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(54) **Title:** SERUM ALBUMIN BINDING PROTEINS

(57) **Abstract:** The present invention relates to amino acid sequences that are capable of binding to serum albumin which, which sequences do not significantly reduce or inhibit the binding of serum albumin to FcRn or significantly reduce the half-life of serum albumin. It further relates to to proteins and polypeptides comprising or essentially consisting of such amino acid sequences; to nucleic acids that encode such amino acid sequences, proteins or polypeptides; to compositions, and in particular pharmaceutical compositions, that comprise such amino acid sequences, proteins and polypeptides; and to uses of such amino acid sequences, proteins and polypeptides.

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Serum albumin binding proteins

The present invention relates to amino acid sequences that are capable of binding to serum albumin; to proteins and polypeptides comprising or essentially consisting of such amino acid sequences; to nucleic acids that encode such amino acid sequences, proteins or polypeptides; to compositions, and in particular pharmaceutical compositions, that comprise such amino acid sequences, proteins and polypeptides; and to uses of such amino acid sequences, proteins and polypeptides.

Other aspects, embodiments, advantages and applications of the invention will become clear from the further description herein.

Amino acid sequences that are capable of binding to human serum albumin and uses thereof in polypeptide constructs in order to increase the half-life of therapeutically relevant proteins and polypeptides are known in the art.

For example, WO 91/01743, WO 01/45746 and WO 02/076489 describe peptide moieties binding to serum albumin that can be fused to therapeutic proteins and other therapeutic compounds and entities in order to increase the half-life thereof. However, these peptide moieties are of bacterial or synthetic origin, which is less preferred for use in therapeutics.

WO 04/041865 by applicant describes Nanobodies® directed against serum albumin (and in particular against human serum albumin) that can be linked to other proteins (such as one or more other Nanobodies® directed against a desired target) in order to increase the half-life of said protein.

The neonatal Fc receptor (FcRn), also termed "Brambell receptor", is involved in prolonging the life-span of albumin in circulation (see Chaudhury et al., The Journal of Experimental Medicine, vol. 3, no. 197, 315-322 (2003)). The FcRn receptor is an integral membrane glycoprotein consisting of a soluble light chain consisting of β2-microglobulin, noncovalently bound to a 43 kD α chain with three extracellular domains, a transmembrane region and a cytoplasmic tail of about 50 amino acids. The cytoplasmic tail contains a dinucleotide motif-based endocytosis signal implicated in the internalization of the receptor. The α chain is a member of the nonclassical MHC I family of proteins. The β2m association with the α chain is critical for correct folding of FcRn and exiting the endoplasmic reticulum for routing to endosomes and the cell surface.

The overall structure of FcRn is similar to that of class I molecules. The α-1 and α-2 regions resemble a platform composed of eight antiparallel β strands forming a single β-sheet topped by two antiparallel α-helices very closely resembling the peptide cleft in MHC I molecules. Owing to an overall repositioning of the α-1 helix and bending of the C-terminal portion of the α-2 helix due to a break in the helix introduced by the presence of Pro162, the FcRn helices are considerably closer together, occluding peptide binding. The side chain of Arg164 of FcRn also occludes the potential interaction of the peptide N-terminus with the MHC pocket. Further, salt bridge and hydrophobic interaction between the α-1 and α-2 helices may also contribute to the groove closure.

FcRn therefore, does not participate in antigen presentation, and the peptide cleft is empty.

FcRn binds and transports IgG across the placental syncytiotrophoblast from maternal circulation to fetal circulation and protects IgG from degradation in adults. In addition to homeostasis, FcRn controls transcytosis of IgG in tissues. FcRn is localized in epithelial cells, endothelial cells and hepatocytes.

According to Chaudhury et al. (supra), albumin binds FcRn to form a tri-molecular complex with IgG. Both albumin and IgG bind noncooperatively to distinct sites on FcRn. Binding of human FcRn to Sepharose-HSA and Sepharose-hIgG was pH dependent, being maximal at pH 5.0 and nil at pH 7.0 through pH 8. The observation that FcRn binds albumin in the same pH dependent fashion as it binds IgG suggests that the mechanism by which albumin interacts with FcRn and thus is protected from degradation is identical to that of IgG, and mediated via a similarly pH-sensitive interaction with FcRn. Using SPR to measure the capacity of individual HSA domains to bind immobilized soluble hFcRn, Chaudhury showed that FcRn and albumin interact via the D-III domain of albumin in a pH-dependent manner, on a site distinct from the IgG binding site (Chaudhury, PhD dissertation, see http://www.andersonlab.com/biosketchCC.htm; Chaudhury et al. Biochemistry, ASAP Article 10.1021/bi052628y S0006-2960(05)02628-0 (Web release date: March 22, 2006)).

It is an object of the present invention to provide amino acid sequences that are an alternative, and in particular an improved alternative, to the albumin-binding amino acid sequences described in the prior art cited above.

In one aspect, the invention achieves this objective by providing amino acid sequences, and in particular immunoglobulin sequences, and more in particular

immunoglobulin variable domain sequences, that can bind to or otherwise associate with serum albumin in such a way that, when the amino acid sequence or polypeptide construct is bound to or otherwise associated with a serum albumin molecule, the binding of said serum albumin molecule to FcRn is not (significantly) reduced or inhibited (i.e. compared to the binding of said serum albumin molecule to FcRn when the amino acid sequence or polypeptide construct is not bound thereto). In this aspect of the invention, by "not significantly reduced or inhibited" is meant that the binding affinity for serum albumin to FcRn (as measured using a suitable assay, such as SPR) is not reduced by more than 50%, preferably not reduced by more than 30 %, even more preferably not reduced by more than 10%, such as not reduced by more than 5%, or essentially not reduced at all. In this aspect of the invention,"not significantly reduced or inhibited" may also mean (or additionally mean) that the half-life of the serum albumin molecule is not significantly reduced (as defined below).

When in this description, reference is made to binding, such binding is preferably specific binding, as normally understood by the skilled person.

When an amino acid sequence as described herein is a monovalent immunoglobulin sequence (for example, a monovalent Nanobody), said monovalent immunoglobulin sequence preferably binds to human serum albumin with a dissociation constant (KD) of 10^{-5} to 10^{-12} moles/liter or less, and preferably 10^{-7} to 10^{-12} moles/liter or less and more preferably 10^{-8} to 10^{-12} moles/liter, and/or with a binding affinity of at least 10^{7} M-1, preferably at least 10^{8} M-1, more preferably at least 10^{9} M-1, such as at least 10^{12} M-1. Any KD value greater than 10^{-4} liters/mol is generally considered to indicate non-specific binding. Preferably, a monovalent immunoglobulin sequence of the invention will bind to the desired antigen with an affinity less than 500 nM, preferably less than 200 nM, more preferably less than 10 nM, such as less than 500 pM. Specific binding of an antigen-binding protein to an antigen or antigenic determinant can be determined in any suitable manner known per se, including, for example, Scatchard analysis and/or competitive binding assays, such as radioimmunoassays (RIA), enzyme immunoassays (EIA) and sandwich competition assays, and the different variants thereof known per se in the art.

In another aspect, the invention provides amino acid sequences, and in particular immunoglobulin sequences, and more in particular immunoglobulin variable domain sequences, that can bind to or otherwise associate with serum albumin in such a way that, when the amino acid sequence or polypeptide construct is bound to or otherwise associated

with a serum albumin molecule, the half-life of the serum albumin molecule is not (significantly) reduced (i.e. compared to the half-life of the serum albumin molecule when the amino acid sequence or polypeptide construct is not bound thereto). In this aspect of the invention, by "not significantly reduced" is meant that the half-life of the serum albumin molecule (as measured using a suitable technique known per se) is not reduced by more than 50%, preferably not reduced by more than 30 %, even more preferably not reduced by more than 10%, such as not reduced by more than 5%, or essentially not reduced at all.

In another aspect, the invention provides amino acid sequences, and in particular immunoglobulin sequences, and more in particular immunoglobulin variable domain sequences, that are capable of binding to amino acid residues on serum albumin that are not involved in binding of serum albumin to FcRn. More in particular, this aspect of the invention provides amino acid sequences that are capable of binding to amino acid sequences of serum albumin that do not form part of domain III of serum albumin. For example, but without being limited thereto, this aspect of the invention provides amino acid sequences that are capable of binding to amino acid sequences of serum albumin that form part of domain I and/or domain II.

The amino acid sequences of the invention are preferably (single) domain antibodies or suitable for use as (single) domain antibodies, and as such may be heavy chain variable domain sequence (VH sequence) or a light chain variable domain sequence (VL sequence), and preferably are VH sequences. The amino acid sequences may for example be so-called "dAb's".

However, according to a particularly preferred embodiment, the amino acid sequences of the present invention are Nanobodies. For a further description and definition of Nanobodies, as well as of some of the further terms used in the present description, reference is made to the copending patent applications by applicant (such as the copending International application by applicant entitled "*Improved Nanobodies™ against Tumor Necrosis Factor-alpha*", which has the same priority and the same international filing date as the present application); as well as the further prior art cited therein.

As such, they may be Nanobodies belonging to the "KERE"-class, to the "GLEW"-class or to the "103-P,R,S"-class (again as defined in the copending patent applications by applicant).

Preferably, the amino acid sequences of the present invention are humanized Nanobodies (again as defined in the copending patent applications by applicant).

The amino acid sequences disclosed herein can be used with advantage as a fusion partner in order to increase the half-life of therapeutic moieties such as proteins, compounds (including, without limitation, small molecules) or other therapeutic entities.

Thus, in another aspect, the invention provides proteins or polypeptides that comprise or essentially consist of an amino acid sequence as disclosed herein. In particular, the invention provides protein or polypeptide constructs that comprise or essentially consist of at least one amino acid sequence of the invention that is linked to at least one therapeutic moiety, optionally via one or more suitable linkers or spacers. Such protein or polypeptide constructs may for example (without limitation) be a fusion protein, as further described herein.

The invention further relates to therapeutic uses of protein or polypeptide constructs or fusion proteins and constructs and to pharmaceutical compositions comprising such protein or polypeptide constructs or fusion proteins.

In some embodiments the at least one therapeutic moiety comprises or essentially consists of a therapeutic protein, polypeptide, compound, factor or other entity. In a preferred embodiment the therapeutic moiety is directed against a desired antigen or target, is capable of binding to a desired antigen (and in particular capable of specifically binding to a desired antigen), and/or is capable of interacting with a desired target. In another embodiment, the at least one therapeutic moiety comprises or essentially consists of a therapeutic protein or polypeptide. In a further embodiment, the at least one therapeutic moiety comprises or essentially consists of an immunoglobulin or immunoglobulin sequence (including but not limited to a fragment of an immunoglobulin), such as an antibody or an antibody fragment (including but not limited to an ScFv fragment). In yet another embodiment, the at least one therapeutic moiety comprises or essentially consists of an antibody variable domain, such as a heavy chain variable domain or a light chain variable domain.

In a preferred embodiment, the at least one therapeutic moiety comprises or essentially consists of at least one domain antibody or single domain antibody, "dAb" or Nanobody ®. According to this embodiment, the amino acid sequence of the invention is preferably also a domain antibody or single domain antibody, "dAb" or Nanobody, so that the resulting construct or fusion protein is a multivalent construct (as described herein) and

preferably a multispecific construct (also as defined herein) comprising at least two domain antibodies, single domain antibodies, "dAbs" or Nanobodies ® (or a combination thereof), at least one of which is directed against (as defined herein) serum albumin.

In a specific embodiment, the at least one therapeutic moiety comprises or essentially consists of at least one monovalent Nanobody® or a bivalent, multivalent, bispecific or multispecific Nanobody® construct. According to this embodiment, the amino acid sequence of the invention is preferably also a Nanobody, so that the resulting construct or fusion protein is a multivalent Nanobody construct (as described herein) and preferably a multispecific Nanobody construct (also as defined herein) comprising at least two Nanobodies, at least one of which is directed against (as defined herein) serum albumin.

According to one embodiment of the invention, the Nanobody against human serum albumin is a humanized Nanobody.

Also, when the amino acid sequences, proteins, polypeptides or constructs of the invention are intended for pharmaceutical or diagnostic use, the aforementioned are preferably directed against human serum albumin. According to one preferred, but non-limiting embodiment, the amino acid sequences, proteins, polypeptides or constructs show an affinity for human serum albumin that is higher than the affinity for mouse serum albumin (determined as described in the Experimental Part).

According to one preferred, but non-limiting embodiment, the amino acid sequence of the invention is directed to the same epitope on human serum albumin as clone PMP6A6 (ALB-1).

According to a specific, but non-limiting embodiment, the amino acid sequence of the invention is an immunoglobulin sequence (and preferably a Nanobody) that is capable of binding to human serum albumin that consists of 4 framework regions (FR1 to FR4 respectively) and 3 complementarity determining regions (CDR1 to CDR3 respectively), in which:

a) CDR1 is an amino acid sequence chosen from the group consisting of the CDR1 sequences of SEQ ID NOS: 8 to 14 and/or from the group consisting of amino acid sequences that have 2 or only 1 "amino acid difference(s)" (as defined herein) with one of the CDR1 sequences of SEQ ID NOS 8 to 14;

and in which:

b) CDR2 is an amino acid sequence chosen from the group consisting of the CDR2 sequences of SEQ ID NOS: 22 to 29; or from the group consisting of amino acid sequences that have at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity (as defined herein) with one of the CDR2 sequences of SEQ ID NOS: 22 to 29; and/or from the group consisting of amino acid sequences that have 2 or only 1 "amino acid difference(s)" (as defined herein) with one of the CDR2 sequences of SEQ ID NOS 22 to 29;

and in which:

c1) CDR3 is an amino acid sequence chosen from the group consisting of the CDR3 sequence of SEQ ID NO: 42; the amino acid sequences that have at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity (as defined herein) with the CDR3 sequence of SEQ ID NO: 42; and the amino acid sequences that have 3, 2 or only 1 "amino acid difference(s)" with the CDR3 sequence of SEQ ID NO:42;

or alternatively in which:

c2) CDR3 is an amino acid sequence chosen from the group consisting of the CDR3 sequences of SEQ ID NOS: 36 to 41 and/or from the group consisting of amino acid sequences that have 2 or only 1 "amino acid difference(s)" (as defined herein) with one of the CDR1 sequences of SEQ ID NOS: 36 to 41;

and in which the framework sequences may be any suitable framework sequences, such as the framework sequences of a (single) domain antibody and in particular of a Nanobody.

In the above amino acid sequences:

(1) any amino acid substitution is preferably a conservative amino acid substitution (as defined herein); and/or

(2) said amino acid sequence preferably only contains amino acid substitutions, and no amino acid deletions or insertions, compared to the above amino acid sequences.

Some preferred combinations of CDR sequences in the Nanobodies of the invention, and some preferred combinations of CDR and framework sequences in the Nanobodies of the invention, can be seen from Table I below.

Table II below lists some preferred Nanobodies of the invention. Table III below lists some preferred humanized Nanobodies of the invention.

Table I: preferred combinations of CDR sequences, and preferred combination of CDR sequence and framework sequences.

CLONE	ID	FR1	ID	CDR1	ID	FR2	ID	CDR2
PMP6A8(ALB2)	1	AVQLVESGGGLVQGGGSLRLACAASERIFD	8	LNLMG	15	WYRQGPGNERELVA	22	TCITVGDSTNYADSVKG
PMP6B4	2	EVQLVESGGGLVQEGGSLRLACAASERIWD	9	INLLG	16	WYRQGPGNERELVA	23	TITVGDSTSYADSVKG
PMP6A6(ALB1)	3	AVQLVESGGGLVQPGNSLRLSCAASGFTFR	10	SFGMS	17	WVRQAPGKEPEWVS	24	SISGSGSDTLYADSVKG
PMP6C1	4	AVQLVDSGGGLVQPGGSLRLSCAASGFSFG	11	SFGMS	18	WVRQYPGKEPEWVS	25	SINGRGDDTRYADSVKG
PMP6G8	5	AVQLVESGGGLVQPGGSLRLTCTASGFTFR	12	SFGMS	19	WVRQAPGKDQEWVS	26	AISADSSTKNYADSVKG
PMP6A5	6	QVQLAESGGGLVQPGGSLRLTCTASGFTFG	13	SFGMS	20	WVRQAPGEGLEWVS	27	AISADSSDKRYADSVKG
PMP6G7	7	QVQLVESGGGLVQPGGSLRLSCAASGFTFS	14	NYWMY	21	WVRVAPGKGLERIS	28	RDISTGGGYSYYADSVKG

CLONE condt...	ID	FR3	ID	CDR3	ID	FR4
PMP6A8(ALB2)	29	RFTISMDYTKQTVYLHMNSLRPEDTGLYYCKI	36	RRTWHSEL	43	WGQGTQVTVSS
PMP6B4	30	RFTISRDYDKNTLYLQMNSLRPEDTGLYYCKI	37	RRTWHSEL	44	WGQGTQVTVSS
PMP6A6(ALB1)	31	RFTISRDNAKTTLYLQMNSLKPEDTAVYYCTI	38	GGSLSR	45	SSQGTQVTVSS
PMP6C1	32	RFSISRDNAKNTLYLQMNSLKPEDTAEYYCTI	39	GRSVSRS	46	RTQGTQVTVSS
PMP6G8	33	RFTISRDNAKKMLYLEMNSLKPEDTAVYYCVI	40	GRGSP	47	SSPGTQVTVSS
PMP6A5	34	RFTISRDNAKKMLYLEMNSLKSEDTAVYYCVI	41	GRGSP	48	ASQGTQVTVSS
PMP6G7	35	RFTISRDNAKNTLYLQMNSLKPEDTALYYCAK	42	DREAQVDTLDFDY	49	RGQGTQVTVSS

Table II: preferred, but non-limiting Nanobodies of the invention.

PMP6A8 (ALB2)	50	AVQLVESGGGLVQGGGSLRLACAASERIFDLNLMGWYRQGPGNERE LVATCITVG.DSTNYADSVKGRFTISMDYTKQTVYLHMNSLRPEDT GLYYCKIRRTWHSELWGQGTQVTVSS
PMP6B4	51	EVQLVESGGGLVQEGGSLRLACAASERIWDINLLGWYRQGPGNERE LVATITVG.DSTSYADSVKGRFTISRDYDKNTLYLQMNSLRPEDTG LYYCKIRRTWHSELWGQGTQVTVSS
PMP6A6 (ALB1)	52	AVQLVESGGGLVQPGNSLRLSCAASGFTFRSFGMSWVRQAPGKEPE WVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKPEDTA VYYCTIGGSLSRSSQGTQVTVSS
PMP6C1	53	AVQLVDSGGGLVQPGGSLRLSCAASGFSFGSFGMSWVRQYPGKEPE WVSSINGRGDDTRYADSVKGRFSISRDNAKNTLYLQMNSLKPEDTA EYYCTIGRSVSRSRTQGTQVTVSS
PMP6G8	54	AVQLVESGGGLVQPGGSLRLTCTASGFTFRSFGMSWVRQAPGKDQE WVSAISADSSTKNYADSVKGRFTISRDNAKKMLYLEMNSLKPEDTA VYYCVIGRGSPSSPGTQVTVSS
PMP6A5	55	QVQLAESGGGLVQPGGSLRLTCTASGFTFGSFGMSWVRQAPGEGLE WVSAISADSSDKRYADSVKGRFTISRDNAKKMLYLEMNSLKSEDTA VYYCVIGRGSPASQGTQVTVSS
PMP6G7	56	QVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMYWVRVAPGKGLE RISRDISTGGGYSYYADSVKGRFTISRDNAKNTLYLQMNSLKPEDT ALYYCAKDREAQVDTLDFDYRGQGTQVTVSS

Table III: preferred. but non-limiting humanized Nanobodies of the invention.

ALB3 (ALB1 HUM1)	57	EVQLVESGGGLVQPGGSLRLSCAASGFTFRSFGMSWVRQAPGKEPE WVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKPEDTA VYYCTIGGSLSRSSQGTQVTVSS
ALB4 (ALB1 HUM2)	58	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSFGMSWVRQAPGKEPE WVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKPEDTA VYYCTIGGSLSRSSQGTQVTVSS
ALB5 (ALB1 HUM3)	59	EVQLVESGGGLVQPGGSLRLSCAASGFTFRSFGMSWVRQAPGKGLE WVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKPEDTA VYYCTIGGSLSRSSQGTQVTVSS
ALB6 (ALB1 HUM1)	60	EVQLVESGGGLVQPGNSLRLSCAASGFTFRSFGMSWVRQAPGKGLE WVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLKPEDTA VYYCTIGGSLSRSSQGTLVTVSS
ALB7 (ALB1 HUM2)	61	EVQLVESGGGLVQPGNSLRLSCAASGFTFRSFGMSWVRQAPGKGLE WVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLRPEDTA VYYCTIGGSLSRSSQGTLVTVSS
ALB8 (ALB1 HUM3)	62	EVQLVESGGGLVQPGNSLRLSCAASGFTFSSFGMSWVRQAPGKGLE WVSSISGSGSDTLYADSVKGRFTISRDNAKTTLYLQMNSLRPEDTA VYYCTIGGSLSRSSQGTLVTVSS
ALB9 (ALB1 HUM4)	63	EVQLVESGGGLVQPGNSLRLSCAASGFTFSSFGMSWVRQAPGKGLE WVSSISGSGSDTLYADSVKGRFTISRDNAKNTLYLQMNSLRPEDTA VYYCTIGGSLSRSSQGTLVTVSS
ALB10 (ALB1 HUM5)	64	EVQLVESGGGLVQPGNSLRLSCAASGFTFSSFGMSWVRQAPGKGLE WVSSISGSGSDTLYADSVKGRFTISRDNAKNTLYLQMNSLRPEDTA VYYCTIGGSLSRSGQGTLVTVSS

Thus, in another aspect, an amino acid sequence of the invention is a Nanobody, which has at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity (as defined herein) with at least one of the amino acid sequences of SEQ ID NO's 50 to 64.

Thus, in another aspect, an amino acid sequence of the invention is a Nanobody, which has at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity (as defined herein) with at least one of the amino acid sequences of SEQ ID NO's 50 to 64, in which:

- the CDR1 sequences present in such Nanobodies are chosen from the CDR1 sequences of SEQ ID NOS: 8 to 14 or from amino acid sequences with only 1 amino acid difference with such a CDR1 sequence;
- the CDR2 sequences present in such Nanobodies are chosen from the CDR1 sequences of SEQ ID NOS: 22 to 28 or from amino acid sequences with only 1 amino acid difference with such a CDR2 sequence;
- and the CDR1 sequences present in such Nanobodies are chosen from the CDR1 sequences of SEQ ID NOS: 23 to 42 or from amino acid sequences with only 1 amino acid difference with such a CDR3 sequence.

In another aspect, an amino acid sequence of the invention is a Nanobody, which has at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity (as defined herein) with at least one of the amino acid sequences of SEQ ID NO's 50 to 64, in which:

- the CDR1 sequences present in such Nanobodies are chosen from the CDR1 sequences of SEQ ID NOS: 8 to 14;
- the CDR2 sequences present in such Nanobodies are chosen from the CDR1 sequences of SEQ ID NOS: 22 to 28;
- and the CDR1 sequences present in such Nanobodies are chosen from the CDR1 sequences of SEQ ID NOS: 23 to 42.

One particularly preferred group of Nanobodies for use in the present invention comprises clone PMP6A6 (ALB1; SEQ ID NO: 52) and humanized variants thereof, including but not limited to the clones ALB 3 (SEQ ID NO: 57); ALB 4 (SEQ ID NO: 58); ALB 5 (SEQ ID NO: 59); ALB 6 (SEQ ID NO: 60); ALB 7 (SEQ ID NO: 61); ALB 8 (SEQ ID NO: 62); ALB 9 (SEQ ID NO: 63); and ALB 10 (SEQ ID NO: 64), of which ALB 8 (SEQ ID NO: 62) is particularly preferred.

Thus, in one preferred aspect, the invention relates to an amino acid sequence, which has at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity (as defined herein) with at least one of the amino acid sequences of SEQ ID NO's 52 and 57 to 64.

In another preferred aspect, the amino acid sequence of the invention is an immunoglobulin sequence (and preferably a Nanobody) that is capable of binding to human serum albumin that consists of 4 framework regions (FR1 to FR4 respectively) and 3 complementarity determining regions (CDR1 to CDR3 respectively), in which:

a) CDR1 comprises, is or essentially consists of:

- the amino acid sequence SFGMS; or
- an amino acid sequence that has at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity with the amino acid sequence SFGMS; or
- an amino acid sequences that has 2 or only 1 amino acid difference(s) with the amino acid sequence SFGMS;

and in which:

b) CDR2 comprises, is or essentially consists of::

- the amino acid sequence SISGSGSDTLYADSVKG; or
- an amino acid sequence that has at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity with the amino acid sequence SISGSGSDTLYADSVKG; or
- an amino acid sequences that has 2 or only 1 amino acid difference(s) with the amino acid sequence SISGSGSDTLYADSVKG;

and in which:

c) CDR3 comprises, is or essentially consists of::

- the amino acid sequence GGSLSR; or
- an amino acid sequence that has at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity with the amino acid sequence GGSLSR; or
- an amino acid sequences that has 2 or only 1 amino acid difference(s) with the amino acid sequence GGSLSR.

In particular, the invention relates to such a Nanobody, in which:

- CDR1 comprises or is the amino acid sequence SFGMS;

or in which

- CDR2 comprises or is the amino acid sequence SISGSGSDTLYADSVKG;

or in which:

- CDR3 comprises or is the amino acid sequence SPSGFN.

More in particular, the invention relates to such a Nanobody, in which

- CDR1 comprises or is the amino acid sequence SFGMS; and CDR3 comprises or is comprises the amino acid sequence GGSLSR;

or in which:

- CDR1 comprises or is the amino acid sequence SFGMS; and CDR2 comprises or is the amino acid sequence SISGSGSDTLYADSVKG;

or in which:

- CDR2 comprises or is the amino acid sequence SISGSGSDTLYADSVKG; and CDR3 comprises or is the amino acid sequence GGSLSR.

Even more in particular, the invention relates to such a Nanobody, in which CDR1 comprises or is the amino acid sequence SFGMS; CDR2 comprises or is the amino acid sequence SISGSGSDTLYADSVKG and CDR3 comprises or is the amino acid sequence GGSLSR.

These amino acid sequences again preferably have at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity (as defined herein) with at least one of the amino acid sequences of SEQ ID NO's 52 and 57 to 64.

Also, again, these amino acid sequences are preferably humanized, as described in the co-pending applications by applicant. Some preferred humanizing substitutions will be clear from the skilled person, for example from comparing the non-humanized sequence of SEQ ID NO: 52 with the corresponding humanized sequences of SEQ ID NOS: 57-64.

When the amino acid sequence is an immunoglobulin sequence such as a immunoglobulin variable domain sequence, a suitable (i.e. suitable for the purposes mentioned herein) fragment of such a sequence may also be used. For example, when the amino acid sequence is a Nanobody, such a fragment may essentially be as described in WO 04/041865.

The invention also relates to a protein or polypeptide that comprises or essentially consists of an amino acid sequence as described herein, or a suitable fragment thereof.

As mentioned herein, the amino acid sequences described herein can be used with advantage as a fusion partner in order to increase the half-life of therapeutic moieties such as proteins, compounds (including, without limitation, small molecules) or other therapeutic entities. Thus, one embodiment of the invention relates to a construct or fusion protein that comprises at least one amino acid sequence of the invention and at least one therapeutic moieties. Such a construct or fusion protein preferably has increased half-life, compared to the therapeutic moiety per se. Generally, such fusion proteins and constructs can be (prepared and used) as described in the prior art cited above, but with an amino acid sequence of the invention instead of the half-life increasing moieties described in the prior art.

Generally, the constructs or fusion proteins described herein preferably have a half-life that is at least 1.5 times, preferably at least 2 times, such as at least 5 times, for example at least 10 times or more than 20 times, greater than the half-life of the corresponding therapeutic moiety per se.

Also, preferably, any such fusion protein or construct has a half-life that is increased with more than 1 hour, preferably more than 2 hours, more preferably of more than 6 hours, such as of more than 12 hours, compared to the half-life of the corresponding therapeutic moiety per se.

Also, preferably, any fusion protein or construct has a half-life that is more than 1 hour, preferably more than 2 hours, more preferably of more than 6 hours, such as of more than 12 hours, and for example of about one day, two days, one week, two weeks or three weeks, and preferably no more than 2 months, although the latter may be less critical.

Half-life can generally be defined as the time taken for the serum concentration of the polypeptide to be reduce by 50%, in vivo, for example due to degradation of the ligand and/or clearance or sequestration of the ligand by natural mechanisms. Methods for pharmacokinetic analysis and determination of half-life are 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, Pharmacokinete analysis: A Practical Approach (1996). Reference is also made to "Pharmacokinetics", M Gibaldi & D Perron, published by Marcel Dekker, 2nd revised edition (1982).

Also, as mentioned above , when the amino acid sequence of the invention is a Nanobody, it can be used to increase the half-life of other immunoglobulin sequences, such as domain antibodies, single domain antibodies, "dAb's" or Nanobodies.

Thus, one embodiment of the invention relates to a construct or fusion protein that comprises at least one amino acid sequence of the invention and at least one immunoglobulin sequence, such as a domain antibodies, single domain antibodies, "dAb's" or Nanobodies. The immunoglobulin sequence is preferably directed against a desired target (which is preferably a therapeutic target), and/or another immunoglobulin sequence that useful or suitable for therapeutic, prophylactic and/or diagnostic purposes.

Thus, in another aspect, the invention relates to a multispecific (and in particular bispecific) Nanobody constructs that comprises at least one Nanobody as described herein, and at least one other Nanobody, in which said at least one other Nanobody is preferably directed against a desired target (which is preferably a therapeutic target), and/or another Nanobody that useful or suitable for therapeutic, prophylactic and/or diagnostic purposes.

For a general description of multivalent and multispecific polypeptides containing one or more Nanobodies and their preparation, reference is also made to Conrath et al., J. Biol. Chem., Vol. 276, 10. 7346-7350, 2001; Muyldermans, Reviews in Molecular Biotechnology 74 (2001), 277-302; as well as to for example WO 96/34103 and WO 99/23221. Some other examples of some specific multispecific and/or multivalent polypeptide of the invention can be found in the co-pending applications by applicant. In particular, for a general description of multivalent and multispecific constructs comprising at least one Nanobody against a serum protein for increasing the half-life, of nucleic acids encoding the same, of compositions comprising the same, of the preparation of the aforementioned, and of uses of the aforementioned, reference is made to the International application WO 04/041865 by applicant mentioned above. The amino acid sequences described herein can generally be used analogously to the half-life increasing Nanobodies described therein.

In one non-limiting embodiment, said other Nanobody is directed against tumor necrosis factor alpha (TNF-alpha), in monomeric and/or multimeric (i.e. trimeric) form. Some examples of such Nanobody constructs can be found in the copending International application by applicant entitled "*Improved Nanobodies™ against Tumor Necrosis Factor-alpha*", which has the same priority and the same international filing date as the present application.

The invention also relates to nucleotide sequences or nucleic acids that encode amino acid sequences, fusion proteins and constructs described herein. The invention further includes genetic constructs that include the foregoing nucleotide sequences or

nucleic acids and one or more elements for genetic constructs known per se. The genetic construct may be in the form of a plasmid or vector. Again, such constructs can be generally as described in the co-pending patent applications by applicant described herein, such as WO 04/041862 or the copending International application by applicant entitled "*Improved Nanobodies™ against Tumor Necrosis Factor-alpha*".

The invention also relates to hosts or host cells that contain such nucleotide sequences or nucleic acids, and/or that express (or are capable of expressing), the amino acid sequences, fusion proteins and constructs described herein. Again, such host cells can be generally as described in the co-pending patent applications by applicant described herein, such as WO 04/041862 or the copending International application by applicant entitled "*Improved Nanobodies™ against Tumor Necrosis Factor-alpha*".

The invention also relates to a method for preparing an amino acid sequence, fusion protein or construct as described herein, which method comprises cultivating or maintaining a host cell as described herein under conditions such that said host cell produces or expresses an amino acid sequence, fusion protein or construct as described herein, and optionally further comprises isolating the amino acid sequence, fusion protein or construct so produced. Again, such methods can be performed as generally described in the co-pending patent applications by applicant described herein, such as WO 04/041862 or the copending International application by applicant entitled "*Improved Nanobodies™ against Tumor Necrosis Factor-alpha*".

The invention also relates to a pharmaceutical composition that comprises at least one amino acid sequence, fusion protein or construct as described herein, and optionally at least one pharmaceutically acceptable carrier, diluent or excipient. Such preparations, carriers, excipients and diluents may generally be as described in the co-pending patent applications by applicant described herein, such as WO 04/041862 or the copending International application by applicant entitled "*Improved Nanobodies™ against Tumor Necrosis Factor-alpha*".

However, since the amino acid sequences, fusion proteins or constructs described herein have an increased half-life, they are preferably administered to the circulation. As such, they can be administered in any suitable manner that allows the amino acid sequences, fusion proteins or constructs to enter the circulation, such as intravenously, via injection or infusion, or in any other suitable manner (including oral administration, administration through the skin, intranasal administration, administration via the lungs, etc)

that allows the amino acid sequences, fusion proteins or constructs to enter the circulation. Suitable methods and routes of administration will be clear to the skilled person, again for example also from the teaching of WO 04/041862 or the copending International application by applicant entitled "*Improved Nanobodies™ against Tumor Necrosis Factor-alpha*

Thus, in another aspect, the invention relates to a method for the prevention and/or treatment of at least one disease or disorder that can be prevented or treated by the use of a fusion protein or construct as described herein, which method comprises administering, to a subject in need thereof, a pharmaceutically active amount of a fusion protein or construct of the invention, and/or of a pharmaceutical composition comprising the same. The diseases and disorders that can be prevented or treated by the use of a fusion protein or construct as described herein will generally be the same as the diseases and disorders that can be prevented or treated by the use of the therapeutic moiety that is present in the fusion protein or construct of the invention.

In the context of the present invention, the term "prevention and/or treatment" not only comprises preventing and/or treating the disease, but also generally comprises preventing the onset of the disease, slowing or reversing the progress of disease, preventing or slowing the onset of one or more symptoms associated with the disease, reducing and/or alleviating one or more symptoms associated with the disease, reducing the severity and/or the duration of the disease and/or of any symptoms associated therewith and/or preventing a further increase in the severity of the disease and/or of any symptoms associated therewith, preventing, reducing or reversing any physiological damage caused by the disease, and generally any pharmacological action that is beneficial to the patient being treated.

The subject to be treated may be any warm-blooded animal, but is in particular a mammal, and more in particular a human being. As will be clear to the skilled person, the subject to be treated will in particular be a person suffering from, or at risk from, the diseases and disorders mentioned herein.

In another embodiment, the invention relates to a method for immunotherapy, and in particular for passive immunotherapy, which method comprises administering, to a subject suffering from or at risk of the diseases and disorders mentioned herein, a pharmaceutically active amount of a fusion protein or construct of the invention, and/or of a pharmaceutical composition comprising the same.

The fusion protein or construct and/or the compositions comprising the same are administered according to a regime of treatment that is suitable for preventing and/or treating the disease or disorder to be prevented or treated. The clinician will generally be able to determine a suitable treatment regimen, depending on factors such as the disease or disorder to be prevented or treated, the severity of the disease to be treated and/or the severity of the symptoms thereof, the specific Nanobody or polypeptide of the invention to be used, the specific route of administration and farmaceutical formulation or composition to be used, the age, gender, weight, diet, general condition of the patient, and similar factors well known to the clinician.

Generally, the treatment regimen will comprise the administration of one or more fusion proteins or constructs of the invention, or of one or more compositions comprising the same, in one or more pharmaceutically effective amounts or doses. The specific amount(s) or doses to administered can be determined by the clinician, again based on the factors cited above.

Generally, for the prevention and/or treatment of the diseases and disorders mentioned herein and depending on the specific disease or disorder to be treated, the potency and/or the half-life of the specific fusion proteins or constructs to be used, the specific route of administration and the specific pharmaceutical formulation or composition used, the Nanobodies and polypeptides of the invention will generally be administered in an amount between 1 gram and 0.01 microgram per kg body weight per day, preferably between 0.1 gram and 0.1 microgram per kg body weight per day, such as about 1, 10, 100 or 1000 microgram per kg body weight per day, either continuously (e.g. by infusion), as a single daily dose or as multiple divided doses during the day. The clinician will generally be able to determine a suitable daily dose, depending on the factors mentioned herein. It will also be clear that in specific cases, the clinician may choose to deviate from these amounts, for example on the basis of the factors cited above and his expert judgment. Generally, some guidance on the amounts to be administered can be obtained from the amounts usually administered for comparable conventional antibodies or antibody fragments against the same target administered via essentially the same route, taking into account however differences in affinity/avidity, efficacy, biodistribution, half-life and similar factors well known to the skilled person.

Usually, in the above method, a single Nanobody or polypeptide of the invention will be used. It is however within the scope of the invention to use two or more Nanobodies and/or polypeptides of the invention in combination.

The Nanobodies and polypeptides of the invention may also be used in combination with one or more further pharmaceutically active compounds or principles, i.e. as a combined treatment regimen, which may or may not lead to a synergistic effect. Again, the clinician will be able to select such further compounds or principles, as well as a suitable combined treatment regimen, based on the factors cited above and his expert judgement.

In particular, the Nanobodies and polypeptides of the invention may be used in combination with other pharmaceutically active compounds or principles that are or can be used for the prevention and/or treatment of the diseases and disorders that can be prevented or treated with the fusion proteins or constructs of the invention, and as a result of which a synergistic effect may or may not be obtained.

The effectiveness of the treatment regimen used according to the invention may be determined and/or followed in any manner known per se for the disease or disorder involved, as will be clear to the clinician. The clinician will also be able, where appropriate and or a case-by-case basis, to change or modify a particular treatment regimen, so as to achieve the desired therapeutic effect, to avoid, limit or reduce unwanted side-effects, and/or to achieve an appropriate balance between achieving the desired therapeutic effect on the one hand and avoiding, limiting or reducing undesired side effects on the other hand.

Generally, the treatment regimen will be followed until the desired therapeutic effect is achieved and/or for as long as the desired therapeutic effect is to be maintained. Again, this can be determined by the clinician.

The subject to be treated may be any warm-blooded animal, but is in particular a mammal, and more in particular a human being. As will be clear to the skilled person, the subject to be treated will in particular be a person suffering from, or at risk from, the diseases and disorders mentioned herein.

Experimental Part

Example 1: Identification of serum albumin specific nanobodies

The albumin specific nanobodies were identified from a llama immunized with human serum albumin. Screening of individual nanobodies was performed by ELISA using human, rhesus and mouse albumin, yielding a panel of nanobodies cross-reacting with the serum albumin of various species.

Example 2: Biacore analysis

Binding of nanobodies to serum albumin was characterised by surface plasmon resonance in a Biacore 3000 instrument. Serum albumin from different species was covalently bound to CM5 sensor chips surface via amine coupling until an increase of 250 response units was reached. Remaining reactive groups were inactivated. Nanobody binding was assessed at one concentration (1 in 20 diluted). Each nanobody was injected for 4 minutes at a flow rate of 45 µl/min to allow for binding to chip-bound antigen. Binding buffer without nanobody was sent over the chip at the same flow rate to allow spontaneous dissociation of bound nanobody for 4 hours. K_{off}-values were calculated from the sensorgrams obtained for the different nanobodies. The nanobodies tested are ranked according to k_{off}-values, see Table IV below:

Table IV:

Class	Human	Rhesus	Mouse
C	PMP6A8	PMP6A8	PMP6B4
C	PMP6B4	PMP6B4	PMP6A8
B	PMP6A6	PMP6A6	PMP6A6
B	PMP6C1	PMP6C1	PMP6C1
A	PMP6G8	PMP6G8	PMP6G8
A	PMP6A5	PMP6A5	PMP6A5
D	PMP6G7	PMP6G7	PMP6G7

In a follow-up experiment, binding was assayed as described above except that series of different concentrations were used. Each concentration was injected for 4 minutes

at a flow rate of 45 µl/min to allow for binding to chip-bound antigen. Binding buffer without analyte was sent over the chip at the same flow rate to allow for dissociation of bound nanobody. After 15 minutes, remaining bound analyte was removed by injection of the regeneration solution (25 mM NaOH).

From the sensorgrams obtained for the different concentrations of each analyte K_D-values were calculated via steady state affinity when equilibrium was reached.

Results are summarized in Table V. Cross-reactivity is observed for both ALB1 and ALB2. The highest affinity is observed for ALB2 on human and rhesus TNFα. However, the difference in affinity for human/rhesus versus mouse serum albumin is more pronounced for ALB2 (factor 400), while for ALB1 a difference of a factor 12 is observed.

Table V:

		Human albumin	**Rhesus albumin**	**Mouse albumin**
ALB1	**KD (nM)**	0,57	0,52	6,5
	ka (1/Ms)	1,11E+06	1,05E+06	1,11E+06
	kd (1/s)	6,30E-04	5,46E-04	7,25E-03
ALB2	**KD (nM)**	0,092	0,036	15,7
	ka (1/Ms)	8,15E+05	1,94E+06	1,95E+05
	kd (1/s)	7,52E-05	7,12E-05	3,07E-03

CLAIMS

1. Amino acid sequence that can bind to or otherwise associate with serum albumin in such a way that, when the amino acid sequence or polypeptide construct is bound to or otherwise associated with a serum albumin molecule, the binding of said serum albumin molecule to FcRn is not (significantly) reduced or inhibited.

2. Amino acid sequence, that can bind to or otherwise associate with serum albumin in such a way that, when the amino acid sequence or polypeptide construct is bound to or otherwise associated with a serum albumin molecule, the half-life of the serum albumin molecule is not (significantly) reduced.

3. Amino acid sequence, that is capable of binding to amino acid residues on serum albumin that are not involved in binding of serum albumin to FcRn.

4. Amino acid sequence, that is capable of binding to amino acid residues on serum albumin that do not form part of domain III of serum albumin

5. Amino acid sequence according to any of claims 1-4, that is an immunoglobulin sequence or a fragment thereof.

6. Amino acid sequence according to claim 5, that is an immunoglobulin variable domain sequence of a fragment thereof.

7. Amino acid sequence according to claim 4, that is a V_H-, V_L- or V_{HH}-sequence or a fragment thereof.

8. Amino acid sequence according to any preceding claim, that is a domain antibody, "dAb", single domain antibody or Nanobody of a fragment thereof.

9. Amino acid sequence according to any of claims 4-8, which consists of 4 framework regions (FR1 to FR4 respectively) and 3 complementarity determining regions (CDR1 to CDR3 respectively), in which:

a) CDR1 is an amino acid sequence chosen from the group consisting of the CDR1 sequences of SEQ ID NOS: 8 to 14 and/or from the group consisting of amino acid sequences that have 2 or only 1 "amino acid difference(s)" (as defined herein) with one of the CDR1 sequences of SEQ ID NOS 8 to 14;

and in which:

b) CDR2 is an amino acid sequence chosen from the group consisting of the CDR2 sequences of SEQ ID NOS: 22 to 29; or from the group consisting of amino acid sequences that have at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity (as defined herein) with one of the CDR2 sequences of SEQ ID NOS: 22 to 29; and/or from the group consisting of amino acid sequences that have 2 or only 1 "amino acid difference(s)" (as defined herein) with one of the CDR2 sequences of SEQ ID NOS 22 to 29;

and in which:

c1) CDR3 is an amino acid sequence chosen from the group consisting of the CDR3 sequence of SEQ ID NO: 42; the amino acid sequences that have at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity (as defined herein) with the CDR3 sequence of SEQ ID NO: 42; and the amino acid sequences that have 3, 2 or only 1 "amino acid difference(s)" with the CDR3 sequence of SEQ ID NO:42;

or alternatively in which:

c2) CDR3 is an amino acid sequence chosen from the group consisting of the CDR3 sequences of SEQ ID NOS: 36 to 41 and/or from the group consisting of amino acid sequences that have 2 or only 1 "amino acid difference(s)" (as defined herein) with one of the CDR1 sequences of SEQ ID NOS: 36 to 41.

10. Amino acid sequence according to claim 10, which is a (single) domain antibody or a Nanobody.

11. Amino acid sequence according to claim 10, which has at least 80%, preferably at least 90%, more preferably at least 95%, even more preferably at least 99% sequence identity (as defined herein) with at least one of the amino acid sequences of SEQ ID NO's 50 to 64.

12. Amino acid sequence according to claim 11, which is chosen from the group consisting of PMP6A6 (ALB1; SEQ ID NO: 52) and humanized variants thereof, including but not limited to the clones ALB 3 (SEQ ID NO: 57); ALB 4 (SEQ ID NO: 58); ALB 5 (SEQ ID NO: 59); ALB 6 (SEQ ID NO: 60); ALB 7 (SEQ ID NO: 61); ALB 8 (SEQ ID NO: 62); ALB 9 (SEQ ID NO: 63); and ALB 10 (SEQ ID NO: 64).

13. Amino acid sequence according to claim 12, which is ALB 8 (SEQ ID NO: 62).

14. Fusion protein or construct, which comprises an amino acid sequence according to any of claims 1-13 and at least one therapeutic moiety.

15. Fusion protein or construct according to claim 14, in which the amino acid sequence according to any of claims 1-13 is either directly linked to the at least one therapeutic moiety or is linked to the at least one therapeutic moiety via a linker or spacer.

16. Fusion protein or construct according to claim 14 or 15, in which the therapeutic moiety comprises an immunoglobulin sequence or a fragment thereof.

17. Fusion protein or construct according to claim 16, in which the therapeutic moiety comprises a (single) domain antibody or a Nanobody.

18. Multivalent and multispecific Nanobody construct, comprising at least one amino acid sequence according to any of claims 1-13 which is a Nanobody and at least one further Nanobody.

19. Multivalent and multispecific Nanobody construct according to claim 18, in which the amino acid sequence according to any of claims 1-13 that is a Nanobody is either directly linked to the at least one further Nanobody or is linked to the at least one further Nanobody via a linker or spacer.

20. Multivalent and multispecific Nanobody construct according to claim 18, in which the amino acid sequence according to any of claims 1-13 that is a Nanobody is is

linked to the at least one further Nanobody via a linker or spacer, and in which the linker is an amino acid sequence.

21. Nucleotide sequence or nucleic acid that encodes an amino acid sequence, fusion protein or construct according to any of claims 1-20.

22. Hosts or host cells that contains a nucleotide sequence or nucleic acid according to claim 20, and/or that express (or are capable of expressing), an amino acid sequence, fusion protein or construct according to any of claims 1-20.

23. Method for preparing an amino acid sequence, fusion protein or construct according to any of claims 1-20, which method comprises cultivating or maintaining a host cell as described herein under conditions such that said host cell produces or expresses an amino acid sequence, fusion protein or construct according to any of claims 1-20, and optionally further comprises isolating the amino acid sequence, fusion protein or construct so produced.

24. Pharmaceutical composition that comprises at least one amino acid sequence, fusion protein or construct according to any of claims 1-20, and optionally at least one pharmaceutically acceptable carrier, diluent or excipient.

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Gly Arg Gly Ser Pro
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<211> 117

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Leu Met Gly Trp Tyr Arg Gln Gly Pro Gly Asn Glu Arg Glu Leu Val
35 40 45

Ala Thr Cys Ile Thr Val Gly Asp Ser Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Met Asp Tyr Thr Lys Gln Thr Val Tyr
65 70 75 80

Leu His Met Asn Ser Leu Arg Pro Glu Asp Thr Gly Leu Tyr Tyr Cys
85 90 95

Lys Ile Arg Arg Thr Trp His Ser Glu Leu Trp Gly Gln Gly Thr Gln
100 105 110

Val Thr Val Ser Ser
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<210> 51

<211> 116

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Leu Leu Gly Trp Tyr Arg Gln Gly Pro Gly Asn Glu Arg Glu Leu Val
35 40 45

Ala Thr Ile Thr Val Gly Asp Ser Thr Ser Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Tyr Asp Lys Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Gly Leu Tyr Tyr Cys Lys
85 90 95

Ile Arg Arg Thr Trp His Ser Glu Leu Trp Gly Gln Gly Thr Gln Val
100 105 110

Thr Val Ser Ser
115

<210> 52

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<400> 52

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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Ser Phe
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Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Glu Pro Glu Trp Val
35 40 45

Ser Ser Ile Ser Gly Ser Gly Ser Asp Thr Leu Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

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Val Ser Ser
115

<210> 53

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Gly Met Ser Trp Val Arg Gln Tyr Pro Gly Lys Glu Pro Glu Trp Val
35 40 45

Ser Ser Ile Asn Gly Arg Gly Asp Asp Thr Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Ser Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Glu Tyr Tyr Cys
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Thr Val Ser Ser
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Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Asp Gln Glu Trp Val
35 40 45

Ser Ala Ile Ser Ala Asp Ser Ser Thr Lys Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys Met Leu Tyr
65 70 75 80

Leu Glu Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
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Ser Leu Arg Leu Thr Cys Thr Ala Ser Gly Phe Thr Phe Gly Ser Phe
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Gly Met Ser Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Ala Asp Ser Ser Asp Lys Arg Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys Met Leu Tyr
65 70 75 80

Leu Glu Met Asn Ser Leu Lys Ser Glu Asp Thr Ala Val Tyr Tyr Cys
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Val Ile Gly Arg Gly Ser Pro Ala Ser Gln Gly Thr Gln Val Thr Val
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Ser Ser

<210> 56

<211> 123

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Trp Met Tyr Trp Val Arg Val Ala Pro Gly Lys Gly Leu Glu Arg Ile
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Ser Arg Asp Ile Ser Thr Gly Gly Gly Tyr Ser Tyr Tyr Ala Asp Ser
50 55 60

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu
65 70 75 80

Tyr Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Leu Tyr Tyr
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Cys Ala Lys Asp Arg Glu Ala Gln Val Asp Thr Leu Asp Phe Asp Tyr
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Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Glu Pro Glu Trp Val
35 40 45

Ser Ser Ile Ser Gly Ser Gly Ser Asp Thr Leu Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Ile Gly Gly Ser Leu Ser Arg Ser Ser Gln Gly Thr Gln Val Thr
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Val Ser Ser
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Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Glu Pro Glu Trp Val
35 40 45

Ser Ser Ile Ser Gly Ser Gly Ser Asp Thr Leu Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
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Thr Ile Gly Gly Ser Leu Ser Arg Ser Ser Gln Gly Thr Gln Val Thr
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Val Ser Ser
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<400> 59

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20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Gly Ser Gly Ser Asp Thr Leu Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Ile Gly Gly Ser Leu Ser Arg Ser Ser Gln Gly Thr Gln Val Thr
100 105 110

Val Ser Ser
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<400> 60

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Ser Phe
20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Gly Ser Gly Ser Asp Thr Leu Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Ile Gly Gly Ser Leu Ser Arg Ser Ser Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
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<400> 61

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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Arg Ser Phe
20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Gly Ser Gly Ser Asp Thr Leu Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

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100 105 110

Val Ser Ser
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<210> 62

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<400> 62

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Gly Ser Gly Ser Asp Thr Leu Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Thr Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Ile Gly Gly Ser Leu Ser Arg Ser Ser Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
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<210> 63

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<400> 63

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Gly Ser Gly Ser Asp Thr Leu Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Ile Gly Gly Ser Leu Ser Arg Ser Ser Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
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<210> 64

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<213> Artificial

<400> 64

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Asn
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Phe
20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Ser Gly Ser Gly Ser Asp Thr Leu Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Ile Gly Gly Ser Leu Ser Arg Ser Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/004679

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/18 C07K19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, Sequence Search, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FERGUSON T A ET AL: "Immunoregulatory properties of antigenic fragments from bovine serum albumin." CELLULAR IMMUNOLOGY. MAY 1983, vol. 78, no. 1, May 1983 (1983-05), pages 1-12, XP009072416 ISSN: 0008-8749 page 2 - page 4 ----- -/--	1-5

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 September 2006	04/10/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Wagner, René

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHAVEZ L G JR ET AL: "Antibody as an immunological probe for studying the refolding of bovine serum albumin. An immunochemical approach to the identification of possible nucleation sites." THE JOURNAL OF BIOLOGICAL CHEMISTRY. 25 NOV 1978, vol. 253, no. 22, 25 November 1978 (1978-11-25), pages 8081-8086, XP002399137 ISSN: 0021-9258 page 8082	1-5
X	WO 2004/003019 A (DOMANTIS LIMITED; WINTER, GREG; TOMLINSON, IAN; IGNATOVICH, OLGA; HOLT) 8 January 2004 (2004-01-08) example 8 page 78 - page 80; example 12	1-24
X	WO 2004/041862 A (ABLYNX N.V; SILENCE, KAREN; LAUWEREYS, MARC; DE HAARD, HANS) 21 May 2004 (2004-05-21) page 65 - page 66; example 2	1-24
A	WO 2004/001064 A (DYAX CORPORATION; SATO, AARON, K; EDGE, ALBERT) 31 December 2003 (2003-12-31) the whole document	1-24
A	WO 01/45746 A (GENENTECH, INC; DELANO, WARREN, L; DENNIS, MARK, S; LOWMAN, HENRY, B) 28 June 2001 (2001-06-28) the whole document	1-24
A	CARTER D C ET AL: "STRUCTURE OF SERUM ALBUMIN" ADVANCES IN PROTEIN CHEMISTRY, ACADEMIC PRESS, NEW YORK, NY, US, vol. 45, 1994, pages 153-203, XP009031387 ISSN: 0065-3233 the whole document	1-24
A	DENNIS M S ET AL: "Albumin binding as a general strategy for improving the pharmacokinetics of proteins" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOCHEMICAL BIOLOGISTS, BIRMINGHAM,, US, vol. 277, no. 38, 20 September 2002 (2002-09-20), pages 35035-35043, XP002285300 ISSN: 0021-9258 the whole document	1-24

-/--

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WUNDER A ET AL: "Albumin-based drug delivery as novel therapeutic approach for rheumatoid arthritis" JOURNAL OF IMMUNOLOGY, THE WILLIAMS AND WILKINS CO. BALTIMORE, US, vol. 170, no. 9, 1 May 2003 (2003-05-01), pages 4793-4801, XP002371816 ISSN: 0022-1767 the whole document	1-24

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/004679

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004003019 A	08-01-2004	AT 328906 T	15-06-2006
		CA 2492092 A1	08-01-2004
		CN 1678634 A	05-10-2005
		EP 1517921 A2	30-03-2005
		JP 2006512895 T	20-04-2006
WO 2004041862 A	21-05-2004	WO 2004041865 A2	21-05-2004
		WO 2004041863 A2	21-05-2004
		CA 2505316 A1	21-05-2004
		CA 2505325 A1	21-05-2004
		CA 2505326 A1	21-05-2004
		MX PA05004955 A	17-11-2005
WO 2004001064 A	31-12-2003	AU 2003245664 A1	06-01-2004
		CA 2490009 A1	31-12-2003
		EP 1576172 A2	21-09-2005
		JP 2006512050 T	13-04-2006
WO 0145746 A	28-06-2001	AU 784285 B2	02-03-2006
		AU 2458701 A	03-07-2001
		CA 2390691 A1	28-06-2001
		EP 1240337 A2	18-09-2002
		JP 2003518075 T	03-06-2003