS

30 DOM7h-88 SEQ ID NO: 112
EVQLLES GGGGLVQPGGSLRLTCAASGFTLNGTSMGWVRQAPGKDLEWVSSIMPVGSHTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKMAHPQSGVAFDYWGQGTLLTVSS

35 DOM7h-89 SEQ ID NO: 113
EVQLLES GGGGLVQPGGSLRLSCAASGFTFDHAPMKWARQAPGKGLEWVSYIGSAGNMNTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKDEGPFYWGQGTLLTVSS

DOM7h-90 SEQ ID NO: 114
EVQLLES GGGGLVQPGGSLRLSCTASGFTFDGMDMSWVRQAPGKGLEWVSSISTTGTTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKPRHPQGGVTFDYWGQGTLLTVSS

40 DOM7h-91 SEQ ID NO: 115
EVQLLES GGGGLVQPGGSLRLSCAASGFTFEAETMAWVRQAPGKGLEWVSTIHSEGSRTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKPRHPQGGVTFDYWGQGTLLTVSS

45 DOM7h-92 SEQ ID NO: 116
EVQLLES GGGGLVQPGGSLRLSCAASGFTFSTGEMAWVRQAPGKGLEWVSSISSSGATTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKPRHPQGGVTFDYWGQGTLLTVSS

50 DOM7h-93 SEQ ID NO: 117
EVQLLES GGGGLVQPGGSLRLSCAASGFTFPSADMVWVRQAPGKGLEWVSRISPEGNHTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAERPPSDYVSFDYWGQGTLLTVSS

DOM7h-94 SEQ ID NO: 118
EVQLLES GGGGLVQPGGSLRLSCAASGFTFANATMSWVRQAPGKGLEWVSDIDQVGHATYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKYSWHPDLFDYWGQGTLLTVSS

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- DOM7h-95 SEQ ID NO: 119
 EVRLLESGGGLVQPGGSLRLSCAASGFTFKDYGMNWVRQAPGKGLEWVSRISRNGTVTYADSVKGRFTI
 5 SRDNSKNTLYLQMNSLRAEDTAVYYCAKLAAPVRQKGMDFDYWGQGTLLVTVSS
- DOM7h-96 SEQ ID NO: 120
 EVQLLESGGGLVQPGGSLRLSCAASGFTFEWYNMSWVRQAPGKDLEWVSSISHDGWNTYYADSVKGRFTI
 SRDNSKNTLYLQMNSLRAEDTAVYYCAKGMIGFDYWGQGTLLVTVSS
- 10 DOM7h-97 SEQ ID NO: 121
 VQLLESGGGLVQPGGSLRLSCAASGFTFDIYTMHWVRQAPGKGLEWVSTIVPQGTPTYADSVKGRFTIS
 RDNSKNTLYLQMNSLRAEDTAVYYCAKSKRRFLKRFDYWGQGTLLVTVSS
- DOM7h-99 SEQ ID NO: 122
 15 EVQLLESGGGLVQPGGSLRLSCAASGFTFARYDMQWVRQAPGKGLEWVSSIKSNGMKTYADSVKGRFTI
 SRDNSKNTLYLQMNSLRAEDTAVYYCAKASMWTFDYWGQGTLLVTVSN
- DOM7h-100 SEQ ID NO: 123
 EVQLLESGGGLVQPGGSLRLSCAASGFTFMLYHMGWVRQAPGKGLEWVSAITGGGYPTYADSVKGRFTI
 20 SRDNSKNTLYLQMNSLRAEDTAVYYCAKLGRLRGVLWRRRFDYWGQGTLLVTVSS
- DOM7h-101 SEQ ID NO: 124
 EVQLLESGGGLVQPGGSLRLSCAASGFTFGAYSMMWVRQAPGKGLEWVSRISRNGTVTYADSVKGRFTI
 25 SRDNSKNTLYLQMNSLRAEDTAVYYCAKIRWNTAQVPVFDYWGQGTLLVTVSS
- DOM7h-102 SEQ ID NO: 125
 EVQLLESGGGLVQPGGSLRLSCAASGFTFGPYWMAWVRQAPGKGLEWVSTITPSGRGTYADSVKGRFTI
 SRDNSKNTLYLQMNSLRAEDTAVYYCAKGRPRVGLWRSQFDYWGQGTLLVTVSS
- 30 DOM7h-103 SEQ ID NO: 126
 EVQLLESGGGLVQPGGSLRLSCAASGFTFGQYAMQWVRQAPGKGLEWVSSINITGSTTYADSVKGRFTI
 SRDNSKNTLYLQMNSLRAEDTAVYYCAKGFRSFDYWGQGTLLVTVSS
- DOM7h-106 SEQ ID NO: 127
 35 VQLLESGGGLVQPGGSLRLSCAASGFTFAGYTMSWVRQAPGKGLEWVSTISGFGWTTYADSVKGRFTIS
 RDNSKNTLYLQMNSLRAEDTAVYYCAKRLGMRFDYWGQGTLLVTVSS
- DOM7h-109 SEQ ID NO: 129
 40 EVQLLESGGGLVQPGGSLRLSCAASGFTFGPYSMGWVRQAPGKGLEWVSFIHSDGRHTYYADSVKGRFTI
 SRDNSKNTLYLQMNSLRAEDTAVYYCAKKTTPYRFDYWGQGTLLVTVSS
- DOM7h-111 SEQ ID NO: 130
 EVQLLESGGGLVQPGGSLRLSCAASGFTFGQYAMQWVRQAPGKGLEWVSSINITGSTTYADSVKGRFTI
 45 SRDNSKNTLYLQMNSLRAEDTAVYYCAKGFRSFDYWGQGTLLVTVSS
- DOM7h-114 SEQ ID NO: 131
 EVQLLESGGGLVQPGGSLRLSCAASGFTFRRYAMSWVRQAPGKGLEWVSTISPYGPVTTYADSVKGRFTI
 SRDNSKNTLYLQMNSLRAEDTAVYYCAKAYYGGFDYWGQGTLLVTVSS
- 50 DOM7r-34 SEQ ID NO: 132
 EVQLLESGGGLVQPGGSLRLSCAASGFTFDAYAMGWVRQAPGKGLEWVSKIDSPGWRTYADSVKGRFTI
 SRDNSKNTLYLQMNSLRAEDTAVYYCAKSARMRSRHFYWGQGTLLVTVSS

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- DOM7r-37 SEQ ID NO: 133
EVQLLESGGGLVQPGGSLRLSCAASGFTTFKDYGMNWVRQAPGKGLEWVSRISRNGTVITYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKIRWNTAQVPVFDYWGQGTLVTVSS
- 5 DOM7r-39 SEQ ID NO: 134
EVQLLESGGGLVQPGGSLRLSCATSGFTFPSYTMGWVRQAPGKGLEWVSRISRTGNYITYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKPMYNRGSSYFDYWGQGTLVTVSS
- 10 DOM7r-40 SEQ ID NO: 135
EVQLLESGGGLVQPGGSLRLSCAASGFTFSQYQMSWVRQAPGKGLEWVSSISPTGIQTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKRLIGMPYVEDTFDYWGQGTLVTVSS
- 15 DOM7r-41 SEQ ID NO: 136
EVQLLESGGGLVQPGGSLRLSCAASGFTFMEYEMEWVRQAPGKGLEWVSGITNSGSGTYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAIMQHQPATGGRVGFYDWGQGTLVTVSS
- 20 DOM7r-42 SEQ ID NO: 137
EVQLLESGGGLVQPGGSLRLSCAASGFTFPRYTMKWVRQAPGKGLEWVSSIDRTGRKTYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKESLVSFYDWGQGTLVTVSS
- DOM7r-43 SEQ ID NO: 138
EVQLLESGGGLVQPGGSLRLSCAASGFTFGGYTMPWVRQAPGKGLEWVSTISRDNITYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKDIGMGFDYGGRTLVTVSS
- 25 DOM7r-44 SEQ ID NO: 139
EVQLLESGGGLVQPGGSLRLSCAASGFTFEIYAMHWVRQAPGKGLEWVSTISSGKGTYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKSRTMYFRVREAFDYWGQGTLVTVSS
- 30 DOM7r-45 SEQ ID NO: 140
EVQLLESGGGLVQPGGSLRLSCAASGFTFRAYRMMWVRQAPGKGLEWVSSIDPDGAVITYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAEHFDLAMPNPNNAKFDYWGQGTLVTVSS
- 35 DOM7r-46 SEQ ID NO: 141
EVQLLESGGGLVQPGGSLRLSCAASGFTFSRYQMSWVRQAPGKGLEWVSSIKSNGSSTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKPSRQSFQYPSFDYWGQGTLVTVSS
- 40 DOM7r-47 SEQ ID NO: 142
EVQLLESGGGLVQPGGSLRLSCAASGFTFGRYKMGWVRQAPGKGLEWVSSISPTGSSTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKTGYVMVEHFDYWGQGTLVTVSS
- DOM7r-48 SEQ ID NO: 143
EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYPMKWVRQAPGKGLEWVSTINSSGTITYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKPLLPFDYWGQGTLVTVSS
- 45 DOM7r-49 SEQ ID NO: 144
EVQLLESGGGLVQPGGSLRLSCAASGFTFARYRMCWVRQAPGKGLEWVSCIRDPGFPTYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKCSPTSQCTGLFDYWGQGTLVTVSS
- 50 DOM7r-50 SEQ ID NO: 145
VQLLESGGGLVQPGGSLRLSCAASGFTFRFYGMAWVRQAPGKGLEWVSLIDPPGGATYYADSVKGRFTIS
RDNSKNTLYLQMNSLRAEDTAVYYCAKMERRHLKSGHKGFYDWGQGTLVTVSS
- DOM7r-51 SEQ ID NO: 146

- 39 -

EVQLLES GGGGLVQPGGSLRLSCAASGFTTFEYDMMWVRQAPGKGLEWVSSISHRGEKTYIYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKDKRYRGSQHYFDYWGQGTLVTVSS

5 DOM7r-52 SEQ ID NO: 147
VQLLES GGGGLVQPGGSLRLSCAASGFTFRSYDMGWARQAPGKGLEWVSTIGSNGANTYYADSVKGRFTIS
RDNSKNTLYLQMNSLRAEDTAVYYCAKLMGMFDYWGQGTLVTVSS

10 DOM7r-53 SEQ ID NO: 148
EVQLLES GGGGLVQPGGSLRLSCAASGFTTFERYSMRWVRQAPGKGLEWVSTIGSTGKWTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKGRGLVSFDYWGQGTLVTVSS

15 DOM7r-54 SEQ ID NO: 149
EVQLLES GGGGLVQPGGSLRLSCAASGFTFRYSMSWVRQAPGKGLEWVSSIDRSGRMTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKSRLSSTGSEGHNFYWGQGTLVTVSS

DOM7r-55 SEQ ID NO: 150
VQLLES GGGGLVQPGGSLRLSCAASGFTFKWYPMKWVRQAPGKGLEWVSTIAYDGVQTYIYADSVKGRFTIS
RDNSKNTLYLQMNSLRAEDTAVYYCAKLGPTSRVFAATDFDYWGQGTLVTVSS

20 DOM7r-56 SEQ ID NO: 151
EVQLLES GGGGLVQPGGSLRLSCAASGFTFPNYAMKWGRQAPGKGLEWVSTIDTSGSTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKLTHPMAPRPAFDYWGQGTLVTVSS

25 DOM7r-57 SEQ ID NO: 152
EVQLLES GGGGLVQPGGSLRLSCAASGFTFDLTEMWVRQAPGKGLEWVSSIGPWGTPTYIYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKISHPQAMYHTFDYWGQGTLVTVSS

30 DOM7r-58 SEQ ID NO: 153
EVQLLES GGGGLVQPGGSLRLSCAASGFTFAHQDMTWVRQAPGKGLEWVSDIDHSGSYTYIYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKWWHPQGGTFDYWGQGTLVTVSS

35 DOM7r-59 SEQ ID NO: 154
EVQLLES GGGGLVQPGGSLRLSCAASGFTFGSKDMSWVRQAPGKGLEWVSTIGANGKATYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAEAGHPQAPSFKSFDYWGQGTLVTVSS

DOM7r-60 SEQ ID NO: 155
EVQLLES GGGGLVQPGGSLRLSCAASGFTFLNAEMSWVRQAPGKGLEWVSTIDRDGANTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKLPPPMSPKKFDYWGQGTLVTVSS

40 DOM7r-61 SEQ ID NO: 156
EVQLLES GGGGLVQPGGSLRLSCAASGFTFEREGMMWVRQAPGKGLEWVSTIDRMGRYTYIYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKRDSPMGFDYRGQGTLVTVSS

45 DOM7r-62 SEQ ID NO: 157
EVQLLES GGGGLVQPGGSLRLSCAASGFTFENEKMSWVRQAPGKGLEWVSSIGPTGSGTYIYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKTPHPQVSSFDYWGQGTLVTVSS

50 DOM7r-63 SEQ ID NO: 158
EVQLLES GGGGLVQPGGSLRLSCAASGFTFEIDHMGWVRQAPGKGLEWVSEIAPSGDRTYIYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKVICQNQCCLFDYWGQGTLVTVSS

DOM7r-64 SEQ ID NO: 159
EVQLLES GGGGLVQPGGSLRLSCAASGFTFRDSEMSWVRQAPGKGLEWVSFITS DGRDYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKPSLPHVTAFDYWGQGTLVTVSS

- 40 -

- DOM7r-65 SEQ ID NO: 160
EVQLLESGGGLVQPGGSLRLSCAASGFTFEDETMSWARQAPGKGLEWVSSIGDAGMPTYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKGEPIYVHTTHFDYWGQGTLLTVSS
- 5
- DOM7r-66 SEQ ID NO: 161
EVQLLESGGGLVQPGGSLRLSCAASGFTFPHGKMGWVRQAPGKGLEWVSWIAGSGDMTYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKLGHPQRGFDYWGQGTLLTVSS
- 10
- DOM7r-67 SEQ ID NO: 162
EVQLLESGGGLVQPGGSLRLSCAASGFTFTGTSMSWVRQAPGKGLEWVSTIDSGGSFTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKPRHPQGGVTFDYWGQGTLLTVSS
- 15
- DOM7r-68 SEQ ID NO: 163
EVQLLESGGGLVQPGGSLRLSCAASGFTFEHVPMAWVRQAPGKGLEWVSRRISEQGSNTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKVQHPMSPHEFDYWGQGTLLTVSS
- 20
- DOM7r-69 SEQ ID NO: 164
EVQLLESGGGLVQPGGSLRLSCAASGFTFEQGMMSWVRQAPGKGLEWVSSINPGGQFTYYADSVKGRFTI
SRDNSRNTLYLQMNSLRAEDTAVYYCAEDLGPGFDYWGQGTLLTVSS
- 25
- DOM7r-70 SEQ ID NO: 165
EVQLLESGGGLVQPGGSLRLSCAASGFTFERWPMWVRQAPGKGLEWVSTIDRSGNTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKVLHPQAGSAFDYWGQGTLLTVSS
- 30
- DOM7r-71 SEQ ID NO: 166
EVQLLESGGGSVQPGGSLRLSCAASGFTFGGSDMGWVRQAPGKGLEWVSYIDNQGYNTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKYKLLGPSTEFDYWGQGTLLTVSS
- 35
- DOM7r-72 SEQ ID NO: 167
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSDVMSWVRQAPGKGLEWVSSITRSGMQTYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKYAHPQSAVEFDYWGQGTLLTVSS
- 40
- DOM7r-73 SEQ ID NO: 168
EVQLLESGGGLVQPGGSLRLSCAASGFTFRNEPMSWVRQAPVKGLEWVSTISPDGSGTYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKHGHPQGARFDYWGQGTLLTVSS
- 45
- DOM7r-74 SEQ ID NO: 169
EVQLLESGGGLVQPGGSLRLSCAASGFTFLNSEMSWVRQAPGKGLEWVSTIGYAGTPTYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKPRHPQGGVTFDYWGQGTLLTVSS
- 50
- DOM7r-75 SEQ ID NO: 170
EVQLLESGGGLVQPGGSLRLSCAASGFTFARGPMSWVRQAPGKGLEWVSTITNDGTSTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAEPPHSGRPMFDYWGQGTLLTVSS
- 55
- DOM7r-76 SEQ ID NO: 171
EVQLLESGGGLVQPGGSLRLSCAASGFTFQRTAMSWVRQAPGKGLEWVSSIEASGRYTYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKQSHPQNGRFDYWGQGTLLTVSS
- 60
- DOM7r-77 SEQ ID NO: 172
EVQLLESGGGLVQPGGSLRLSCAASGFTFDASEMAWVRQAPGKGLEWVSSITVYGDRTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKPRHPQGGVTFDYWGQGTLLTVSS
- 65
- DOM7r-78 SEQ ID NO: 173

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EVQLLES GGGGLVQP GGS LRLSCAASGFTFDDSHMAWVRQAPGKGLEWVSRISREGKATYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAAPNDQSAAFDYWGQGLTVTVSS

5 DOM7r-79 SEQ ID NO: 174
EVQLLES GGGGLVQP GGS LRLSCAASGFTFDMSEMSWVRQAPGKGLEWVSAITSDGSSTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKPSLPHVTAFDYWGQGLTVTVSS

10 DOM7r-80 SEQ ID NO: 175
EVQLLES GGGGLVQP GGS LRLSCAASGFTFERSTMHWVRQAPGKGLEWVSEIDALGTDITYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKSSDHPQNSFDYWGQGLTVTVSS

15 DOM7r-81 SEQ ID NO: 176
EVQLLES GGGGLVQP GGS LRLSCAASGFTFEPREMYWARQAPGKGLEWVARIGWDGHTTYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKQLGQFDYWGQGLTVTVSS

DOM7r-82 SEQ ID NO: 177
EVQLLES GGGGLVQP GGS LRLSCAASGFTFDAYSMMWVRQAPGKGLEWVSTIGRWGEITYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKRRYIGPYMLSGRFDYWGQGLTVTVSS

20 DOM7r-83 SEQ ID NO: 178
EVQLLES GGGGLVQP GGS LRLSCAASGFTFMRYPMVWVRQAPGRGLEWVSSISPAGYGTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKGHEISRFSRWSSFDYWGQGLTVTVSS

25 DOM7r-84 SEQ ID NO: 179
EVQLLES GGGGLVQP GGS LRLSCAASGFTFRKYRMSWVRQAPGKGLEWVSSIARNRSTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKTTSGFDYWGQGLTVTVSS

30 DOM7r-85 SEQ ID NO: 180
EVQLLES GGGGLVQP GGS LRLSCAASGFTFNKKEMGWVRQAPGKGLEWVSSIDVSGNVTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKMAHPQSGVAFDYWGQGLTVTVSS

35 DOM7r-88 SEQ ID NO: 181
EVQLLES GGGGLVQP GGS LRLSCAASGFTFRMYDMAWVRQAPGKGLKWVSTILSSGKGTYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKLAHPQKGSIFDYRGQGLTVTVSS

DOM7r-89 SEQ ID NO: 182
EVQLLES GGGGLVQP GGS LRLSCAASGFTFHQGPWGVRQAPGKGLEWVSWIQATGGATYYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKGMHPQSGTLFDYWGQGLTVTVSS

40 DOM7r-90 SEQ ID NO: 183
EVQLLES GGGGLVQP GGS LRLSCAASGFTFDVADMDWVRQAPGKGLEWVSGISSGGYTYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKNLGQGFYWGQGLTVTVSS

45 DOM7r-92 SEQ ID NO: 184
EVQLLES GGGGLVQP GGS LRLSCAASGFTFDTSSMLWVRQAPGKGLEWVSVIHQSGTPTYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKFPFTHGKFDYWGQGLTVTVSS

50 DOM7r-93 SEQ ID NO: 185
EVQLLES GGGGLVQP GGS LRLSCAASGFTFNNTYTMGWVRQAPGKGLEWVSLIHTSGTVTYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKWSSRAFDYWGQGLTVTVSS

DOM7r-94 SEQ ID NO: 186
EVQLLES GGGGLVQP GGS LRLSCAASGFTFGNYRMTWVRQAPGKGLEWVSTISPLGTYTYADSVKGRFTI
SRDNSKNTLYLQMNSLRAEDTAVYYCAKGRWSIFDYWGQGLTVTVSS

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DOM7r-95 SEQ ID NO: 187
 EVQLLES GGGGLVQPGGSLRLSCAASGFTFGSYPMGWVRQAPGKGLEWVSWIRGRGLATYYADSVKGRFTI
 SRDNSKNTLYLQMNSLRAEDTAVYYCAKYFHGKFDYWGQGT LVT VSS

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DOM7r-96 SEQ ID NO: 188
 EVQLLES GGGGLVQPGGSLRLSCAASGFTFSAYVMGWVRQAPGKGLEWVSSIRMPGYLTYADSVKGRFTI
 SRDNSKNTLYLQMNSLRAEDTAVYYCAKRTPFDFDYWGQGT LVT VSS

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DOM7r-97 SEQ ID NO: 189
 EVQLLES GGGGLVQPGGSLRLSCAASGFTFEHYSMGWVRQAPGKGLEWVSEIDPDGIMTYADSVKGRFTI
 SRDNSKNTLYLQMNSLRAEDTAVYYCAKAPGVLEMWITHFDYWGQGT LVT VSS

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DOM7r-98 SEQ ID NO: 190
 EVQLLES GGGGLVQPGGSLRLSCAASGFTFRHYVMGWVRQAPGKGLEWVSAISAHGNRTYYADSVKGRFTI
 SRDNSKNTLYLQMNSLRAEDTAVYYCAKSYSLALTPFDYWGQGT LVT VSS

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DOM7r-99 SEQ ID NO: 191
 EVQLLES GGGGLVQPGGSLRLSCAASGFTFTVYEMKWVRQAPGKGLEWVSAISAGGKYTYADSVKGRFTI
 SRDNSKNTLYLQMNSLRAEDTAVYYCAKEIRHLDNAVEFDYWGQGT LVT VSS

EXEMPLIFICATION

25

Example 1

Biophysical Characterisation:

30 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
 35 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
 40 measured as a function of angle. This measurement taken together with the protein

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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-
5 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
10 native conformation and the other 50% is denatured. Here, DSC determined the apparent transition midpoint ($_{app}T_m$) as most of the proteins examined do not fully refold. The higher the T_m , the more stable the molecule. The software package used was Origin^R v7.0383.

15 Characteristics of the VH dAbs are summarised in Table 1 below. Cross-reactivity of the AlbudAbsTM (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, BiacoreTM was used. The epitope mapping to domain 1, 2 and/or 3 (D1,2,3) of human serum albumin (HSA) was
20 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-
25 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
30 could explain in part the presence of two $_{app}T_m$ s for some AlbudAbs as seen in table1;

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

Table 1

*	x- reactivity	MALLS	DSC [°C]		Expression	Binding to D1/2/3 of HSA
	(4AGs)	[kDa]	appTm1	appTm2	(<i>E.coli</i>) 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

5 *: 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
 10 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.

15 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
 5 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
 10 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.
 15 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 T_{1/2} of 20mins in rat) to varying
 degrees; this trend can also be seen in the calculated AUC being the highest value for
 20 the longest t_{1/2}. The longest serum half-life with 34.5hrs approximates the serum half-
 life of rat serum albumin.

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

25 **Table 2**

VH dAb	T _{1/2} *	AUC 0-inf
	[hr]	[hr*ug/mL]
DOM7h-98	13.5	577.5
DOM7r-29	21.9	697.6

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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.

$T_{1/2}$ is a measure of the circulation time of the molecule in the subjects.

AUC=area under the curve, which is a PK profile parameter

5

Anti-myc ELISA method using MSD

The AlbuAb 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%

10 BSA/PBS + 1% TWEEN™. Serum samples were added at a range of dilutions alongside a standard at known concentrations. Bound myc-tagged AlbuAb 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;

15 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

20 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.

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Example 3: Affinity maturation of naïve VH AlbuAbs™

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12 VH AlbuAb 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 2×10^9 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 μ M (HSA or RSA), Round 2 at 1 μ M (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

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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

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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		5	15	25	35	45	55
	A	EVQLLES	GGG LVQPGGSLRL	SCAASGFTFS	SYAMSWVRQA	PGKGLEWVSA	ISGSGGSTYY
	B	EVQLLES	GGG LVQPGGSLRL	SCAASGFTFN	HYTMGWVRQA	PGKGLEWVSL	IHPSGTVIYY
	C	EVQLLES	GGG LVQPGGSLRL	SCAASGFTFN	HYTMGWVRQA	PGKGREWVSL	IHPSGTVIYY
	D	EVQLLES	GGG LVQPGGSLRL	SCAASGFTFN	HYTMGWVRQA	PGKGLEWVSL	IHPSGTVIYY
10	E	EVQLLES	GGG LVQPGGSLRL	SCAASGFTFD	<u>TSSMLWVRQA</u>	PGKGLEWVSV	<u>IHQSGTPTY</u>
	F	EVQLLES	GGG LVQPGGSLRL	SCAASGFTFG	<u>NYAMAWVRQA</u>	PGKGLEWVSS	<u>IDMVGIKTY</u>
	G	EVQLLES	GGG LVQPGGSLRL	SCTASGFTFR	<u>HYRMGWVRQA</u>	PGKGLEWVSW	<u>IRPDGTFTYY</u>
15		65	75	85	95	105	115
	A	<u>ADSVKGRFTI</u>	SRDNSKNTLY	LQMNSLRAED	TAVYYCAKSY	<u>GA~~~FDYWG</u>	QGTTLTVSS
	B	<u>ADSVKGRFTI</u>	SRDNSKNTLY	LQMNSLRAED	TAVYYCAKWS	<u>SRA~~~FDYWG</u>	QGTTLTVSS
	C	<u>ADSVKGRFTI</u>	SRDNSKNTLY	LQMNSLRAED	TAVYYCAKWS	<u>SRA~~~FDYWG</u>	QGTTLTVSS
	D	<u>ADSVKGRFTI</u>	SRDNSKNTLY	LQMNSLRAED	TAVYYCARWS	<u>SRA~~~FDYWG</u>	QGTTLTVSS
	E	<u>ADSVKGRFTI</u>	SRDNSKNTLY	LQMNSLRAED	TAVYYCAKFP	<u>STHGKFDYWG</u>	QGTTLTVSS
20	F	<u>ADSVKGRFTN</u>	SRDNSKNTLY	LQMNSLRAED	TAVYYCARGF	<u>RI~~~FDYWG</u>	QGTTLTVSS
	G	<u>ADSVKGRFTI</u>	SRDNSKNTLY	LQMNSLRAED	TAVYYCAKSY	<u>MADR~FDYWG</u>	QGTTLTVSS

A= VH dummy

B= DOM7r-201

25 C= DOM7r-36-2

D= DOM7r-36-8

E= DOM7r-92-4

F= DOM7h-98-4

G= DOM7r-31-1

30

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

35 Nucleotide sequences

DOM7r-201 SEQ ID NO: 192

GAGGTGCAACTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTGC
 CCTGCGTCTCTCCTGTGCAGCCTCCGGATTACCTTTAATCATTATACGA
 40 TGGGTTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCATTG
 ATTCATCCGAGTGGTACGGTGATATACTACGCAGACTCCGTGAAGGGCCG
 GTTCAACATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGA
 ACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAATGGAGT
 TCGAGGGCATTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCTAG
 45 C

DOM7r-36-2 SEQ ID NO: 193

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5 GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTC
CCTGCGTCTCTCCTGTGCAGCCTCCGGATTACCTTTAATCATTATACGA
TGGGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCATTG
ATTTCATCCGAGTGGTACGGTGACATACTACGCAGACTCCGTGAAGGGCCG
GTTTACCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGA
ACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAATGGAGT
TCGAGGGCGTTTGGTACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAG
C

10 DOM7r-36-8 SEQ ID NO: 194
GAGGTGCAACTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTC
CCTGCGTCTCTCCTGTGCAGCCTCCGGATTACCTTTAATCATTATACGA
TGGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCATTG
ATTCATCCGAGTGGTACGGTGATATACTACGCAGACTCCGTGAAGGGCCG
15 GTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGA
ACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAGATGGAGT
TCGAGGGCGTTTGGTACTACTGGGGTCAGGGGACCCTGGTCACCGTCTCGAG
C

20 DOM7r-92-4 SEQ ID NO: 195
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTC
CCTGCGTCTCTCCTGTGCAGCCTCCGGATTACCTTTGATACGAGTAGTA
TGTTGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCAGTT
ATTCATCAGAGTGGTACGCCACATACTACGCAGACTCCGTGAAGGGCCG
25 GTTCACCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGA
ACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAATTTCCG
TCTACTCATGGTAAGTTTGGTACTACTGGGGTCAGGGAACCCTGGTCACCGT
CTCGAGC

30 DOM7h-98-4 SEQ ID NO: 196
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTC
CCTGCGTCTCTCCTGTGCAGCCTCCGGATTACCTTTGGTAATTATGCGA
TGGCGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCATCG
ATTGATATGGTTGGTATTAAGACATACTACGCAGACTCCGTGAAGGGCCG
35 GTTCACCAATTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGA
ACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAGAGGTTTT
CGTATTTTTGACTACTGGGGTCAGGGAACCCTGGTCACCGTCTCGAGC

40 DOM7r-31-14 SEQ ID NO: 197
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTC
CCTGCGTCTCTCCTGTACAGCCTCCGGATTACCTTTAGGCATTATCGTA
TGGGTGGGTCCGCCAGGCTCCAGGGAAGGGTCTAGAGTGGGTCTCATGG
ATTCGTCCGGATGGTACGTTTACATACTACGCAGACTCCGTGAAGGGCCG
GTTTACCATCTCCCGCGACAATTCCAAGAACACGCTGTATCTGCAAATGA
45 ACAGCCTGCGTGCCGAGGACACCGCGGTATATTACTGTGCGAAATCTTAT
ATGGCTGATAGTTTGGTACTACTGGGGTCAGGGAACCCTGGTCACCGTCTC
GAGC

Amino Acid Sequences

50 DOM7r-201 SEQ ID NO: 198
EVQLLESGLVQPGGSLRLSCAASGFTFNHYTMGWVRQAPGKGLEWVSL
IHPSGTVIYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKWS

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SRAFDYWGQGTTLVTVSS

DOM7r-36-2 SEQ ID NO: 199

5 EVQLLESGGGLVQPGGSLRLSCAASGFTFNHYTMGWVRQAPGKGREWVSL
IHPSGTVTYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKWS
SRAFDYWGQGTTLVTVSS

DOM7r-36-8 SEQ ID NO: 200

10 EVQLLESGGGLVQPGGSLRLSCAASGFTFNHYTMGWVRQAPGKGLEWVSL
IHPSGTVIYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARWS
SRAFDYWGQGTTLVTVSS

DOM7r-92-4 SEQ ID NO: 201

15 EVQLLESGGGLVQPGGSLRLSCAASGFTFDTSSMLWVRQAPGKGLEWVSV
IHQSGTPTYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKFP
STHGKFDYWGQGTTLVTVSS

DOM7h-98-4 SEQ ID NO: 202

20 EVQLLESGGGLVQPGGSLRLSCAASGFTFGNYAMAWVRQAPGKGLEWVSS
IDMVGIKTYADSVKGRFTNSRDN SKNTLYLQMNSLRAEDTAVYYCARGF
RIFDYWGQGTTLVTVSS

DOM7r-31-14 SEQ ID NO: 203

25 EVQLLESGGGLVQPGGSLRLSCTASGFTFRHYRMGWVRQAPGKGLEWVSW
IRPDGTFITYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKSY
MADRFDYWGQGTTLVTVSS

CLAIMS:

1. An anti-serum albumin (SA) immunoglobulin single variable domain
5 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
10 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
15 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
20 198 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.
- 25 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 1.5×10^{-4} to about 0.1 sec^{-1} , optionally from about 3×10^{-4} to about 0.1 sec^{-1} as
determined by surface plasmon resonance.

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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 2×10^6 to about $1 \times 10^4 \text{ M}^{-1}\text{sec}^{-1}$, optionally from about 1×10^6 to about $2 \times 10^4 \text{ M}^{-1}\text{sec}^{-1}$ as determined by surface plasmon resonance.

5

8. The variable domain of any preceding claim, comprising a binding site that specifically binds *Cynomolgus* monkey SA with a dissociation constant (K_D) of from about 0.1 to about 10000 nM, optionally from about 1 to about 6000 nM, as determined by surface plasmon resonance.

10

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 1.5×10^{-4} to about 0.1 sec^{-1} , optionally from about 3×10^{-4} to about 0.1 sec^{-1} as determined by surface plasmon resonance.

15

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 2×10^6 to about $1 \times 10^4 \text{ M}^{-1}\text{sec}^{-1}$, optionally from about 1×10^6 to about $5 \times 10^3 \text{ M}^{-1}\text{sec}^{-1}$ as determined by surface plasmon resonance.

20

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

25

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).

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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.
- 5 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.
- 10 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.
- 15 16. A composition comprising a variable domain, fusion protein or ligand of any preceding claim and a pharmaceutically acceptable diluent, carrier, excipient or vehicle.
- 20 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.
- 25 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

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