DESCRIPTION

Reference to a Sequence Listing

[0001] This application contains a Sequence Listing in computer readable form.

Background of the Invention

Field of the Invention

[0002] The invention relates to variants of albumin or fragments thereof or fusion polypeptides comprising variant albumin or fragments thereof having a change in binding affinity to FcRn and/or a change in half-life compared to the albumin, fragment thereof or fusion polypeptide comprising albumin or a fragment thereof. The invention allows tailoring of binding affinity and/or half-life of an albumin to the requirements and desires of a user or application.

Description of the Related Art

[0003] Albumin is a protein naturally found in the blood plasma of mammals where it is the most abundant protein. It has important roles in maintaining the desired osmotic pressure of the blood and also in transport of various substances in the blood stream. Albumins have been characterized from many species including human, pig, mouse, rat, rabbit and goat and they share a high degree of sequence and structural homology.

[0004] Albumin binds *in vivo* to its receptor, the neonatal Fc receptor (FcRn) "Brambell" and this interaction is known to be important for the plasma half-life of albumin. FcRn is a membrane bound protein, expressed in many cell and tissue types. FcRn has been found to salvage albumin from intracellular degradation (Roopenian D. C. and Akilesh, S. (2007), Nat. Rev. Immunol 7, 715-725.). FcRn is a bifunctional molecule that contributes to maintaining a high level of IgGs and albumin in serum in mammals such as human beings.

[0005] Whilst the FcRn-immunoglobulin (IgG) interaction has been characterized in the prior art, the FcRn-albumin interaction is less well characterized. The major FcRn binding site is localized within DIII (381-585), (Andersen et al (2010), Clinical Biochemistry 43,367-372). A number of key amino acids have been shown to be important in binding, notably histidines H464, H510 and H536 and Lys500 (Andersen et al (2010), Nat. Commun. 3:610. DOI:10.1038/ncomms1607). Data indicates that IgG and albumin bind non-cooperatively to distinct sites on FcRn (Andersen et al. (2006), Eur. J. Immunol 36, 3044-3051; Chaudhury et al. (2006), Biochemistry 45, 4983-4990.).

[0006] It is known that mouse FcRn binds IgG from mice and humans whereas human FcRn appears to be more discriminating (Ober et al. (2001) Int. Immunol 13, 1551-1559). Andersen et al. (2010) Journal of Biological Chemistry 285(7):4826-36, describes the affinity of human and mouse FcRn for each mouse and human albumin (all possible combinations). No binding of albumin from either species was observed at physiological pH to either receptor. At acidic pH, a 100-fold difference in binding affinity was observed. In all cases, binding of albumin and IgG from either species to both receptors were additive.

[0007] Human serum albumin (HSA) has been well characterized as a polypeptide of 585 amino acids, the sequence of which can be found in Peters, T., Jr. (1996) All about Albumin: Biochemistry, Genetics and Medical, Applications pp10, Academic Press, Inc., Orlando (ISBN 0-12-552110-3). It has a characteristic binding to its receptor FcRn, where it binds at pH 6.0 but not at pH 7.4.

[0008] The plasma half-life of HSA has been found to be approximately 19 days. A natural variant having lower plasma half-life has been identified (Peach, R. J. and Brennan, S. 0., (1991) Biochim Biophys Acta.1097:49-54) having the substitution D494N. This substitution generated an N-glycosylation site in this variant, which is not present in the wild-type albumin. It is not known whether the glycosylation or the amino acid change is responsible for the change in plasma half-life.

[0009] Albumin has a long plasma half-life and because of this property it has been suggested for use in drug delivery. Albumin has been conjugated to pharmaceutically beneficial compounds (WO2000/69902), and it was found that the conjugate maintained the long plasma half-life of albumin. The resulting plasma half-life of the conjugate was generally considerably longer than the plasma half-life of the beneficial therapeutic compound alone.

[0010] Further, albumin has been genetically fused to therapeutically beneficial peptides (WO 2001/79271 A and WO2003/59934) with the typical result that the fusion has the activity of the therapeutically beneficial peptide and a considerably longer plasma half-life than the plasma half-life of the therapeutically beneficial peptides alone.

[0011] Otagiri et al (2009), Biol. Pharm. Bull. 32(4), 527-534, discloses more than 70 albumin variants, of these 25 of these are found to be mutated in domain III. A natural variant lacking the last 175 amino acids at the carboxy termini has been shown to have reduced half-life (Andersen et al (2010), Clinical Biochemistry 43, 367-372). Iwao *et al* (2007) studied the half-life of naturally occurring human albumin variants using a mouse model, and found that K541E and K560E had reduced half-life, E501K and E570K had increased half-life and K573E had almost no effect on half-life (Iwao, et. al. (2007) B.B.A. Proteins and Proteomics 1774, 1582-1590). Galliano et al (1993) Biochim. Biophys. Acta 1225, 27-32 discloses a natural variant E505K. Minchiotti *et al* (1990) discloses a natural variant K536E. Minchiotti et al (1987) Biochim. Biophys. Acta 916, 411-418, discloses a natural variant K574N. Takahashi et al (1987) Proc. Natl. Acad. Sci. USA 84, 4413-4417, discloses a natural variant D550G. Carlson et al (1992). Proc. Nat. Acad. Sci. USA 89, 8225- 8229, discloses a natural variant D550A. Database entry NCBI Accession

Number 103600 discloses several mutations of albumin. Chen et al 2003 Proteins 52(1): 80-87 discloses a protein-docking algorithm. Sugio et al 1999 Protein Engineering 12(6): 439-446 discloses a crystal structure of human serum albumin.

[0012] WO2011/051489 and WO 2012/150319 (PCT/EP2012/058206) disclose a number of point mutations in albumin which modulate the binding of albumin to FcRn, WO2010/092135 discloses a number of point mutations in albumin which increase the number of thiols available for conjugation in the albumin, the disclosure is silent about the effect of the mutations on the binding of the albumin to FcRn. WO2011/103076 discloses albumin variants, each containing a substitution in Domain III of HSA. WO2012/112188 discloses albumin variants containing substitutions in Domain III of HSA. WO2009/126920 discloses variants of human albumin wherein one or more surface-exposed amino acid residue is substituted by cysteine.

[0013] Albumin has the ability to bind a number of ligands and these become associated (associates) with albumin. This property has been utilized to extend the plasma half-life of drugs having the ability to non-covalently bind to albumin. This can also be achieved by binding a pharmaceutical beneficial compound, which has little or no albumin binding properties, to a moiety having albumin binding properties, see review article and reference therein, Kratz (2008) Journal of Controlled Release 132, 171-183.

[0014] Albumin is used in preparations of pharmaceutically beneficial compounds, in which such a preparation maybe for example, but not limited to, a nanoparticle or microparticle of albumin. In these examples the delivery of a pharmaceutically beneficial compound or mixture of compounds may benefit from alteration in the albumin's affinity to its receptor where the beneficial compound has been shown to associate with albumin for the means of delivery. It is not clear what determines the plasma half-life of the formed associates (for example but not limited to Levemir®, Kurtzhals P et al. Biochem. J. 1995; 312:725-731), conjugates or fusion polypeptides but it appears to be a result of the combination of the albumin and the selected pharmaceutically beneficial compound/polypeptide. It would be desirable to be able to control the plasma half-life of given albumin conjugates, associates or albumin fusion polypeptides so that a longer or shorter plasma half-life can be achieved than given by the components of the association, conjugation or fusion, in order to be able to design a particular drug according to the particulars of the indication intended to be treated.

[0015] Albumin is known to accumulate and be catabolized in tumors; it has also been shown to accumulate in inflamed joints of rheumatoid arthritis sufferers. See review article and reference therein, Kratz (2008) Journal of Controlled Release 132, 171-183. It is envisaged that HSA variants with increased affinity for FcRn would be advantageous for the delivery of pharmaceutically beneficial compounds.

[0016] It may even be desirable to have variants of albumin that have little or no binding to FcRn in order to provide shorter half-lives or controlled serum pharmacokinetics as described by Kenanova et al (2009) J. Nucl. Med.; 50 (Supplement 2):1582).

[0017] Kenanova et al (2010, Protein Engineering, Design & Selection 23(10): 789-798;

WO2010/118169) discloses a docking model comprising a structural model of domain III of HSA (solved at pH 7 to 8) and a structural model of FcRn (solved at pH 6.4). Kenanova *et al* discloses that positions 464, 505, 510, 531 and 535 in domain III potentially interact with FcRn. The histidines at positions 464, 510 and 535 were identified as being of particular interest by Chaudhury *et al.,* (2006, *op. cit.*) and these were shown to have a significant reduction in affinity and shorter half-life in mouse by Kenanova (2010, *op. cit.*). However, the studies of Kenanova *et al* are limited to domain III of HSA and therefore do not consider HSA in its native intact configuration. Furthermore, the identified positions result in a decrease in affinity for the FcRn receptor.

[0018] The present invention provides further variants having modulated (i.e. altered) binding affinity to the FcRn receptor. The albumin moiety or moieties may therefore be used to tailor the binding affinity to FcRn and/or half-life of fusion polypeptides, conjugates, associates, nanoparticles and compositions comprising the albumin moiety.

Summary of the Invention

[0019] The present invention relates to a polypeptide which is a variant of albumin, fragment thereof or fusion polypeptide comprising said variant albumin or a fragment thereof, which polypeptide has at least 80% identity to the full length of SEQ ID NO: 2, and comprises substitutions, at positions corresponding to positions 83, 111 and 573 of SEQ ID NO: 2, and has a stronger binding affinity to FcRn and/or longer plasma half-life compared with the binding affinity to FcRn or plasma half-life of a parent albumin which comprises the same sequence as the polypeptide with the exception that it does not comprise the substitutions at positions corresponding to positions 83, 111 and 573 of SEQ ID NO: 2.

[0020] The present invention also relates to isolated polynucleotides encoding the variants; nucleic acid constructs, vectors, and host cells comprising the polynucleotides; and methods of producing the variants.

[0021] The invention also relates to conjugates or associates comprising the variant albumin or fragment thereof according to the invention and a beneficial therapeutic moiety or to a fusion polypeptide comprising a variant albumin or fragment thereof of the invention and a fusion partner polypeptide.

[0022] The invention further relates to compositions comprising the variant albumin, fragment thereof, fusion polypeptide comprising variant albumin or fragment thereof or conjugates comprising the variant albumin or fragment thereof, according to the invention or associates comprising the variant albumin or fragment thereof, according to the invention. The compositions are preferably pharmaceutical compositions.

[0023] The invention further relates to a pharmaceutical composition comprising a variant albumin, fragment thereof, fusion polypeptide comprising variant albumin or fragment thereof or conjugates comprising the variant albumin or fragment thereof, or associates comprising the

variant albumin or fragment thereof.

[0024] The invention also relates to the use of the variants, fragments, fusion polypeptides, conjugates, associates, nanoparticles and microparticles.

[0025] The invention also relates to a method for preparing a variant albumin, fragment thereof, fusion polypeptide comprising variant albumin or fragment thereof or conjugates comprising the variant albumin or fragment thereof, or associates comprising the variant albumin or fragment thereof.

Brief Description of the Figures

[0026]

Figure 1: Multiple alignment of amino acid sequences of (i) full length mature HSA (Hu_1_2_3), (ii) an albumin variant comprising domain I and domain III of HSA (Hu_1_3), (iii) an albumin variant comprising domain II and domain III of HSA (Hu_2_3), (iv) full-length Macaca *mulatta* albumin (Mac_mul), (v) full-length *Rattus norvegicus* albumin (Rat) and (vi) full-length *Mus musculus* albumin (Mouse). Positions 500, 550 and 573 (relative to full length HSA) are indicated by arrows. In Figure 1 Domains I, II and III are referred to as 1, 2 and 3 (respectively).

Figure 2: Multiple alignment of amino acid sequence of mature albumin from human, sheep, mouse, rabbit and goat and immature albumins from chimpanzee ("Chimp"), macaque, hamster, guinea pig, rat, cow, horse, donkey, dog, chicken, and pig. The Start and End amino acids of domains 1, 2 and 3 (as defined by Dockal et al (The Journal of Biological Chemistry, 1999, Vol. 274(41): 29303-29310)) are indicated with respect to mature human albumin.

Figure 3: Conserved groups of amino acids based on their properties.

Figure 4: Representation of shFcRn-HSA docking model. (A-B) Two orientations of the complex are shown. Albumin is shown by a space-filling diagram, FcRn is shown as a ribbon diagram. The core binding interface of HSA is highlighted in pink (in grey-scale this is seen as the darkest (almost black) region; DI (CBI)), while the area distally localized from the interface is shown as DII (orange) and DIII is split into sub-domains DIIIa (in colour, this is cyan) and DIIIb (in colour, this is blue).

Figure 5: shFcRn binding of WT HSA, HSA K573P and HSA N111Q/K573P at pH5.5, samples were injected over immobilized shFcRn-HIS (~1500-2500 RU) at pH 5.5.

Figure 6: A proposed shFcRn-HSA docking model, showing the spatial relationship between shFcRn (space filling diagram) and HSA (ribbon diagram) DI, DII and DIII including loops of HSA comprising positions 78 to 88 and 108 to 112.

Definitions

[0027] Variant: The term "variant" means a polypeptide derived from a parent albumin by one or more (several) alteration(s), *i.e.*, a substitution, insertion, and/or deletion, at one or more (several) positions. A substitution means a replacement of an amino acid occupying a position with a different amino acid; a deletion means removal of an amino acid occupying a position; and an insertion means adding 1 or more (several), such as 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, preferably 1 to 3 amino acids immediately adjacent an amino acid occupying a position. In relation to substitutions, 'immediately adjacent' may be to the N-side ('upstream') or C-side ('downstream') of the amino acid occupying a position ('the named amino acid'). Therefore, for an amino acid named/numbered 'X', the insertion may be at position 'X+1' ('downstream') or at position 'X-1' ('upstream').

[0028] Mutant: The term "mutant" means a polynucleotide encoding a variant.

[0029] Wild-Type Albumin: The term "wild-type" (WT) albumin means albumin having the same amino acid sequence as naturally found in an animal or in a human being.

[0030] Parent Albumin: The term "parent" or "parent albumin" means an albumin to which an alteration is made by the hand of man to produce the albumin variants of the invention. The parent may be a naturally occurring (wild-type) polypeptide or an allele thereof, or even a variant thereof.

[0031] Albumin: Albumins are proteins and constitute the most abundant protein in plasma in mammals and albumins from a long number of mammals have been characterized by biochemical methods and/or by sequence information. Several albumins, *e.g.*, human serum albumin (HSA), have also been characterized crystallographically and the structure determined (HSA: He XM, Carter DC (July 1992). "Atomic structure and chemistry of human serum albumin". Nature 358 (6383): 209-15; horse albumin: Ho, J.X. et al. (2001). X-ray and primary structure of horse serum albumin (Equus caballus) at 0.27-nm resolution. Eur J Biochem. 215(1):205-12).

[0032] The term "albumin" means a protein having the same and/or very similar three dimensional (tertiary) structure as HSA or HSA domains and has similar properties to HSA or to the relevant domains. Similar three dimensional structures are for example the structures of the albumins from the species mentioned herein. Some of the major properties of albumin are i) its ability to regulate plasma volume (oncotic activity), ii) a long plasma half-life of around 19 days ± 5 days, iii) binding to FcRn, iv) ligand-binding, *e.g.* binding of endogenous molecules such as acidic, lipophilic compounds including bilirubin, fatty acids, hemin and thyroxine (see also Table 1 of Kragh-Hansen et al, 2002, Biol. Pharm. Bull. 25, 695), v) binding of small organic compounds with acidic or electronegative features *e.g.* drugs such as warfarin, diazepam, ibuprofen and paclitaxel (see also Table 1 of Kragh-Hansen et al, 2002, Biol. Pharm. Bull. 25, 695). Not all of these properties need to be fulfilled in order to characterize a protein or fragment as an albumin. If a fragment, for example, does not comprise a domain responsible for binding of certain ligands or organic compounds the variant of such a fragment will not be expected to have these properties either.

[0033] Albumins have generally a long plasma half-life of approximately 20 days or longer, *e.g.*, HSA has a plasma half-life of 19 days. It is known that the long plasma half-life of HSA is mediated *via* interaction with its receptor FcRn, however, an understanding or knowledge of the exact mechanism behind the long half-life of HSA is not essential for the invention.

[0034] As examples of albumin proteins according to the invention can be mentioned human serum albumin (*e.g.* AAA98797 or P02768-1, SEQ ID NO: 2 (mature), SEQ ID NO: 4 (immature)), primate serum albumin, (such as chimpanzee serum albumin (*e.g.* predicted sequence XP_517233.2 SEQ ID NO: 5), gorilla serum albumin or macaque serum albumin (*e.g.* NP_001182578, SEQ ID NO: 6), rodent serum albumin (such as hamster serum albumin (*e.g.* A6YF56, SEQ ID NO: 7), guinea pig serum albumin (*e.g.* Q6WDN9-1, SEQ ID NO: 8), mouse serum albumin (*e.g.* AAH49971 or P07724-1 Version 3, SEQ ID NO: 9) and rat serum albumin (*e.g.* AAH85359 or P02770-1 Version 2, SEQ ID NO: 10), bovine serum albumin (*e.g.* cow serum albumin P02769-1, SEQ ID NO: 11), equine serum albumin such as horse serum albumin (*e.g.* P35747-1, SEQ ID NO: 12) or donkey serum albumin (*e.g.* Q5XLE4-1, SEQ ID NO: 13), rabbit serum albumin (*e.g.* P49065-1 Version 2, SEQ ID NO: 14), goat serum albumin (*e.g.* ACF10391, SEQ ID NO: 15), sheep serum albumin (*e.g.* P14639-1, SEQ ID NO: 16), dog serum albumin (*e.g.* P49822-1, SEQ ID NO: 17), chicken serum albumin (*e.g.* P19121-1 Version 2, SEQ ID NO: 18) and pig serum albumin (*e.g.* P08835-1 Version 2, SEQ ID NO: 19) or a polypeptide having at least 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98 or at least 99% amino acid identity to such an albumin. The parent or reference albumin may be an artificial variant such as HSA K573P (SEQ ID NO: 3) or a chimeric albumin such as the N-terminal of HSA and the C-terminal of macaca albumin (SEQ ID NO: 20), N-terminal of HSA and the C-terminal of mouse albumin (SEQ ID NO: 21), N-terminal of HSA and the C-terminal of rabbit albumin (SEQ ID NO: 22), N-terminal of HSA and the C-terminal of sheep albumin (SEQ ID NO: 23).

[0035] Other examples of albumin, which are also included in the scope of this application, include ovalbumin (*e.g.* P01012.pro: chicken ovalbumin; O73860.pro: turkey ovalbumin).

[0036] HSA as disclosed in SEQ ID NO: 2 or any naturally occurring allele thereof, is the preferred albumin (parent albumin) according to the invention. HSA is a protein consisting of 585 amino acid residues and has a molecular weight of 67 kDa. In its natural form it is not glycosylated. The skilled person will appreciate that natural alleles may exist having essentially the same properties as HSA but having one or more (several) amino acid changes compared to SEQ ID NO: 2, and the inventors also contemplate the use of such natural alleles as parent albumin according to the invention.

[0037] The parent albumin, a fragment thereof, or albumin part of a fusion polypeptide comprising albumin or a fragment thereof according to the invention preferably has a sequence identity to the sequence of HSA shown in SEQ ID NO: 2 of at least 60%, preferably at least 70%, preferably at least 80%, preferably at least 85%, preferably at least 86%, preferably at least 87%, preferably at least 88%, preferably at least 89%, preferably at least 90%, preferably at least 91%, preferably at least 92%, preferably at least 93%, preferably at least 94%, preferably at least 95%, more preferred at least 96%, more preferred at least 97%, more preferred at least 98% and most

preferred at least 99%. It is preferred that the parent albumin maintains at least one of the major properties of albumin or a similar tertiary structure as an albumin, such as HSA The sequence identity may be over the full-length of SEQ ID NO: 2 or over a molecule consisting or comprising of a fragment such as one or more (several) domains of SEQ ID NO: 2 such as a molecule consisting of or comprising domain III (*e.g.* SEQ ID NO: 27), a molecule consisting of or comprising domain II and domain III (*e.g.* SEQ ID NO: 25), a molecule consisting of or comprising domain I and domain III (*e.g.* SEQ ID NO: 24), a molecule consisting of or comprising two copies of domain III (*e.g.* SEQ ID NO: 26), a molecule consisting of or comprising three copies of domain III (*e.g.* SEQ ID NO: 28) or a molecule consisting of or comprising domain I and two copies of domain III (*e.g.* SEQ ID NO: 29).

[0038] The parent preferably comprises or consists of the amino acid sequence of SEQ ID NO: 4 (immature sequence of HSA) or SEQ ID NO: 2 (mature sequence of HSA).

[0039] In another embodiment, the parent is an allelic variant of the mature polypeptide of SEQ ID NO: 2.

[0040] The parent albumin may be encoded by a polynucleotide that hybridizes under very low stringency conditions, low stringency conditions, medium stringency conditions, medium-high stringency conditions, high stringency conditions, or very high stringency conditions with (i) the mature polypeptide coding sequence of SEQ ID NO: 1, or (ii) the full-length complementary strand of (i) (J. Sambrook, E.F. Fritsch, and T. Maniatis, 1989, Molecular Cloning, A Laboratory Manual, 2d edition, Cold Spring Harbor, New York).

[0041] The polynucleotide of SEQ ID NO: 1 or a subsequence thereof, as well as the amino acid sequence of SEQ ID NO: 2 or a fragment thereof, may be used to design nucleic acid probes to identify and clone DNA encoding a parent from strains of different genera or species according to methods well known in the art. In particular, such probes can be used for hybridization with the genomic or cDNA of the genus or species of interest, following standard Southern blotting procedures, in order to identify and isolate the corresponding gene therein. Such probes can be considerably shorter than the entire sequence, but should be at least 14, *e.g.*, at least 25, at least 35, or at least 70 nucleotides in length. Preferably, the nucleic acid probe is at least 100 nucleotides in length, *e.g.*, at least 200 nucleotides, at least 300 nucleotides, at least 400 nucleotides, at least 500 nucleotides, at least 600 nucleotides, at least 700 nucleotides, at least 800 nucleotides, or at least 900 nucleotides in length. Both DNA and RNA probes can be used. The probes are typically labelled for detecting the corresponding gene (for example, with ^{32}P, ^{3}H, ^{35}S, biotin, or avidin). Such probes are encompassed by the invention.

[0042] A genomic DNA or cDNA library prepared from such other organisms may be screened for DNA that hybridizes with the probes described above and encodes a parent. Genomic or other DNA from such other organisms may be separated by agarose or polyacrylamide gel electrophoresis, or other separation techniques. DNA from the libraries or the separated DNA may be transferred to and immobilized on nitrocellulose or other suitable carrier material. In order to identify a clone or DNA that is homologous with SEQ ID NO: 1 or a subsequence

thereof, the carrier material is used in a Southern blot.

[0043] For purposes of the invention, hybridization indicates that the polynucleotide hybridizes to a labelled nucleotide probe corresponding to the polynucleotide shown in SEQ ID NO: 1, its complementary strand, or a subsequence thereof, under low to very high stringency conditions. Molecules to which the probe hybridizes can be detected using, for example, X-ray film or any other detection means known in the art.

[0044] The nucleic acid probe may comprise or consist of the mature polypeptide coding sequence of SEQ ID NO: 1, *i.e.* nucleotides 1 to 1785 of SEQ ID NO: 1. The nucleic acid probe may comprise or consist of a polynucleotide that encodes the polypeptide of SEQ ID NO: 2 or a fragment thereof.

[0045] For long probes of at least 100 nucleotides in length, very low to very high stringency conditions are defined as pre-hybridization and hybridization at 42°C in 5X SSPE, 0.3% SDS, 200 micrograms/ml sheared and denatured salmon sperm DNA, and either 25% formamide for very low and low stringencies, 35% formamide for medium and medium-high stringencies, or 50% formamide for high and very high stringencies, following standard Southern blotting procedures for 12 to 24 hours optimally. The carrier material is finally washed three times each for 15 minutes using 2X SSC, 0.2% SDS at 45°C (very low stringency), 50°C (low stringency), 55°C (medium stringency), 60°C (medium-high stringency), 65°C (high stringency), or 70°C (very high stringency).

[0046] For short probes that are about 15 nucleotides to about 70 nucleotides in length, stringency conditions are defined as pre-hybridization and hybridization at about 5°C to about 10°C below the calculated T_m using the calculation according to Bolton and McCarthy (1962, Proc. Natl. Acad. Sci. USA 48: 1390) in 0.9 M NaCl, 0.09 M Tris-HCl pH 7.6, 6 mM EDTA, 0.5% NP-40, 1X Denhardt's solution, 1 mM sodium pyrophosphate, 1 mM sodium monobasic phosphate, 0.1 mM ATP, and 0.2 mg of yeast RNA per ml following standard Southern blotting procedures for 12 to 24 hours optimally. The carrier material is finally washed once in 6X SCC plus 0.1% SDS for 15 minutes and twice each for 15 minutes using 6X SSC at 5°C to 10°C below the calculated T_m.

[0047] The parent may be encoded by a polynucleotide with a sequence identity to the mature polypeptide coding sequence of SEQ ID NO: 1 of at least 60%, e.g., at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%, which encodes a polypeptide which is able to function as an albumin. In an embodiment, the parent is encoded by a polynucleotide comprising or consisting of SEQ ID NO: 1.

[0048] **Albumin moiety:** The albumin part of a fusion polypeptide, conjugate, associate, nanoparticle or composition comprising the albumin variant or fragment thereof according to the invention, may be referred to as an 'albumin moiety' or 'albumin component'. A polypeptide according to the invention may comprise or consist of an albumin moiety.

[0049] FcRn and shFcRn: The term "FcRn" means the human neonatal Fc receptor (FcRn). shFcRn is a soluble recombinant form of FcRn. hFcRn is a heterodimer of SEQ ID NO: 30 (truncated heavy chain of the major histocompatibility complex class I-like Fc receptor (FCGRT)) and SEQ ID NO: 31 (beta-2-microglobulin). Together, SEQ ID NO: 30 and 31 form hFcRn.

[0050] Isolated variant: The term "isolated variant" means a variant that is modified by the hand of man and separated completely or partially from at least one component with which it naturally occurs. The term "isolated variant" means a variant in a form or environment which does not occur in nature. Non-limiting examples of isolated substances include (1) any non-naturally occurring variant, (2) any variant that is at least partially removed from one or more (several) or all of the naturally occurring constituents with which it is associated in nature; (3) any variant modified by the hand of man relative to the polypeptide from which it is derived (*e.g.* the polypeptide from which it is derived as found in nature); or (4) any variant modified by increasing the amount of the variant relative to other components with which it is naturally associated (*e.g.,* multiple copies of a gene encoding the substance; use of a stronger promoter than the promoter naturally associated with the gene encoding the substance). An isolated variant may be present in a fermentation broth sample. The variant may be at least 1% pure, e.g., at least 5% pure, at least 10% pure, at least 20% pure, at least 40% pure, at least 60% pure, at least 80% pure, and at least 90% pure, as determined by SDS-PAGE or GP-HPLC.

[0051] Substantially pure variant: The term "substantially pure variant" means a preparation that contains at most 10%, at most 8%, at most 6%, at most 5%, at most 4%, at most 3%, at most 2%, at most 1 %, and at most 0.5% by weight of other polypeptide material with which it is natively or recombinantly associated. Preferably, the variant is at least 92% pure, *e.g.*, at least 94% pure, at least 95% pure, at least 96% pure, at least 97% pure, at least 98% pure, at least 99%, at least 99.5% pure, and 100% pure by weight of the total polypeptide material present in the preparation. Purity may be determined by SDS-PAGE or GP-HPLC. The variants of the invention are preferably in a substantially pure form. This can be accomplished, for example, by preparing the variant by well-known recombinant methods and by purification methods.

[0052] Mature polypeptide: The term "mature polypeptide" means a polypeptide in its final form following translation and any post-translational modifications, such as N-terminal processing, C-terminal truncation, glycosylation, phosphorylation, etc. The mature polypeptide may be amino acids 1 to 585 of SEQ ID NO: 2, *e.g.* with alterations according to the invention and/or with the inclusion of any post-translational modifications.

[0053] Mature polypeptide coding sequence: The term "mature polypeptide coding sequence" means a polynucleotide that encodes a mature albumin polypeptide. The mature polypeptide coding sequence may be nucleotides 1 to 1758 of SEQ ID NO: 1 *e.g.* with inclusions required to encode a variant according to the invention.

[0054] Sequence Identity: The relatedness between two amino acid sequences or between two nucleotide sequences is described by the parameter "sequence identity".

[0055] For purposes of the invention, the degree of sequence identity between two amino acid

sequences is determined using the Needleman-Wunsch algorithm (Needleman and Wunsch, 1970, J. Mol. Biol. 48: 443-453) as implemented in the Needle program of the EMBOSS package (EMBOSS: The European Molecular Biology Open Software Suite, Rice et al., 2000, Trends Genet. 16: 276-277), preferably version 3.0.0 or later, more preferably version 5.0.0 or later. The optional parameters used are gap open penalty of 10, gap extension penalty of 0.5, and the EBLOSUM62 (EMBOSS version of BLOSUM62) substitution matrix. The output of Needle labelled "longest identity" (obtained using the -nobrief option) is used as the percent identity and is calculated as follows:

(Identical Residues x 100)/(Length of Alignment – Total Number of Gaps in Alignment)

[0056] For purposes of the invention, the degree of sequence identity between two deoxyribonucleotide sequences is determined using the Needleman-Wunsch algorithm (Needleman and Wunsch, 1970, *supra*) as implemented in the Needle program of the EMBOSS package (EMBOSS: The European Molecular Biology Open Software Suite, Rice *et al.,* 2000, *supra*), preferably version 3.0.0 or later, more preferably version 5.0.0 or later. The optional parameters used are gap open penalty of 10, gap extension penalty of 0.5, and the EDNAFULL (EMBOSS version of NCBI NUC4.4) substitution matrix. The output of Needle labelled "longest identity" (obtained using the -nobrief option) is used as the percent identity and is calculated as follows:

(Identical Deoxyribonucleotides x 100)/(Length of Alignment – Total Number of Gaps in Alignment)

[0057] Fragment: The term "fragment" means a polypeptide having one or more (several) amino acids deleted from the amino and/or carboxyl terminus of an albumin and/or an internal region of albumin that has retained the ability to bind to FcRn. Fragments may consist of one uninterrupted sequence derived from HSA or it may comprise two or more (several) sequences derived from HSA. The fragments according to the invention have a size of more than approximately 20 amino acid residues, preferably more than 30 amino acid residues, more preferred more than 40 amino acid residues, more preferred more than 50 amino acid residues, more preferred more than 75 amino acid residues, more preferred more than 100 amino acid residues, more preferred more than 200 amino acid residues, more preferred more than 300 amino acid residues, even more preferred more than 400 amino acid residues and most preferred more than 500 amino acid residues. A fragment may comprise or consist of one more domains of albumin such as DI + DII, DI + DIII, DII + DIII, DIII + DIII, DI + DIII + DIII, DIII + DIII +DIII, or fragments of such domains or combinations of domains.

[0058] Domains I, II and III may be defined with reference to HSA (SEQ ID NO: 2). For example, HSA domain I may consist of or comprise amino acids 1 to 194 (± 1 to 15 amino acids) of SEQ ID NO: 2, HSA domain II may consist of or comprise amino acids 192 (± 1 to 15 amino acids) to 387 (± 1 to 15 amino acids) of SEQ ID NO: 2 and domain III may consist of or comprise amino acid residues 381 (± 1 to 15 amino acids) to 585 (± 1 to 15 amino acids) of SEQ ID NO: 2. "± 1 to 15 amino acids" means that the residue number may deviate by 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acids to the C-terminus and/or to the N-terminus of the stated amino

acid position. Examples of domains I, II and III are described by Dockal et al (The Journal of Biological Chemistry, 1999, Vol. 274(41): 29303-29310) and Kjeldsen et al (Protein Expression and Purification, 1998, Vol 13: 163-169) and are tabulated below.

Amino acid residues of HSA domains I, II and III with reference to SEQ ID NO: 2	**Dockal *et al***	**Kjeldsen *et al***
Domain I	1 to 197	1 to 192
Domain II	189 to 385	193 to 382
Domain III	381 to 585	383 to 585

[0059] The skilled person can identify domains I, II and III in non-human albumins by amino acid sequence alignment with HSA, for example using the Needleman-Wunsch algorithm (Needleman and Wunsch, 1970, J. Mol. Biol. 48: 443-453) as implemented in the Needle program of the EMBOSS package (EMBOSS: The European Molecular Biology Open Software Suite, Rice et al., 2000, Trends Genet. 16: 276-277), preferably version 3.0.0 or later, more preferably version 5.0.0 or later. The optional parameters used are gap open penalty of 10, gap extension penalty of 0.5, and the EBLOSUM62 (EMBOSS version of BLOSUM62) substitution matrix. Other suitable software includes MUSCLE ((Multiple sequence comparison by log-expectation, Robert C. Edgar, Version 3.6, http://www.drive5.com/muscle; Edgar (2004) Nucleic Acids Research 32(5), 1792-97 and Edgar (2004) BMC Bioinformatics, 5(1):113) which may be used with the default settings as described in the User Guide (Version 3.6, September 2005). Versions of MUSCLE later than 3.6 may also be used for any aspect of the invention). Examples of suitable alignments are provided in Figures 1 and 2.

[0060] It is preferred that domains have at least 70, 75, 80, 85, 90, 95, 96, 97, 98, 99, 99.5 % identity or 100% identity to Domain I, II or III of HSA (SEQ ID NO: 2).

[0061] Allelic variant: The term "allelic variant" means any of two or more (several) alternative forms of a gene occupying the same chromosomal locus. Allelic variation arises naturally through mutation, and may result in polymorphism within populations. Gene mutations can be silent (no change in the encoded polypeptide) or may encode polypeptides having altered amino acid sequences. An allelic variant of a polypeptide is a polypeptide encoded by an allelic variant of a gene.

[0062] Coding sequence: The term "coding sequence" means a polynucleotide, which directly specifies the amino acid sequence of its translated polypeptide product. The boundaries of the coding sequence are generally determined by an open reading frame, which usually begins with the ATG start codon or alternative start codons such as GTG and TTG and ends with a stop codon such as TAA, TAG, and TGA. The coding sequence may be a DNA, cDNA, synthetic, or recombinant polynucleotide.

[0063] cDNA: The term "cDNA" means a DNA molecule that can be prepared by reverse transcription from a mature, spliced, mRNA molecule obtained from a eukaryotic cell. cDNA lacks intron sequences that may be present in the corresponding genomic DNA. The initial, primary

RNA transcript is a precursor to mRNA that is processed through a series of steps, including splicing, before appearing as mature spliced mRNA.

[0064] Nucleic acid construct: The term "nucleic acid construct" means a nucleic acid molecule, either single- or double-stranded, which is isolated from a naturally occurring gene or is modified to contain segments of nucleic acids in a manner that would not otherwise exist in nature or which is synthetic. The term nucleic acid construct is synonymous with the term "expression cassette" when the nucleic acid construct contains the control sequences required for expression of a coding sequence of the invention.

[0065] Control sequences: The term "control sequences" means all components (*e.g.* nucleic acid sequences) necessary for the expression of a polynucleotide encoding a variant of the invention. Each control sequence may be native (*i.e.* from the same gene) or foreign (*i.e.* from a different gene) to the polynucleotide encoding the variant or native or foreign to each other. Such control sequences include, but are not limited to, a leader, polyadenylation sequence, propeptide sequence, promoter, signal peptide sequence, and transcription terminator. At a minimum, the control sequences include a promoter, and transcriptional and translational stop signals. The control sequences may be provided with linkers for the purpose of introducing specific restriction sites facilitating ligation of the control sequences within the coding region of the polynucleotide encoding a variant.

[0066] Operably linked: The term "operably linked" means a configuration in which a control sequence is placed at an appropriate position relative to the coding sequence of a polynucleotide such that the control sequence directs the expression of the coding sequence.

[0067] Expression: The term "expression" includes any step involved in the production of the variant including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and secretion.

[0068] Expression vector: The term "expression vector" means a linear or circular DNA molecule that comprises a polynucleotide encoding a variant and is operably linked to additional nucleotides (*e.g.* control sequences) that provide for its expression.

[0069] Host cell: The term "host cell" means any cell type that is susceptible to transformation, transfection, transduction, and/or the like with a nucleic acid construct or expression vector comprising a polynucleotide of the present invention. The term "host cell" encompasses any progeny of a parent cell that is not identical to the parent cell due to mutations that occur during replication.

[0070] Plasma half-life: Plasma half-life is ideally determined *in vivo* in suitable individuals. However, since it is time consuming and expensive and there are inevitably ethical concerns connected with doing experiments in animals or man it is desirable to use an *in vitro* assay for determining whether plasma half-life is extended or reduced. It is known that the binding of albumin to its receptor FcRn is important for plasma half-life and the correlation between receptor binding and plasma half-life is that a higher affinity of albumin to its receptor leads to

longer plasma half-life. Thus for the invention a higher affinity of albumin to FcRn is considered indicative of an increased plasma half-life and a lower affinity of albumin to its receptor is considered indicative of a reduced plasma half-life.

[0071] In this application and claims the binding of albumin to its receptor FcRn is described using the term affinity and the expressions "stronger" or "weaker". Thus, it should be understood that a molecule having a higher affinity to FcRn than HSA is considered to bind stronger to FcRn than HSA and a molecule having a lower affinity to FcRn than HSA is considered to bind weaker to FcRn than HSA.

[0072] The terms "longer plasma half-life" or "shorter plasma half-life" and similar expressions are understood to be in relationship to the corresponding parent or reference or corresponding albumin molecule. Thus, a longer plasma half-life with respect to a variant albumin of the invention means that the variant has longer plasma half-life than the corresponding albumin having the same sequences except for the alteration(s) described herein, *e.g.* at one or more (several) positions in Domain I and one or more (several) positions in Domain III (*e.g.* in SEQ ID NO: 2).

[0073] **Reference:** a reference is an albumin, fusion, conjugate, composition, associate or nanoparticle to which an albumin variant, fusion, conjugate, composition, associate or nanoparticle is compared. The reference may comprise or consist of full length albumin (such as HSA or a natural allele thereof) of a fragment thereof. A reference may also be referred to as a 'corresponding' albumin, fusion, conjugate, composition, associate or nanoparticle to which an albumin variant, fusion, conjugate, composition, associate or nanoparticle is compared. A reference may comprise or consist of HSA (SEQ ID NO: 2) or a fragment, fusion, conjugate, associate, nanoparticle or microparticle thereof. Preferably, the reference is identical to the polypeptide, fusion polypeptide, conjugate, composition, associate, nanoparticle or microparticle according to the invention ("being studied") with the exception of the albumin moiety. Preferably the albumin moiety of the reference comprises or consists of an albumin (*e.g.* HSA, SEQ ID NO: 2) or a fragment thereof. The amino acid sequence of the albumin moiety of the reference may be longer than, shorter than or, preferably, the same (± 1 to 15 amino acids) length as the amino sequence of the albumin moiety of the polypeptide, fusion polypeptide, conjugate, composition, associate, nanoparticle or microparticle according to the invention ("being studied").

[0074] **Equivalent amino acid positions**: Throughout this specification amino acid positions are defined in relation to full-length mature human serum albumin (*i.e.* without leader sequence, SEQ ID NO: 2). However, the skilled person understands that the invention also relates to variants of non-human albumins *e.g.* those disclosed herein and/or fragments of a human or non-human albumin. Equivalent positions can be identified in fragments of human serum albumin, in animal albumins and in fragments, fusions and other derivative or variants thereof by comparing amino acid sequences using pairwise (*e.g.* ClustalW) or multiple (*e.g.* MUSCLE) alignments. For example, Fig. 1 shows that positions equivalent to 500, 550 and 573 in full length human serum albumin are easily identified in fragments of human serum albumin and in albumins of other species. Positions 500, 550 and 573 are indicated by arrows. Further details are provided in the table below.

Example of identification of equivalent positions in HSA, animal albumins and albumin fragments

Organism (accession number of protein)	Albumin			Position equivalent to human serum albumin (native amino acid):		
	Full length or fragment	Fragment details	Total length of mature protein	500 (K)	550 (D)	573 (K)
Homo sapiens (AAA98797)	Full length	-	585	500 (K)	550 (D)	573 (K)
Homo sapiens	Fragment	DI, DIII	399	314 (K)	364 (D)	387 (K)
Homo sapiens	Fragment	DI, DIII	403	318 (K)	368 (D)	391 (K)
Macaca mulatta (NP_001182578)	Full length	-	584	500 (K)	550 (N)	573 (P)
Rattus norvegicus (AAH85359)	Full length	-	584	500 (K)	550 (D)	573 (P)
Mus musculus (AAH49971)	Full length	-	584	500 (K)	550 (D)	573 (P)

[0075] Fig. 1 was generated by MUSCLE using the default parameters including output in ClustalW 1.81 format. The raw output data was shaded using BoxShade 3.21 (http://www.ch.embnet.org/software/BOX_form.html) using Output Format: RTF_new; Font Size: 10; Consensus Line: no consensus line; Fraction of sequences (that must agree for shading): 0.5; Input sequence format: ALN. Therefore, throughout this specification amino acid positions defined in human serum albumin also apply to equivalent positions in fragments, derivatives or variants and fusions of human serum albumin, animals from other species and fragments and fusions thereof. Such equivalent positions may have (i) a different residue number in its native protein and/or (ii) a different native amino acid in its native protein.

[0076] Likewise, Fig. 2 shows that equivalent positions can be identified in fragments (*e.g.* domains) of an albumin with reference to SEQ ID NO: 2 (HSA).

Conventions for Designation of Variants

[0077] For purposes of the present invention, the mature polypeptide disclosed in SEQ ID NO: 2 is used to determine the corresponding amino acid residue in another albumin. The amino acid sequence of another albumin is aligned with the mature polypeptide disclosed in SEQ ID NO: 2, and based on the alignment, the amino acid position number corresponding to any amino acid residue in the mature polypeptide disclosed in SEQ ID NO: 2 is determined using the Needleman-Wunsch algorithm (Needleman and Wunsch, 1970, J. Mol. Biol. 48: 443-453) as implemented in the Needle program of the EMBOSS package (EMBOSS: The European

Molecular Biology Open Software Suite, Rice et al., 2000, Trends Genet. 16: 276-277), preferably version 3.0.0 or later, more preferably version 5.0.0 or later.

[0078] Identification of the corresponding amino acid residue in another albumin can be determined or confirmed by an alignment of multiple polypeptide sequences using a suitable computer program including, but not limited to, "ClustalW" (Larkin et al., 2007, Bioinformatics 23: 2947-2948), MUSCLE (multiple sequence comparison by log-expectation; version 3.5 or later; Edgar, 2004, Nucleic Acids Research 32: 1792-1797), MAFFT (version 6.857 or later; Katoh and Kuma, 2002, Nucleic Acids Research 30: 3059-3066; Katoh et al., 2005, Nucleic Acids Research 33: 511-518; Katoh and Toh, 2007, Bioinformatics 23: 372-374; Katoh et al., 2009, Methods in Molecular Biology 537:39-64; Katoh and Toh, 2010, Bioinformatics 26: 1899-1900), and EMBOSS EMMA employing ClustalW (1.83 or later; Thompson et al., 1994, Nucleic Acids Research 22: 4673-4680), using their respective default parameters.

[0079] When the other polypeptide (or protein) has diverged from the mature polypeptide of SEQ ID NO: 2 such that traditional sequence-based comparison fails to detect their relationship (Lindahl and Elofsson, 2000, J. Mol. Biol. 295: 613-615), other pairwise sequence comparison algorithms can be used. Greater sensitivity in sequence-based searching can be attained using search programs that utilize probabilistic representations of polypeptide families (profiles) to search databases. For example, the PSI-BLAST program generates profiles through an iterative database search process and is capable of detecting remote homologs (Atschul et al., 1997, Nucleic Acids Res. 25: 3389-3402). Even greater sensitivity can be achieved if the family or superfamily for the polypeptide has one or more (several) representatives in the protein structure databases. Programs such as GenTHREADER (Jones, 1999, J. Mol. Biol. 287: 797-815; McGuffin and Jones, 2003, Bioinformatics 19: 874-881) utilize information from a variety of sources (PSI-BLAST, secondary structure prediction, structural alignment profiles, and solvation potentials) as input to a neural network that predicts the structural fold for a query sequence. Similarly, the method of Gough et al., 2000, J. Mol. Biol. 313: 903-919, can be used to align a sequence of unknown structure with the superfamily models present in the SCOP database. These alignments can in turn be used to generate homology models for the polypeptide, and such models can be assessed for accuracy using a variety of tools developed for that purpose.

[0080] For proteins of known structure, several tools and resources are available for retrieving and generating structural alignments. For example the SCOP superfamilies of proteins have been structurally aligned, and those alignments are accessible and downloadable. Two or more protein structures can be aligned using a variety of algorithms such as the distance alignment matrix (Holm and Sander, 1998, Proteins 33: 88-96) or combinatorial extension (Shindyalov and Bourne, 1998, Protein Engineering 11: 739-747), and implementation of these algorithms can additionally be utilized to query structure databases with a structure of interest in order to discover possible structural homologs (*e.g.*, Holm and Park, 2000, Bioinformatics 16: 566-567).

[0081] In describing the albumin variants of the present invention, the nomenclature described below is adapted for ease of reference. The accepted IUPAC single letter or three letter amino acid abbreviation is employed. The term 'point mutation' and/or 'alteration' includes deletions, insertions and substitutions.

[0082] Substitutions. For an amino acid substitution, the following nomenclature is used: Original amino acid, position, substituted amino acid. Accordingly, for example the substitution of threonine with alanine at position 226 is designated as "Thr226Ala" or "T226A". Multiple mutations (or alterations) are separated by addition marks ("+"), *e.g.*, "Gly205Arg + Ser411 Phe" or "G205R + S411F", representing substitutions at positions 205 and 411 of glycine (G) with arginine (R) and serine (S) with phenylalanine (F), respectively. The Figures also use ("/"), *e.g.,* "E492T/N503D" this should be viewed as interchangeable with ("+").

[0083] Deletions. For an amino acid deletion, the following nomenclature is used: Original amino acid, position*. Accordingly, the deletion of glycine at position 195 is designated as "Gly195*" or "G195*". Multiple deletions are separated by addition marks ("+"), *e.g.*, "Gly195* + Ser411*" or "G195* + S411*".

[0084] Insertions. As disclosed above, an insertion may be to the N-side ('upstream', 'X-1') or C-side ('downstream', 'X+1') of the amino acid occupying a position ('the named (or original) amino acid', 'X').

[0085] For an amino acid insertion to the C-side ('downstream', `X+1') of the original amino acid ('X'), the following nomenclature is used: Original amino acid, position, original amino acid, inserted amino acid. Accordingly the insertion of lysine after glycine at position 195 is designated "Gly195GlyLys" or "G195GK". An insertion of multiple amino acids is designated [Original amino acid, position, original amino acid, inserted amino acid #1, inserted amino acid #2; etc.]. For example, the insertion of lysine and alanine after glycine at position 195 is indicated as "Gly195GlyLysAla" or "G195GKA".

[0086] In such cases the inserted amino acid residue(s) are numbered by the addition of lower case letters to the position number of the amino acid residue preceding the inserted amino acid residue(s). In the above example, the sequence would thus be:

Parent:	Variant:
195	195 195a 195b
G	G - K - A

[0087] For an amino acid insertion to the N-side ('upstream', 'X-1') of the original amino acid (X), the following nomenclature is used: Original amino acid, position, inserted amino acid, original amino acid. Accordingly the insertion of lysine (K) before glycine (G) at position 195 is designated "Gly195LysGly" or "G195KG". An insertion of multiple amino acids is designated [Original amino acid, position, inserted amino acid #1, inserted amino acid #2; etc., original amino acid]. For example, the insertion of lysine (K) and alanine (A) before glycine at position 195 is indicated as "Gly195LysAlaGly" or "G195KAG". In such cases the inserted amino acid residue(s) are numbered by the addition of lower case letters with prime to the position number of the amino acid residue following the inserted amino acid residue(s). In the above example, the sequence would thus be:

Parent:	Variant:
195	195a' 195b' 195
G	K - A - G

[0088] Multiple alterations. Variants comprising multiple alterations are separated by addition marks ("+"), *e.g.*, "Arg170Tyr+Gly195Glu" or "R170Y+G195E" representing a substitution of tyrosine and glutamic acid for arginine and glycine at positions 170 and 195, respectively.

[0089] Different alterations (*e.g.* substitutions). Where different alterations (*e.g.* substitutions) can be introduced at a position, the different alterations (*e.g.* substitutions) are separated by a comma, *e.g.*, "Arg170Tyr,Glu" represents a substitution of arginine with tyrosine or glutamic acid at position 170. Thus, "Tyr167Gly,Ala + Arg170Gly,Ala" designates the following variants: "Tyr167Gly+Arg170Gly", "Tyr167Gly+Arg170Ala", "Tyr167Ala+Arg170Gly", and "Tyr167Ala+Arg170Ala".

Detailed Description of the Invention

[0090] The present invention relates to a polypeptide which is a variant of albumin, fragment thereof or fusion polypeptide comprising said variant albumin or a fragment thereof, which polypeptide has at least 80% identity to the full length of SEQ ID NO: 2, and comprises substitutions, at positions corresponding to positions 83, 111 and 573 of SEQ ID NO: 2, and has a stronger binding affinity to FcRn and/or longer plasma half-life compared with the binding affinity to FcRn or plasma half-life of a parent albumin which comprises the same sequence as the polypeptide with the exception that it does not comprise the substitutions at positions corresponding to positions 83, 111 and 573 of SEQ ID NO: 2.

Variants

[0091] A first aspect of the invention provides a polypeptide which is a variant of albumin, fragment thereof or fusion polypeptide comprising said variant albumin or a fragment thereof, which polypeptide has at least 80% identity to the full length of SEQ ID NO: 2, and comprises substitutions, at positions corresponding to positions 83, 111 and 573 of SEQ ID NO: 2, and has a stronger binding affinity to FcRn and/or longer plasma half-life compared with the binding affinity to FcRn or plasma half-life of a parent albumin which comprises the same sequence as the polypeptide with the exception that it does not comprise the substitutions at positions corresponding to positions 83, 111 and 573 of SEQ ID NO: 2. The alterations may be made in SEQ ID NO: 2.

[0092] It is preferred that the parent albumin and/or the variant albumin comprises or consists of:

1. (a) a polypeptide having at least 60% sequence identity to the mature polypeptide of SEQ ID NO: 2;
2. (b) a polypeptide encoded by a polynucleotide that hybridizes under low stringency conditions with (i) the mature polypeptide coding sequence of SEQ ID NO: 1, or (ii) the full-length complement of (i);
3. (c) a polypeptide encoded by a polynucleotide having at least 60% identity to the mature polypeptide coding sequence of SEQ ID NO: 1; and/or
4. (d) a fragment of the mature polypeptide of SEQ ID NO: 2.

[0093] The variants of albumin or fragments thereof or fusion polypeptides comprising albumin or fragments thereof comprise one or more (several) alterations, such as substitutions, deletions or insertions at positions in Domain I and one or more (several) alterations, such as substitutions, deletions or insertions at positions in Domain III of the mature polypeptide of SEQ ID NO: 2 or in equivalent positions of other albumins or variants or fragments thereof. A stop codon may be introduced in addition to the alterations described herein and if introduced is at position 574 or further downstream (*e.g.* in SEQ ID NO: 2 it is introduced at from position 574 to 585).

[0094] The variant albumin, a fragment thereof, or albumin part of a fusion polypeptide comprising variant albumin or a fragment thereof according to the invention has generally a sequence identity to the sequence of HSA shown in SEQ ID NO: 2 of at least 80%, preferably at least 85%, preferably at least 90 %, more preferred at least 95%, more preferred at least 96%, more preferred at least 97%, more preferred at least 98% and most preferred at least 99%. The variant has less than 100% identity to SEQ ID NO: 2.

[0095] The variant albumin, a fragment thereof, or albumin part of a fusion polypeptide comprising variant albumin or a fragment thereof according to the invention has generally a sequence identity to the sequence of the parent albumin of at least 80%, preferably at least 85%, preferably at least 90 %, more preferred at least 95%, more preferred at least 96%, more preferred at least 97%, more preferred at least 98% and most preferred at least 99%. The variant has less than 100% identity to the sequence of the parent albumin.

[0096] In one aspect, the number of alterations in the variants of the invention is 1 to 20, *e.g.,* 1 to 10 and 1 to 5, such as 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 alterations relative to SEQ ID NO: 2 or relative to the sequence of the parent albumin.

[0097] The one or more (several) alterations in Domain I may be selected from positions corresponding to positions from 78 to 88 (i.e. 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88) and/or from 105 to 120 (*i.e.* 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120) of HSA (SEQ ID NO: 2). In HSA positions 78 to 88 form a loop and positions 105 to 120 form a loop. Therefore, positions in equivalent loops of other albumins are also included in the invention. Preferred residues are residues 81 to 85, particularly 82 and 83, and residues 110 to 114, particularly 111 and 112.

[0098] At position 82 of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof), it is preferred that the alteration is a substitution, such as from the native amino acid to A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y, more preferred to Q, D or A, even more preferred to D or A and most preferred to A. In SEQ ID NO: 2 the native amino acid at position 82 is glutamic acid, therefore a substitution to glutamic acid is not preferred.

[0099] At position 83 of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof), it is preferred that the alteration is a substitution, such as from the native amino acid to A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y, more preferred to N, K or S, even more preferred to N or K and most preferred to N. In SEQ ID NO: 2 the native amino acid at position 82 is threonine, therefore a substitution to threonine is not preferred.

[0100] At position 111 of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof), it is preferred that the alteration is a substitution, such as from the native amino acid to A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y, more preferred to N, E, Q, D, G or H, even more preferred to E or Q and most preferred to E. In SEQ ID NO: 2 the native amino acid at position 111 is asparagine, therefore a substitution to asparagine is not preferred.

[0101] At position 112 of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof), it is preferred that the alteration is a substitution, such as from the native amino acid to A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y, more preferred to F, Y or W, even more preferred to F or Y and most preferred to F. In SEQ ID NO: 2 the native amino acid at position 112 is leucine, therefore a substitution to leucine is not preferred.

[0102] At position 573 of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof), it is preferred that the alteration is a substitution, such as from the native amino acid to A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y, more preferred to P, Y, W, H, F, T, I or V, even more preferred to P, Y or W and most preferred to P. In SEQ ID NO: 2 the native amino acid at position 573 is lysine, therefore a substitution to lysine is not preferred.

[0103] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 82 and 83; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0104] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 82 and 111; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0105] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 82 and 112; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0106] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 82 and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an

albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0107] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 83 and 111; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0108] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 83 and 112; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0109] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 83 and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0110] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 111 and 112; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0111] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 111 and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0112] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 112 and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0113] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 82, 83, and 111; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0114] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 82, 83, 112; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0115] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 82, 83, and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0116] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 82, 111, and 112; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0117] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 82, 111, and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0118] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 82, 112, and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0119] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 83, 111, and 112; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0120] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 83, 111, and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0121] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 83, 112, and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0122] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 111, 112, and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0123] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 82, 83, 111, and 112; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0124] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 82, 83, 111, and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0125] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 82, 83, 112, and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0126] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 82, 111, 112, and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0127] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 83, 111, 112, and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0128] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 82, 83, 111, 112, and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0129] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 425 and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0130] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 505 and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0131] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 527 and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0132] An albumin variant may comprise alterations, *e.g.* substitutions, at positions 534 and 573; of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof) of an albumin, variant or fragment thereof, especially SEQ ID NO: 2.

[0133] Particularly preferred albumin variants comprise substitutions T83N/N111E (*e.g.* SEQ ID NO: 32); T83N/N111E/K573P (*e.g.* SEQ ID NO: 33); T83N/K573P (*e.g.* SEQ ID NO: 34); T83K/K573P (*e.g.* SEQ ID NO: 38); E82A/K573P (*e.g.* SEQ ID NO: 39); L112F/K573P (*e.g.* SEQ ID NO: 40); E82D/K573P (*e.g.* SEQ ID NO: 43); P110G/K573P (*e.g.* SEQ ID NO: 44); N111D/K573P (*e.g.* SEQ ID NO: 60); N111G/K573P (*e.g.* SEQ ID NO: 61); N111H/K573P (*e.g.* SEQ ID NO: 62); E425A/K573P (*e.g.* SEQ ID NO: 64); E505Q/K573P (*e.g.* SEQ ID NO: 65); T527M/K573P (*e.g.* SEQ ID NO: 66); N111E/K573P (*e.g.* SEQ ID NO: 68); K534V/K573P (*e.g.* SEQ ID NO: 73); N111Q/K573P (*e.g.* SEQ ID NO: 74) which are described with reference to HSA (SEQ ID NO: 2). Other preferred albumin variants comprise equivalent substitutions in albumins other than HSA (SEQ ID NO: 2).

[0134] Also, an albumin variant according to the invention may comprise one or more (several) alterations at positions selected from 78 to 88 (78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91) and/or 105 to 120 (105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120) and/or 425, 505, 510, 512, 524, 527, 531, 534, 569, 575 of HSA (SEQ ID NO: 2) or equivalent positions of other albumins. Preferred alterations are substitutions such as those described for these positions in the first aspect of the invention. Particularly preferred substitutions include D108A (SEQ ID NO: 59); D108E (*e.g.* SEQ ID NO: 70); N109K (*e.g.* SEQ ID NO: 69); P110G (*e.g.* SEQ ID NO: 42); N111D (*e.g.* SEQ ID NO: 46); N111E (*e.g.* SEQ ID NO: 67); N111G (*e.g.* SEQ ID NO: 48); N111H (*e.g.* SEQ ID NO: 49); N111K (*e.g.* SEQ ID NO: 54); L112F (*e.g.* SEQ ID NO: 37); E425A (*e.g.* SEQ ID NO: 63); E425K (*e.g.* SEQ ID NO: 55); E505Q (*e.g.* SEQ ID NO: 45); H510D (*e.g.* SEQ ID NO: 57); D512E (*e.g.* SEQ ID NO: 50); K524A (*e.g.* SEQ ID NO: 51); T527A (*e.g.* SEQ ID NO: 52); T527M (*e.g.* SEQ ID NO: 47); E531 H (*e.g.* SEQ ID NO: 53); K534V (*e.g.* SEQ ID NO: 56); A569S (*e.g.* SEQ ID NO: 58); L575F (*e.g.* SEQ ID NO: 72); E82A (*e.g.* SEQ ID NO: 36); E82D (*e.g.* SEQ ID NO: 41); T83K (*e.g.* SEQ ID NO: 35); T83N (*e.g.* SEQ ID NO: 71) which are described with reference to HSA (SEQ ID NO: 2). Other preferred albumin variants comprising one or more (several) alterations may comprise equivalent substitutions in albumins other than HSA (SEQ ID NO: 2).

[0135] It is preferred that the variant albumin, a fragment thereof or fusion polypeptide comprising the variant albumin or fragment thereof has altered binding affinity to FcRn and/or an altered plasma half-life compared with the corresponding parent or reference albumin, fragment thereof, or fusion polypeptide comprising the variant albumin or fragment thereof and/or an altered binding affinity to FcRn.

[0136] In a particularly preferred embodiment the parent or reference albumin is HSA (SEQ ID NO: 2) and the variant albumin, a fragment thereof or fusion polypeptide comprising the variant albumin or fragment thereof has altered binding affinity to FcRn and/or an altered plasma half-life compared with the HSA, the corresponding fragment or fusion polypeptide comprising HSA or fragment thereof and/or an altered binding affinity to FcRn.

[0137] The correlation between binding of albumin to its receptor and plasma half-life has been realized by the present inventors based on the natural occurring allele of HSA D494N. The inventors have previously analyzed this allele and found that it has a lower affinity to its receptor FcRn than the affinity of WT HSA to FcRn.

[0138] Further, it has been disclosed that a transgenic mouse having the natural mouse FcRn replaced with human FcRn has a higher serum albumin level than normal mouse (J Exp Med. (2003) 197(3):315-22). The inventors have previously discovered that human FcRn has a higher affinity to mouse serum albumin than mouse FcRn has to mouse serum albumin and, therefore, the observed increase in serum albumin in the transgenic mice corresponds with a higher affinity between serum albumin and its receptor, confirming the correlation between albumin binding to FcRn and plasma half-life. In addition, variants of albumin that have little or no binding to FcRn have been shown to have reduced half-life in a mouse model, Kenanova et al (2009) J. Nucl. Med.; 50 (Supplement 2):1582).

[0139] One way to determine whether the affinity of a variant albumin to FcRn is higher or lower than the parent or reference albumin is to use the Surface Plasmon Resonance assay (SPR) as described below. The skilled person will understand that other methods might be useful to determine whether the affinity of a variant albumin to FcRn is higher or lower than the affinity of the parent or reference albumin to FcRn, *e.g.*, determination and comparison of the binding constants KD. The binding affinity (KD) between a first molecule (*e.g.* ligand) and a second molecule (*e.g.* receptor) is a function of the kinetic constants for association (on rate, k_a) and dissociation (off-rate, k_d) according to KD= k_d/k_a. Thus, according to the invention variant albumins having a KD that is lower than the KD for natural HSA is considered to have a higher plasma half-life than HSA and variant albumins having a KD that is higher than the KD for natural HSA is considered to have a lower plasma half-life than HSA.

[0140] In an embodiment of the invention, the variants of albumin or fragments thereof, or fusion polypeptides comprising variant albumin or a fragment thereof according to the invention have a plasma half-life that is longer than the plasma half-life of the parent or reference albumin fragment thereof or fusion polypeptide comprising the parent or reference albumin or a fragment thereof and/or an stronger binding affinity to FcRn.

[0141] In a further embodiment the variants of albumin or fragments thereof, or fusion polypeptides comprising variant albumin or fragments thereof according to the invention have a plasma half-life that is shorter than the plasma half-life of the parent or reference albumin fragment thereof or fusion polypeptide comprising the parent or reference albumin or a fragment thereof and/or an weaker binding affinity to FcRn.

[0142] In addition to alterations at positions in Domains I (such as within loop 78 to 88 and/or within loop 105 to 120 as described herein) and III (or equivalent position of other albumins or variants of fragments thereof) the variant albumin or fragments thereof, or fusion polypeptides comprising variant albumin or fragments thereof according to the invention may contain additional substitutions, deletions or insertions in other positions of the molecules. Such additional substitutions, deletions or insertions may be useful in order to alter other properties of the molecules such as but not limited to altered glycosylation; introduction of reactive groups of the surface such a thiol groups, removing/generating a carbamoylation site; etc.

[0143] Residues that might be altered in order to provide reactive residues on the surface and which advantageously could be applied to the invention have been disclosed in WO2010/092135. Particular preferred residues include the positions corresponding to positions in SEQ ID NO: 2.

[0144] As examples of alterations that can be made in SEQ ID NO: 2 or in corresponding positions in other albumins in order to provide a reactive thiol group on the surface includes alterations corresponding to following alterations in SEQ ID NO: 2: L585C, D1C, A2C, D562C, A364C, A504C, E505C, T79C, E86C, D129C, D549C, A581C, D121C, E82C, S270C, A578C, L595LC, D1DC, A2AC, D562DC, A364AC, A504AC, E505EC, T79TC, E86EC, D129DC, D549DC, A581AC, A581AC, D121DC, E82EC, S270SC, S579AC, C360*, C316*, C75*, C168*, C558*, C361*, C91*, C124*, C169* and C567*. Alternatively a cysteine residue may be added to the N or C terminal of albumin. The term 'reactive thiol' means and/or includes a thiol group provided by a Cys which is not disulphide bonded to a Cysteine and/or which is sterically available for binding to a partner such as a conjugation partner.

Fusion polypeptides

[0145] A second aspect of the invention relates to fusion polypeptides. Therefore, the variants of albumin or fragments thereof according to the invention may be fused with a non-albumin polypeptide fusion partner. The fusion partner may in principle be any polypeptide but generally it is preferred that the fusion partner is a polypeptide having therapeutic, prophylactic (including vaccine), diagnostic, imaging or other beneficial properties. Such properties may be referred to as 'pharmaceutically beneficial properties'. Fusion polypeptides comprising albumin or fragments thereof are known in the art. It has been found that such fusion polypeptides comprising albumin or a fragment thereof and a fusion partner polypeptide have a longer plasma half-life compared to the unfused fusion partner polypeptide alone. According to the invention it is possible to alter the plasma half-life of the fusion polypeptides according to the invention compared to the corresponding fusion polypeptides of the prior art. 'Alter' includes both increasing the plasma

half-life and decreasing the plasma half-life. Increasing the plasma half-life is preferred. The invention allows tailoring of half-life to a term desired.

[0146] One or more (several) therapeutic, prophylactic (including vaccine), diagnostic, imaging or other beneficial may be fused to the N-terminus, the C-terminus of albumin, inserted into a loop in the albumin structure or any combination thereof. It may or it may not comprise linker sequences separating the various components of the fusion polypeptide.

[0147] Teachings relating to fusions of albumin or a fragment thereof are known in the art and the skilled person will appreciate that such teachings can also be applied to the invention. WO 2001/79271A (particularly page 9 and/or Table 1), WO 2003/59934 (particularly Table 1), WO03/060071 (particularly Table 1) and WO01/079480 (particularly Table 1) also contain examples of therapeutic, prophylactic (including vaccine), diagnostic, imaging or other beneficial polypeptides that may be fused to albumin or fragments thereof, and these examples apply also to the invention.

[0148] Further preferences for the second aspect of the invention include those of the first aspect of the invention and those provided below the twelfth aspect of the invention. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

Polynucleotides

[0149] A third aspect of the invention relates to isolated polynucleotides that encode any of the variants or fusion polypeptides of the invention. The polynucleotide may be an isolated polynucleotide. The polynucleotide may be comprised in a vector (such as a plasmid) and/or in a host cell.

[0150] Further preferences for the third aspect of the invention include those of the first aspect of the invention and those provided below the twelfth aspect of the invention. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

Nucleic Acid Constructs

[0151] A fourth aspect of the invention relates to nucleic acid constructs comprising a polynucleotide encoding a variant or fusion polypeptide of the invention operably linked to one or more (several) control sequences that direct the expression of the coding sequence in a suitable host cell under conditions compatible with the control sequences.

[0152] A polynucleotide may be manipulated in a variety of ways to provide for expression of a variant. Manipulation of the polynucleotide prior to its insertion into a vector may be desirable or necessary depending on the expression vector. The techniques for modifying polynucleotides utilizing recombinant DNA methods are well known in the art.

[0153] The control sequence may be a promoter sequence, which is recognized by a host cell for expression of the polynucleotide. The promoter sequence contains transcriptional control sequences that mediate the expression of the variant. The promoter may be any nucleic acid sequence that shows transcriptional activity in the host cell including mutant, truncated, and hybrid promoters, and may be obtained from genes encoding extracellular or intracellular polypeptides either homologous or heterologous to the host cell.

[0154] In a yeast host, useful promoters are obtained from the genes for *Saccharomyces cerevisiae* enolase (ENO-1), *Saccharomyces cerevisiae* protease A (PRA1), *Saccharomyces cerevisiae* protease B (PRB1), *Saccharomyces cerevisiae* translation elongation factor (TEF1), *Saccharomyces cerevisiae* translation elongation factor (TEF2), *Saccharomyces cerevisiae* galactokinase (GAL1), *Saccharomyces cerevisiae* alcohol dehydrogenase/glyceraldehyde-3-phosphate dehydrogenase (ADH1, ADH2/GAP), *Saccharomyces cerevisiae* triose phosphate isomerase (TPI), *Saccharomyces cerevisiae* metallothionein (CUP1), and *Saccharomyces cerevisiae* 3-phosphoglycerate kinase. Other useful promoters for yeast host cells are described by Romanos et al., 1992, Yeast 8: 423-488.

[0155] The skilled person knows useful promoters for use in rice and mammalian cells, such as CHO or HEK. In a rice host, useful promoters are obtained from cauliflower mosaic virus 35S RNA gene (CaMV35S), maize alcohol dehydrogenase (Adh1) and alpha Amy3.

[0156] In a mammalian host cell, such as CHO or HEK, useful promoters are obtained from Cytomegalovirus (CMV) and CAG hybrid promoter (hybrid of CMV early enhancer element and chicken beta-actin promoter), Simian vacuolating virus 40 (SV40).

[0157] The control sequence may also be a suitable transcription terminator sequence, which is recognized by a host cell to terminate transcription. The terminator sequence is operably linked to the 3'-terminus of the polynucleotide encoding the variant. Any terminator that is functional in the host cell may be used.

[0158] Preferred terminators for yeast host cells are obtained from the genes for *Saccharomyces cerevisiae* enolase, *Saccharomyces cerevisiae* cytochrome C (CYC1), *Saccharomyces cerevisiae* alcohol dehydrogenase (ADH1) and *Saccharomyces cerevisiae* glyceraldehyde-3-phosphate dehydrogenase. Other useful terminators for yeast host cells are described by Romanos *et al.,* 1992, *supra*. The skilled person knows useful terminators for use in rice and mammalian cells, such as CHO or HEK. For example, in a rice host, preferred terminators are obtained from Agrobacterium tumefaciens nopaline synthase (Nos) and cauliflower mosaic virus 35S RNA gene (CaMV35S)

[0159] The control sequence may also be a suitable leader sequence, a nontranslated region of

an mRNA that is important for translation by the host cell. The leader sequence is operably linked to the 5'-terminus of the polynucleotide encoding the variant. Any leader sequence that is functional in the host cell may be used.

[0160] Suitable leaders for yeast host cells are obtained from the genes for *Saccharomyces cerevisiae* enolase (ENO-1), *Saccharomyces cerevisiae* 3-phosphoglycerate kinase, *Saccharomyces cerevisiae* alpha-factor, and *Saccharomyces cerevisiae* alcohol dehydrogenase/glyceraldehyde-3-phosphate dehydrogenase (ADH2/GAP).

[0161] The control sequence may also be a polyadenylation sequence, a sequence operably linked to the 3'-terminus of the variant-encoding sequence and, when transcribed, is recognized by the host cell as a signal to add polyadenosine residues to transcribed mRNA. Any polyadenylation sequence that is functional in the host cell may be used.

[0162] Useful polyadenylation sequences for yeast host cells are described by Guo and Sherman, 1995, Mol. Cellular Biol. 15: 5983-5990.

[0163] The control sequence may also be a signal peptide coding region that encodes a signal peptide linked to the N-terminus of a variant and directs the variant into the cell's secretory pathway. The 5'-end of the coding sequence of the polynucleotide may inherently contain a signal peptide coding region naturally linked in translation reading frame with the segment of the coding region that encodes the variant. Alternatively, the 5'-end of the coding sequence may contain a signal peptide coding region that is foreign to the coding sequence. The foreign signal peptide coding region may be required where the coding sequence does not naturally contain a signal peptide coding region. Alternatively, the foreign signal peptide coding region may simply replace the natural signal peptide coding region in order to enhance secretion of the variant. However, any signal peptide coding region that directs the expressed variant into the secretory pathway of a host cell may be used.

[0164] Useful signal peptides for yeast host cells are obtained from the genes for *Saccharomyces cerevisiae* alpha-factor and *Saccharomyces cerevisiae* invertase. Other useful signal peptide coding sequences are described by Romanos *et al.,* 1992, *supra.* The skilled person knows useful signal peptides for use in rice and mammalian cells, such as CHO or HEK.

[0165] Where both signal peptide and propeptide regions are present at the N-terminus of a variant, the propeptide region is positioned next to the N-terminus of the variant and the signal peptide region is positioned next to the N-terminus of the propeptide region.

[0166] Further preferences for the fourth aspect of the invention include those of the first aspect of the invention and those provided below the twelfth aspect of the invention. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

Preparation of Variants

[0167] A fifth aspect of the invention relates to a method for preparing or obtaining a variant albumin or fragment thereof, or fusion polypeptides comprising the variant albumin or fragments thereof, or associates of variant albumin or fragment thereof comprising:

1. (a) introducing into a parent albumin or fragments thereof, or fusion polypeptides comprising the parent albumin or fragments thereof the alterations as described for the first aspect of the invention; and
2. (b) recovering the variant albumin or fragment thereof, or fusion polypeptides comprising the variant albumin or fragment thereof.

[0168] Preferred alterations are as described in relation to the first aspect of the invention. The resultant variant albumin or fragment thereof may have altered FcRn-binding affinity compared to the FcRn-binding affinity of a reference such as a parent albumin or fragment which does not comprise the alterations. More preferably, the resultant variant albumin or fragment thereof has a stronger FcRn-binding affinity.

[0169] The invention includes a method for preparing a polypeptide which is a variant of albumin, fragment thereof or fusion polypeptide comprising said variant albumin or fragment thereof having a binding affinity to FcRn which is altered compared to the binding affinity of a reference albumin, fragment or fusion thereof to FcRn, comprising:

1. (a) providing a nucleic acid encoding a parent albumin such as an albumin having at least 60% sequence identity to SEQ ID NO: 2;
2. (b) modifying the sequence of step (a), to encode a polypeptide which is a variant albumin, fragment thereof or fusion polypeptide comprising said variant albumin or fragment thereof comprising:
    1. (i) alterations at positions corresponding to one or more (several) positions in Domain I of the parent albumin and one or more (several) positions in Domain III (Domain 3), or
    2. (ii) alterations at positions corresponding to one of more (several) of any of positions 78 to 120 of Domain I of SEQ ID NO: 2 or at positions corresponding to one or more (several) of any of positions 425, 505, 510, 512, 524, 527, 531, 534, 569, 573, 575 of Domain III of SEQ ID NO: 2;
3. (c) optionally, introducing the modified sequence of step (b) in a suitable host cell;
4. (d) optionally, growing the cells in a suitable growth medium under condition leading to expression of the polypeptide; and
5. (e) optionally, recovering the polypeptide from the growth medium;

wherein the polypeptide has an altered binding affinity to FcRn and/or an altered plasma half-life compared with the half-life of a parent albumin, reference albumin, fragment thereof or fusion polypeptide comprising said parent albumin, reference albumin or fragment or fusion thereof.

[0170] It is preferred that the parent albumin and/or the variant albumin comprises or consists of:

1. (a) a polypeptide having at least 80% sequence identity to the mature polypeptide of SEQ ID NO: 2;
2. (b) a polypeptide encoded by a polynucleotide that hybridizes under low stringency conditions with (i) the mature polypeptide coding sequence of SEQ ID NO: 1, or (ii) the full-length complement of (i);
3. (c) a polypeptide encoded by a polynucleotide having at least 60% identity to the mature polypeptide coding sequence of SEQ ID NO: 1; and/or
4. (d) a fragment of the mature polypeptide of SEQ ID NO: 2.

[0171] The variants can be prepared by those skilled persons using any mutagenesis procedure known in the art, such as site-directed mutagenesis, synthetic gene construction, semi-synthetic gene construction, random mutagenesis, shuffling, etc.

[0172] Site-directed mutagenesis is a technique in which one or more (several) mutations (alterations) are created at one or more (several) defined sites in a polynucleotide encoding the parent.

[0173] Site-directed mutagenesis can be accomplished *in vitro* by PCR involving the use of oligonucleotide primers containing the desired mutation. Site-directed mutagenesis can also be performed *in vitro* by cassette mutagenesis involving the cleavage by a restriction enzyme at a site in the plasmid comprising a polynucleotide encoding the parent and subsequent ligation of an oligonucleotide containing the mutation in the polynucleotide. Usually the restriction enzyme that digests at the plasmid and the oligonucleotide is the same, permitting ligation of the plasmid and insert to one another. See, *e.g.*, Scherer and Davis, 1979, Proc. Natl. Acad. Sci. USA 76: 4949-4955; and Barton et al., 1990, Nucleic Acids Res. 18: 7349-4966.

[0174] Site-directed mutagenesis can also be accomplished *in vivo* by methods known in the art. See, *e.g.*, U.S. Patent Application Publication NO: 2004/0171154; Storici et al., 2001, Nature Biotechnol. 19: 773-776; Kren et al., 1998, Nat. Med. 4: 285-290; and Calissano and Macino, 1996, Fungal Genet. Newslett. 43: 15-16.

[0175] Any site-directed mutagenesis procedure can be used in the invention. There are many commercial kits available that can be used to prepare variants.

[0176] Synthetic gene construction entails *in vitro* synthesis of a designed polynucleotide molecule to encode a polypeptide of interest. Gene synthesis can be performed utilizing a number of techniques, such as the multiplex microchip-based technology described by Tian et al. (2004, Nature 432: 1050-1054) and similar technologies wherein oligonucleotides are synthesized and assembled upon photo-programmable microfluidic chips.

[0177] Single or multiple amino acid substitutions, deletions, and/or insertions can be made and

tested using known methods of mutagenesis, recombination, and/or shuffling, followed by a relevant screening procedure, such as those disclosed by Reidhaar-Olson and Sauer, 1988, Science 241: 53-57; Bowie and Sauer, 1989, Proc. Natl. Acad. Sci. USA 86: 2152-2156; WO 95/17413; or WO 95/22625. Other methods that can be used include error-prone PCR, phage display (*e.g.*, Lowman et al., 1991, Biochemistry 30: 10832-10837; U.S. Patent NO: 5,223,409; WO 92/06204) and region-directed mutagenesis (Derbyshire et al., 1986, Gene 46: 145; Ner et al., 1988, DNA 7: 127).

[0178] Mutagenesis/shuffling methods can be combined with high-throughput, automated screening methods to detect activity of cloned, mutagenized polypeptides expressed by host cells (Ness et al., 1999, Nature Biotechnology 17: 893-896). Mutagenized DNA molecules that encode active polypeptides can be recovered from the host cells and rapidly sequenced using standard methods in the art. These methods allow the rapid determination of the importance of individual amino acid residues in a polypeptide.

[0179] Semi-synthetic gene construction is accomplished by combining aspects of synthetic gene construction, and/or site-directed mutagenesis, and/or random mutagenesis, and/or shuffling. Semi-synthetic construction is typified by a process utilizing polynucleotide fragments that are synthesized, in combination with PCR techniques. Defined regions of genes may thus be synthesized *de novo,* while other regions may be amplified using site-specific mutagenic primers, while yet other regions may be subjected to error-prone PCR or non-error prone PCR amplification. Polynucleotide sub sequences may then be shuffled.

[0180] Further preferences for the fifth aspect of the invention include those of the first aspect of the invention and those provided below the twelfth aspect of the invention. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

Methods of Production

[0181] A sixth aspect of the invention relates to methods of preparation of a variant according to the invention. The variants of the invention can be prepared using techniques well known to the skilled person. One convenient way is by cloning nucleic acid encoding the parent albumin or a fragment thereof or fusion polypeptide comprising albumin or a fragment thereof, modifying said nucleic acid to introduce the desired substitution(s) at positions in Domain I and Domain III of the mature polypeptide of SEQ ID NO: 2 (or equivalent positions in other albumins or fragments thereof), preparing a suitable genetic construct where the modified nucleic acid is placed in operative connection with suitable regulatory genetic elements, such as promoter, terminator, activation sites, ribosome binding sites etc., introducing the genetic construct into a suitable host organism, culturing the transformed host organism under conditions leading to expression of the variant and recovering the variant. All these techniques are known in the art and it is within the skills of the average practitioner to design a suitable method for preparing a particular variant

according to the invention.

[0182] The variant polypeptide of the invention may also be connected to a signal sequence in order to have the variant polypeptide secreted into the growth medium during culturing of the transformed host organism. It is generally advantageous to have the variant polypeptide secreted into the growth medium in order to ease recovery and purification.

[0183] Techniques for preparing variant polypeptides have also been disclosed in WO 2009019314 (included by reference) and these techniques may also be applied to the invention.

[0184] Albumins have been successfully expressed as recombinant proteins in a range of hosts including fungi (including but not limited to *Aspergillus* (WO06066595), *Kluyveromyces* (Fleer 1991, Bio/technology 9, 968-975), *Pichia* (Kobayashi 1998 Therapeutic Apheresis 2, 257-262) and *Saccharomyces* (Sleep 1990, Bio/technology 8, 42-46)), bacteria (Pandjaitab 2000, J. Allergy Clin. Immunol. 105, 279-285)), animals (Barash 1993, Transgenic Research 2, 266-276) and plants (including but not limited to potato and tobacco (Sijmons 1990, Bio/technology 8, 217 and Farran 2002, Transgenic Research 11, 337-346) and rice *e.g. Oryza sativa*) and mammalian cells such as CHO and HEK. The variant polypeptide of the invention is preferably produced recombinantly in a suitable host cell. In principle any host cell capable of producing a polypeptide in suitable amounts may be used and it is within the skills of the average practitioner to select a suitable host cell according to the invention. A preferred host organism is yeast, preferably selected among *Saccharomycacae,* more preferred *Saccharomyces cerevisiae.*

[0185] The variant polypeptides of the invention may be recovered and purified from the growth medium using a combination of known separation techniques such as filtration, centrifugation, chromatography, and affinity separation techniques etc. It is within the skills of the average practitioner to purify the variants of the invention using a particular combination of such known separation steps. As an example of purification techniques that may be applied to the variants of the invention can be mentioned the teaching of WO00/44772.

[0186] The variant polypeptides of the invention may be used for delivering a therapeutically beneficial compound (including prophylactically beneficial compound such as a vaccine) to an animal or a human individual in need thereof. Such therapeutically beneficial compounds include, but are not limited, to labels and readily detectable compounds for use in diagnostics, such as various imaging techniques; pharmaceutical active compounds such as drugs, or specifically binding moieties such as antibodies. The variants of the invention may even be connected to two or more (several) different therapeutically beneficial compounds, e.g., an antibody and a drug, which gives the combined molecule the ability to bind specifically to a desired target and thereby provide a high concentration of the connected drug at that particular target.

[0187] Further preferences for the sixth aspect of the invention include those of the first aspect of the invention and those provided below the twelfth aspect of the invention. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

Conjugates

[0188] A seventh aspect of the invention relates to conjugates (conjugations).Therefore, the variants of albumin or fragments thereof or fusion polypeptides according to the invention may be conjugated to a second molecule ('conjugation partner') using techniques known within the art. The conjugation partner may be a therapeutic, prophylactic (including vaccine), diagnostic, imaging or other beneficial moiety. Said conjugation partner may be a polypeptide or a non-polypeptide chemical. The conjugation partner may be a polypeptide, a chemical (*e.g.* chemically synthesized drug) or a nucleic acid (*e.g.* DNA, RNA, siRNA).

[0189] Said second molecule may comprise a diagnostic or imaging moiety, and in this embodiment the conjugate may be useful as a diagnostic tool such as in imaging; or the second molecule may be a therapeutic or prophylactic (*e.g.* vaccine) compound and in this embodiment the conjugate may be used for therapeutic or prophylactic (*e.g.* vaccination) purposes where the conjugate will have the therapeutic or prophylactic properties of the therapeutic or prophylactic compound as well as the desirable plasma half-life provided by the albumin part of the conjugate. Conjugates of albumin and a therapeutic molecule are known in the art and it has been verified that such conjugates have long plasma half-life compared with the nonconjugated, free therapeutic molecule as such. According to the invention it is possible to alter the binding affinity to FcRn and/or plasma half-life of the conjugate according to the invention compared to the corresponding conjugates of the prior art. 'Alter' includes both increasing the plasma half-life and decreasing the plasma half-life binding affinity to FcRn and/or increasing the binding affinity and decreasing the binding affinity to FcRn. Increasing the plasma half-life and/or binding affinity to FcRn is preferred. The conjugates may conveniently be linked *via a* free thiol group present on the surface of HSA (amino acid residue 34 of mature HSA) using well known chemistry.

[0190] In one particular preferred aspect the variant albumin or fragment thereof is conjugated to a beneficial therapeutic or prophylactic (including vaccine) compound and the conjugate is used for treatment of a condition in a patient in need thereof, which condition is responsive to the particular selected therapeutic compound. Techniques for conjugating such a therapeutically useful compound to the variant albumin or fragment thereof are known in the art. WO 2009/019314 discloses examples of techniques suitable for conjugating a therapeutically useful compound to a polypeptide which techniques can also be applied to the invention. Further WO 2009/019314 discloses examples of compounds and moieties that may be conjugated to substituted transferrin and these examples may also be applied to the invention. The teaching of WO 2009/019314 is included herein by reference.

[0191] HSA contains in its natural form one free thiol group (at Cys34) that conveniently may be used for conjugation. As a particular embodiment within this aspect the variant albumin or fragment thereof may comprise further modifications provided to generate additional free thiol groups on the surface. This has the benefit that the payload of the variant albumin or fragment thereof is increased so that more than one molecule of the therapeutic (e.g. prophylactic) compound can be conjugated to each molecule of variant albumin or fragment thereof, or two or

more (several) different therapeutic compounds may be conjugated to each molecule of variant albumin or fragment thereof, *e.g.*, a compound having targeting properties such as an antibody specific for example a tumor; and a cytotoxic drug conjugated to the variant albumin or fragment thereof thereby creating a highly specific drug against a tumor. Teaching of particular residues that may be modified to provide for further free thiol groups on the surface can be found in copending patent application WO 2010/092135.

[0192] The conjugation partner may alternatively be conjugated to a fusion polypeptide (described herein), resulting in a molecule comprising a fusion partner fused to the albumin as well as a conjugation partner conjugated to the same albumin or even to the fusion partner.

[0193] Further preferences for the seventh aspect of the invention include those of the first aspect of the invention and those provided below the twelfth aspect of the invention. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

Associates

[0194] An eighth aspect of the invention relates to associates. Therefore, the variants of albumin or fragments thereof or fusion polypeptides may further be used in the form of "associates". In this connection the term "associate" is intended to mean a compound comprising a variant of albumin or a fragment thereof and another compound bound or associated to the variant albumin or fragment thereof by non-covalent binding. As an example of such an associate can be mentioned an associate consisting variant albumin and a lipid associated to albumin by a hydrophobic interaction. Such associates are known in the art and they may be prepared using well known techniques. As an example of a preferred associate according to the invention, can be mentioned an associate comprising variant albumin and a taxane, a taxol or taxol derivative (e.g. paclitaxel). Further examples of associates comprise a therapeutic, prophylactic (including vaccine), diagnostic, imaging or other beneficial moiety.

[0195] The half-life of an albumin associate according to the invention may be longer or shorter than the half-life of the 'other compound' alone. The half-life of an albumin associate according to the invention may be longer or shorter than the half-life of the analogous / equivalent albumin associate comprising or consisting of a reference albumin such as native HSA (instead of an albumin variant or derivative according to the invention) and the 'other compound'. Likewise, the binding affinity to FcRn an albumin associate according to the invention may be stronger or weaker than the binding affinity to FcRn of the analogous / equivalent albumin associate comprising or consisting of a reference albumin such as native HSA (instead of an albumin variant or derivative according to the invention) and the 'other compound'. Methods for the preparation of associates are well-known to the skilled person, for example, formulation (by association) of HSA with Lipo-compounds is described in Hussain, R. and Siligardi, G. (2006) International Journal of Peptide Research and Therapeutics, Vol. 12, NO: 3, pp. 311-315.

[0196] Further preferences for the eighth aspect of the invention include those of the first aspect of the invention and those provided below the twelfth aspect of the invention. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

Compositions

[0197] A ninth aspect of the invention relates to compositions. Therefore the invention is also directed to the use of a variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, or a conjugate comprising a variant of albumin or a fragment thereof, or an associate comprising a variant of albumin or a fragment thereof for the manufacture of a pharmaceutical composition, wherein the variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, or a conjugate comprising a variant of albumin or a fragment thereof, or an associate comprising a variant of albumin or a fragment thereof has an altered binding affinity to FcRn and/or an altered plasma half-life compared with HSA or the corresponding fragment thereof or fusion polypeptide comprising HSA or fragment thereof or conjugate comprising HSA.

[0198] In this connection the corresponding fragment of HSA is intended to mean a fragment of HSA that aligns with and has same number of amino acids as the fragment of the variant albumin with which it is compared. Similarly the corresponding fusion polypeptide comprising HSA or conjugate comprising HSA is intended to mean molecules having same size and amino acid sequence as the fusion polypeptide of conjugate comprising variant albumin, with which it is compared.

[0199] The composition may comprise a pharmaceutically acceptable carrier or excipient such as water, polysorbate 80 or those specified in the US Pharmacopoeia for human albumin.

[0200] Further preferences for the ninth aspect of the invention include those of the first aspect of the invention and those provided below the twelfth aspect of the invention. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

Nanoparticles

[0201] A tenth aspect of the invention relates to a nanoparticle comprising a variant, fusion, conjugate, associate, nanoparticle, composition or polynucleotide as disclosed herein.

[0202] Techniques for incorporation of a molecule into nano- or microparticles are known in the art. Preferred methods for preparing nano- or microparticles that may be applied to the albumin,

variant, fragment, fusion, conjugate or associate thereof according to the invention is disclosed in WO 2004/071536 or WO2008/007146 or Oner & Groves (Pharmaceutical Research, Vol 10(9), 1993, pages 1387 to 1388). Preferably the average diameter of a nano-particle is from 5 to 1000 nm, more preferably 5, 10, 20, 30, 40, 50, 80, 100, 130, 150, 200, 300, 400, 500, 600, 700, 800, 900, or 999 to 5, 10, 20, 30, 40, 50, 80, 100, 130, 150, 200, 300, 400, 500, 600, 700, 800, 900, or 1000 nm. An advantage of a microparticle less than 200 nm diameter, and more particularly less than 130 nm, is that it is amenable to sterilization by filtration through a 0.2 μm (micron) filter. Preferably, the average diameter of a micro-particle is from 1000 nm (1 μm (micron)) to 100 μm (micron), more preferably from 1, 2, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 to 1, 2, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 μm (micron).

[0203] Further preferences for the tenth aspect of the invention include those of the first aspect of the invention and those provided below the twelfth aspect of the invention. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

Uses

[0204] An eleventh aspect of the invention relates to use of a variant albumin, fragment, fusion or conjugate thereof or nanoparticle or associate thereof. Use may be, for example, in a method of treatment, prophylaxis, diagnosis or imaging. The variant albumin or fragments thereof or fusion polypeptides comprising variant albumin or fragments thereof according to the invention have the benefit that their binding affinity to FcRn and/or plasma half-life is altered compared to the parent or reference albumin or fragments thereof or fusion polypeptides comprising parent or reference albumin or fragments thereof. This has the advantage that the binding affinity to FcRn and/or plasma half-life of conjugates comprising variant albumin or a fragment thereof or fusion polypeptide comprising variant albumin or a fragment thereof, or an associate comprising variant albumin or a fragment thereof according to the invention can be selected in accordance with the particular therapeutic purpose.

[0205] In some situations, it would be advantageous to use an albumin, variant, fragment, fusion, conjugate or associate or composition thereof having a longer plasma half-life than the reference molecule or composition since this would have the benefit that the administration of the albumin, variant, fragment, fusion, conjugate or associate or composition thereof would be needed less frequently or at a reduced dose (and consequently with fewer side effects) compared to the situation where the reference molecule or composition was used. With respect to the use of a variant, fusion, conjugate, associate, nanoparticle, composition or polynucleotide the albumin moiety may comprise one more alterations as disclosed herein.

[0206] In other situations, it would be advantageous to use an albumin, variant, fragment, fusion, conjugate or associate or composition thereof having a shorter plasma half-life than the reference molecule or composition since this would have the benefit that the administration of the albumin, variant, fragment, fusion, conjugate or associate or composition thereof can be

carried out at a higher dose compared to the situation where the reference molecule or composition was used with the benefit that the administered compound clears from the recipient more quickly than if the reference molecule or composition was used. With respect to the use of a variant, fusion, conjugate, associate, nanoparticle, composition or polynucleotide the albumin moiety may comprise one more alterations as disclosed herein.

[0207] For example, for a conjugate, associate or fusion polypeptide used for imaging purposes in animals or human beings, where the imaging moiety has a very short half-life and a conjugate or a fusion polypeptide comprising HSA has a plasma half-life that is far longer than needed for the imaging purposes it would be advantageous to use a variant albumin or fragment thereof of the invention having a shorter plasma half-life than the parent or reference albumin or fragment thereof, to provide conjugates of fusion polypeptides having a plasma half-life that is sufficiently long for the imaging purpose but sufficiently short to be cleared form the body of the particular patient on which it is applied.

[0208] In another example for a conjugate, an associate or fusion polypeptide comprising a therapeutic compound effective to treat or alleviate a particular condition in a patient in need for such a treatment it would be advantageous to use the variant albumin or fragment thereof having a longer plasma half-life than the parent or reference albumin or fragment thereof, to provide associates or conjugates or fusion polypeptides having longer plasma half-lives which would have the benefit that the administration of the associate or conjugate or fusion polypeptide of the invention would be needed less frequently or reduced dose with less side effects compared to the situation where the parent or reference albumin or associates thereof or fragment thereof was used. For example, the invention provides a method of treating a proliferative disease in an individual, comprising administering the individual an effective amount of an associate according to the invention in which the associate comprises a taxane, a taxol or taxol derivative (*e.g.* paclitaxel).

[0209] In a further aspect the invention relates to compositions comprising the variant albumin, associates thereof or fragment thereof, variant albumin fragment or associates thereof or fusion polypeptide comprising variant albumin or fragment thereof according to the invention. The compositions are preferably pharmaceutical compositions. The composition may be prepared using techniques known in the area such as disclosed in recognized handbooks within the pharmaceutical field. Since the albumin, variant, fragment, fusion, conjugate or associate thereof has a binding affinity to FcRn and/or plasma half-life which is modulated (*i.e.* stronger or weaker and/or longer or shorter) than that of a reference molecule, the composition also has a binding affinity to FcRn and/or modulated (*i.e.* altered) plasma half-life relative to an equivalent composition comprising the reference molecule in place of the albumin, variant, fragment, fusion, conjugate or associate thereof as described herein. The composition may be a vaccine. The polypeptide according to the invention may be an active pharmaceutical or an excipient. Optionally, the composition is provided in unit dosage form.

[0210] Preferably the albumin, variant, fragment, fusion, conjugate or associate thereof has a plasma half-life that is longer than the plasma half-life of the reference molecule *e.g.* the same composition except that the albumin component (*e.g.* albumin, variant, fragment, fusion,

conjugate or associate) is wild-type albumin (*e.g.* HSA) or a variant, fragment, fusion, conjugate or associate.

[0211] In a particular embodiment the compositions comprise a variant albumin or a fragment thereof according to the invention and a compound comprising a pharmaceutically beneficial moiety and an albumin binding domain (ABD). According to the invention ABD means a site, moiety or domain capable of binding to circulating albumin *in vivo* and thereby conferring transport in the circulation of the ABD and any compound or moiety bound to said ABD. ABD's are known in the art and have been shown to bind very tight to albumin so a compound comprising an ABD bound to albumin will to a certain extent behave as a single molecule. The inventors have realized by using the variant albumin or fragment thereof according to the invention together with a compound comprising a pharmaceutically beneficial moiety and an ABD makes it possible to alter the binding affinity to FcRn and/or plasma half-life of the compound comprising a pharmaceutically beneficial moiety and an ABD compared to the situation where said compound were injected as such in a patient having need thereof or administered in a formulation comprising natural albumin or a fragment thereof.

[0212] The variant albumin or fragments thereof, conjugates comprising variant albumin or a fragment thereof or fusion polypeptide comprising variant albumin or a fragment thereof, or an associate comprising variant albumin or a fragment thereof according to the invention may also be incorporated into nano- or microparticles using techniques well known within the art. A preferred method for preparing nano- or microparticles that may be applied to the variant albumins or fragments thereof according to the invention is disclosed in WO 2004/071536 or WO2008/007146 or Oner & Groves (Pharmaceutical Research, Vol 10(9), 1993, pages 1387 to 1388).

[0213] Further preferences for the eleventh aspect of the invention include those of the first aspect of the invention and those provided below the twelfth aspect of the invention. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

Method for altering the FcRn-binding affinity or half-life of a molecule

[0214] A twelfth aspect of the invention provides a method for altering the FcRn-binding affinity or half-life of a molecule comprising:

1. (a) where the molecule is a polypeptide, fusing or conjugating the molecule to a polypeptide disclosed herein or to a conjugate disclosed herein; associating the molecule to a polypeptide disclosed herein or to a conjugate disclosed herein; incorporating the molecule in a nanoparticle disclosed herein or a composition disclosed herein;
2. (b) where the molecule is not a polypeptide, conjugating the molecule to a polypeptide disclosed herein or to a conjugate disclosed herein; associating the molecule to a polypeptide disclosed herein or to a conjugate a disclosed herein; incorporating the

molecule in a nanoparticle disclosed herein or a composition disclosed herein.

[0215] Examples of 'molecule' include those useful in therapy, prophylaxis (including those used in vaccines either as an active pharmaceutical ingredient or as an excipient), imaging and diagnosis, such as those described herein.

[0216] Further preferences for the twelfth aspect of the invention include those of the first aspect of the invention and those provided below this twelfth aspect of the invention. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

[0217] Preferences for all aspects of the invention are provided below. The skilled person understands that any aspect of the invention may be combined with another aspect or aspects of the invention and/or with one or more (several) of the preferences for the aspects of the invention and/or other disclosures made herein.

[0218] The variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition may have a plasma half-life that is either longer or shorter, preferably longer, than the plasma half-life than a corresponding albumin or a fragment thereof or fusion polypeptides comprising albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition or a binding to FcRn that is stronger or weaker, preferably weaker. Preferably the variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition has a plasma half-life that is longer than the plasma half-life of HSA or the corresponding albumin or a fragment thereof or fusion polypeptides comprising albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition.

[0219] Alternatively, this may be expressed as the variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition having a KD to FcRn (*e.g.* shFcRn) that is lower than the corresponding KD for HSA to FcRn or the corresponding fragment thereof or fusion polypeptide comprising HSA or fragment thereof. Preferably, the KD for the variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition is less than 0.9X KD for HSA to FcRn, more preferred less than 0.5X KD for HSA to FcRn, more preferred less than 0.1X KD for HSA to FcRn, even more preferred less than 0.05X KD for HSA to FcRn, even more preferred less than 0.02X KD for HSA to FcRn and most preferred less than 0.01X KD for HSA to FcRn (where X means 'multiplied by'). The KD of the variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition may be between the KD of WT albumin (*e.g.* SEQ ID No. 2) for FcRn and the KD of HSA K573P (SEQ ID No. 3) for FcRn. Such KDs represent

binding affinities that are higher than the binding affinity between HSA and FcRn. A higher binding affinity indicates a longer half-life, for example plasma half-life.

[0220] Alternatively, the variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition has a plasma half-life that is shorter than the plasma half-life of HSA or the corresponding fragment thereof or fusion polypeptide comprising HSA or fragment thereof.

[0221] This may be expressed as the variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition having a KD to FcRn that is higher than the corresponding KD for HSA to FcRn or the corresponding of albumin or a fragment thereof or fusion polypeptides comprising albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition. Preferably, the KD for the variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, or a conjugate comprising a variant of albumin or a fragment thereof is more than 2X KD for HSA to FcRn, more preferred more than 5X KD for HSA to FcRn, more preferred more than 10X KD for HSA to FcRn, even more preferred more than 25X KD for HSA to FcRn, even most preferred more than 50X KD for HSA to FcRn. The variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition may be a null binder to FcRn.

[0222] The variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, or a conjugate or nanoparticle or associate or composition comprising a variant of albumin or a fragment thereof is preferably the variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, or a conjugate or nanoparticle or associate or composition comprising a variant of albumin or a fragment thereof according to the invention. A lower binding affinity indicates a shorter half-life, for example plasma half-life.

[0223] One advantage of the invention is that it allows the half-life of albumin, a variant of albumin or a fragment thereof or fusion polypeptides comprising variant albumin or fragments thereof, fragment thereof, conjugate, nanoparticle, associate or composition to be tailored in order to achieve a binding affinity or half-life which meets the needs of the user.

[0224] When determining and/or comparing KD, one or more (and preferably all) of the following parameters may be used:

Instrument: Biacore 3000 instrument (GE Healthcare)

Flow cell: CM5 sensor chip

FcRn: human FcRn, preferably soluble human FcRn, optionally coupled to a tag such as GST or His, most preferably His such as 6 histidines at the C-terminus of the beta-2-microglobulin (SEQ ID NO: 31).

Quantity of FcRn: 1200-2500 RU

Coupling chemistry: amine coupling chemistry (*e.g.* as described in the protocol provided by the manufacturer of the instrument).

Coupling method: The coupling may be performed by injecting 20 µg/ml of the protein in 10 mM sodium acetate pH 5.0 (GE Healthcare). Phosphate buffer (67 mM phosphate buffer, 0.15 M NaCl, 0.005% Tween 20) at pH 5.5 may be used as running buffer and dilution buffer. Regeneration of the surfaces may be done using injections of HBS-EP buffer (0.01 M HEPES, 0.15 M NaCl, 3 mM EDTA, 0.005% surfactant P20) at pH 7.4 (Biacore AB).

Quantity of injection of test molecule (*e.g.* HSA or variant) 20-0.032µM

Flow rate of injection: constant, *e.g.* 30 µl/ml

Temperature of injection: 25 °C

Data evaluation software: BIAevaluation 4.1 software (BIAcore AB).

The preferred method for determining KD is provided in Example 2.

[0225] The invention discloses that one or more (several) positions in Domain I in combination with one or more (several) positions in Domain III in SEQ ID NO: 2 (and therefore equivalent positions in albumins and fragments from human serum and albumin and non-human serum albumins) may be altered in order to modulate (increase of decrease) the binding affinity and/or half-life e.g. plasma half-life of an albumin, fragment, fusion, conjugate, associate, nanoparticle or composition. An alteration may be a substitution, insertion or deletion. Substitution is preferred.

[0226] A substitution or insertion may or may not comprise introduction of a conserved amino acid, i.e. conserved in relation to the amino acid at the position of interest. Examples of conserved amino acids are shown by the groups of Fig. 3: aliphatic, aromatic, hydrophobic, charged, polar, positive, tiny and small.

[0227] At position 82 of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof), it is preferred that the alteration is a substitution, such as from the native amino acid to A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y, more preferred to Q, D, A, even more preferred to D, A and most preferred to A. In SEQ ID NO: 2 the native amino acid at position 82 is glutamic acid, therefore a substitution to glutamic acid is not preferred.

[0228] At position 83 of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof), it is preferred that the alteration is a substitution, such as from the native amino acid to A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y, more preferred to N, K, S, even more preferred to N, K and most preferred to N. In SEQ ID NO: 2 the native amino acid at position 83 is threonine, therefore a substitution to threonine is not preferred.

[0229] At position 111 of SEQ ID NO: 2 (or equivalent position of other albumins or variants of

fragments thereof), it is preferred that the alteration is a substitution, such as from the native amino acid to A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y, more preferred to N, E, Q, D, G, H, even more preferred to E, Q and most preferred to E. In SEQ ID NO: 2 the native amino acid at position 111 is asparagine, therefore a substitution to asparagine is not preferred.

[0230] At position 112 of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof), it is preferred that the alteration is a substitution, such as from the native amino acid to A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y, more preferred to F, Y, W, even more preferred to F, Y and most preferred to F. In SEQ ID NO: 2 the native amino acid at position 112 is leucine, therefore a substitution to leucine is not preferred.

[0231] At position 573 of SEQ ID NO: 2 (or equivalent position of other albumins or variants of fragments thereof), it is preferred that the alteration is a substitution, such as from the native amino acid to A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y, more preferred to P, Y, W, H, F, T, I or V, even more preferred to P, Y or W and most preferred to P. In SEQ ID NO: 2 the native amino acid at position 573 is lysine, therefore a substitution to lysine is not preferred.

[0232] It is preferred that the alteration at position 82 is conserved relative to A. It is preferred that the alteration at position 83 is conserved relative to N. It is preferred that the alteration at position 111 is conserved relative to E. It is preferred that the alteration at position 112 is conserved relative to F. It is preferred that the alteration at position 573 is conserved relative to P.

[0233] Particularly preferred albumin variants comprise substitutions T83N/N111E (*e.g.* SEQ ID NO: 32); T83N/N111E/K573P (*e.g.* SEQ ID NO: 33); T83N/K573P (*e.g.* SEQ ID NO: 34); T83K/K573P (*e.g.* SEQ ID NO: 38); E82A/K573P (*e.g.* SEQ ID NO: 39); L112F/K573P (*e.g.* SEQ ID NO: 40); E82D/K573P (*e.g.* SEQ ID NO: 43); P110G/K573P (*e.g.* SEQ ID NO: 44); N111D/K573P (*e.g.* SEQ ID NO: 60); N111G/K573P (*e.g.* SEQ ID NO: 61); N111H/K573P (*e.g.* SEQ ID NO: 62); E425A/K573P (*e.g.* SEQ ID NO: 64); E505Q/K573P (*e.g.* SEQ ID NO: 65); T527M/K573P (*e.g.* SEQ ID NO: 66); N111E/K573P (*e.g.* SEQ ID NO: 68); K534V/K573P (*e.g.* SEQ ID NO: 73); N111Q/K573P (*e.g.* SEQ ID NO: 74) which are descried with reference to HSA (SEQ ID NO: 2). Other preferred albumin variants comprise equivalent substitutions in albumins other than HSA (SEQ ID NO: 2).

[0234] Also, an albumin variant according to the invention may comprise one or more (several) alterations at positions selected from 78 to 88 and/or 105 to 120 and/or 425, 505, 510, 512, 524, 527, 531, 534, 569, 575 of HSA (SEQ ID NO: 2) or equivalent positions of other albumins. Preferred alterations are substitutions such as those described for these positions in the first aspect of the invention. Particularly preferred substitutions include D108A (SEQ ID NO: 59); D108E (*e.g.* SEQ ID NO: 70); N109K (*e.g.* SEQ ID NO: 69); P110G (*e.g.* SEQ ID NO: 42); N111D (*e.g.* SEQ ID NO: 46); N111E (*e.g.* SEQ ID NO: 67); N111G (*e.g.* SEQ ID NO: 48); N111H (*e.g.* SEQ ID NO: 49); N111K (*e.g.* SEQ ID NO: 54); L112F (*e.g.* SEQ ID NO: 37); E425A (*e.g.* SEQ ID NO: 63); E425K (*e.g.* SEQ ID NO: 55); E505Q (*e.g.* SEQ ID NO: 45); H510D (*e.g.* SEQ ID NO: 57); D512E (*e.g.* SEQ ID NO: 50); K524A (*e.g.* SEQ ID NO: 51); T527A (*e.g.* SEQ ID NO: 52); T527M (*e.g.* SEQ ID NO: 47); E531H (*e.g.* SEQ ID NO: 53); K534V (*e.g.* SEQ ID NO: 56); A569S

(*e.g.* SEQ ID NO: 58); L575F (*e.g.* SEQ ID NO: 72); E82A (*e.g.* SEQ ID NO: 36); E82D (*e.g.* SEQ ID NO: 41); T83K (*e.g.* SEQ ID NO: 35); T83N (*e.g.* SEQ ID NO: 71) which are descried with reference to HSA (SEQ ID NO: 2). Other preferred albumin variants comprising one or more (several) alterations may comprise equivalent substitutions in albumins other than HSA (SEQ ID NO: 2).

[0235] Advantageously, the polypeptide retains substantially the same tertiary structure (or, for a fragment, the relevant part of the structure) as a reference or parent albumin such as HSA. The skilled person understands the term 'substantially the same tertiary structure' bearing in mind that some degree of variation in tertiary structure is expected as all proteins have some degree of structural flexibility. This applies particularly to polypeptides having a higher binding affinity to FcRn than the parent or reference albumin (*e.g.* HSA) has to FcRn.

[0236] One or more (several) of the His residues may or may not be maintained relative to the parent albumin. For example, with reference to SEQ ID NO: 2, one or more (several) of the following His residues may be maintained: 3, 9, 39, 67, 105, 128, 146, 242, 247, 288, 338, 367, 440, 464, 510, and/or 535. One or more (several), preferably all, of the His residues in domain I are maintained (*i.e.* 3, 9, 39, 67, 105, 128, 146.). One or more (several), preferably all, of the His residues in domain II are maintained (*i.e.* 242, 247, 288, 338, 367). One or more (several), preferably all, of the His residues in domain III are maintained (*i.e.* 440, 464, 510, 535). One or more (several) or all three of His 464, 510, 535 may be maintained.

[0237] It is preferred that at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 or 17 of the disulphide bonds of the albumin are maintained in the polypeptide. For a polypeptide derived from a full length albumin, it is preferred that all disulphide bonds usually present in that albumin are maintained. For a polypeptide derived from a fragment of albumin, it is preferred that all disulphide bonds usually present in that fragment are maintained. It is preferred that Cys34 (or equivalent in non-human albumins) is maintained.

[0238] For all aspects of the invention fusion partner polypeptides and/or conjugates may comprise one or more (several) of: 4-1BB ligand, 5-helix, A human C-C chemokine, A human L105 chemokine, A human L105 chemokine designated huL105_3., A monokine induced by gamma-interferon (MIG), A partial CXCR4B protein, A platelet basic protein (PBP), α1-antitrypsin, ACRP-30 Homologue; Complement Component C1q C, Adenoid-expressed chemokine (ADEC), aFGF; FGF-1, AGF, AGF Protein, albumin, an etoposide, angiostatin, Anthrax vaccine, Antibodies specific for collapsin, antistasin, Anti-TGF beta family antibodies, antithrombin III, APM-1; ACRP-30; Famoxin, apo-lipoprotein species, Arylsulfatase B, b57 Protein, BCMA, Beta-thromboglobulin protein (beta-TG), bFGF; FGF2, Blood coagulation factors, BMP Processing Enzyme Furin, BMP-10, BMP-12, BMP-15, BMP-17, BMP-18, BMP-2B, BMP-4, BMP-5, BMP-6, BMP-9, Bone Morphogenic Protein-2, calcitonin, Calpain-10a, Calpain-10b, Calpain-10c, Cancer Vaccine, Carboxypeptidase, C-C chemokine, MCP2, CCR5 variant, CCR7, CD11a Mab, CD137; 4-1 BB Receptor Protein, CD20 Mab, CD27, CD27L, CD30, CD30 ligand, CD33 immunotoxin, CD40, CD40L, CD52 Mab, Cerebus Protein, Chemokine Eotaxin, Chemokine hIL-8, Chemokine hMCP1, Chemokine hMCP1a, Chemokine hMCP1b, Chemokine hMCP2, Chemokine hMCP3, Chemokine hSDF1b, Chemokine MCP-4, chemokine TECK and

TECK variant, Chemokine-like protein IL-8M1 Full-Length and Mature, Chemokine-like protein IL-8M10 Full-Length and Mature, Chemokine-like protein IL-8M3, Chemokine-like protein IL-8M8 Full-Length and Mature, Chemokine-like protein IL-8M9 Full-Length and Mature, Chemokine-like protein PF4-414 Full-Length and Mature, Chemokine-like protein PF4-426 Full-Length and Mature, Chemokine-like protein PF4-M2 Full-Length and Mature, Cholera vaccine, Chondromodulin-like protein, c-kit ligand; SCF; Mast cell growth factor; MGF; Fibrosarcoma-derived stem cell factor, CNTF and fragment thereof (such as CNTFAx15'(Axokine™)), coagulation factors in both pre and active forms, collagens, Complement C5 Mab, Connective tissue activating protein-III, CTAA16.88 Mab, CTAP-III, CTLA4-Ig, CTLA-8, CXC3, CXC chemokine receptor 3, cyanovirin-N, Darbepoetin, designated exodus, designated huL105_7, DIL-40, DNase, EDAR, EGF Receptor Mab, ENA-78, Endostatin, Eotaxin, Epithelial neutrophil activating protein-78, EPO receptor; EPOR, erythropoietin (EPO) and EPO mimics, Eutropin, Exodus protein, Factor IX, Factor VII, Factor VIII, Factor X and Factor XIII, FAS Ligand Inhibitory Protein (DcR3), FasL, FGF, FGF-12; Fibroblast growth factor homologous factor-1, FGF-15, FGF-16, FGF-18, FGF-3; INT-2, FGF-4; gelonin, HST-1; HBGF-4, FGF-5, FGF-6; Heparin binding secreted transforming factor-2, FGF-8, FGF-9; Glia activating factor, fibrinogen, flt-1, flt-3 ligand, Follicle stimulating hormone Alpha subunit, Follicle stimulating hormone Beta subunit, Follitropin, Fractalkine, fragment. myofibrillar protein Troponin I, FSH, Galactosidase, Galectin-4, G-CSF, GDF-1, Gene therapy, Glioma-derived growth factor, glucagon, glucagon-like peptides, Glucocerebrosidase, glucose oxidase, Glucosidase, Glycodelin-A; Progesterone-associated endometrial protein, GM-CSF, gonadotropin, Granulocyte chemotactic protein-2 (GCP-2), Granulocyte-macrophage colony stimulating factor, growth hormone, Growth related oncogene-alpha (GRO-alpha), Growth related oncogene-beta (GRO-beta), Growth related oncogene-gamma (GRO-gamma), hAPO-4; TROY, hCG, Hepatitus B surface Antigen, Hepatitus B Vaccine, HER2 Receptor Mab, hirudin, HIV gp120, HIV gp41, HIV Inhibitor Peptide, HIV protease inhibiting peptides, HIV-1 protease inhibitors, HPV vaccine, Human 6CKine protein, Human Act-2 protein, Human adipogenesis inhibitory factor, human B cell stimulating factor-2 receptor, Human beta-chemokine H1305 (MCP-2), Human C-C chemokine DGWCC, Human CC chemokine ELC protein, Human CC type chemokine interleukin C, Human CCC3 protein, Human CCF18 chemokine, Human CC-type chemokine protein designated SLC (secondary lymphoid chemokine), Human chemokine beta-8 short forms, Human chemokine C10, Human chemokine CC-2, Human chemokine CC-3, Human chemokine CCR-2, Human chemokine Ckbeta-7, Human chemokine ENA-78, Human chemokine eotaxin, Human chemokine GROalpha, Human chemokine GRObeta, Human chemokine HCC-1, Human chemokine I-309, Human chemokine IP-10, Human chemokine L105_3, Human chemokine L105_7, Human chemokine MIG, Human chemokine MIG-beta protein, Human chemokine MIP-1alpha, Human chemokine MIP1beta, Human chemokine MIP-3alpha, Human chemokine MIP-3beta, Human chemokine PF4, Human chemokine protein 331D5, Human chemokine protein 61164, Human chemokine receptor CXCR3, Human chemokine SDF1alpha, Human chemokine SDF1beta, Human chemokine ZSIG-35, Human Chr19Kine protein, Human CKbeta-9, Human CX3C 111 amino acid chemokine, Human DNAX interleukin-40, Human DVic-1 C-C chemokine, Human EDIRF I protein sequence, Human EDIRF II protein sequence, Human eosinocyte CC type chemokine eotaxin, Human eosinophil-expressed chemokine (EEC), Human fast twitch skeletal muscle troponin C, Human fast twitch skeletal muscle troponin I, Human fast twitch skeletal muscle Troponin subunit C, Human fast twitch skeletal muscle Troponin subunit I Protein, Human fast twitch skeletal muscle

Troponin subunit T, Human fast twitch skeletal muscle troponin T, Human foetal spleen expressed chemokine, FSEC, Human GM-CSF receptor, Human gro-alpha chemokine, Human gro-beta chemokine, Human gro-gamma chemokine, Human IL-16 protein, Human IL-1RD10 protein sequence, Human IL-1RD9, Human IL-5 receptor alpha chain, Human IL-6 receptor, Human IL-8 receptor protein hIL8RA, Human IL-8 receptor protein hIL8RB, Human IL-9 receptor protein, Human IL-9 receptor protein variant #3, Human IL-9 receptor protein variant fragment, Human IL-9 receptor protein variant fragment#3, Human interleukin 1 delta, Human Interleukin 10, Human interleukin 18, Human interleukin 18 derivatives, Human interleukin-1 beta precursor., Human interleukin-1 receptor accessory protein, Human interleukin-1 receptor antagonist beta, Human interleukin-1 type-3 receptor, Human Interleukin-10 (precursor), Human interleukin-11 receptor, Human interleukin-12 40 kD subunit, Human interleukin-12 beta-1 receptor, Human interleukin-12 beta-2 receptor, Human Interleukin-12 p35 protein, Human Interleukin-12 p40 protein, Human interleukin-12 receptor, Human interleukin-13 alpha receptor, Human interleukin-13 beta receptor, Human interleukin-15, Human interleukin-15 receptor from clone P1, Human interleukin-17 receptor, Human interleukin-18 protein (IL-18), Human interleukin-3, human interleukin-3 receptor, Human interleukin-3 variant, Human interleukin-4 receptor, Human interleukin-5, Human interleukin-6, Human interleukin-7, Human interleukin-8 (IL-8), Human intracellular IL-1 receptor antagonist, Human IP-10 and HIV-1 gp120 hypervariable region fusion protein, Human IP-10 and human Muc-1 core epitope (VNT) fusion protein, human liver and activation regulated chemokine (LARC), Human Lkn-1 Full-Length and Mature protein, Human mammary associated chemokine (MACK) protein Full-Length and Mature, Human mature chemokine Ckbeta-7, Human mature gro-alpha, Human mature gro-gamma polypeptide used to treat sepsis, Human MCP-3 and human Muc-1 core epitope (VNT) fusion protein, Human MI10 protein, Human MI1A protein, Human monocyte chemoattractant factor hMCP-1, Human monocyte chemoattractant factor hMCP-3, Human monocyte chemotactic proprotein (MCPP) sequence, Human neurotactin chemokine like domain, Human non-ELR CXC chemokine H174, Human non-ELR CXC chemokine IP10, Human non-ELR CXC chemokine Mig, Human PAI-1 mutants, Human protein with IL-16 activity, Human secondary lymphoid chemokine (SLC), Human SISD protein, Human STCP-1, Human stromal cell-derived chemokine, SDF-1, Human T cell mixed lymphocyte reaction expressed chemokine (TMEC), Human thymus and activation regulated cytokine (TARC), Human thymus expressed, Human TNF-alpha, Human TNF-beta (LT-alpha), Human type CC chemokine eotaxin 3 protein sequence, Human type II interleukin-1 receptor, Human wild-type interleukin-4 (hIL-4) protein, Human ZCHEMO-8 protein, Humanized Anti-VEGF Antibodies, and fragments thereof, Hyaluronidase, ICE 10 kD subunit, ICE 20 kD subunit, ICE 22 kD subunit, Iduronate-2-sulfatase, Iduronidase, IL-1 alpha, IL-1 beta, IL-1 inhibitor (IL-1i), IL-1 mature, IL-10 receptor, IL-11, IL-12 p40 subunit, IL-13, IL-14, IL-15, IL-15 receptor, IL-17, IL-17 receptor, IL-19, IL-1i fragments, IL1-receptor antagonist, IL-21 (TIF), IL-3 containing fusion protein., IL-3 mutant proteins, IL-3 variants, IL-4, IL-4 mutein, IL-4 mutein Y124G, IL-4 mutein Y124X, IL-4 muteins, Il-5 receptor, IL-6, Il-6 receptor, IL-7 receptor clone, IL-8 receptor, IL-9 mature protein variant (Met117 version), immunoglobulins or immunoglobulin-based molecules or fragment of either (*e.g.* a Small Modular ImmunoPharmaceutical™ ("SMIP") or dAb, Fab' fragments, F(ab')2, scAb, scFv or scFv fragment), including but not limited to plasminogen, Influenza Vaccine, Inhibin alpha, Inhibin beta, insulin, insulin-like growth factor, Integrin Mab, inter-alpha trypsin inhibitor, inter-alpha trypsin inhibitor, Interferon gamma-inducible protein (IP-10), interferons (such as interferon

alpha species and sub-species, interferon beta species and sub-species, interferon gamma species and sub-species), Interleukin 6, Interleukin 8 (IL-8) receptor, Interleukin 8 receptor B, Interleukin-1alpha, Interleukin-2 receptor associated protein p43, interleukin-3, interleukin-4 muteins, Interleukin-8 (IL-8) protein., interleukin-9, Interleukin-9 (IL-9) mature protein (Thr117 version), interleukins (such as IL10, IL11 and IL2), Japanese encephalitis vaccine, Kalikrein Inhibitor, Keratinocyte growth factor, Kunitz domain protein (such as aprotinin, amyloid precursor protein and those described in WO 03/066824, with or without albumin fusions), Kunitz domain protein (such as aprotinin, amyloid precursor protein and those described in WO 03/066824, with or without albumin fusions), LACI, lactoferrin, Latent TGF-beta binding protein II, leptin, Liver expressed chemokine-1 (LVEC-1), Liver expressed chemokine-2 (LVEC-2), LT-alpha, LT-beta, Luteinization Hormone, Lyme Vaccine, Lymphotactin, Macrophage derived chemokine analogue MDC (n+1), Macrophage derived chemokine analogue MDC-eyfy, Macrophage derived chemokine analogue MDC-yl, Macrophage derived chemokine, MDC, Macrophage-derived chemokine (MDC), Maspin; Protease Inhibitor 5, MCP-1 receptor, MCP-1a, MCP-1b, MCP-3, MCP-4 receptor, M-CSF, Melanoma inhibiting protein, Membrane-bound proteins, Met117 human interleukin 9, MIP-3 alpha, MIP-3 beta, MIP-Gamma, MIRAP, Modified Rantes, monoclonal antibody, MP52, Mutant Interleukin 6 S176R, myofibrillar contractile protein Troponin I, Natriuretic Peptide, Nerve Growth Factor-beta, Nerve Growth Factor-beta2, Neuropilin-1, Neuropilin-2, Neurotactin, Neurotrophin-3, Neurotrophin-4, Neurotrophin-4a, Neurotrophin-4b, Neurotrophin-4c, Neurotrophin-4d, Neutrophil activating peptide-2 (NAP-2), NOGO-66 Receptor, NOGO-A, NOGO-B, NOGO-C, Novel beta-chemokine designated PTEC, N-terminal modified chemokine GroHEK/hSDF-1 alpha, N-terminal modified chemokine GroHEK/hSDF-1beta., N-terminal modified chemokine met-hSDF-1 alpha, N-terminal modified chemokine met-hSDF-1 beta, OPGL, Osteogenic Protein-1; OP-1; BMP-7, Osteogenic Protein-2, OX40; ACT-4, OX40L, Oxytocin (Neurophysin I), parathyroid hormone, Patched, Patched-2, PDGF-D, Pertussis toxoid, Pituitary expressed chemokine (PGEC), Placental Growth Factor, Placental Growth Factor-2, Plasminogen Activator Inhibitor-1; PAI-1, Plasminogen Activator Inhibitor-2; PAI-2, Platelet derived growth factor, Platelet derived growth factor Bv-sis, Platelet derived growth factor precursor A, Platelet derived growth factor precursor B, Platelet Mab, platelet-derived endothelial cell growth factor (PD-ECGF), Platelet-Derived Growth Factor A chain, Platelet-Derived Growth Factor B chain, polypeptide used to treat sepsis, Preproapolipoprotein "milano" variant, Preproapolipoprotein "paris" variant, pre-thrombin, Primate CC chemokine "ILINCK", Primate CXC chemokine "IBICK", proinsulin, Prolactin, Prolactin2, prosaptide, Protease inhibitor peptides, Protein C, Protein S, pro-thrombin, prourokinase, RANTES, RANTES 8-68, RANTES 9-68, RANTES peptide, RANTES receptor, Recombinant interleukin-16, Resistin, restrictocin, Retroviral protease inhibitors, ricin, Rotavirus Vaccine, RSV Mab, saporin, sarcin, Secreted and Transmembrane polypeptides, serum cholinesterase, serum protein (such as a blood clotting factor), Soluble BMP Receptor Kinase Protein-3, Soluble VEGF Receptor, Stem Cell Inhibitory Factor, Straphylococcus Vaccine, Stromal Derived Factor-1 alpha, Stromal Derived Factor-1 beta, Substance P (tachykinin), T1249 peptide, T20 peptide, T4 Endonuclease, TACI, Tarc, TGF-beta 1, TGF-beta 2, Thr117 human interleukin 9, thrombin, thrombopoietin, Thrombopoietin derivative1, Thrombopoietin derivative2, Thrombopoietin derivative3, Thrombopoietin derivative4, Thrombopoietin derivative5, Thrombopoietin derivative6, Thrombopoietin derivative7, Thymus expressed chemokine (TECK), Thyroid stimulating Hormone, tick anticoagulant peptide, Tim-1 protein, TNF-alpha precursor, TNF-R, TNF-RII; TNF p75 Receptor;

Death Receptor, tPA, transferrin, transforming growth factor beta, Troponin peptides, Truncated monocyte chemotactic protein 2 (6-76), Truncated monocyte chemotactic protein 2 (6-76), Truncated RANTES protein (3-68), tumour necrosis factor, Urate Oxidase, urokinase, Vasopressin (Neurophysin II), VEGF R-3; flt-4, VEGF Receptor; KDR; flk-1, VEGF-110, VEGF-121, VEGF-138, VEGF-145, VEGF-162, VEGF-165, VEGF-182, VEGF-189, VEGF-206, VEGF-D, VEGF-E; VEGF-X, von Willebrand's factor, Wild type monocyte chemotactic protein 2, ZTGF-beta 9, alternative antibody scaffolds e.g. anticalin(s), adnectin(s), fibrinogen fragment(s), nanobodies such as camelid nanobodies, infestin, and/or any of the molecules mentioned in WO01/79271 (particularly page 9 and/or Table 1 WO 2003/59934 (particularly Table 1), WO03/060071 (particularly Table 1) or WO01/079480 (particularly Table 1).

[0239] Furthermore, conjugates may comprise one or more (several) of chemotherapy drugs such as: 13-cis-Retinoic Acid, 2-CdA, 2-Chlorodeoxyadenosine, 5-Azacitidine, 5-Fluorouracil, 5-FU, 6-Mercaptopurine, 6-MP, 6-TG, 6-Thioguanine, Abraxane, Accutane®, Actinomycin-D, Adriamycin®, Adrucil®, Agrylin®, Ala-Cort®, Aldesleukin, Alemtuzumab, ALIMTA, Alitretinoin, Alkaban-AQ®, Alkeran®, All-transretinoic Acid, Alpha Interferon, Altretamine, Amethopterin, Amifostine, Aminoglutethimide, Anagrelide, Anandron®, Anastrozole, Arabinosylcytosine, Ara-C, Aranesp®, Aredia®, Arimidex®, Aromasin®, Arranon®, Arsenic Trioxide, Asparaginase, ATRA, Avastin®, Azacitidine, BCG, BCNU, Bevacizumab, Bexarotene, BEXXAR®, Bicalutamide, BiCNU, Blenoxane®, Bleomycin, Bortezomib, Busulfan, Busulfex®, C225, Calcium Leucovorin, Campath®, Camptosar®, Camptothecin-11, Capecitabine, Carac™, Carboplatin, Carmustine, Carmustine Wafer, Casodex®, CC-5013, CCNU, CDDP, CeeNU, Cerubidine®, Cetuximab, Chlorambucil, Cisplatin, Citrovorum Factor, Cladribine, Cortisone, Cosmegen®, CPT-11, Cyclophosphamide, Cytadren®, Cytarabine, Cytarabine Liposomal, Cytosar-U®, Cytoxan®, Dacarbazine, Dacogen, Dactinomycin, Darbepoetin Alfa, Dasatinib, Daunomycin, Daunorubicin, Daunorubicin Hydrochloride, Daunorubicin Liposomal, DaunoXome®, Decadron, Decitabine, Delta-Cortef®, Deltasone®, Denileukin diftitox, DepoCyt™, Dexamethasone, Dexamethasone acetate, Dexamethasone Sodium Phosphate, Dexasone, Dexrazoxane, DHAD, DIC, Diodex, Docetaxel, Doxil®, Doxorubicin, Doxorubicin liposomal, Droxia™, DTIC, DTIC-Dome®, Duralone®, Efudex®, Eligard™, Ellence™, Eloxatin™, Elspar®, Emcyt®, Epirubicin, Epoetin alfa, Erbitux™, Erlotinib, Erwinia L-asparaginase, Estramustine, Ethyol, Etopophos®, Etoposide, Etoposide Phosphate, Eulexin®, Evista®, Exemestane, Fareston®, Faslodex®, Femara®, Filgrastim, Floxuridine, Fludara®, Fludarabine, Fluoroplex®, Fluorouracil, Fluorouracil (cream), Fluoxymesterone, Flutamide, Folinic Acid, FUDR®, Fulvestrant, G-CSF, Gefitinib, Gemcitabine, Gemtuzumab ozogamicin, Gemzar®, Gleevec™, Gliadel® Wafer, GM-CSF, Goserelin, Granulocyte - Colony Stimulating Factor, Granulocyte Macrophage Colony Stimulating Factor, Halotestin®, Herceptin®, Hexadrol, Hexalen®, Hexamethylmelamine, HMM, Hycamtin®, Hydrea®, Hydrocort Acetate®, Hydrocortisone, Hydrocortisone Sodium Phosphate, Hydrocortisone Sodium Succinate, Hydrocortone Phosphate, Hydroxyurea, Ibritumomab, Ibritumomab Tiuxetan, Idamycin®, Idarubicin, Ifex®, IFN-alpha, Ifosfamide, IL-11, IL-2, Imatinib mesylate, Imidazole Carboxamide, Interferon alfa, Interferon Alfa-2b (PEG Conjugate), Interleukin-2, Interleukin-11, Intron A® (interferon alfa-2b), Iressa®, Irinotecan, Isotretinoin, Kidrolase®, Lanacort®, Lapatinib, L-asparaginase, LCR, Lenalidomide, Letrozole, Leucovorin, Leukeran, Leukine™, Leuprolide, Leurocristine, Leustatin™, Liposomal Ara-C, Liquid Pred®, Lomustine, L-PAM, L-Sarcolysin, Lupron®, Lupron Depot®, Matulane®, Maxidex,

Mechlorethamine, Mechlorethamine Hydrochloride, Medralone®, Medrol®, Megace®, Megestrol, Megestrol Acetate, Melphalan, Mercaptopurine, Mesna, Mesnex™, Methotrexate, Methotrexate Sodium, Methylprednisolone, Meticorten®, Mitomycin, Mitomycin-C, Mitoxantrone, M-Prednisol®, MTC, MTX, Mustargen®, Mustine, Mutamycin®, Myleran®, Mylocel™, Mylotarg®, Navelbine®, Nelarabine, Neosar®, Neulasta™, Neumega®, Neupogen®, Nexavar®, Nilandron®, Nilutamide, Nipent®, Nitrogen Mustard, Novaldex®, Novantrone®, Octreotide, Octreotide acetate, Oncospar®, Oncovin®, Ontak®, Onxal™, Oprevelkin, Orapred®, Orasone®, Oxaliplatin, a taxol or taxol derivative e.g. Paclitaxel or Paclitaxel Protein-bound, Pamidronate, Panitumumab, Panretin®, Paraplatin®, Pediapred®, PEG Interferon, Pegaspargase, Pegfilgrastim, PEG-INTRON™, PEG-L-asparaginase, PEMETREXED, Pentostatin, Phenylalanine Mustard, Platinol®, Platinol-AQ®, Prednisolone, Prednisone, Prelone®, Procarbazine, PROCRIT®, Proleukin®, Prolifeprospan 20 with Carmustine Implant, Purinethol®, Raloxifene, Revlimid®, Rheumatrex®, Rituxan®, Rituximab, Roferon-A® (Interferon Alfa-2a), Rubex®, Rubidomycin hydrochloride, Sandostatin®, Sandostatin LAR®, Sargramostim, Solu-Cortef®, Solu-Medrol®, Sorafenib, SPRYCEL™, STI-571, Streptozocin, SU11248, Sunitinib, Sutent®, Tamoxifen, Tarceva®, Targretin®, Taxol®, Taxotere®, Temodar®, Temozolomide, Teniposide, TESPA, Thalidomide, Thalomid®, TheraCys®, Thioguanine, Thioguanine Tabloid®, Thiophosphoamide, Thioplex®, Thiotepa, TICE®, Toposar®, Topotecan, Toremifene, Tositumomab, Trastuzumab, Tretinoin, Trexall™, Trisenox®, TSPA, TYKERB®, VCR, Vectibix™, Velban®, Velcade®, VePesid®, Vesanoid®, Viadur™, Vidaza®, Vinblastine, Vinblastine Sulfate, Vincasar Pfs®, Vincristine, Vinorelbine, Vinorelbine tartrate, VLB, VM-26, Vorinostat, VP-16, Vumon®, Xeloda®, Zanosar®, Zevalin™, Zinecard®, Zoladex®, Zoledronic acid, Zolinza, Zometa®; radiopharmaceuticals such as: Carbon-11, Carbon-14, Chromium-51, Cobalt-57, Cobalt-58, Erbium-169, Fluorine-18, Gallium-67, Gold-198, Indium-111, Indium-113m, Iodine-123, Iodine-125, Iodine-131, Iron-59, Krypton-81m, Nitrogen-13, Oxygen-15, Phosphorous-32, Rhenium-186, Rubidium-82, Samarium-153, Selenium-75, Strontium-89, Technetium-99m, Thallium-201, Tritium, Xenon-127, Xenon-133, Yttrium-90; imaging agents such as Gadolinium, magnetite, manganese, technetium, 1125, 1131, P32, TI201, Iopamidol, PET-FDG.

[0240] Further fusion partners, conjugation partners and/or molecules for inclusion in a nanoparticle, associate or composition according to the invention include: acromegaly drugs *e.g.* somatuline, lanreotide, octreotide, Sandostatin; antithrombotics *e.g.* bivalirudin, Angiomax, dalteparin, Fragmin, enoxaparin, Lovenox, Drotrecogin alfa (*e.g.* Activated), Xigris, heparin; assisted reproductive therapy compounds *e.g.* choriogonadotropin, Ovidrel, follitropin, alpha/beta; enzymes *e.g.* hyaluronidase, Hylenex; diabetes drugs *e.g.* exenatide, Byetta, glucagon, insulin, liraglutide, albiglutide, GLP-1 agonists, exendin or an exendin analog; compounds useful in diagnosis *e.g.* protirelin, Thyrel TRH Thypinone, secretin (*e.g.* synthetic human), Chirhostim, thyrotropin (*e.g.* alpha), Thyrogen' erythropoiesis drugs *e.g.* Darbepoetin alfa, Aranesp, Epoetin alfa, Epogen, Eprex, drugs for the treatment of genetic defects *e.g.* pegademase, drugs for the treatment of growth failure *e.g.* Adagen, mecasermin, rinfabate, drugs for the treatment of cystic fibrosis *e.g.* Dornase alfa, Pulmozyme, drugs for the treatment of metaoblic disorders *e.g.* Agalsidase beta, Fabrazyme, alglucosidase alpha, Myozyme, Laronidase, Aldurazyme, drugs for the treatment of genital wart intralesional *e.g.* Interferon alfa-n3, Alferon N, drugs for the treatment of granulomatous disease *e.g.* Interferon gamma-1b, Actimmune; drugs for the treatment of growth failure *e.g.* pegvisomant, Somavert, somatropin,

Genotropin, Nutropin, Humatrope, Serostim, Protropin; drugs for the treatment of heart failure *e.g.* nesiritide, Natrecor; drugs for the treatment of hemophilia *e.g.* a coagulation factor *e.g.* Factor VIII, Helixate FS, Kogenate FS, Factor IX, BeneFIX, Factor VIIa, Novoseven, desmopressin, Stimate, DDAVP; hemopoetic drugs *e.g.* Filgrastim (G-CSF), Neupogen, Oprelvekin, Neumega, Pegfilgrastim, Neulasta, Sargramostim, Leukine; drugs for the treatment of hepatitis C *e.g.* Interferon alfa-2a, Roferon A, Interferon alfa-2b, Intron A, Interferon alfacon-1, Infergen, Peginterferon alfa-2a, Pegasys, Peginterferon alfa-2b, PEG-Intron; drugs for the treatment of HIV *e.g.* enfuvirtide, Fuzeon; Fabs *e.g.* Fab (antithrombin), Abciximab, ReoPro; monoclonal antibodies *e.g.* Daclizumab, Zenapax; antiviral monoclonal antibodies *e.g.* Palivizumab, Synagis; monoclonal antibodies for the treatment of asthma *e.g.* Omalizumab, Xolair; monoclonal antibodies for use in diagnostic imaging *e.g.* Arcitumomab, CEA-Scan, Capromab Pendetide, ProstaScint, Satumomab Pendetide, OncoScint CR/OV, Fabs for use in diagnostic imaging *e.g.* Nofetumomab, Verluma; immuno-supressant monoclonal antibodies *e.g.* Basiliximab, Simulect, Muromonab-CD3, Orthoclone OKT3; monoclonal antibodies for the treatment of malignancy *e.g.* Alemtuzumab, Campath, Ibritumomab tiuxetan, Zevalin, Rituximab, Rituxan, Trastuzumab, Herceptin; monoclonal antibodies for the treatment of rheumatoid arthritis (RA) *e.g.* Adalimumab, Humira, Infliximab, Remicade; monoclonal antibodies for use as a radio-immuno-therapeutic *e.g.* Tositumomab and Iodine I^{131}, Tositumomab, Bexxar; drugs for the treatment of macular degeneration *e.g.* pegaptanib, Macugen; drugs for the treatment of malignancy *e.g.* Aldesleukin, Proleukin, Interleukin-2, Asparaginase, Elspar, Rasburicase, Elitek, Denileukin diftitox, Ontak, Pegaspargase, Oncaspar, goserelin, leuprolide; drugs for the treatment of multiple sclerosis (MS) *e.g.* Glatiramer acetate (*e.g.* copolymer-1), Copaxone, Interferon beta-1a, Avonex, Rebif, Interferon beta-1 b, Betaseron; drugs for the treatment of mucositis *e.g.* palifermin, Kepivance; drug for the treatment of dystonia *e.g.*, neurotoxin, Botulinum Toxin Type A, BOTOX, BOTOX Cosmetic, Botulinum Toxin Type B, MYOBLOC; drugs for the treatment of osteoporosis *e.g.* teriparatide, Forteo; drugs for the treatment of psoriasis *e.g.* Alefacept, Amevive; drugs for the treatment of RA *e.g.* abatacept, Orencia, Anakinra, Kineret, Etanercept, Enbrel; thrombolytics *e.g.* Alteplase, Activase, recombinant tissue plasminogen activator (rtPA), Anistreplase, Eminase, Reteplase, Retavase, Streptokinase, Streptase, Tenecteplase, TNKase (tenecteplase), Urokinase, Abbokinase, Kinlytic; drugs for the treatment of osteoporosis *e.g.* calcitonin (*e.g.* salmon), Miacalcin, Fortical, drugs for the treatment of skin ulcers *e.g.* Becaplermin, Regranex, Collagenase, Santyl.

[0241] Such polypeptides and chemical compounds may be referred to as diagnostic moieties, therapeutic moieties, prophylactic moieties or beneficial moieties.

[0242] Preferably the fusion partner and/or conjugation partner is not an albumin, variant or fragment thereof.

[0243] One or more (several) therapeutic or prophylactic polypeptides may be fused to the N-terminus, the C-terminus of albumin, inserted into a loop in the albumin structure or any combination thereof. It may or it may not comprise linker sequences separating the various components of the fusion polypeptide.

[0244] Teachings relating to fusions of albumin or a fragment thereof are known in the art and

the skilled person will appreciate that such teachings can also be applied to the invention. WO 2001/79271A and WO 2003/59934 also contain examples of therapeutic and prophylactic polypeptides that may be fused to albumin or fragments thereof, and these examples apply also to the invention.

[0245] The invention is further described by the following examples that should not be construed as limiting the scope of the invention.

Examples

Example 1: Preparation of HSA mutein expression plasmids.

[0246] HSA variants were expressed using standard molecular biology techniques, such as described in Sambrook, J. and D.W. Russell, 2001 (Molecular Cloning: a laboratory manual, 3rd ed. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y).

[0247] Construction of the K573P expression plasmid is described in WO2011/051489. Construction of the remaining expression plasmids was performed as described in WO 2012/150319 (PCT/EP12/058206). Variants HSA T83K, HSA E82A, HSA E82D, HSA P110G, HSA L112F and HSA T83N/N111 E were produced as described in Example 6, Method 2 of WO 2012/150319 (PCT/EP12/058206). Combination mutants containing the K573P substitution were produced as described in "Production of combination mutants with K573P" (WO 2012/150319 (PCT/EP12/058206)), where the required fragments were inserted into appropriately digested pDB4852 (described in WO 2012/150319 (PCT/EP12/058206,)). Fragments containing T83N/N111E, T83K, E82A, E82D, P110G and L112F were removed from synthetic constructs *via* the indicated restriction sites (Table 1). The fragment containing the T83N substitution was removed from pDB4874 (described in WO 2012/150319 (PCT/EP12/058206)). Ligation of the polynucleotides encoding HSA variants and plasmids pDB3964/pDB4852 produced plasmids, which were used to express the desired mutants (Table 1). All plasmids were sequenced to confirm that the HSA sequence was only mutated at the desired position(s).

[0248] Construction of HSA T83N, HSA N111E and HSA N111E/K573P was as described in WO 2012/150319 (PCT/EP12/058206).

[0249] Transformation of *S. cerevisiae* was performed as described in WO 2012/150319 (PCT/EP12/058206), employing the 24 hour stocking method described in WO 2011/051489, with the exception that the host strain was S. *cerevisiae* DYB7 (Payne et al (2008) Applied and Environmental Microbiology Vol. 74(24): 7759-7766) with four copies of PDI integrated into the genome.

Table 1: Construction of HSA mutein expression plasmids.

Variant	Restriction enzymes	Digested fragment size (kb)	Plasmid	SEQ ID NO
HSA T83N/N111E	SacII/NheI	0.395	pDB4966	32
HSA T83N/N111E/K573P	SacII/NheI	0.395	pDB4967	33
HSA T83N/K573P	SacII/NheI	0.395	pDB4968	34
HSA T83K	SacII/NheI	0.395	pDB4903	35
HSA E82A	SacII/NheI	0.395	pDB4904	36
HSA L112F	SacII/NheI	0.395	pDB4907	37
HSA T83K/K573P	SacII/NheI	0.395	pDB4908	38
HSA E82A/K573P	SacII/NheI	0.395	pDB4909	39
HSA L112F/K573P	SacII/NheI	0.395	pDB4912	40
HSA E82D	SacII/NheI	0.395	pDB4905	41
HSA P110G	SacII/NheI	0.395	pDB4906	42
HSA E82D/K573P	SacII/NheI	0.395	pDB4910	43
HSA P110G/K573P	SacII/NheI	0.395	pDB4911	44

Example 2: SPR analysis of binding affinity of albumin variants to FcRn

[0250] SPR analyses were performed as described in WO 2012/150319 (PCT/EP12/058206).

[0251] The variants were albumin (SEQ ID NO: 2), each with one point mutation selected from: D108A, N111D, N111G, N111H, N111K, K190A, R197A, K276N, R410A, Y411A, P416A, E425A, E425K, K466A, D471A, R472A, N503D, N503K, E505K, E505Q, H510D, H510E, D512A, D512E, K524A, K525A, T527A, T527D, T527M, E531A, E531H, K534V, H535F, E565V, A569L, A569S, A569V, and V576F.

[0252] Firstly, the variants were analyzed by SPR to determine their binding response (RU) to shFcRn. Only variants showing a binding response more than 20% higher or lower than the binding response of wild-type albumin were analyzed to identify the KD (Table 2, below). Wild-type HSA and HSA with mutation K573P were used as controls.

Table 2: Binding affinity of albumin variants to shFcRn

Molecule	SEQ ID NO:	Ka (10^3/Ms)	Kd (10^{-3}/s)	KD (μM)
WT rHSA	2	-	-	3.1± 0.4*
HSA K573P	3	-	-	0.4± 0.1 *
HSA E505Q	45	2.1	2.9	1.4
HSA N111D	46	0.8	4.4	5.2
HSA T527M	47	2.7	3.3	1.2

Molecule	SEQ ID NO:	Ka (10^3/Ms)	Kd (10^{-3}/s)	KD (μM)
HSA N111G	48	1.6	5.2	3.3
HSA N111H	49	0.5	2.4	5.0
HSA D512E	50	2.7	10.9	4.1
HSA K524A	51	3.3	11.6	3.5
HSA T527A	52	2.6	13.7	5.2
HSA E531H	53	3.5	20.8	6.2
HSA N111K	54	0.5	8.3	17.3
HSA E425K	55	3.6	12.4	3.5
HSA K534V	56	4.8	5.5	1.1
HSA H510D	57	0.2	0.4	0.2
HSA A569S	58	0.7	4.8	6.8
HSA D108A	59	0.9	12.7	13.7
* Mean of five repeats, therefore Ka and Kd data are not provided				

[0253] Variants with a lower KD than wild-type HSA have a higher binding affinity to shFcRn. Conversely, variants with a higher KD than wild-type HSA have a lower binding affinity to shFcRn.

[0254] The data for positions 108 and 111 support the involvement of a loop including positions 105 to 120 in interaction with FcRn and therefore that alteration at any position within this loop will modulate the binding affinity of albumin to FcRn.

Example 3. SPR analysis of binding affinity of albumin variants to FcRn

[0255] The variants were albumin (SEQ ID NO: 2), each with one point mutation selected from: N111D, N111G, N111H, N111D/K573P, N111G/K573P, N111H/K573P, E505Q, E425A, T527M, E505Q/K573P, E425A/K573P and T527M/K573P were prepared as described in above.

Table 3: Binding affinity of albumin variants to shFcRn-HIS

Molecule	SEQ ID NO:	Ka (10^3/Ms)		Kd (10^{-3}/s)		KD (μM)	
WT rHSA	2	-		-		3.6±0.54*	
HSA K573P	3	-		-		0.6±0.12**	
HSA N111D	46	9.8	9.1	17.9	17.9	1.8	2.0
HSA N111G	48	7.4	7.4	20.5	19.2	2.7	2.6
HSA N111H	49	4.4	4.0	15.6	14.2	3.5	3.6
HSA N111D/K573P	60	4.0	4.2	1.9	2.2	0.5	0.5

Molecule	SEQ ID NO:	Ka (10^3/Ms)		Kd (10^{-3}/s)		KD (μM)	
HSA N111G/K573P	61	4.1	4.7	1.7	2.3	0.4	0.5
HSA N111H/K573P	62	2.9	3.0	1.7	2.2	0.6	0.7
HSA E505Q	45	5.1	5.0	4.9	6.0	1.0	1.2
HSA E425A	63	6.6	7.9	34.1	28.1	5.1	3.6
HSA T527M	47	4.9	4.8	4.4	5.1	0.9	1.1
HSA E425A/K573P	64	3.4	3.6	2.5	3.2	0.7	0.9
HSA E505Q/K573P	65	0.4	0.4	0.5	1.1	1.6	2.5
HSA T527M/K573P	66	2.6	2.8	1.2	2.2	0.5	0.8
* Mean of 8 and standard deviation ** Mean of 5 and standard deviation. Variants with a lower KD than wild-type HSA have a higher binding affinity to shFcRn. Conversely, variants with a higher KD than wild-type HSA have a lower binding affinity to shFcRn.							

[0256] The data for variants including K573P generate increases in affinity consistent with the K573P substitution only.

Example 4. SPR analysis of binding affinity of albumin variants to FcRn

[0257] The variants were albumin (SEQ ID NO: 2), each with one point mutation selected from: N111R, N111Q, N111E, N111R/K573P, N111Q/K573P, N111E/K573P, N109D, N109E, N109Q, N109R, N109K, N109H, N109G, D108E, T83N, L575F and K534V/K573P were prepared as described above.

Table 4a: Binding affinity of albumin variants to shFcRn-HIS

Molecule	SEQ ID NO:	Ka (10^3/Ms)		Kd (10^{-3}/s)		KD (μM)	
WT HSA	2	-		-		2.0±0.3*	
HSA K573P	3	-		-		0.3±0.0**	
HSA N111E	67	15.3	14.3	13.1	15.2	0.8	1.1
HSA N111E/K573P	68	4.2	-	2.4	-	0.6	-
HSA N109K	69	9.7	6.3	18.3	21.6	1.9	3.4
HSA D108E	70	13.9	7.5	16.6	19.5	1.2	2.6
HSA T83N	71	17.7	15.2	15.6	16.8	0.9	1.1
HSA L575F	72	11.8	8.3	31.3	32.2	2.7	4.0

Molecule	SEQ ID NO:	Ka (10^3/Ms)		Kd (10^{-3}/s)		KD (µM)	
HSA K534V/K573P	73	4.7	4.5	6.9	6.9	1.5	1.5
* Mean of 11 and standard deviation ** Mean of 5 and standard deviation.							

Table 4b

Molecule	SEQ ID NO:	Ka (10^3/Ms)		Kd (10^{-3}/s)		KD (µM)	
WT rHSA	2	-		-		3.6±0.54*	
HSA K573P	3	-		-		0.6±0.12**	
HSA N111D	46	9.8	9.1	17.9	17.9	1.8	2.0
HSA N111G	48	7.4	7.4	20.5	19.2	2.7	2.6
HSA N111H	49	4.4	4.0	15.6	14.2	3.5	3.6
* Mean of 8 and standard deviation ** Mean of 5 and standard deviation.							

The data demonstrate a role for the 108 to 111 loop in binding of HSA to FcRn, with reduced binding affinity observed in the D108A and N111K variants (Table 2). Additional mutations at position 111 demonstrated a range of binding affinities, from the reduced affinity observed for the N111K variant through to the N111E variant, which displayed an increased affinity for FcRn as compared to WT HSA (Table 4). Variant N111Q/K573P (Figure 5, SEQ ID NO: 74) shows a binding curve with increased response compared to wt HSA and slower dissociation compared to wt HSA, this is consistent with the K573P substitution. The relative position of loop region 108 to 112 of HSA and FcRn (Figure 6) suggests that this region has potential to contribute to FcRn binding as predicted in Example 2. Further details regarding Figures 5 and 6 are provided in WO 2012/150319 (PCT/EP12/058206).

[0258] The relative position of adjacent loop region of Domain I (domain 1), comprising residues 78 to 88 (Figure 6), suggests that this region has potential to contribute to FcRn binding. This is supported by the observation that the T83N variant shows increased affinity for FcRn compared to WT HSA (Table 4).

[0259] Mutation of the adjacent residues, particularly E82, P110 and L112 (Figure 6), would be predicted to alter the binding affinity of HSA for FcRn.

Example 5: SPR analysis of binding affinity of albumin variants to FcRn

[0260] SPR analyses were performed on a Biacore 3000 instrument (GE Healthcare). Immobilization was carried out on CM5 chips coupled with shFcRn (GeneArt 1177525) using GE Healthcare amine coupling chemistry as per manufacturer's instructions. Immobilized levels of shFcRn-HIS (shFcRn with a 6-His tail on the C-terminus of beta-2-microglobulin) were "~1200R, and achieved by injecting 20µg/mL shFcRn in sodium acetate pH4.5 (G E Healthcare). Chip surface was left to stabilize with a constant flow (5µL/min) of running buffer - Di-basic/Mono-basic phosphate buffer pH5.5 at 25 °C overnight. After ligand stabilization, the chip surface was conditioned by injecting 3 x 45µL Di-basic/Mono-basic phosphate buffer at 30µL/min followed by HBS_EP (0.01 M HEPES, 0.15 M NaCl, 3mM EDTA, 0.005% surfactant P20) at pH 7.4 (GE

Healthcare)) regeneration steps (12s) in between each injection. Surfaces were then checked for activity by injecting 3x45µL positive control at 30µL/min, followed by 12s regeneration pulse.

[0261] pH 5.5 Binding Analysis: Sensorgrams for binding data were obtained by injecting 45µL of 20µM (diluted in pH 5.5 buffer) of analytes in pH 5.5 running buffer at 30µL/min in duplicate. 2 x 12s regeneration pulses post injection were performed to restore the baseline (HBS-EP pH 7.4; 10µL at 50µL/min). The reference was then subtracted and BiaEvaluation software 4.1 used to obtain binding analysis data.

[0262] pH 5.5 Kinetic Analysis: Sensorgrams for kinetic data were obtained by injecting 45µL of five concentrations: 20µM, 4µM, 0.8µM 0.16µM and 0.032µM of analytes in pH 5.5 running buffer at 30µL/min with a 90s delay post injection (to allow smooth dissociation for kinetic modelling). 2 x 12s regeneration pulses post injection were performed to restore the baseline (HBS-EP pH 7.4; 10µL at 50µL/min). Analysis was performed on two separate occasions. The reference cell value was then subtracted and Biaevaluation software 4.1 used to obtain kinetic data and confirm KD values.

[0263] SPR was used to identify the binding response of variants to FcRn, the results are shown in Tables 5a and 5b.

Table 5a:

Molecule	**SEQ ID NO**	**Binding Response (RU)**
WT rHSA	2	229
HSA K573P	3	300
HSA T83K	35	194
HSA T83K/K573P	38	285
HSA E82A	36	221
HSA E82A/K573P	39	275
HSA E82D	41	227
HSA E82D/K573P	43	269
HSA P110G	42	235
HSA P110G/K573P	44	284
HSA L112F	37	253
HSA L112F/K573P	40	290
Values shown are a mean of two runs.		

Table 5b:

Molecule	**SEQ ID NO**	**Binding Response (RU)**
WT rHSA	2	148
HSA K573P	3	181
HSA T83N/N111E	32	167
Values shown are a mean of two runs.		

[0264] KD analysis was performed on variants to assess variant-FcRn binding affinity relative to HSA-K573-FcRn binding affinity. The results are shown in Table 6. Further analysis was carried out to calculate binding affinities (Table 7).

Table 6:

Molecule	SEQ ID NO:	KD (μM)	Binding affinity (fold difference, relative to HSA wild-type)
WT rHSA	2	3.82	-
HSA L112F	37	1.44	2.7
HSA T83K	35	1.42	2.7
HSA E82A	36	2.81	1.4
HSA K573P	3	0.18	21.2
HSA L112F/K573P	40	0.108	35.4
HSA T83K/K573P	38	0.147	26.0
HSA E82A/K573P	39	0.174	22.0

Table 7

Molecule	SEQ ID NO:	Ka (1/Ms)	Kd (1/s)	KD (μM)	Mean KD (μM)	Fold difference compared to HSA wild-type
WT rHSA	2	0.63 $x10^4$	0.0133	2.11	1.97	-
		0.78 $x10^4$	0.0141	1.83		
HSA K573P	3	0.81 $x10^4$	1.32 $x10^{-3}$	0.162	0.20	9.9
		0.74 $x10^4$	1.77 $x10^{-3}$	0.238		
HSA T83N/N 111 E/K573P	33	2.28 $x10^4$	1.16 $x10^{-3}$	0.051	0.061	32.3
		2.28 $x10^4$	1.59 $x10^{-3}$	0.070		
HSA T83N/K573P	34	1.55 $x10^4$	1.3 $x10^{-3}$	0.084	0.12	16.4
		1.22 $x10^4$	1.84 $x10^{-3}$	0.15		

[0265] The data show that HSA T83N/N111E/K573P and HSA T83N/K573P have high FcRn binding affinities relative to wild-type HSA. HSA E82A and HSA L112F both show improved binding to FcRn compared to wild-type HSA binding to FcRn and this suggests that the loops comprising amino acids 78 to 88 of HSA (SEQ ID NO: 2) and 105 to 120 of HSA (SEQ ID NO: 2) are involved in the binding of HSA to FcRn.

[0266] HSA with single mutations at position L112 or T83 show similar FcRn binding affinities to each other. However, the double mutation of L112 and K573 has a stronger binding affinity to FcRn than the double mutation of T83 and K573.

Table 8

Molecule	**SEQ ID NO:**	**Ka (10^3/MS)**	**Kd (10^3/s)**	**KD (μM)**	**Mean KD (μM)**
WT HSA	2	4.3	63.6	13.7	13.8
		5.6	77.6	13.9	
HSA-K573P	3	4.3	6.2	1.4	1.1
		5.2	4.6	0.89	
HSA-E82D	41	2.3	84.3	36.9	24.1
		6.5	73.0	11.3	
HSA-E82D/K573P	43	4.9	6.7	1.4	1.1
		5.5	5.0	0.9	

[0267] The data of Table 8 show that HSA-E82D has a low FcRn binding affinity relative to wild-type albumin and HSA-K573P has a high FcRn binding relative to wild-type albumin. However, the double mutant HSA-E82D/K573P shows the same FcRn binding affinity as HSA-K573P, i.e. inclusion of the E82D substitution does not adversely affect FcRn binding.

SEQUENCE MISTING

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gacttgcctt cattagctgc tgattttgtt gaaagtaagg atgtttgcaa aaactatgct      960

gaggcaaagg atgtcttcct gggcatgttt ttgtatgaat atgcaagaag gcatcctgat     1020

tactctgtcg tgctgctgct gagacttgcc aagacatatg aaaccactct agagaagtgc     1080

tgtgccgctg cagatcctca tgaatgctat gccaaagtgt tcgatgaatt taaacctctt     1140
```

```
gtggaagagc ctcagaattt aatcaaacaa aattgtgagc tttttgagca gcttggagag     1200

tacaaattcc agaatgcgct attagttcgt tacaccaaga aagtacccca agtgtcaact     1260

ccaactcttg tagaggtctc aagaaaccta ggaaaagtgg gcagcaaatg ttgtaaacat     1320

cctgaagcaa aaagaatgcc ctgtgcagaa gactatctat ccgtggtcct gaaccagtta     1380

tgtgtgttgc atgagaaaac gccagtaagt gacagagtca ccaaatgctg cacagaatcc     1440

ttggtgaaca ggcgaccatg cttttcagct ctggaagtcg atgaaacata cgttcccaaa     1500

gagtttaatg ctgaaacatt caccttccat gcagatatat gcacactttc tgagaaggag     1560

agacaaatca agaaacaaac tgcacttgtt gagctcgtga aacacaagcc caaggcaaca     1620

aaagagcaac tgaaagctgt tatggatgat ttcgcagctt ttgtagagaa gtgctgcaag     1680

gctgacgata aggagacctg ctttgccgag gagggtaaaa aacttgttgc tgcaagtcaa     1740

gctgccttag gcttataa                                                  1758
```

<210> 2

<211> 585

<212> PRT

<213> Homo sapiens

<400> 2

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                  10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175
```

```
Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg

                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480
```

```
Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 3

<211> 585

<212> PRT

<213> Artificial Sequence

<220>

<223> HSA K573P

<400> 3

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140
```

```
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu

        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430
```

```
Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 4

<211> 609

<212> PRT

<213> Homo sapiens

<400> 4

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu
        35                  40                  45

Ile Ala Phe Ala Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110
```

```
Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Glu Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Lys Arg Tyr Lys Ala Ala Phe Thr Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Asn Asp
305                 310                 315                 320

Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430
```

420 425 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
435 440 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
450 455 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465 470 475 480

Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg
485 490 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
500 505 510

Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
515 520 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu
530 535 540

Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545 550 555 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala
565 570 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe
580 585 590

Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly
595 600 605

Leu

<210> 5

<211> 621

<212> PRT

<213> Pan troglodytes

<400> 5

Met Asn Glu Ser Ser Cys Cys Ser Thr Ser Leu Pro Ala Phe Gly Val
1 5 10 15

Ser Val Leu Asp Ser Gly His Ser Ser Ser Ser Ala Tyr Ser Arg Gly
20 25 30

Val Phe Arg Arg Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys
35 40 45

Asp Leu Gly Glu Glu Asn Phe Lys Ala Leu Val Leu Val Ala Phe Ala
50 55 60

Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn
65 70 75 80

```
Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu
                85                  90                  95

Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr
            100                 105                 110

Val Ala Thr Leu Arg Glu Lys Tyr Gly Glu Met Ala Asp Cys Cys Ala
        115                 120                 125

Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp
    130                 135                 140

Asn Pro Asn Leu Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys
145                 150                 155                 160

Thr Ala Phe His Asp Asn Glu Gly Thr Phe Leu Lys Lys Tyr Leu Tyr
                165                 170                 175

Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe
            180                 185                 190

Phe Ala Glu Arg Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala
        195                 200                 205

Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu
    210                 215                 220

Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln
225                 230                 235                 240

Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser
                245                 250                 255

Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr
            260                 265                 270

Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu
        275                 280                 285

Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln
    290                 295                 300

Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu
305                 310                 315                 320

Glu Lys Ser His Cys Leu Ala Glu Val Glu Asn Asp Glu Met Pro Ala
                325                 330                 335

Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Ser Lys Glu Val Cys
            340                 345                 350

Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr
        355                 360                 365

Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg
    370                 375                 380
```

```
Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala
385                 390                 395                 400

Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu
                405                 410                 415

Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
            420                 425                 430

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr

        435                 440                 445

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
    450                 455                 460

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
465                 470                 475                 480

Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu
                485                 490                 495

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys
            500                 505                 510

Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu
        515                 520                 525

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
    530                 535                 540

Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
545                 550                 555                 560

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
                565                 570                 575

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu
            580                 585                 590

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
        595                 600                 605

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
    610                 615                 620
```

<210> 6

<211> 608

<212> PRT

<213> Macaca mulatta

<400> 6

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Thr His Lys Ser Glu Val Ala
```

```
                20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu His Phe Lys Gly Leu Val Leu

        35                  40                  45

Val Ala Phe Ser Gln Tyr Leu Gln Gln Cys Pro Phe Glu Glu His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Glu Thr Tyr Gly Glu Met Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Pro Leu Val Arg Pro Glu Val
    130                 135                 140

Asp Val Met Cys Thr Ala Phe His Asp Asn Glu Ala Thr Phe Leu Lys
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Phe Phe Ala Ala Arg Tyr Lys Ala Ala Phe Ala Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Leu Asp Glu
        195                 200                 205

Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Asp Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Lys Phe Pro Lys Ala Glu Phe Ala Glu Val Ser
                245                 250                 255

Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Met
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Asp
    290                 295                 300

Lys Pro Leu Leu Glu Lys Ser His Cys Leu Ala Glu Val Glu Asn Asp
305                 310                 315                 320
```

```
Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Tyr Val Glu Ser
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Met
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Ala Tyr Glu Ala Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Phe Gln Pro Leu Val Glu Glu Pro Gln Asn Leu Val Lys Gln Asn Cys
                405                 410                 415

Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ala Lys Cys Cys Lys Leu
    450                 455                 460

Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Arg Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Glu Lys
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Glu Leu Asp Glu Ala Tyr Val Pro Lys Ala Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Met Cys Thr Leu Ser Glu Lys Glu
    530                 535                 540

Lys Gln Val Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Lys Glu Gln Leu Lys Gly Val Met Asp Asn Phe Ala
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Ala Cys Phe
            580                 585                 590

Ala Glu Glu Gly Pro Lys Phe Val Ala Ala Ser Gln Ala Ala Leu Ala
        595                 600                 605
```

<210> 7

<211> 608

<212> PRT

<213> Mesocricetus auratus

<400> 7

```
Met Lys Trp Val Thr Phe Leu Leu Leu Leu Phe Val Ser Asp Ser Ala
1               5                   10                  15

Phe Ser Arg Gly Leu Phe Arg Arg Asp Ala His Lys Ser Glu Ile Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu
        35                  40                  45

Ile Ala Phe Ser Gln Phe Leu Gln Lys Cys Pro Tyr Glu Glu His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Ala Ile Pro Thr Leu Arg Asp Ser Tyr Gly Glu Leu Ala
            100                 105                 110

Asp Cys Cys Ala Lys Lys Glu Pro Glu Arg Asn Glu Cys Phe Leu Lys
        115                 120                 125

His Lys Asp Asp His Pro Asn Leu Pro Pro Phe Val Arg Pro Asp Ala
    130                 135                 140

Glu Ala Met Cys Thr Ser Phe Gln Glu Asn Ala Val Thr Phe Met Gly
145                 150                 155                 160

His Tyr Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Tyr Tyr Ala Glu Lys Tyr Ser Ala Ile Met Thr Glu Cys
            180                 185                 190

Cys Gly Glu Ala Asp Lys Ala Ala Cys Ile Thr Pro Lys Leu Asp Ala
        195                 200                 205

Leu Lys Glu Lys Ala Leu Ala Ser Ser Val Asn Gln Arg Leu Lys Cys
    210                 215                 220

Ser Ser Leu Gln Arg Phe Gly Gln Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Met Ser Gln Lys Phe Pro Lys Ala Asp Phe Ala Glu Ile Thr
                245                 250                 255

Lys Leu Ala Thr Asp Leu Thr Lys Leu Thr Glu Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met
        275                 280                 285

Cys Glu Asn Gln Ala Ser Ile Ser Ser Lys Leu Gln Ala Cys Cys Asp
```

```
Cys Glu Asn Gln Ala Ser Ile Ser Ser Lys Leu Gln Ala Cys Cys Asp
    290                 295                 300

Lys Pro Val Leu Lys Lys Ser His Cys Leu Ser Glu Val Glu Asn Asp
305                 310                 315                 320

Asp Leu Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Asp
                325                 330                 335

Lys Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Thr Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser Val Ala
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Glu Ala Asp Pro Ser Ala Cys Tyr Gly Lys Val Leu Asp Glu
385                 390                 395                 400

Phe Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Ala Asn Cys
                405                 410                 415

Glu Leu Phe Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Leu Ile
            420                 425                 430

Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Ala Ala Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Val Leu
    450                 455                 460

Pro Glu Ala Gln Arg Leu Pro Cys Val Glu Asp Tyr Ile Ser Ala Ile
465                 470                 475                 480

Leu Asn Arg Val Cys Val Leu His Glu Lys Thr Pro Val Ser Glu Gln
                485                 490                 495

Val Thr Lys Cys Cys Thr Gly Ser Val Val Glu Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Pro Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Ser Leu Pro Glu Lys Glu
    530                 535                 540

Lys Gln Met Lys Lys Gln Ala Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Gly Pro Gln Leu Arg Thr Val Leu Gly Glu Phe Thr
                565                 570                 575

Ala Phe Leu Asp Lys Cys Cys Lys Ala Glu Asp Lys Glu Ala Cys Phe
            580                 585                 590

Ser Glu Asp Gly Pro Lys Leu Val Ala Ser Ser Gln Ala Ala Leu Ala
```

595 600 605

<210> 8

<211> 608

<212> PRT

<213> Cavia porcellus

<400> 8

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Val
1               5                  10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala
            20                  25                  30

His Arg Phe Asn Asp Leu Gly Glu Gly His Phe Lys Gly Leu Val Leu
        35                  40                  45

Ile Thr Leu Ser Gln His Leu Gln Lys Ser Pro Phe Glu Glu His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Asp Phe Ala Lys Ala Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Gln Asn Cys Gly Lys Ala Ile Ala Thr Leu Phe Gly Asp
                85                  90                  95

Lys Val Cys Ala Ile Pro Ser Leu Arg Glu Thr Tyr Gly Glu Leu Ala
            100                 105                 110

Asp Cys Cys Ala Lys Glu Asp Pro Asp Arg Val Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Pro Phe Glu Arg Pro Glu Pro
    130                 135                 140

Glu Ala Leu Cys Thr Ala Phe Lys Glu Asn Asn Asp Arg Phe Ile Gly
145                 150                 155                 160

His Tyr Leu Tyr Glu Val Ser Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Tyr Tyr Ala Glu Lys Tyr Lys Asn Ala Leu Thr Glu Cys
            180                 185                 190

Cys Glu Ala Ala Asp Lys Ala Ala Cys Leu Thr Pro Lys Leu Asp Ala
        195                 200                 205

Ile Lys Glu Lys Ala Leu Val Ser Ser Ala Gln Gln Arg Leu Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ser Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Lys Phe Pro Lys Ala Glu Phe Ala Glu Ile Ser
                245                 250                 255

Thr Ile Val Thr Ser Leu Thr Lys Val Thr Lys Glu Cys Cys His Gly
```

```
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Gln Glu Leu Ala Lys Tyr Met

        275                 280                 285

Cys Glu His Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys Cys Val
    290                 295                 300

Lys Pro Thr Leu Gln Lys Ala His Cys Ile Leu Glu Ile Gln Arg Asp
305                 310                 315                 320

Glu Leu Pro Thr Glu Leu Pro Asp Leu Ala Val Asp Phe Val Glu Asp
                325                 330                 335

Lys Glu Val Cys Lys Asn Phe Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Glu Tyr Ser Ile Gly
        355                 360                 365

Met Leu Leu Arg Ile Ala Lys Gly Tyr Glu Ala Lys Leu Glu Lys Cys
    370                 375                 380

Cys Ala Glu Ala Asp Pro His Ala Cys Tyr Ala Lys Val Phe Asp Glu
385                 390                 395                 400

Leu Gln Pro Leu Ile Asp Glu Pro Lys Lys Leu Val Gln Gln Asn Cys
                405                 410                 415

Glu Leu Phe Asp Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Leu Ala
            420                 425                 430

Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Tyr Ala Arg Lys Leu Gly Ser Val Gly Thr Lys Cys Cys Ser Leu
    450                 455                 460

Pro Glu Thr Glu Arg Leu Ser Cys Thr Glu Asn Tyr Leu Ala Leu Ile
465                 470                 475                 480

Leu Asn Arg Leu Cys Ile Leu His Glu Lys Thr Pro Val Ser Glu Arg
                485                 490                 495

Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu His Val Asp Glu Thr Tyr Val Pro Lys Pro Phe His Ala
        515                 520                 525

Asp Ser Phe Thr Phe His Ala Asp Ile Cys Thr Leu Pro Glu Lys Glu
    530                 535                 540

Lys Gln Val Lys Lys Gln Met Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560
```

```
Pro Lys Ala Ser Glu Glu Gln Met Lys Thr Val Met Gly Asp Phe Ala
                565                 570                 575

Ala Phe Leu Lys Lys Cys Cys Asp Ala Asp Asn Lys Glu Ala Cys Phe
            580                 585                 590

Thr Glu Asp Gly Pro Lys Leu Val Ala Lys Cys Gln Ala Thr Leu Ala
        595                 600                 605
```

<210> 9

<211> 608

<212> PRT

<213> Mus musculus

<400> 9

```
Met Lys Trp Val Thr Phe Leu Leu Leu Leu Phe Val Ser Gly Ser Ala
1               5                   10                  15

Phe Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala
            20                  25                  30

His Arg Tyr Asn Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu
        35                  40                  45

Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Ser Tyr Asp Glu His Ala
    50                  55                  60

Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Ala Ile Pro Asn Leu Arg Glu Asn Tyr Gly Glu Leu Ala
            100                 105                 110

Asp Cys Cys Thr Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Ser Leu Pro Pro Phe Glu Arg Pro Glu Ala
    130                 135                 140

Glu Ala Met Cys Thr Ser Phe Lys Glu Asn Pro Thr Thr Phe Met Gly
145                 150                 155                 160

His Tyr Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Tyr Tyr Ala Glu Gln Tyr Asn Glu Ile Leu Thr Gln Cys
            180                 185                 190

Cys Ala Glu Ala Asp Lys Glu Ser Cys Leu Thr Pro Lys Leu Asp Gly
        195                 200                 205

Val Lys Glu Lys Ala Leu Val Ser Ser Val Arg Gln Arg Met Lys Cys
    210                 215                 220
```

```
Ser Ser Met Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Thr Phe Pro Asn Ala Asp Phe Ala Glu Ile Thr
                245                 250                 255

Lys Leu Ala Thr Asp Leu Thr Lys Val Asn Lys Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met
        275                 280                 285

Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Thr Cys Cys Asp
    290                 295                 300

Lys Pro Leu Leu Lys Lys Ala His Cys Leu Ser Glu Val Glu His Asp
305                 310                 315                 320

Thr Met Pro Ala Asp Leu Pro Ala Ile Ala Ala Asp Phe Val Glu Asp
                325                 330                 335

Gln Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Glu Ala Asn Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu
385                 390                 395                 400

Phe Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys
                405                 410                 415

Asp Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Ile Leu
            420                 425                 430

Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu
    450                 455                 460

Pro Glu Asp Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile
465                 470                 475                 480

Leu Asn Arg Val Cys Leu Leu His Glu Lys Thr Pro Val Ser Glu His
                485                 490                 495

Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys Glu
```

```
Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Glu Lys Glu
    530                 535                 540

Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Ala Glu Gln Leu Lys Thr Val Met Asp Asp Phe Ala
                565                 570                 575

Gln Phe Leu Asp Thr Cys Cys Lys Ala Ala Asp Lys Asp Thr Cys Phe
            580                 585                 590

Ser Thr Glu Gly Pro Asn Leu Val Thr Arg Cys Lys Asp Ala Leu Ala
        595                 600                 605
```

<210> 10

<211> 608

<212> PRT

<213> Rattus norvegicus

<400> 10

```
Met Lys Trp Val Thr Phe Leu Leu Leu Leu Phe Ile Ser Gly Ser Ala
1               5                   10                  15

Phe Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Gln His Phe Lys Gly Leu Val Leu
        35                  40                  45

Ile Ala Phe Ser Gln Tyr Leu Gln Lys Cys Pro Tyr Glu Glu His Ile
    50                  55                  60

Lys Leu Val Gln Glu Val Thr Asp Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Asn Ala Glu Asn Cys Asp Lys Ser Ile His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Ala Ile Pro Lys Leu Arg Asp Asn Tyr Gly Glu Leu Ala
            100                 105                 110

Asp Cys Cys Ala Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asp Asp Asn Pro Asn Leu Pro Pro Phe Gln Arg Pro Glu Ala
    130                 135                 140

Glu Ala Met Cys Thr Ser Phe Gln Glu Asn Pro Thr Ser Phe Leu Gly
145                 150                 155                 160

His Tyr Leu His Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Tyr Tyr Ala Glu Lys Tyr Asn Glu Val Leu Thr Gln Cys
            180                 185                 190

Cys Thr Glu Ser Asp Lys Ala Ala Cys Leu Thr Pro Lys Leu Asp Ala
```

```
        195                 200                 205

Val Lys Glu Lys Ala Leu Val Ala Ala Val Arg Gln Arg Met Lys Cys
    210                 215                 220

Ser Ser Met Gln Arg Phe Gly Glu Arg Ala Phe Lys Ala Trp Ala Val
225                 230                 235                 240

Ala Arg Met Ser Gln Arg Phe Pro Asn Ala Glu Phe Ala Glu Ile Thr
                245                 250                 255

Lys Leu Ala Thr Asp Val Thr Lys Ile Asn Lys Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Glu Leu Ala Lys Tyr Met
        275                 280                 285

Cys Glu Asn Gln Ala Thr Ile Ser Ser Lys Leu Gln Ala Cys Cys Asp
    290                 295                 300

Lys Pro Val Leu Gln Lys Ser Gln Cys Leu Ala Glu Ile Glu His Asp
305                 310                 315                 320

Asn Ile Pro Ala Asp Leu Pro Ser Ile Ala Ala Asp Phe Val Glu Asp
                325                 330                 335

Lys Glu Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Thr Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Lys Tyr Glu Ala Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Glu Gly Asp Pro Pro Ala Cys Tyr Gly Thr Val Leu Ala Glu
385                 390                 395                 400

Phe Gln Pro Leu Val Glu Glu Pro Lys Asn Leu Val Lys Thr Asn Cys
                405                 410                 415

Glu Leu Tyr Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Val Leu
            420                 425                 430

Val Arg Tyr Thr Gln Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Ala Ala Arg Asn Leu Gly Arg Val Gly Thr Lys Cys Cys Thr Leu
    450                 455                 460

Pro Glu Ala Gln Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Ala Ile
465                 470                 475                 480

Leu Asn Arg Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Glu Lys
                485                 490                 495

Val Thr Lys Cys Cys Ser Gly Ser Leu Val Glu Arg Arg Pro Cys Phe
            500                 505                 510
```

```
Ser Ala Leu Thr Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Lys Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ser Asp Ile Cys Thr Leu Pro Asp Lys Glu
    530                 535                 540

Lys Gln Ile Lys Lys Gln Thr Ala Leu Ala Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Glu Asp Gln Leu Lys Thr Val Met Gly Asp Phe Ala
                565                 570                 575

Gln Phe Val Asp Lys Cys Cys Lys Ala Ala Asp Lys Asp Asn Cys Phe
            580                 585                 590

Ala Thr Glu Gly Pro Asn Leu Val Ala Arg Ser Lys Glu Ala Leu Ala
        595                 600                 605
```

<210> 11

<211> 607

<212> PRT

<213> Bos taurus

<400> 11

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Leu Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Thr His Lys Ser Glu Ile Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Glu His Phe Lys Gly Leu Val Leu
        35                  40                  45

Ile Ala Phe Ser Gln Tyr Leu Gln Gln Cys Pro Phe Asp Glu His Val
    50                  55                  60

Lys Leu Val Asn Glu Leu Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser His Ala Gly Cys Glu Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Glu Leu Cys Lys Val Ala Ser Leu Arg Glu Thr Tyr Gly Asp Met Ala
            100                 105                 110

Asp Cys Cys Glu Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Ser
        115                 120                 125

His Lys Asp Asp Ser Pro Asp Leu Pro Lys Leu Lys Pro Asp Pro Asn

    130                 135                 140

Thr Leu Cys Asp Glu Phe Lys Ala Asp Glu Lys Lys Phe Trp Gly Lys
```

145 150 155 160

Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
165 170 175

Leu Leu Tyr Tyr Ala Asn Lys Tyr Asn Gly Val Phe Gln Glu Cys Cys
180 185 190

Gln Ala Glu Asp Lys Gly Ala Cys Leu Leu Pro Lys Ile Glu Thr Met
195 200 205

Arg Glu Lys Val Leu Ala Ser Ser Ala Arg Gln Arg Leu Arg Cys Ala
210 215 220

Ser Ile Gln Lys Phe Gly Glu Arg Ala Leu Lys Ala Trp Ser Val Ala
225 230 235 240

Arg Leu Ser Gln Lys Phe Pro Lys Ala Glu Phe Val Glu Val Thr Lys
245 250 255

Leu Val Thr Asp Leu Thr Lys Val His Lys Glu Cys Cys His Gly Asp
260 265 270

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
275 280 285

Asp Asn Gln Asp Thr Ile Ser Ser Lys Leu Lys Glu Cys Cys Asp Lys
290 295 300

Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu Lys Asp Ala
305 310 315 320

Ile Pro Glu Asn Leu Pro Pro Leu Thr Ala Asp Phe Ala Glu Asp Lys
325 330 335

Asp Val Cys Lys Asn Tyr Gln Glu Ala Lys Asp Ala Phe Leu Gly Ser
340 345 350

Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Glu Tyr Ala Val Ser Val
355 360 365

Leu Leu Arg Leu Ala Lys Glu Tyr Glu Ala Thr Leu Glu Glu Cys Cys
370 375 380

Ala Lys Asp Asp Pro His Ala Cys Tyr Ser Thr Val Phe Asp Lys Leu
385 390 395 400

Lys His Leu Val Asp Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Asp
405 410 415

Gln Phe Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Leu Ile Val
420 425 430

Arg Tyr Thr Arg Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu
435 440 445

Val Ser Arg Ser Leu Gly Lys Val Gly Thr Arg Cys Cys Thr Lys Pro
450 455 460

```
Glu Ser Glu Arg Met Pro Cys Thr Glu Asp Tyr Leu Ser Leu Ile Leu
465                 470                 475                 480

Asn Arg Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Glu Lys Val
                485                 490                 495

Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser
            500                 505                 510

Ala Leu Thr Pro Asp Glu Thr Tyr Val Pro Lys Ala Phe Asp Glu Lys
        515                 520                 525

Leu Phe Thr Phe His Ala Asp Ile Cys Thr Leu Pro Asp Thr Glu Lys
    530                 535                 540

Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Leu Lys His Lys Pro
545                 550                 555                 560

Lys Ala Thr Glu Glu Gln Leu Lys Thr Val Met Glu Asn Phe Val Ala
                565                 570                 575

Phe Val Asp Lys Cys Cys Ala Ala Asp Asp Lys Glu Ala Cys Phe Ala
            580                 585                 590

Val Glu Gly Pro Lys Leu Val Val Ser Thr Gln Thr Ala Leu Ala
        595                 600                 605
```

<210> 12

<211> 607

<212> PRT

<213> Equus caballus

<400> 12

```
Met Lys Trp Val Thr Phe Val Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Gly Val Leu Arg Arg Asp Thr His Lys Ser Glu Ile Ala
            20                  25                  30

His Arg Phe Asn Asp Leu Gly Glu Lys His Phe Lys Gly Leu Val Leu
        35                  40                  45

Val Ala Phe Ser Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Lys Cys Ala Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Thr Leu Arg Ala Thr Tyr Gly Glu Leu Ala
            100                 105                 110

Asp Cys Cys Glu Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Thr
        115                 120                 125
```

```
His Lys Asp Asp His Pro Asn Leu Pro Lys Leu Lys Pro Glu Pro Asp
    130                 135                 140

Ala Gln Cys Ala Ala Phe Gln Glu Asp Pro Asp Lys Phe Leu Gly Lys
145                 150                 155                 160

Tyr Leu Tyr Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Gly Pro Glu
                165                 170                 175

Leu Leu Phe His Ala Glu Glu Tyr Lys Ala Asp Phe Thr Glu Cys Cys
            180                 185                 190

Pro Ala Asp Asp Lys Leu Ala Cys Leu Ile Pro Lys Leu Asp Ala Leu
        195                 200                 205

Lys Glu Arg Ile Leu Leu Ser Ser Ala Lys Glu Arg Leu Lys Cys Ser
    210                 215                 220

Ser Phe Gln Asn Phe Gly Glu Arg Ala Val Lys Ala Trp Ser Val Ala
225                 230                 235                 240

Arg Leu Ser Gln Lys Phe Pro Lys Ala Asp Phe Ala Glu Val Ser Lys
                245                 250                 255

Ile Val Thr Asp Leu Thr Lys Val His Lys Glu Cys Cys His Gly Asp
            260                 265                 270

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
        275                 280                 285

Glu His Gln Asp Ser Ile Ser Gly Lys Leu Lys Ala Cys Cys Asp Lys
    290                 295                 300

Pro Leu Leu Gln Lys Ser His Cys Ile Ala Glu Val Lys Glu Asp Asp
305                 310                 315                 320

Leu Pro Ser Asp Leu Pro Ala Leu Ala Ala Asp Phe Ala Glu Asp Lys
                325                 330                 335

Glu Ile Cys Lys His Tyr Lys Asp Ala Lys Asp Val Phe Leu Gly Thr
            340                 345                 350

Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser Leu
        355                 360                 365

Leu Leu Arg Ile Ala Lys Thr Tyr Glu Ala Thr Leu Glu Lys Cys Cys
    370                 375                 380

Ala Glu Ala Asp Pro Pro Ala Cys Tyr Arg Thr Val Phe Asp Gln Phe
385                 390                 395                 400

Thr Pro Leu Val Glu Glu Pro Lys Ser Leu Val Lys Lys Asn Cys Asp
                405                 410                 415

Leu Phe Glu Glu Val Gly Glu Tyr Asp Phe Gln Asn Ala Leu Ile Val
            420                 425                 430
```

```
Arg Tyr Thr Lys Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu
        435                 440                 445

Ile Gly Arg Thr Leu Gly Lys Val Gly Ser Arg Cys Cys Lys Leu Pro
    450                 455                 460

Glu Ser Glu Arg Leu Pro Cys Ser Glu Asn His Leu Ala Leu Ala Leu
465                 470                 475                 480

Asn Arg Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Glu Lys Ile
                485                 490                 495

Thr Lys Cys Cys Thr Asp Ser Leu Ala Glu Arg Arg Pro Cys Phe Ser
            500                 505                 510

Ala Leu Glu Leu Asp Glu Gly Tyr Val Pro Lys Glu Phe Lys Ala Glu
        515                 520                 525

Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Pro Glu Asp Glu Lys
    530                 535                 540

Gln Ile Lys Lys Gln Ser Ala Leu Ala Glu Leu Val Lys His Lys Pro
545                 550                 555                 560

Lys Ala Thr Lys Glu Gln Leu Lys Thr Val Leu Gly Asn Phe Ser Ala
                565                 570                 575

Phe Val Ala Lys Cys Cys Gly Arg Glu Asp Lys Glu Ala Cys Phe Ala
            580                 585                 590

Glu Glu Gly Pro Lys Leu Val Ala Ser Ser Gln Leu Ala Leu Ala
        595                 600                 605
```

<210> 13

<211> 607

<212> PRT

<213> Equus asinus

<400> 13

```
Met Lys Trp Val Thr Phe Val Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Phe Arg Gly Val Leu Arg Arg Asp Thr His Lys Ser Glu Ile Ala
            20                  25                  30

His Arg Phe Asn Asp Leu Gly Glu Lys His Phe Lys Gly Leu Val Leu
        35                  40                  45

Val Ala Phe Ser Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Val Asn Glu Val Thr Glu Phe Ala Lys Lys Cys Ala Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95
```

```
Lys Leu Cys Thr Val Ala Thr Leu Arg Ala Thr Tyr Gly Glu Leu Ala
            100                 105                 110

Asp Cys Cys Glu Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Thr
        115                 120                 125

His Lys Asp Asp His Pro Asn Leu Pro Lys Leu Lys Pro Glu Pro Asp
    130                 135                 140

Ala Gln Cys Ala Ala Phe Gln Glu Asp Pro Asp Lys Phe Leu Gly Lys
145                 150                 155                 160

Tyr Leu Tyr Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Gly Pro Glu
                165                 170                 175

Leu Leu Phe His Ala Glu Glu Tyr Lys Ala Asp Phe Thr Glu Cys Cys
            180                 185                 190

Pro Ala Asp Asp Lys Ala Gly Cys Leu Ile Pro Lys Leu Asp Ala Leu
        195                 200                 205

Lys Glu Arg Ile Leu Leu Ser Ser Ala Lys Glu Arg Leu Lys Cys Ser
    210                 215                 220

Ser Phe Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ser Val Ala
225                 230                 235                 240

Arg Leu Ser Gln Lys Phe Pro Lys Ala Asp Phe Ala Glu Val Ser Lys
                245                 250                 255

Ile Val Thr Asp Leu Thr Lys Val His Lys Glu Cys Cys His Gly Asp
            260                 265                 270

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Thr Lys Tyr Ile Cys
        275                 280                 285

Glu His Gln Asp Ser Ile Ser Gly Lys Leu Lys Ala Cys Cys Asp Lys
    290                 295                 300

Pro Leu Leu Gln Lys Ser His Cys Ile Ala Glu Val Lys Glu Asp Asp
305                 310                 315                 320

Leu Pro Ser Asp Leu Pro Ala Leu Ala Ala Asp Phe Ala Glu Asp Lys
                325                 330                 335

Glu Ile Cys Lys His Tyr Lys Asp Ala Lys Asp Val Phe Leu Gly Thr
            340                 345                 350

Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser Leu
        355                 360                 365

Leu Leu Arg Ile Ala Lys Thr Tyr Glu Ala Thr Leu Glu Lys Cys Cys

    370                 375                 380

Ala Glu Ala Asp Pro Pro Ala Cys Tyr Ala Thr Val Phe Asp Gln Phe
385                 390                 395                 400
```

```
Thr Pro Leu Val Glu Glu Pro Lys Ser Leu Val Lys Lys Asn Cys Asp
                405                 410                 415

Leu Phe Glu Glu Val Gly Glu Tyr Asp Phe Gln Asn Ala Leu Ile Val
            420                 425                 430

Arg Tyr Thr Lys Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu
        435                 440                 445

Ile Gly Arg Thr Leu Gly Lys Val Gly Ser Arg Cys Cys Lys Leu Pro
    450                 455                 460

Glu Ser Glu Arg Leu Pro Cys Ser Glu Asn His Leu Ala Leu Ala Leu
465                 470                 475                 480

Asn Arg Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Glu Lys Ile
                485                 490                 495

Thr Lys Cys Cys Thr Asp Ser Leu Ala Glu Arg Arg Pro Cys Phe Ser
            500                 505                 510

Ala Leu Glu Leu Asp Glu Gly Tyr Ile Pro Lys Glu Phe Lys Ala Glu
        515                 520                 525

Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Pro Glu Asp Glu Lys
    530                 535                 540

Gln Ile Lys Lys Gln Ser Ala Leu Ala Glu Leu Val Lys His Lys Pro
545                 550                 555                 560

Lys Ala Thr Lys Glu Gln Leu Lys Thr Val Leu Gly Asn Phe Ser Ala
                565                 570                 575

Phe Val Ala Lys Cys Cys Gly Ala Glu Asp Lys Glu Ala Cys Phe Ala
            580                 585                 590

Glu Glu Gly Pro Lys Leu Val Ala Ser Ser Gln Leu Ala Leu Ala
        595                 600                 605
```

<210> 14

<211> 608

<212> PRT

<213> Oryctolagus cuniculus

<400> 14

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Glu Ala His Lys Ser Glu Ile Ala
            20                  25                  30

His Arg Phe Asn Asp Val Gly Glu Glu His Phe Ile Gly Leu Val Leu
        35                  40                  45

Ile Thr Phe Ser Gln Tyr Leu Gln Lys Cys Pro Tyr Glu Glu His Ala
```

```
    50                  55                  60

Lys Leu Val Lys Glu Val Thr Asp Leu Ala Lys Ala Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Ala Asn Cys Asp Lys Ser Leu His Asp Ile Phe Gly Asp
                85                  90                  95

Lys Ile Cys Ala Leu Pro Ser Leu Arg Asp Thr Tyr Gly Asp Val Ala
            100                 105                 110

Asp Cys Cys Glu Lys Lys Glu Pro Glu Arg Asn Glu Cys Phe Leu His
        115                 120                 125

His Lys Asp Asp Lys Pro Asp Leu Pro Pro Phe Ala Arg Pro Glu Ala
    130                 135                 140

Asp Val Leu Cys Lys Ala Phe His Asp Asp Glu Lys Ala Phe Phe Gly
145                 150                 155                 160

His Tyr Leu Tyr Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Tyr Tyr Ala Gln Lys Tyr Lys Ala Ile Leu Thr Glu Cys
            180                 185                 190

Cys Glu Ala Ala Asp Lys Gly Ala Cys Leu Thr Pro Lys Leu Asp Ala
        195                 200                 205

Leu Glu Gly Lys Ser Leu Ile Ser Ala Ala Gln Glu Arg Leu Arg Cys
    210                 215                 220

Ala Ser Ile Gln Lys Phe Gly Asp Arg Ala Tyr Lys Ala Trp Ala Leu
225                 230                 235                 240

Val Arg Leu Ser Gln Arg Phe Pro Lys Ala Asp Phe Thr Asp Ile Ser
                245                 250                 255

Lys Ile Val Thr Asp Leu Thr Lys Val His Lys Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Met
        275                 280                 285

Cys Glu His Gln Glu Thr Ile Ser Ser His Leu Lys Glu Cys Cys Asp
    290                 295                 300

Lys Pro Ile Leu Glu Lys Ala His Cys Ile Tyr Gly Leu His Asn Asp
305                 310                 315                 320

Glu Thr Pro Ala Gly Leu Pro Ala Val Ala Glu Glu Phe Val Glu Asp
                325                 330                 335

Lys Asp Val Cys Lys Asn Tyr Glu Glu Ala Lys Asp Leu Phe Leu Gly
            340                 345                 350

Lys Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Val
        355                 360                 365
```

```
Leu Leu Leu Arg Leu Gly Lys Ala Tyr Glu Ala Thr Leu Lys Lys Cys
    370                 375                 380

Cys Ala Thr Asp Asp Pro His Ala Cys Tyr Ala Lys Val Leu Asp Glu
385                 390                 395                 400

Phe Gln Pro Leu Val Asp Glu Pro Lys Asn Leu Val Lys Gln Asn Cys
                405                 410                 415

Glu Leu Tyr Glu Gln Leu Gly Asp Tyr Asn Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Ile Ser Arg Ser Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His
    450                 455                 460

Pro Glu Ala Glu Arg Leu Pro Cys Val Glu Asp Tyr Leu Ser Val Val
465                 470                 475                 480

Leu Asn Arg Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Glu Lys
                485                 490                 495

Val Thr Lys Cys Cys Ser Glu Ser Leu Val Asp Arg Arg Pro Cys Phe
            500                 505                 510

Ser Ala Leu Gly Pro Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Pro Glu Thr Glu
    530                 535                 540

Arg Lys Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys
545                 550                 555                 560

Pro His Ala Thr Asn Asp Gln Leu Lys Thr Val Val Gly Glu Phe Thr
                565                 570                 575

Ala Leu Leu Asp Lys Cys Cys Ser Ala Glu Asp Lys Glu Ala Cys Phe
            580                 585                 590

Ala Val Glu Gly Pro Lys Leu Val Glu Ser Ser Lys Ala Thr Leu Gly
        595                 600                 605
```

<210> 15

<211> 583

<212> PRT

<213> Capra hircus

<400> 15

```
Asp Thr His Lys Ser Glu Ile Ala His Arg Phe Asn Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Gln Gly Leu Val Leu Ile Ala Phe Ser Gln Tyr Leu Gln
            20                  25                  30
```

```
Gln Cys Pro Phe Asp Glu His Val Lys Leu Val Lys Glu Leu Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser His Ala Gly Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Glu Leu Cys Lys Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Asp Met Ala Asp Cys Cys Glu Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Lys His Lys Asp Asp Ser Pro Asp Leu
            100                 105                 110

Pro Lys Leu Lys Pro Glu Pro Asp Thr Leu Cys Ala Glu Phe Lys Ala
        115                 120                 125

Asp Glu Lys Lys Phe Trp Gly Lys Tyr Leu Tyr Glu Val Ala Arg Arg
    130                 135                 140

His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Tyr Tyr Ala Asn Lys Tyr
145                 150                 155                 160

Asn Gly Val Phe Gln Glu Cys Cys Gln Ala Glu Asp Lys Gly Ala Cys
                165                 170                 175

Leu Leu Pro Lys Ile Glu Thr Met Arg Glu Lys Val Leu Ala Ser Ser
            180                 185                 190

Ala Arg Gln Arg Leu Arg Cys Ala Ser Ile Gln Lys Phe Gly Glu Arg
        195                 200                 205

Ala Leu Lys Ala Trp Ser Val Ala Arg Leu Ser Gln Lys Phe Pro Lys
    210                 215                 220

Ala Asp Phe Thr Asp Val Thr Lys Ile Val Thr Asp Leu Thr Lys Val
225                 230                 235                 240

His Lys Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg
                245                 250                 255

Ala Asp Leu Ala Lys Tyr Ile Cys Asp His Gln Asp Thr Leu Ser Ser
            260                 265                 270

Lys Leu Lys Glu Cys Cys Asp Lys Pro Val Leu Glu Lys Ser His Cys
        275                 280                 285

Ile Ala Glu Ile Asp Lys Asp Ala Val Pro Glu Asn Leu Pro Pro Leu
    290                 295                 300

Thr Ala Asp Phe Ala Glu Asp Lys Glu Val Cys Lys Asn Tyr Gln Glu
305                 310                 315                 320

Ala Lys Asp Val Phe Leu Gly Ser Phe Leu Tyr Glu Tyr Ser Arg Arg
                325                 330                 335
```

```
His Pro Glu Tyr Ala Val Ser Val Leu Leu Arg Leu Ala Lys Glu Tyr
            340                 345                 350

Glu Ala Thr Leu Glu Asp Cys Cys Ala Lys Glu Asp Pro His Ala Cys
        355                 360                 365

Tyr Ala Thr Val Phe Asp Lys Leu Lys His Leu Val Asp Glu Pro Gln
    370                 375                 380

Asn Leu Ile Lys Lys Asn Cys Glu Leu Phe Glu Lys His Gly Glu Tyr
385                 390                 395                 400

Gly Phe Gln Asn Ala Leu Ile Val Arg Tyr Thr Arg Lys Ala Pro Gln
                405                 410                 415

Val Ser Thr Pro Thr Leu Val Glu Ile Ser Arg Ser Leu Gly Lys Val
            420                 425                 430

Gly Thr Lys Cys Cys Ala Lys Pro Glu Ser Glu Arg Met Pro Cys Thr
        435                 440                 445

Glu Asp Tyr Leu Ser Leu Ile Leu Asn Arg Leu Cys Val Leu His Glu
    450                 455                 460

Lys Thr Pro Val Ser Glu Lys Val Thr Lys Cys Cys Thr Glu Ser Leu
465                 470                 475                 480

Val Asn Arg Arg Pro Cys Phe Ser Asp Leu Thr Leu Asp Glu Thr Tyr
                485                 490                 495

Val Pro Lys Pro Phe Asp Gly Glu Ser Phe Thr Phe His Ala Asp Ile
            500                 505                 510

Cys Thr Leu Pro Asp Thr Glu Lys Gln Ile Lys Lys Gln Thr Ala Leu
        515                 520                 525

Val Glu Leu Leu Lys His Lys Pro Lys Ala Thr Asp Glu Gln Leu Lys
    530                 535                 540

Thr Val Met Glu Asn Phe Val Ala Phe Val Asp Lys Cys Cys Ala Ala
545                 550                 555                 560

Asp Asp Lys Glu Gly Cys Phe Leu Leu Glu Gly Pro Lys Leu Val Ala
                565                 570                 575

Ser Thr Gln Ala Ala Leu Ala
            580
```

<210> 16

<211> 607

<212> PRT

<213> Ovis aries

<400> 16

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Leu Leu Phe Ser Ser Ala
1               5                  10                  15
```

```
Tyr Ser Arg Gly Val Phe Arg Arg Asp Thr His Lys Ser Glu Ile Ala
            20                  25                  30

His Arg Phe Asn Asp Leu Gly Glu Glu Asn Phe Gln Gly Leu Val Leu
        35                  40                  45

Ile Ala Phe Ser Gln Tyr Leu Gln Gln Cys Pro Phe Asp Glu His Val
    50                  55                  60

Lys Leu Val Lys Glu Leu Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser His Ala Gly Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Glu Leu Cys Lys Val Ala Thr Leu Arg Glu Thr Tyr Gly Asp Met Ala
            100                 105                 110

Asp Cys Cys Glu Lys Gln Glu Pro Glu Arg Asn Glu Cys Phe Leu Asn
        115                 120                 125

His Lys Asp Asp Ser Pro Asp Leu Pro Lys Leu Lys Pro Glu Pro Asp
    130                 135                 140

Thr Leu Cys Ala Glu Phe Lys Ala Asp Glu Lys Lys Phe Trp Gly Lys
145                 150                 155                 160

Tyr Leu Tyr Glu Val Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
                165                 170                 175

Leu Leu Tyr Tyr Ala Asn Lys Tyr Asn Gly Val Phe Gln Glu Cys Cys
            180                 185                 190

Gln Ala Glu Asp Lys Gly Ala Cys Leu Leu Pro Lys Ile Asp Ala Met
        195                 200                 205

Arg Glu Lys Val Leu Ala Ser Ser Ala Arg Gln Arg Leu Arg Cys Ala
    210                 215                 220

Ser Ile Gln Lys Phe Gly Glu Arg Ala Leu Lys Ala Trp Ser Val Ala
225                 230                 235                 240

Arg Leu Ser Gln Lys Phe Pro Lys Ala Asp Phe Thr Asp Val Thr Lys

                245                 250                 255

Ile Val Thr Asp Leu Thr Lys Val His Lys Glu Cys Cys His Gly Asp
            260                 265                 270

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
        275                 280                 285

Asp His Gln Asp Ala Leu Ser Ser Lys Leu Lys Glu Cys Cys Asp Lys
    290                 295                 300

Pro Val Leu Glu Lys Ser His Cys Ile Ala Glu Val Asp Lys Asp Ala
```

305 310 315 320

Val Pro Glu Asn Leu Pro Pro Leu Thr Ala Asp Phe Ala Glu Asp Lys
325 330 335

Glu Val Cys Lys Asn Tyr Gln Glu Ala Lys Asp Val Phe Leu Gly Ser
340 345 350

Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Glu Tyr Ala Val Ser Val
355 360 365

Leu Leu Arg Leu Ala Lys Glu Tyr Glu Ala Thr Leu Glu Asp Cys Cys
370 375 380

Ala Lys Glu Asp Pro His Ala Cys Tyr Ala Thr Val Phe Asp Lys Leu
385 390 395 400

Lys His Leu Val Asp Glu Pro Gln Asn Leu Ile Lys Lys Asn Cys Glu
405 410 415

Leu Phe Glu Lys His Gly Glu Tyr Gly Phe Gln Asn Ala Leu Ile Val
420 425 430

Arg Tyr Thr Arg Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val Glu
435 440 445

Ile Ser Arg Ser Leu Gly Lys Val Gly Thr Lys Cys Cys Ala Lys Pro
450 455 460

Glu Ser Glu Arg Met Pro Cys Thr Glu Asp Tyr Leu Ser Leu Ile Leu
465 470 475 480

Asn Arg Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Glu Lys Val
485 490 495

Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser
500 505 510

Asp Leu Thr Leu Asp Glu Thr Tyr Val Pro Lys Pro Phe Asp Glu Lys
515 520 525

Phe Phe Thr Phe His Ala Asp Ile Cys Thr Leu Pro Asp Thr Glu Lys
530 535 540

Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Leu Lys His Lys Pro
545 550 555 560

Lys Ala Thr Asp Glu Gln Leu Lys Thr Val Met Glu Asn Phe Val Ala
565 570 575

Phe Val Asp Lys Cys Cys Ala Ala Asp Asp Lys Glu Gly Cys Phe Val
580 585 590

Leu Glu Gly Pro Lys Leu Val Ala Ser Thr Gln Ala Ala Leu Ala
595 600 605

<210> 17

<211> 608

<212> PRT

<213> canis lupus familiaris

<400> 17

```
Met Lys Trp Val Thr Phe Ile Ser Leu Phe Phe Leu Phe Ser Ser Ala
1               5                  10                  15

Tyr Ser Arg Gly Leu Val Arg Arg Glu Ala Tyr Lys Ser Glu Ile Ala
            20                  25                  30

His Arg Tyr Asn Asp Leu Gly Glu Glu His Phe Arg Gly Leu Val Leu
        35                  40                  45

Val Ala Phe Ser Gln Tyr Leu Gln Gln Cys Pro Phe Glu Asp His Val
    50                  55                  60

Lys Leu Ala Lys Glu Val Thr Glu Phe Ala Lys Ala Cys Ala Ala Glu
65                  70                  75                  80

Glu Ser Gly Ala Asn Cys Asp Lys Ser Leu His Thr Leu Phe Gly Asp
                85                  90                  95

Lys Leu Cys Thr Val Ala Ser Leu Arg Asp Lys Tyr Gly Asp Met Ala
            100                 105                 110

Asp Cys Cys Glu Lys Gln Glu Pro Asp Arg Asn Glu Cys Phe Leu Ala
        115                 120                 125

His Lys Asp Asp Asn Pro Gly Phe Pro Pro Leu Val Ala Pro Glu Pro
    130                 135                 140

Asp Ala Leu Cys Ala Ala Phe Gln Asp Asn Glu Gln Leu Phe Leu Gly
145                 150                 155                 160

Lys Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro
                165                 170                 175

Glu Leu Leu Tyr Tyr Ala Gln Gln Tyr Lys Gly Val Phe Ala Glu Cys
            180                 185                 190

Cys Gln Ala Ala Asp Lys Ala Ala Cys Leu Gly Pro Lys Ile Glu Ala
        195                 200                 205

Leu Arg Glu Lys Val Leu Leu Ser Ser Ala Lys Glu Arg Phe Lys Cys
    210                 215                 220

Ala Ser Leu Gln Lys Phe Gly Asp Arg Ala Phe Lys Ala Trp Ser Val
225                 230                 235                 240

Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Asp Phe Ala Glu Ile Ser
                245                 250                 255

Lys Val Val Thr Asp Leu Thr Lys Val His Lys Glu Cys Cys His Gly
            260                 265                 270

Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Met
```

```
        275                 280                 285

Cys Glu Asn Gln Asp Ser Ile Ser Thr Lys Leu Lys Glu Cys Cys Asp
    290                 295                 300

Lys Pro Val Leu Glu Lys Ser Gln Cys Leu Ala Glu Val Glu Arg Asp
305                 310                 315                 320

Glu Leu Pro Gly Asp Leu Pro Ser Leu Ala Ala Asp Phe Val Glu Asp
                325                 330                 335

Lys Glu Val Cys Lys Asn Tyr Gln Glu Ala Lys Asp Val Phe Leu Gly
            340                 345                 350

Thr Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Glu Tyr Ser Val Ser
        355                 360                 365

Leu Leu Leu Arg Leu Ala Lys Glu Tyr Glu Ala Thr Leu Glu Lys Cys
    370                 375                 380

Cys Ala Thr Asp Asp Pro Pro Thr Cys Tyr Ala Lys Val Leu Asp Glu
385                 390                 395                 400

Phe Lys Pro Leu Val Asp Glu Pro Gln Asn Leu Val Lys Thr Asn Cys
                405                 410                 415

Glu Leu Phe Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Leu Leu
            420                 425                 430

Val Arg Tyr Thr Lys Lys Ala Pro Gln Val Ser Thr Pro Thr Leu Val
        435                 440                 445

Glu Val Ser Arg Lys Leu Gly Lys Val Gly Thr Lys Cys Cys Lys Lys
    450                 455                 460

Pro Glu Ser Glu Arg Met Ser Cys Ala Glu Asp Phe Leu Ser Val Val
465                 470                 475                 480

Leu Asn Arg Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Glu Arg
                485                 490                 495

Val Thr Lys Cys Cys Ser Glu Ser Leu Val Asn Arg Arg Pro Cys Phe
            500                 505                 510

Ser Gly Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala
        515                 520                 525

Glu Thr Phe Thr Phe His Ala Asp Leu Cys Thr Leu Pro Glu Ala Glu
    530                 535                 540

Lys Gln Val Lys Lys Gln Thr Ala Leu Val Glu Leu Leu Lys His Lys
545                 550                 555                 560

Pro Lys Ala Thr Asp Glu Gln Leu Lys Thr Val Met Gly Asp Phe Gly
                565                 570                 575

Ala Phe Val Glu Lys Cys Cys Ala Ala Glu Asn Lys Glu Gly Cys Phe
            580                 585                 590
```

580 585 590

Ser Glu Glu Gly Pro Lys Leu Val Ala Ala Ala Gln Ala Ala Leu Val
595 600 605

<210> 18

<211> 615

<212> PRT

<213> Gallus gallus

<400> 18

Met Lys Trp Val Thr Leu Ile Ser Phe Ile Phe Leu Phe Ser Ser Ala
1 5 10 15

Thr Ser Arg Asn Leu Gln Arg Phe Ala Arg Asp Ala Glu His Lys Ser
20 25 30

Glu Ile Ala His Arg Tyr Asn Asp Leu Lys Glu Glu Thr Phe Lys Ala
35 40 45

Val Ala Met Ile Thr Phe Ala Gln Tyr Leu Gln Arg Cys Ser Tyr Glu
50 55 60

Gly Leu Ser Lys Leu Val Lys Asp Val Val Asp Leu Ala Gln Lys Cys
65 70 75 80

Val Ala Asn Glu Asp Ala Pro Glu Cys Ser Lys Pro Leu Pro Ser Ile
85 90 95

Ile Leu Asp Glu Ile Cys Gln Val Glu Lys Leu Arg Asp Ser Tyr Gly
100 105 110

Ala Met Ala Asp Cys Cys Ser Lys Ala Asp Pro Glu Arg Asn Glu Cys
115 120 125

Phe Leu Ser Phe Lys Val Ser Gln Pro Asp Phe Val Gln Pro Tyr Gln
130 135 140

Arg Pro Ala Ser Asp Val Ile Cys Gln Glu Tyr Gln Asp Asn Arg Val
145 150 155 160

Ser Phe Leu Gly His Phe Ile Tyr Ser Val Ala Arg Arg His Pro Phe
165 170 175

Leu Tyr Ala Pro Ala Ile Leu Ser Phe Ala Val Asp Phe Glu His Ala
180 185 190

Leu Gln Ser Cys Cys Lys Glu Ser Asp Val Gly Ala Cys Leu Asp Thr
195 200 205

Lys Glu Ile Val Met Arg Glu Lys Ala Lys Gly Val Ser Val Lys Gln
210 215 220

Gln Tyr Phe Cys Gly Ile Leu Lys Gln Phe Gly Asp Arg Val Phe Gln
225 230 235 240

Ala Arg Gln Leu Ile Tyr Leu Ser Gln Lys Tyr Pro Lys Ala Pro Phe

```
                245                 250                 255

Ser Glu Val Ser Lys Phe Val His Asp Ser Ile Gly Val His Lys Glu
            260                 265                 270

Cys Cys Glu Gly Asp Met Val Glu Cys Met Asp Asp Met Ala Arg Met
        275                 280                 285

Met Ser Asn Leu Cys Ser Gln Gln Asp Val Phe Ser Gly Lys Ile Lys
    290                 295                 300

Asp Cys Cys Glu Lys Pro Ile Val Glu Arg Ser Gln Cys Ile Met Glu
305                 310                 315                 320

Ala Glu Phe Asp Glu Lys Pro Ala Asp Leu Pro Ser Leu Val Glu Lys
                325                 330                 335

Tyr Ile Glu Asp Lys Glu Val Cys Lys Ser Phe Glu Ala Gly His Asp
            340                 345                 350

Ala Phe Met Ala Glu Phe Val Tyr Glu Tyr Ser Arg Arg His Pro Glu
        355                 360                 365

Phe Ser Ile Gln Leu Ile Met Arg Ile Ala Lys Gly Tyr Glu Ser Leu
    370                 375                 380

Leu Glu Lys Cys Cys Lys Thr Asp Asn Pro Ala Glu Cys Tyr Ala Asn
385                 390                 395                 400

Ala Gln Glu Gln Leu Asn Gln His Ile Lys Glu Thr Gln Asp Val Val
                405                 410                 415

Lys Thr Asn Cys Asp Leu Leu His Asp His Gly Glu Ala Asp Phe Leu
            420                 425                 430

Lys Ser Ile Leu Ile Arg Tyr Thr Lys Lys Met Pro Gln Val Pro Thr
        435                 440                 445

Asp Leu Leu Leu Glu Thr Gly Lys Lys Met Thr Thr Ile Gly Thr Lys
    450                 455                 460

Cys Cys Gln Leu Gly Glu Asp Arg Arg Met Ala Cys Ser Glu Gly Tyr
465                 470                 475                 480

Leu Ser Ile Val Ile His Asp Thr Cys Arg Lys Gln Glu Thr Thr Pro

                485                 490                 495

Ile Asn Asp Asn Val Ser Gln Cys Cys Ser Gln Leu Tyr Ala Asn Arg
            500                 505                 510

Arg Pro Cys Phe Thr Ala Met Gly Val Asp Thr Lys Tyr Val Pro Pro
        515                 520                 525

Pro Phe Asn Pro Asp Met Phe Ser Phe Asp Glu Lys Leu Cys Ser Ala
    530                 535                 540
```

```
Pro Ala Glu Glu Arg Glu Val Gly Gln Met Lys Leu Leu Ile Asn Leu
545                 550                 555                 560

Ile Lys Arg Lys Pro Gln Met Thr Glu Glu Gln Ile Lys Thr Ile Ala
                565                 570                 575

Asp Gly Phe Thr Ala Met Val Asp Lys Cys Cys Lys Gln Ser Asp Ile
            580                 585                 590

Asn Thr Cys Phe Gly Glu Glu Gly Ala Asn Leu Ile Val Gln Ser Arg
        595                 600                 605

Ala Thr Leu Gly Ile Gly Ala
    610                 615
```

<210> 19

<211> 607

<212> PRT

<213> Sus scrofa

<400> 19

```
Met Lys Trp Val Thr Phe Ile Ser Leu Leu Phe Leu Phe Ser Ser Ala
1               5                   10                  15

Tyr Ser Arg Gly Val Phe Arg Arg Asp Thr Tyr Lys Ser Glu Ile Ala
            20                  25                  30

His Arg Phe Lys Asp Leu Gly Glu Gln Tyr Phe Lys Gly Leu Val Leu
        35                  40                  45

Ile Ala Phe Ser Gln His Leu Gln Gln Cys Pro Tyr Glu Glu His Val
    50                  55                  60

Lys Leu Val Arg Glu Val Thr Glu Phe Ala Lys Thr Cys Val Ala Asp
65                  70                  75                  80

Glu Ser Ala Glu Asn Cys Asp Lys Ser Ile His Thr Leu Phe Gly Asp

                85                  90                  95

Lys Leu Cys Ala Ile Pro Ser Leu Arg Glu His Tyr Gly Asp Leu Ala
            100                 105                 110

Asp Cys Cys Glu Lys Glu Glu Pro Glu Arg Asn Glu Cys Phe Leu Gln
        115                 120                 125

His Lys Asn Asp Asn Pro Asp Ile Pro Lys Leu Lys Pro Asp Pro Val
    130                 135                 140

Ala Leu Cys Ala Asp Phe Gln Glu Asp Glu Gln Lys Phe Trp Gly Lys
145                 150                 155                 160

Tyr Leu Tyr Glu Ile Ala Arg Arg His Pro Tyr Phe Tyr Ala Pro Glu
                165                 170                 175

Leu Leu Tyr Tyr Ala Ile Ile Tyr Lys Asp Val Phe Ser Glu Cys Cys
```

```
Leu Leu Tyr Tyr Ala Ile Ile Tyr Lys Asp Val Phe Ser Glu Cys Cys
            180                 185                 190

Gln Ala Ala Asp Lys Ala Ala Cys Leu Leu Pro Lys Ile Glu His Leu
        195                 200                 205

Arg Glu Lys Val Leu Thr Ser Ala Ala Lys Gln Arg Leu Lys Cys Ala
    210                 215                 220

Ser Ile Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp Ser Leu Ala
225                 230                 235                 240

Arg Leu Ser Gln Arg Phe Pro Lys Ala Asp Phe Thr Glu Ile Ser Lys
                245                 250                 255

Ile Val Thr Asp Leu Ala Lys Val His Lys Glu Cys Cys His Gly Asp
            260                 265                 270

Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys Tyr Ile Cys
        275                 280                 285

Glu Asn Gln Asp Thr Ile Ser Thr Lys Leu Lys Glu Cys Cys Asp Lys
    290                 295                 300

Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Ala Lys Arg Asp Glu
305                 310                 315                 320

Leu Pro Ala Asp Leu Asn Pro Leu Glu His Asp Phe Val Glu Asp Lys
                325                 330                 335

Glu Val Cys Lys Asn Tyr Lys Glu Ala Lys His Val Phe Leu Gly Thr
            340                 345                 350

Phe Leu Tyr Glu Tyr Ser Arg Arg His Pro Asp Tyr Ser Val Ser Leu
        355                 360                 365

Leu Leu Arg Ile Ala Lys Ile Tyr Glu Ala Thr Leu Glu Asp Cys Cys
    370                 375                 380

Ala Lys Glu Asp Pro Pro Ala Cys Tyr Ala Thr Val Phe Asp Lys Phe
385                 390                 395                 400

Gln Pro Leu Val Asp Glu Pro Lys Asn Leu Ile Lys Gln Asn Cys Glu
                405                 410                 415

Leu Phe Glu Lys Leu Gly Glu Tyr Gly Phe Gln Asn Ala Leu Ile Val
            420                 425                 430

Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu
        435                 440                 445

Val Ala Arg Lys Leu Gly Leu Val Gly Ser Arg Cys Cys Lys Arg Pro
    450                 455                 460

Glu Glu Glu Arg Leu Ser Cys Ala Glu Asp Tyr Leu Ser Leu Val Leu
465                 470                 475                 480

Asn Arg Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Glu Lys Val
                485                 490                 495
```

```
Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser
            500                 505                 510

Ala Leu Thr Pro Asp Glu Thr Tyr Lys Pro Lys Glu Phe Val Glu Gly
        515                 520                 525

Thr Phe Thr Phe His Ala Asp Leu Cys Thr Leu Pro Glu Asp Glu Lys
    530                 535                 540

Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Leu Lys His Lys Pro
545                 550                 555                 560

His Ala Thr Glu Glu Gln Leu Arg Thr Val Leu Gly Asn Phe Ala Ala
                565                 570                 575

Phe Val Gln Lys Cys Cys Ala Ala Pro Asp His Glu Ala Cys Phe Ala
            580                 585                 590

Val Glu Gly Pro Lys Phe Val Ile Glu Ile Arg Gly Ile Leu Ala
        595                 600                 605
```

<210> 20

<211> 584

<212> PRT

<213> artificial sequence

<220>

<223> N terminal is residues 1 to 572 of HSA. C terminal is residues 573 to 584 of Macaque albumin.

<400> 20

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125
```

```
Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
```

```
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Phe Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Ala
            580
```

<210> 21

<211> 584

<212> PRT

<213> Artificial Sequence

<220>

<223> N terminal is residues 1 to 572 from HSA. C terminal is residues 573 to 584 from mouse albumin.

<400> 21

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95
```

```
Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala

305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
```

```
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Asn Leu Val
                565                 570                 575

Thr Arg Cys Lys Asp Ala Leu Ala
            580
```

<210> 22

<211> 584

<212> PRT

<213> Artificial Sequence

<220>

<223> N terminal is residues 1 to 572 of HSA. C terminal is residues 573 to 584 of rabbit albumin.

<400> 22

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45
```

```
Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350
```

```
Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
                565                 570                 575

Glu Ser Ser Lys Ala Thr Leu Gly
            580
```

<210> 23

<211> 584

<212> PRT

<213> Artificial Sequence

<220>

<223> N-terminal is residues 1 to 572 of HSA. C-terminal is residues 573 to 583 of sheep albumin.

<400> 23

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                  10                  15
```

```
1               5                  10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320
```

```
Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys

545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
                565                 570                 575

Ala Ser Thr Gln Ala Ala Leu Ala
            580
```

<210> 24

<211> 399

<212> PRT

<213> Artificial sequence

<220>

<223> Artificial albumin variant: human serum albumin domain 1 and human serum albumin domain 3

<400> 24

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala

                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
        195                 200                 205

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
    210                 215                 220

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
225                 230                 235                 240

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
                245                 250                 255

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
```

```
Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
            260                 265                 270

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
        275                 280                 285

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
    290                 295                 300

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
305                 310                 315                 320

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
                325                 330                 335

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
            340                 345                 350

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
        355                 360                 365

Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
    370                 375                 380

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
385                 390                 395
```

<210> 25

<211> 403

<212> PRT

<213> Artificial sequence

<220>

<223> Artificial albumin variant: human serum albumin domain 2 and human serum albumin domain 3

<400> 25

```
Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser Ser Ala Lys Gln Arg Leu
1               5                   10                  15

Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu Arg Ala Phe Lys Ala Trp
            20                  25                  30

Ala Val Ala Arg Leu Ser Gln Arg Phe Pro Lys Ala Glu Phe Ala Glu
        35                  40                  45

Val Ser Lys Leu Val Thr Asp Leu Thr Lys Val His Thr Glu Cys Cys
    50                  55                  60

His Gly Asp Leu Leu Glu Cys Ala Asp Asp Arg Ala Asp Leu Ala Lys
65                  70                  75                  80

Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser Ser Lys Leu Lys Glu Cys
                85                  90                  95

Cys Glu Lys Pro Leu Leu Glu Lys Ser His Cys Ile Ala Glu Val Glu
```

```
            100                 105                 110

Asn Asp Glu Met Pro Ala Asp Leu Pro Ser Leu Ala Ala Asp Phe Val
        115                 120                 125

Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala Glu Ala Lys Asp Val Phe
    130                 135                 140

Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg Arg His Pro Asp Tyr Ser
145                 150                 155                 160

Val Val Leu Leu Leu Arg Leu Ala Lys Thr Tyr Glu Thr Thr Leu Glu
                165                 170                 175

Lys Cys Cys Ala Ala Ala Asp Pro His Glu Cys Tyr Ala Lys Val Phe
            180                 185                 190

Asp Glu Phe Lys Pro Leu Val Glu Glu Pro Gln Asn Leu Ile Lys Gln
        195                 200                 205

Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala
    210                 215                 220

Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr
225                 230                 235                 240

Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys
                245                 250                 255

Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser
            260                 265                 270

Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser
        275                 280                 285

Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro
    290                 295                 300

Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe
305                 310                 315                 320

Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu
                325                 330                 335

Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys
            340                 345                 350

His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp
        355                 360                 365

Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr
    370                 375                 380

Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala
385                 390                 395                 400

Leu Gly Leu
```

-

<210> 26

<211> 410

<212> PRT

<213> Artificial sequence

<220>

<223> Artificial albumin variant: two consecutive copies of human serum albumin domain 3

<400> 26

```
Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
1               5                  10                  15

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr
            20                  25                  30

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
        35                  40                  45

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
    50                  55                  60

Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu
65                  70                  75                  80

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys
                85                  90                  95

Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu
            100                 105                 110

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
        115                 120                 125

Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
    130                 135                 140

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
145                 150                 155                 160

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu
                165                 170                 175

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
            180                 185                 190

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Val Glu Glu
        195                 200                 205

Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly
    210                 215                 220

Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val
225                 230                 235                 240

Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly
                245                 250                 255
```

```
Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro
            260                 265                 270

Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu
        275                 280                 285

His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu
    290                 295                 300

Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu
305                 310                 315                 320

Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala
                325                 330                 335

Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr
            340                 345                 350

Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln
        355                 360                 365

Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys
    370                 375                 380

Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu
385                 390                 395                 400

Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
                405                 410
```

<210> 27

<211> 205

<212> PRT

<213> Artificial sequence

<220>

<223> Artificial albumin variant: human serum albumin domain 3

<400> 27

```
Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
1               5                   10                  15

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr
            20                  25                  30

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
        35                  40                  45

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
    50                  55                  60

Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu
65                  70                  75                  80

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys
```

```
                85                  90                  95

Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu
            100                 105                 110

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
        115                 120                 125

Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
    130                 135                 140

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
145                 150                 155                 160

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu
                165                 170                 175

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
            180                 185                 190

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
        195                 200                 205
```

<210> 28

<211> 615

<212> PRT

<213> Artificial Sequence

<220>

<223> HSA Domain III + HSA Domain III + HSA Domain III

<400> 28

```
Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu
1               5                   10                  15

Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr
            20                  25                  30

Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg
        35                  40                  45

Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys
    50                  55                  60

Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu

65                  70                  75                  80

Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys
                85                  90                  95

Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu
            100                 105                 110

Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr
        115                 120                 125
```

```
Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys
    130                 135                 140

Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr
145                 150                 155                 160

Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu
                165                 170                 175

Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly
            180                 185                 190

Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Val Glu Glu
        195                 200                 205

Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly
    210                 215                 220

Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val
225                 230                 235                 240

Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly
                245                 250                 255

Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro
            260                 265                 270

Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu
        275                 280                 285

His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu
    290                 295                 300

Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu
305                 310                 315                 320

Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala
                325                 330                 335

Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr
            340                 345                 350

Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln
        355                 360                 365

Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys
    370                 375                 380

Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu
385                 390                 395                 400

Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Val Glu Glu Pro Gln Asn
                405                 410                 415

Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu Tyr Lys
            420                 425                 430
```

```
Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro Gln Val
        435                 440                 445

Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys Val Gly
    450                 455                 460

Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys Ala Glu
465                 470                 475                 480

Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His Glu Lys
                485                 490                 495

Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser Leu Val
            500                 505                 510

Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr Tyr Val
        515                 520                 525

Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp Ile Cys
    530                 535                 540

Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala Leu Val
545                 550                 555                 560

Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu Lys Ala
                565                 570                 575

Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys Ala Asp
            580                 585                 590

Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val Ala Ala
        595                 600                 605

Ser Gln Ala Ala Leu Gly Leu
    610                 615
```

<210> 29

<211> 604

<212> PRT

<213> Artificial Sequence

<220>

<223> HSA Domain I + HSA Domain III + HSA Domain III

<400> 29

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60
```

```
Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Val Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu
        195                 200                 205

Phe Glu Gln Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg
    210                 215                 220

Tyr Thr Lys Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val
225                 230                 235                 240

Ser Arg Asn Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu
                245                 250                 255

Ala Lys Arg Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn
            260                 265                 270

Gln Leu Cys Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr
        275                 280                 285

Lys Cys Cys Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala
    290                 295                 300

Leu Glu Val Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr
305                 310                 315                 320

Phe Thr Phe His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln
                325                 330                 335

Ile Lys Lys Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys
            340                 345                 350

Ala Thr Lys Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe
        355                 360                 365
```

```
Val Glu Lys Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu
    370                 375                 380

Glu Gly Lys Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu Val
385                 390                 395                 400

Glu Glu Pro Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln
                405                 410                 415

Leu Gly Glu Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys
            420                 425                 430

Lys Val Pro Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn
        435                 440                 445

Leu Gly Lys Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg
    450                 455                 460

Met Pro Cys Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys
465                 470                 475                 480

Val Leu His Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys
                485                 490                 495

Thr Glu Ser Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val
            500                 505                 510

Asp Glu Thr Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe
        515                 520                 525

His Ala Asp Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys
    530                 535                 540

Gln Thr Ala Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys
545                 550                 555                 560

Glu Gln Leu Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys
                565                 570                 575

Cys Cys Lys Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys
            580                 585                 590

Lys Leu Val Ala Ala Ser Gln Ala Ala Leu Gly Leu
        595                 600
```

<210> 30

<211> 290

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)..(290)

<223> Truncated heavy chain of the major histocompatibility complex class I-like Fc receptor (FCGRT) (together, SEQ ID No. 30 and SEQ ID No. 31 form FcRN)

<400> 30

```
Met Gly Val Pro Arg Pro Gln Pro Trp Ala Leu Gly Leu Leu Leu Phe
1               5                  10                  15

Leu Leu Pro Gly Ser Leu Gly Ala Glu Ser His Leu Ser Leu Leu Tyr
            20                  25                  30

His Leu Thr Ala Val Ser Ser Pro Ala Pro Gly Thr Pro Ala Phe Trp
        35                  40                  45

Val Ser Gly Trp Leu Gly Pro Gln Gln Tyr Leu Ser Tyr Asn Ser Leu
    50                  55                  60

Arg Gly Glu Ala Glu Pro Cys Gly Ala Trp Val Trp Glu Asn Gln Val
65                  70                  75                  80

Ser Trp Tyr Trp Glu Lys Glu Thr Thr Asp Leu Arg Ile Lys Glu Lys
                85                  90                  95

Leu Phe Leu Glu Ala Phe Lys Ala Leu Gly Gly Lys Gly Pro Tyr Thr
            100                 105                 110

Leu Gln Gly Leu Leu Gly Cys Glu Leu Gly Pro Asp Asn Thr Ser Val
        115                 120                 125

Pro Thr Ala Lys Phe Ala Leu Asn Gly Glu Glu Phe Met Asn Phe Asp
    130                 135                 140

Leu Lys Gln Gly Thr Trp Gly Gly Asp Trp Pro Glu Ala Leu Ala Ile
145                 150                 155                 160

Ser Gln Arg Trp Gln Gln Gln Asp Lys Ala Ala Asn Lys Glu Leu Thr
                165                 170                 175

Phe Leu Leu Phe Ser Cys Pro His Arg Leu Arg Glu His Leu Glu Arg
            180                 185                 190

Gly Arg Gly Asn Leu Glu Trp Lys Glu Pro Pro Ser Met Arg Leu Lys
        195                 200                 205

Ala Arg Pro Ser Ser Pro Gly Phe Ser Val Leu Thr Cys Ser Ala Phe
    210                 215                 220

Ser Phe Tyr Pro Pro Glu Leu Gln Leu Arg Phe Leu Arg Asn Gly Leu
225                 230                 235                 240

Ala Ala Gly Thr Gly Gln Gly Asp Phe Gly Pro Asn Ser Asp Gly Ser
                245                 250                 255

Phe His Ala Ser Ser Ser Leu Thr Val Lys Ser Gly Asp Glu His His
            260                 265                 270

Tyr Cys Cys Ile Val Gln His Ala Gly Leu Ala Gln Pro Leu Arg Val
        275                 280                 285

Glu Leu
    290
```

<210> 31

<211> 119

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)..(119)

<223> Beta-2-microglobulin (together, SEQ ID No. 30 and SEQ ID No. 31 form FcRN)

<400> 31

```
Met Ser Arg Ser Val Ala Leu Ala Val Leu Ala Leu Leu Ser Leu Ser
1               5                  10                  15

Gly Leu Glu Ala Ile Gln Arg Thr Pro Lys Ile Gln Val Tyr Ser Arg
            20                  25                  30

His Pro Ala Glu Asn Gly Lys Ser Asn Phe Leu Asn Cys Tyr Val Ser
        35                  40                  45

Gly Phe His Pro Ser Asp Ile Glu Val Asp Leu Leu Lys Asn Gly Glu
    50                  55                  60

Arg Ile Glu Lys Val Glu His Ser Asp Leu Ser Phe Ser Lys Asp Trp
65                  70                  75                  80

Ser Phe Tyr Leu Leu Tyr Tyr Thr Glu Phe Thr Pro Thr Glu Lys Asp
                85                  90                  95

Glu Tyr Ala Cys Arg Val Asn His Val Thr Leu Ser Gln Pro Lys Ile
            100                 105                 110

Val Lys Trp Asp Arg Asp Met
        115
```

<210> 32

<211> 585

<212> PRT

<213> Artificial Sequence

<220>

<223> HSA T83N, N111E

<400> 32

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                  10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60
```

```
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Asn Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Glu Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365
```

```
Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 33

<211> 585

<212> PRT

<213> Artificial Sequence

<220>

<223> HSA T83N, N111E, K573P

<400> 33

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30
```

```
Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Asn Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Glu Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335
```

```
Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 34

<211> 585

<212> PRT

<213> Artificial Sequence

<220>

<223> HSA T83N, K573P

<400> 34

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                  10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Asn Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300
```

```
Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 35

<211> 585

<212> PRT

<213> Artificial Sequence

<220>

<223> HSA T83K

<400> 35

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Lys Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270
```

```
Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575
```

```
Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 36

<211> 585

<212> PRT

<213> Artificial Sequence

<220>

<223> HSA E82A

<400> 36

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                  10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Ala Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240
```

```
Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser

465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525
```

```
Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 37

<211> 585

<212> PRT

<213> Artificial Sequence

<220>

<223> HSA L112F

<400> 37

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Phe
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190
```

```
Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr

            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495
```

```
Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 38

<211> 585

<212> PRT

<213> Artificial Sequence

<220>

<223> HSA T83K, K573P

<400> 38

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Lys Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
```

```
Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445
```

```
Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 39

<211> 585

<212> PRT

<213> Artificial Sequence

<220>

<223> HSA E82A, K573P

<400> 39

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Ala Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro

                85                  90                  95
```

```
Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
```

```
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 40

<211> 585

<212> PRT

<213> Artificial Sequence

<220>

<223> HSA L112F, K573P

<400> 40

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
```

```
--- --- --- --- --- --- --- --- --- --- --- --- --- --- --- ---
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Phe
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380
```

```
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 41

<211> 585

<212> PRT

<213> Artificial Sequence

<220>

<223> HSA E82D

<400> 41

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
```

35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Asp Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

```
Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 42

<211> 585

<212> PRT

<213> Artificial Sequence

<220>

<223> HSA P110G

<400> 42

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15
```

```
Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Gly Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320
```

```
Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 43

<211> 585

<212> PRT

<213> Artificial Sequence

<220>

<223> HSA E82D, K573P

<400> 43

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                  10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Asp Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285
```

```
Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu

580                 585
```

<210> 44

<211> 585

<212> PRT

<213> Artificial Sequence

<220>

<223> HSA P110G, K573P

<400> 44

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                  10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Gly Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
```

```
               245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His

    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540
```

```
Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 45

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA E505Q

<400> 45

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205
```

```
Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg

                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Gln Thr Phe Thr Phe His Ala Asp
```

```
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 46

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA N111D

<400> 46

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asp Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160
```

```
Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu

        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460
```

```
Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 47

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA T527M

<400> 47

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu

65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110
```

```
Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
```

```
                420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Met Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 48

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA N111G

<400> 48

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80
```

```
Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Gly Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400
```

385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 49

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA N111H

<400> 49

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys

```
Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro His Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365
```

```
Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 50

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA H512E

<400> 50

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30
```

```
Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335
```

```
Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Glu
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 51

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA K524A

<400> 51

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                  10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300
```

```
Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Ala Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val

                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 52

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA T527A

<400> 52

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270
```

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys

435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Ala Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

```
Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 53

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA E531H

<400> 53

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220
```

```
Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala

305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525
```

```
Leu Val His Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 54

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA N111K

<400> 54

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Lys Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
```

180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

```
Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 55

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA E425K

<400> 55

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys

    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125
```

```
Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Lys Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445
```

```
Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 56

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA K534V

<400> 56

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
```

```
           100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415
```

```
Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Val His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 57

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA H510D

<400> 57

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80
```

```
Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380
```

```
Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe Asp Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 58

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA A569S

<400> 58

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45
```

```
Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
```

```
       355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ser Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 59

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA D108A

<400> 59

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15
```

```
Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Ala Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335
```

```
Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys

545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 60

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA N111D, K573P

<400> 60

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                  10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asp Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285
```

```
Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys

            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 61

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA N111G, K573P

<400> 61

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Gly Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
```

```
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser

    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540
```

```
Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 62

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA N111H, K573P

<400> 62

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro His Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala

                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
```

```
Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
```

```
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 63

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA E425A

<400> 63

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu

        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160
```

```
Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Ala Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460
```

```
Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 64

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA E425A, K573P

<400> 64

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125
```

```
Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Ala Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Glu Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
```

```
Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 65

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA E505Q, K573P

<400> 65

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95
```

```
Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415
```

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Gln Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 66

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA T527M, K573P

<400> 66

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu

65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

```
Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Met Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 67

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA N111E

<400> 67

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45
```

```
Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Glu Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350
```

```
Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu

    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 68

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA N111E, K573P

<400> 68

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
```

```
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Glu Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
```

305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro

405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 69

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA N109K

<400> 69

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                  10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Lys Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270
```

```
Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His

        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
```

```
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 70

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA N108E

<400> 70

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Glu Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg

145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220
```

```
Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525
```

```
Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 71

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA T83N

<400> 71

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln

            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Asn Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175
```

```
Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
```

485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 72

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA L575F

<400> 72

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

```
Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460
```

```
Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Phe Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
```

<210> 73

<211> 585

<212> PRT

<213> Artificial sequence

<220>

<223> HSA K534V, K573P

<400> 73

```
Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1               5                   10                  15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
```

```
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430
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Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Val His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
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Ala Ala Ser Gln Ala Ala Leu Gly Leu
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<211> 585

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<213> Artificial Sequence

<220>

<223> HSA N111Q, K573P

<400> 74

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Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
            20                  25                  30

Gln Cys Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
        35                  40                  45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
    50                  55                  60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65                  70                  75                  80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
                85                  90                  95
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Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Gln Leu
            100                 105                 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
        115                 120                 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
    130                 135                 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145                 150                 155                 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
                165                 170                 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser
            180                 185                 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
        195                 200                 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
    210                 215                 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225                 230                 235                 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
                245                 250                 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
            260                 265                 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
        275                 280                 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
    290                 295                 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305                 310                 315                 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
                325                 330                 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
            340                 345                 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
        355                 360                 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
    370                 375                 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385                 390                 395                 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
```

```
Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
                405                 410                 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
            420                 425                 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
        435                 440                 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His
    450                 455                 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465                 470                 475                 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
                485                 490                 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
            500                 505                 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
        515                 520                 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
    530                 535                 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545                 550                 555                 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Pro Lys Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585
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Titel: Albuminvarianter

KRAV

1. Et polypeptid, som er en variant af albumin, et fragment deraf eller et fusionspolypeptid omfattende nævnte variant af albumin eller et fragment deraf, hvilket polypeptid:

har mindst 80% identitet med den fulde længde af SEQ ID NO: 2 og omfatter substitutioner ved positioner svarende til positionerne 83, 111 og 573 i SEQ ID NO: 2, og

har en stærkere bindingsaffinitet til FcRn og/eller længere plasmahalveringstid sammenlignet med bindingsaffiniteten til FcRn eller plasmahalveringstid for et moderalbumin, som omfatter den samme sekvens som polypeptidet med den undtagelse, at den ikke omfatter substitutionerne ved positioner svarende til positionerne 83, 111 og 573 i SEQ ID NO: 2.

2. Polypeptid ifølge krav 1 omfattende substitutioner ved positioner svarende til positionerne (a) 83, 111, 112 og 573; eller (b) 82, 83, 111, 112 og 573 i SEQ ID NO: 2.

3. Polypeptid ifølge krav 1 eller 2, hvor substitutionen ved positionen svarende til position 83 er en substitution til N, K eller S.

4. Polypeptid ifølge et hvilket som helst af kravene 1 til 3, hvor substitutionen ved positionen svarende til position 111 er en substitution til D, G, H, R, Q eller E.

5. Polypeptid ifølge et hvilket som helst af kravene 1 til 4, hvor substitutionen ved positionen svarende til position 573 er en substitution til P, Y, W, H, F, T, I eller V.

6. Polypeptid ifølge et hvilket som helst af kravene 1 til 5, hvor polypeptidets sekvensidentitet med den fulde længde af SEQ ID NO: 2 er mere end 90%.

7. Fusionspolypeptid omfattende et polypeptid ifølge et hvilket som helst af kravene 1 til 6 og et fusionspartnerpolypeptid valgt blandt en terapeutisk, profylaktisk, diagnostisk, imagografisk eller anden fordelagtig del.

8. Fremgangsmåde til fremstilling af et polypeptid, hvilken fremgangsmåde omfatter:

(a) tilvejebringelse af en nukleinsyre kodende for et moderalbumin med mindst 80% sekvensidentitet med den fulde længde af SEQ ID NO: 2; og

(b) modifikation af nukleinsyresekvensen ifølge trin (a) til kodning af et polypeptid ifølge et hvilket som helst af kravene 1 til 7.

9. Fremgangsmåde ifølge krav 8, der yderligere omfatter indføring af den modificerede sekvens fra trin (b) i en egnet værtscelle.

10. Fremgangsmåde ifølge krav 9, der yderligere omfatter dyrkning af cellerne i et egnet vækstmedium under betingelser, der fører til ekspression af polypeptidet.

11. Fremgangsmåde ifølge krav 10, der yderligere omfatter udvinding af polypeptidet fra vækstmediet.

12. Konjugat omfattende et polypeptid ifølge et hvilket som helst af kravene 1 til 7 og en konjugationspartner.

13. Konjugat ifølge krav 12, hvor konjugationspartneren er en terapeutisk, profylaktisk, diagnostisk, imagografisk eller anden fordelagtig del.

14. Et associeret middel indeholdende et polypeptid ifølge et hvilket som helst af kravene 1 til 7 og en terapeutisk, profylaktisk, diagnostisk, imagografisk eller anden fordelagtig del.

15. Nanopartikel eller mikropartikel omfattende et polypeptid ifølge et hvilket som helst af kravene 1 til 7, et konjugat ifølge krav 12 eller 13 eller et associeret middel ifølge krav 14.

16. Sammensætning omfattende et polypeptid ifølge et hvilket som helst af kravene 1 til 7, et konjugat ifølge krav 12 eller 13, et associeret middel ifølge krav 14 eller en nanopartikel eller mikropartikel ifølge krav 15, hvor bindingsaffiniteten af polypeptidet, fusionspolypeptidet, konjugatet, det associerede middel, eller nanopartiklen eller mikropartiklen til FcRn er stærkere end bindingsaffiniteten af en sammensætning, der omfatter det tilsvarende moderalbumin til FcRn, hvor moderalbuminet omfatter den samme sekvens som polypeptidet med undtagelse af, at den

ikke omfatter substitutionerne ved positioner svarende til positioner 83, 111 og 573 i SEQ ID NO: 2.

17. Sammensætning ifølge krav 16, hvor bindingsaffinitet af polypeptidet, fusionspolypeptidet, konjugatet, det associerede middel, eller nanopartiklen eller mikropartiklen til FcRn er stærkere end bindingsaffiniteten af HSA (SEQ ID NO: 2) til FcRn.

18. Sammensætning ifølge krav 16 eller 17, hvor bindingskoefficienten af varianten til polypeptidet, fusionspolypeptidet, konjugatet, det associerede middel eller nanopartiklen eller mikropartiklen til FcRn er mindre end 0,9X KD af HSA (SEQ ID NO: 2) til FcRn.

19. Sammensætning ifølge et hvilket som helst af kravene 16 til 18, omfattende et polypeptid ifølge et hvilket som helst af kravene 1 til 7, et konjugat ifølge krav 12 eller 13, et associeret middel ifølge krav 14 eller en nanopartikel eller mikropartikel ifølge krav 15, der yderligere omfatter en forbindelse omfattende et antistofbindende domæne (ABD) og en terapeutisk, profylaktisk, diagnostisk, imagografisk eller anden fordelagtig del.

20. Sammensætning ifølge et hvilket som helst af kravene 16 til 19, omfattende en farmaceutisk acceptabel bærer eller excipiens.

21. Anvendelse af et polypeptid ifølge et hvilket som helst af kravene 1 til 7, et konjugat ifølge krav 12 eller 13, et associeret middel ifølge krav 14 eller en nanopartikel eller mikropartikel ifølge krav 15 eller en sammensætning ifølge et hvilket som helst af kravene 16 til 20 *in vitro* med henblik på at ændre bindingsaffiniteten til FcRn eller halveringstiden for en terapeutisk, profylaktisk, diagnostisk, imagografisk eller anden fordelagtig del.

22. En fremgangsmåde til ændring af bindingsaffiniteten til FcRn eller halveringstiden for et molekyle *in vitro* omfattende:

(a) hvor molekylet er et polypeptid, at fusionere eller konjugere molekylet til et polypeptid ifølge et hvilket som helst af kravene 1 til 7 eller til et konjugat ifølge krav 12 eller 13; at associere molekylet til et polypeptid ifølge et hvilket som helst af kravene 1 til 7 eller til et konjugat ifølge krav 12 eller 13; at inkorporere molekylet i et associeret middel ifølge krav 14, i en nanopartikel eller mikropartikel ifølge krav 15 eller en sammensætning ifølge et hvilket som helst af kravene 16 til 20;

(b) hvor molekylet ikke er et polypeptid, at konjugere molekylet til et polypeptid ifølge et hvilket som helst af kravene 1 til 7 eller til et konjugat ifølge krav 12 eller 13; at associere molekylet til et polypeptid ifølge et hvilket som helst af kravene 1 til 7 eller til et konjugat ifølge krav 12 eller 13; at inkorporere molekylet i et associeret middel ifølge 14, i en nanopartikel eller mikropartikel ifølge 15 eller en sammensætning ifølge et hvilket som helst af kravene 16 til 20.

23. Fremgangsmåde ifølge krav 22, hvor molekylet er en terapeutisk, profylaktisk, diagnostisk, imagografisk eller anden fordelagtig del.

24. Nukleinsyre kodende for polypeptidet eller fusionspolypeptidet ifølge et hvilket som helst af kravene 1 til 7.

25. Vektor omfattende en nukleinsyre ifølge krav 24.

26. Værtscelle omfattende en nukleinsyre ifølge krav 24 eller en vektor ifølge krav 25.

27. Værtscelle ifølge krav 26, hvor værtscellen er en eukaryot.

28. Et polypeptid, fusionspolypeptid, konjugat, sammensætning, associeret middel, nanopartikel eller mikropartikel eller polynukleotid ifølge et hvilket som helst af kravene 1 til 7 eller 12 til 20 til anvendelse ved profylakse, behandling eller diagnose.