BISPECIFIC ANTIBODY CONSTRUCTS BINDING MESOTHELIN AND CD3

The present invention relates to a bispecific antibody construct comprising a first binding domain which binds to human MSLN on the surface of a target cell and a second binding domain which binds to human CD3 on the surface of a T cell. Moreover, the invention provides a polynucleotide encoding the antibody construct, a vector comprising said polynucleotide and a host cell transformed or transfected with said polynucleotide or vector. Furthermore, the invention provides a process for the production of the antibody construct of the invention, a medical use of said antibody construct and a kit comprising said antibody construct.

INTRODUCTION:

Mesothelin is a cell surface protein that was initially discovered as an antigen recognized by K1, a monoclonal antibody derived by immunization of mice with the OVCAR-3 human ovarian cancer cell line (Chang et al., Int. J. Cancer 1992). Expression cloning was used to identify the mesothelin cDNA from a HeLa library (Chang et al., PNAS 1996). Molecular analysis demonstrated that the mesothelin gene is encoded within a 69 kD precursor protein, which is cleaved by furin to give two distinct proteins: megakaryocyte potentiating factor (MPF), a 31 kD protein that is shed, and mesothelin, a 40 kD protein that associates with the cell membrane through a glycophosphatidylinositol linkage (GPI anchor) (Chang et al., PNAS 1996). The mesothelin protein is organized into superhelical domains, with ARM-type repeats.

Mesothelin is highly expressed in ovarian cancer as well as in other tumor types, including pancreatic cancer, mesothelioma, lung cancer, gastric cancer and triple negative breast cancer. In normal tissues, mesothelin is mainly expressed in the mesothelial cell layer of the pleural, pericardial, and peritoneal cavities. Mesothelin is also expressed on the surface epithelia of normal ovary, Fallopian tube and tonsil.

In addition to its expression on the cell surface, mesothelin is also shed into serum through the action of ADAM17/TACE. Serum levels of shed mesothelin are elevated in patients with ovarian cancer and other cancer. MESOMARK®, an ELISA test for shed serum mesothelin, is approved by the FDA for humanitarian use and may help in the diagnosis or monitoring of mesothelioma. Shed mesothelin has also been used, alone or together with other markers, to aid in diagnosis or prognosis of other cancer types.

The correlation of serum levels of shed mesothelin with disease suggested a potential role for the mesothelin protein in cancer progression. While the biological function of mesothelin is not well understood – knockout mice appear normal – mesothelin has been shown to bind the mucin MUC16/CA-125. The mesothelin-CA-125 interaction has been proposed to function in cell adhesion, invasion and metastasis.

The first antibodies generated against mesothelin for therapeutic intervention were designed to interfere with the interaction between mesothelin and CA-125. Phage display identified the Fv SS, which was affinity optimized and used to generate a recombinant immunotoxin targeting mesothelin, SS1P. The MORAb-009 antibody amatuximab, which also uses SS1, recognizes a non-linear epitope in the amino terminal 64 amino acids of mesothelin. The SS1 Fv was also used to generate chimeric antigen receptor-engineered T cells. Anti-mesothelin antibodies have also been used to generate drug conjugates, such as Anetumab ravtansine, containing the MF-T antibody coupled to DM4, and the 7D9 antibody conjugated to monomethyl auristatin E. These anti-mesothelin antibodies also recognize the amino terminal region of the protein (amino acids 296-390) although they do not compete with. These anti-mesothelin targeted therapeutics that are currently in clinical trials have shown limited efficacy as single agents.

Very recently, new anti-mesothelin antibodies have been reported that recognize other regions of the mesothelin protein. There still remains a need to understand whether antibodies against different epitopes of mesothelin than SS1/ MORAb-009 (for example, antibodies that are not competed by shed mesothelin or shed CA-125) would have improved efficacy in patients.

As there is still a need for having available further options for the treatment of solid tumor diseases diseases related to the overexpression of MSLN, such as ovarian cancer, pancreatic cancer, mesothelioma, lung cancer, gastric cancer and triple negative breast cancer, there are provided herewith means and methods for the solution of this problem in the form of a bispecific antibody construct having a binding domain directed to MSLN on the surface of tumor target cells and a second binding domain directed to CD3 on the surface of T cells.

Thus, in a first aspect, the present invention provides a bispecific antibody construct comprising a first binding domain which binds to human MSLN on the surface of a target cell and a second binding domain which binds to human CD3 on the surface of a T cell, wherein the first binding domain binds to an epitope of MSLN which is comprised within the MSLN variants as depicted in SEQ ID NOs: 231, 232, and 233 and further binds to *Macaca fascicularis* MSLN as depicted in SEQ ID NOs: 234.

It must be noted that as used herein, the singular forms “a”, “an”, and “the” include plural references unless the context clearly indicates otherwise. Thus, for example, reference to “a reagent” includes one or more of such different reagents and reference to “the method” includes reference to equivalent steps and methods known to those of ordinary skill in the art that could be modified or substituted for the methods described herein.

Unless otherwise indicated, the term “at least” preceding a series of elements is to be understood to refer to every element in the series. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the present invention.

The term “and/or” wherever used herein includes the meaning of “and”, “or” and “all or any other combination of the elements connected by said term”.

The term “about” or “approximately” as used herein means within ±20%, preferably within ±15%, more preferably within ±10%, and most preferably within ±5% of a given value or range.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word “comprise”, and variations such as “comprises” and “comprising”, will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integer or step. When used herein the term “comprising” can be substituted with the term “containing” or “including” or sometimes when used herein with the term “having”.

When used herein “consisting of” excludes any element, step, or ingredient not specified in the claim element. When used herein, “consisting essentially of” does not exclude materials or steps that do not materially affect the basic and novel characteristics of the claim.

In each instance herein any of the terms “comprising”, “consisting essentially of” and “consisting of” may be replaced with either of the other two terms.

The term “antibody construct” refers to a molecule in which the structure and/or function is/are based on the structure and/or function of an antibody, e.g., of a full-length or whole immunoglobulin molecule. An antibody construct is hence capable of binding to its specific

target or antigen. Furthermore, an antibody construct according to the invention comprises the minimum structural requirements of an antibody which allow for the target binding. This minimum requirement may e.g. be defined by the presence of at least the three light chain CDRs (i.e. CDR1, CDR2 and CDR3 of the VL region) and/or the three heavy chain CDRs (i.e. CDR1, CDR2 and CDR3 of the VH region), preferably of all six CDRs. The antibodies on which the constructs according to the invention are based include for example monoclonal, recombinant, chimeric, deimmunized, humanized and human antibodies.

Within the definition of “antibody constructs” according to the invention are full-length or whole antibodies also including camelid antibodies and other immunoglobulin antibodies generated by biotechnological or protein engineering methods or processes. These full-length antibodies may be for example monoclonal, recombinant, chimeric, deimmunized, humanized and human antibodies. Also within the definition of “antibody constructs” are fragments of full-length antibodies, such as VH, VHH, VL, (s)dAb, Fv, Fd, Fab, Fab’, F(ab')2 or “r IgG” (“half antibody”). Antibody constructs according to the invention may also be modified fragments of antibodies, also called antibody variants, such as scFv, di-scFv or bi(s)-scFv, scFv-Fc, scFv-zipper, scFab, Fab2, Fab3, diabodies, single chain diabodies, tandem diabodies (Tandab’s), tandem di-scFv, tandem tri-scFv, „minibodies“ exemplified by a structure which is as follows: (VH-VL-CH3)2, (scFv-CH3)2 , ((scFv)2-CH3 + CH3), ((scFv)2-CH3) or (scFv-CH3-scFv)2, multibodies such as triabodies or tetrabodies, and single domain antibodies such as nanobodies or single variable domain antibodies comprising merely one variable domain, which might be VHH, VH or VL, that specifically bind an antigen or epitope independently of other V regions or domains.

A binding domain may typically comprise an antibody light chain variable region (VL) and an antibody heavy chain variable region (VH); however, it does not have to comprise both. Fd fragments, for example, have two VH regions and often retain some antigen-binding function of the intact antigen-binding domain. Additional examples for the format of antibody fragments, antibody variants or binding domains include (1) a Fab fragment, a monovalent fragment having the VL, VH, CL and CH1 domains; (2) a F(ab')2 fragment, a bivalent fragment having two Fab fragments linked by a disulfide bridge at the hinge region; (3) an Fd fragment having the two VH and CH1 domains; (4) an Fv fragment having the VL and VH domains of a single arm of an antibody, (5) a dAb fragment (Ward et al., (1989) Nature 341 :544-546), which has a VH domain; (6) an isolated complementarity determining region (CDR), and (7) a single chain Fv (scFv) , the latter being preferred (for example, derived from an scFV-library). Examples for embodiments of antibody constructs according to the invention are e.g. described in

WO 00/006605, WO 2005/040220, WO 2008/119567, WO 2010/037838, WO 2013/026837, WO 2013/026833, US 2014/0308285, US 2014/0302037, W O2014/144722, WO 2014/151910, and WO 2015/048272.

Furthermore, the definition of the term "antibody construct" includes monovalent, bivalent and polyvalent / multivalent constructs and, thus, monospecific constructs, specifically binding to only one antigenic structure, as well as bispecific and polyspecific / multispecific constructs, which specifically bind more than one antigenic structure, e.g. two, three or more, through distinct binding domains. Moreover, the definition of the term "antibody construct" includes molecules consisting of only one polypeptide chain as well as molecules consisting of more than one polypeptide chain, which chains can be either identical (homodimers, homotrimers or homo oligomers) or different (heterodimer, heterotrimer or heterooligomer). Examples for the above identified antibodies and variants or derivatives thereof are described inter alia in Harlow and Lane, Antibodies a laboratory manual, CSHL Press (1988) and Using Antibodies: a laboratory manual, CSHL Press (1999), Kontermann and Dübel, Antibody Engineering, Springer, 2nd ed. 2010 and Little, Recombinant Antibodies for Immunotherapy, Cambridge University Press 2009.

The antibody constructs of the present invention are preferably "in vitro generated antibody constructs". This term refers to an antibody construct according to the above definition where all or part of the variable region (e.g., at least one CDR) is generated in a non-immune cell selection, e.g., an in vitro phage display, protein chip or any other method in which candidate sequences can be tested for their ability to bind to an antigen. This term thus preferably excludes sequences generated solely by genomic rearrangement in an immune cell in an animal. A "recombinant antibody" is an antibody made through the use of recombinant DNA technology or genetic engineering.

The term "monoclonal antibody" (mAb) or monoclonal antibody construct as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations and/or post-translation modifications (e.g., isomerizations, amidations) that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site or determinant on the antigen, in contrast to conventional (polyclonal) antibody preparations which typically include different antibodies directed against different determinants (or epitopes). In addition to their specificity, the monoclonal antibodies

are advantageous in that they are synthesized by the hybridoma culture, hence uncontaminated by other immunoglobulins. The modifier “monoclonal” indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method.

For the preparation of monoclonal antibodies, any technique providing antibodies produced by continuous cell line cultures can be used. For example, monoclonal antibodies to be used may be made by the hybridoma method first described by Koehler et al., Nature, 256: 495 (1975), or may be made by recombinant DNA methods (see, e.g., U.S. Patent No. 4,816,567). Examples for further techniques to produce human monoclonal antibodies include the trioma technique, the human B-cell hybridoma technique (Kozbor, Immunology Today 4 (1983), 72) and the EBV-hybridoma technique (Cole et al., Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc. (1985), 77-96).

Hybridomas can then be screened using standard methods, such as enzyme-linked immunosorbent assay (ELISA) and surface plasmon resonance (BIACORE™) analysis, to identify one or more hybridomas that produce an antibody that specifically binds with a specified antigen. Any form of the relevant antigen may be used as the immunogen, e.g., recombinant antigen, naturally occurring forms, any variants or fragments thereof, as well as an antigenic peptide thereof. Surface plasmon resonance as employed in the BIAcore system can be used to increase the efficiency of phage antibodies which bind to an epitope of a target antigen, such as MSLN or CD3 epsilon (Schier, Human Antibodies Hybridomas 7 (1996), 97-105; Malmborg, J. Immunol. Methods 183 (1995), 7-13).

Another exemplary method of making monoclonal antibodies includes screening protein expression libraries, e.g., phage display or ribosome display libraries. Phage display is described, for example, in Ladner et al., U.S. Patent No. 5,223,409; Smith (1985) Science 228:1315-1317, Clackson et al., Nature, 352: 624-628 (1991) and Marks et al., J. Mol. Biol., 222: 581-597 (1991).

In addition to the use of display libraries, the relevant antigen can be used to immunize a non-human animal, e.g., a rodent (such as a mouse, hamster, rabbit or rat). In one embodiment, the non-human animal includes at least a part of a human immunoglobulin gene. For example, it is possible to engineer mouse strains deficient in mouse antibody production with large fragments of the human Ig (immunoglobulin) loci. Using the hybridoma technology, antigen-specific

monoclonal antibodies derived from the genes with the desired specificity may be produced and selected. See, e.g., XENOMOUSE™, Green et al. (1994) Nature Genetics 7:13-21, US 2003-0070185, WO 96/34096, and WO 96/33735.

A monoclonal antibody can also be obtained from a non-human animal, and then modified, e.g., humanized, deimmunized, rendered chimeric etc., using recombinant DNA techniques known in the art. Examples of modified antibody constructs include humanized variants of non-human antibodies, "affinity matured" antibodies (see, e.g. Hawkins et al. J. Mol. Biol. 254, 889-896 (1992) and Lowman et *al.*, Biochemistry 30, 10832- 10837 (1991)) and antibody mutants with altered effector function(s) (see, *e.g.*, US Patent 5,648,260, Kontermann and Dübel (2010), *loc. cit.* and Little (2009), *loc. cit.*).

In immunology, affinity maturation is the process by which B cells produce antibodies with increased affinity for antigen during the course of an immune response. With repeated exposures to the same antigen, a host will produce antibodies of successively greater affinities. Like the natural prototype, the *in vitro* affinity maturation is based on the principles of mutation and selection. The *in vitro* affinity maturation has successfully been used to optimize antibodies, antibody constructs, and antibody fragments. Random mutations inside the CDRs are introduced using radiation, chemical mutagens or error-prone PCR. In addition, the genetical diversity can be increased by chain shuffling. Two or three rounds of mutation and selection using display methods like phage display usually results in antibody fragments with affinities in the low nanomolar range.

A preferred type of an amino acid substitutional varianation of the antibody constructs involves substituting one or more hypervariable region residues of a parent antibody (e. g. a humanized or human antibody). Generally, the resulting variant(s) selected for further development will have improved biological properties relative to the parent antibody from which they are generated. A convenient way for generating such substitutional variants involves affinity maturation using phage display. Briefly, several hypervariable region sites (e. g. 6-7 sites) are mutated to generate all possible amino acid substitutions at each site. The antibody variants thus generated are displayed in a monovalent fashion from filamentous phage particles as fusions to the gene III product of M13 packaged within each particle. The phage-displayed variants are then screened for their biological activity (e. g. binding affinity) as herein disclosed. In order to identify candidate hypervariable region sites for modification, alanine scanning mutagenesis can be performed to identify hypervariable region residues contributing

significantly to antigen binding. Alternatively, or additionally, it may be beneficial to analyze a crystal structure of the antigen-antibody complex to identify contact points between the binding domain and, *e.g.*, human MSLN. Such contact residues and neighbouring residues are candidates for substitution according to the techniques elaborated herein. Once such variants are generated, the panel of variants is subjected to screening as described herein and antibodies with superior properties in one or more relevant assays may be selected for further development.

The monoclonal antibodies and antibody constructs of the present invention specifically include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is/are identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Patent No. 4,816,567; Morrison et al., Proc. Natl. Acad. Sci. USA, 81: 6851-6855 (1984)). Chimeric antibodies of interest herein include "primitized" antibodies comprising variable domain antigen-binding sequences derived from a non-human primate (e.g., Old World Monkey, Ape etc.) and human constant region sequences. A variety of approaches for making chimeric antibodies have been described. See *e.g.*, Morrison *et al.*, Proc. Natl. Acad. ScL U.S.A. 81:6851 , 1985; Takeda *et al.*, Nature 314:452, 1985, Cabilly *et al.*, U.S. Patent No. 4,816,567; Boss *et al.*, U.S. Patent No. 4,816,397; Tanaguchi *et al.*, EP 0171496; EP 0173494; and GB 2177096.

An antibody, antibody construct, antibody fragment or antibody variant may also be modified by specific deletion of human T cell epitopes (a method called "deimmunization") by the methods disclosed for example in WO 98/52976 or WO 00/34317. Briefly, the heavy and light chain variable domains of an antibody can be analyzed for peptides that bind to MHC class II; these peptides represent potential T cell epitopes (as defined in WO 98/52976 and WO 00/34317). For detection of potential T cell epitopes, a computer modeling approach termed "peptide threading" can be applied, and in addition a database of human MHC class II binding peptides can be searched for motifs present in the VH and VL sequences, as described in WO 98/52976 and WO 00/34317. These motifs bind to any of the 18 major MHC class II DR allotypes, and thus constitute potential T cell epitopes. Potential T cell epitopes detected can be eliminated by substituting small numbers of amino acid residues in the variable domains, or preferably, by single amino acid substitutions. Typically, conservative substitutions are made. Often, but not

exclusively, an amino acid common to a position in human germline antibody sequences may be used. Human germline sequences are disclosed *e.g.* in Tomlinson, *et al.* (1992) J. Mol. Biol. 227:776-798; Cook, G.P. *et al.* (1995) Immunol. Today Vol. 16 (5): 237-242; and Tomlinson et al. (1995) EMBO J. 14: 14:4628-4638. The V BASE directory provides a comprehensive directory of human immunoglobulin variable region sequences (compiled by Tomlinson, LA. *et al.* MRC Centre for Protein Engineering, Cambridge, UK). These sequences can be used as a source of human sequence, *e.g.*, for framework regions and CDRs. Consensus human framework regions can also be used, for example as described in US Patent No. 6,300,064.

"Humanized" antibodies, antibody constructs, variants or fragments thereof (such as Fv, Fab, Fab', F(ab')2 or other antigen-binding subsequences of antibodies) are antibodies or immunoglobulins of mostly human sequences, which contain (a) minimal sequence(s) derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region (also CDR) of the recipient are replaced by residues from a hypervariable region of a non-human (*e.g.*, rodent) species (donor antibody) such as mouse, rat, hamster or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, "humanized antibodies" as used herein may also comprise residues which are found neither in the recipient antibody nor the donor antibody. These modifications are made to further refine and optimize antibody performance. The humanized antibody may also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones *et al.*, Nature, 321: 522-525 (1986); Reichmann *et al.*, Nature, 332: 323-329 (1988); and Presta, Curr. Op. Struct. Biol., 2: 593-596 (1992).

Humanized antibodies or fragments thereof can be generated by replacing sequences of the Fv variable domain that are not directly involved in antigen binding with equivalent sequences from human Fv variable domains. Exemplary methods for generating humanized antibodies or fragments thereof are provided by Morrison (1985) Science 229:1202-1207; by Oi *et al.* (1986) BioTechniques 4:214; and by US 5,585,089; US 5,693,761; US 5,693,762; US 5,859,205; and US 6,407,213. Those methods include isolating, manipulating, and expressing the nucleic acid sequences that encode all or part of immunoglobulin Fv variable domains from at least one of a heavy or light chain. Such nucleic acids may be obtained from a hybridoma producing an antibody against a predetermined target, as described above, as well as from other sources.

The recombinant DNA encoding the humanized antibody molecule can then be cloned into an appropriate expression vector.

Humanized antibodies may also be produced using transgenic animals such as mice that express human heavy and light chain genes, but are incapable of expressing the endogenous mouse immunoglobulin heavy and light chain genes. Winter describes an exemplary CDR grafting method that may be used to prepare the humanized antibodies described herein (U.S. Patent No. 5,225,539). All of the CDRs of a particular human antibody may be replaced with at least a portion of a non-human CDR, or only some of the CDRs may be replaced with non-human CDRs. It is only necessary to replace the number of CDRs required for binding of the humanized antibody to a predetermined antigen.

A humanized antibody can be optimized by the introduction of conservative substitutions, consensus sequence substitutions, germline substitutions and/or back mutations. Such altered immunoglobulin molecules can be made by any of several techniques known in the art, (*e.g.*, Teng *et al.*, Proc. Natl. Acad. Sci. U.S.A., 80: 7308-7312, 1983; Kozbor *et al.*, Immunology Today, 4: 7279, 1983; Olsson *et al.*, Meth. Enzymol., 92: 3-16, 1982, and EP 239 400).

The term "human antibody", “human antibody construct” and “human binding domain” includes antibodies, antibody constructs and binding domains having antibody regions such as variable and constant regions or domains which correspond substantially to human germline immunoglobulin sequences known in the art, including, for example, those described by Kabat *et al.* (1991) (*loc. cit.*). The human antibodies, antibody constructs or binding domains of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs, and in particular, in CDR3. The human antibodies, antibody constructs or binding domains can have at least one, two, three, four, five, or more positions replaced with an amino acid residue that is not encoded by the human germline immunoglobulin sequence. The definition of human antibodies, antibody constructs and binding domains as used herein also contemplates fully human antibodies, which include only non-artificially and/or genetically altered human sequences of antibodies as those can be derived by using technologies or systems such as the Xenomouse.

In some embodiments, the antibody constructs of the invention are “isolated” or “substantially pure” antibody constructs. “Isolated” or “substantially pure”, when used to describe the antibody

constructs disclosed herein, means an antibody construct that has been identified, separated and/or recovered from a component of its production environment. Preferably, the antibody construct is free or substantially free of association with all other components from its production environment. Contaminant components of its production environment, such as that resulting from recombinant transfected cells, are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. The antibody constructs may e.g constitute at least about 5%, or at least about 50% by weight of the total protein in a given sample. It is understood that the isolated protein may constitute from 5% to 99.9% by weight of the total protein content, depending on the circumstances. The polypeptide may be made at a significantly higher concentration through the use of an inducible promoter or high expression promoter, such that it is made at increased concentration levels. The definition includes the production of an antibody construct in a wide variety of organisms and/or host cells that are known in the art. In preferred embodiments, the antibody construct will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Ordinarily, however, an isolated antibody construct will be prepared by at least one purification step.

The term "binding domain" characterizes in connection with the present invention a domain which (specifically) binds to / interacts with / recognizes a given target epitope or a given target site on the target molecules (antigens), here: MSLN and CD3, respectively. The structure and function of the first binding domain (recognizing MSLN), and preferably also the structure and/or function of the second binding domain (recognizing CD3), is/are based on the structure and/or function of an antibody, e.g. of a full-length or whole immunoglobulin molecule. According to the invention, the first binding domain is characterized by the presence of three light chain CDRs (i.e. CDR1, CDR2 and CDR3 of the VL region) and/or three heavy chain CDRs (i.e. CDR1, CDR2 and CDR3 of the VH region). The second binding domain preferably also comprises the minimum structural requirements of an antibody which allow for the target binding. More preferably, the second binding domain comprises at least three light chain CDRs (i.e. CDR1, CDR2 and CDR3 of the VL region) and/or three heavy chain CDRs (i.e. CDR1, CDR2 and CDR3 of the VH region). It is envisaged that the first and/or second binding domain is produced by or obtainable by phage-display or library screening methods rather than by grafting CDR sequences from a pre-existing (monoclonal) antibody into a scaffold.

According to the present invention, binding domains are in the form of one or more polypeptides. Such polypeptides may include proteinaceous parts and non-proteinaceous parts (e.g. chemical linkers or chemical cross-linking agents such as glutaraldehyde). Proteins (including fragments thereof, preferably biologically active fragments, and peptides, usually having less than 30 amino acids) comprise two or more amino acids coupled to each other via a covalent peptide bond (resulting in a chain of amino acids). The term "polypeptide" as used herein describes a group of molecules, which usually consist of more than 30 amino acids. Polypeptides may further form multimers such as dimers, trimers and higher oligomers, *i.e.*, consisting of more than one polypeptide molecule. Polypeptide molecules forming such dimers, trimers etc. may be identical or non-identical. The corresponding higher order structures of such multimers are, consequently, termed homo- or heterodimers, homo- or heterotrimers etc. An example for a hereteromultimer is an antibody molecule, which, in its naturally occurring form, consists of two identical light polypeptide chains and two identical heavy polypeptide chains. The terms “peptide”, "polypeptide" and "protein" also refer to naturally modified peptides / polypeptides / proteins wherein the modification is effected *e.g.* by post-translational modifications like glycosylation, acetylation, phosphorylation and the like. A “peptide”, "polypeptide" or "protein" when referred to herein may also be chemically modified such as pegylated. Such modifications are well known in the art and described herein below.

Preferably the binding domain which binds to MSLN and/or the binding domain which binds to CD3 is/are human binding domains. Antibodies and antibody constructs comprising at least one human binding domain avoid some of the problems associated with antibodies or antibody constructs that possess non-human such as rodent (*e.g.* murine, rat, hamster or rabbit) variable and/or constant regions. The presence of such rodent derived proteins can lead to the rapid clearance of the antibodies or antibody constructs or can lead to the generation of an immune response against the antibody or antibody construct by a patient. In order to avoid the use of rodent derived antibodies or antibody constructs, human or fully human antibodies / antibody constructs can be generated through the introduction of human antibody function into a rodent so that the rodent produces fully human antibodies.

The ability to clone and reconstruct megabase-sized human loci in YACs and to introduce them into the mouse germline provides a powerful approach to elucidating the functional components of very large or crudely mapped loci as well as generating useful models of human disease. Furthermore, the use of such technology for substitution of mouse loci with their human equivalents could provide unique insights into the expression and regulation of human gene

products during development, their communication with other systems, and their involvement in disease induction and progression.

An important practical application of such a strategy is the “humanization” of the mouse humoral immune system. Introduction of human immunoglobulin (Ig) loci into mice in which the endogenous Ig genes have been inactivated offers the opportunity to study the mechanisms underlying programmed expression and assembly of antibodies as well as their role in B-cell development. Furthermore, such a strategy could provide an ideal source for production of fully human monoclonal antibodies (mAbs) – an important milestone towards fulfilling the promise of antibody therapy in human disease. Fully human antibodies or antibody constructs are expected to minimize the immunogenic and allergic responses intrinsic to mouse or mouse-derivatized mAbs and thus to increase the efficacy and safety of the administered antibodies / antibody constructs. The use of fully human antibodies or antibody constructs can be expected to provide a substantial advantage in the treatment of chronic and recurring human diseases, such as inflammation, autoimmunity, and cancer, which require repeated compound administrations.

One approach towards this goal was to engineer mouse strains deficient in mouse antibody production with large fragments of the human Ig loci in anticipation that such mice would produce a large repertoire of human antibodies in the absence of mouse antibodies. Large human Ig fragments would preserve the large variable gene diversity as well as the proper regulation of antibody production and expression. By exploiting the mouse machinery for antibody diversification and selection and the lack of immunological tolerance to human proteins, the reproduced human antibody repertoire in these mouse strains should yield high affinity antibodies against any antigen of interest, including human antigens. Using the hybridoma technology, antigen-specific human mAbs with the desired specificity could be readily produced and selected. This general strategy was demonstrated in connection with the generation of the first XenoMouse mouse strains (see Green et al. Nature Genetics 7:13-21 (1994)). The XenoMouse strains were engineered with yeast artificial chromosomes (YACs) containing 245 kb and 190 kb-sized germline configuration fragments of the human heavy chain locus and kappa light chain locus, respectively, which contained core variable and constant region sequences. The human Ig containing YACs proved to be compatible with the mouse system for both rearrangement and expression of antibodies and were capable of substituting for the inactivated mouse Ig genes. This was demonstrated by their ability to induce B cell development, to produce an adult-like human repertoire of fully human antibodies, and to generate antigen-specific human mAbs. These results also suggested that introduction of larger

portions of the human Ig loci containing greater numbers of V genes, additional regulatory elements, and human Ig constant regions might recapitulate substantially the full repertoire that is characteristic of the human humoral response to infection and immunization. The work of Green et al. was recently extended to the introduction of greater than approximately 80% of the human antibody repertoire through introduction of megabase sized, germline configuration YAC fragments of the human heavy chain loci and kappa light chain loci, respectively. See Mendez *et al.* Nature Genetics 15:146-156 (1997) and U.S. patent application Ser. No. 08/759,620.

The production of the XenoMouse mice is further discussed and delineated in U.S. patent applications Ser. No. 07/466,008, Ser. No. 07/610,515, Ser. No. 07/919,297, Ser. No. 07/922,649, Ser. No. 08/031,801, Ser. No. 08/112,848, Ser. No. 08/234,145, Ser. No. 08/376,279, Ser. No. 08/430,938, Ser. No. 08/464,584, Ser. No. 08/464,582, Ser. No. 08/463,191, Ser. No. 08/462,837, Ser. No. 08/486,853, Ser. No. 08/486,857, Ser. No. 08/486,859, Ser. No. 08/462,513, Ser. No. 08/724,752, and Ser. No. 08/759,620; and U.S. Pat. Nos. 6,162,963; 6,150,584; 6,114,598; 6,075,181, and 5,939,598 and Japanese Patent Nos. 3 068 180 B2, 3 068 506 B2, and 3 068 507 B2. See also Mendez *et al.* Nature Genetics 15:146-156 (1997) and Green and Jakobovits J. Exp. Med. 188:483-495 (1998), EP 0 463 151 B1, WO 94/02602, WO 96/34096, WO 98/24893, WO 00/76310, and WO 03/47336.

In an alternative approach, others, including GenPharm International, Inc., have utilized a "minilocus" approach. In the minilocus approach, an exogenous Ig locus is mimicked through the inclusion of pieces (individual genes) from the Ig locus. Thus, one or more VH genes, one or more DH genes, one or more JH genes, a mu constant region, and a second constant region (preferably a gamma constant region) are formed into a construct for insertion into an animal. This approach is described in U.S. Pat. No. 5,545,807 to Surani *et al.* and U.S. Pat. Nos. 5,545,806; 5,625,825; 5,625,126; 5,633,425; 5,661,016; 5,770,429; 5,789,650; 5,814,318; 5,877,397; 5,874,299; and 6,255,458 each to Lonberg and Kay, U.S. Pat. Nos. 5,591,669 and 6,023.010 to Krimpenfort and Berns, U.S. Pat. Nos. 5,612,205; 5,721,367; and 5,789,215 to Berns *et al.*, and U.S. Pat. No. 5,643,763 to Choi and Dunn, and GenPharm International U.S. patent application Ser. No. 07/574,748, Ser. No. 07/575,962, Ser. No. 07/810,279, Ser. No. 07/853,408, Ser. No. 07/904,068, Ser. No. 07/990,860, Ser. No. 08/053,131, Ser. No. 08/096,762, Ser. No. 08/155,301, Ser. No. 08/161,739, Ser. No. 08/165,699, Ser. No. 08/209,741. See also EP 0 546 073 B1, WO 92/03918, WO 92/22645, WO 92/22647, WO 92/22670, WO 93/12227, WO 94/00569, WO 94/25585,

WO 96/14436, WO 97/13852, and WO 98/24884 and U.S. Pat. No. 5,981,175. See further Taylor *et al.* (1992), Chen *et al.* (1993), Tuaillon *et al.* (1993), Choi *et al.* (1993), Lonberg *et al.* (1994), Taylor *et al.* (1994), and Tuaillon *et al.* (1995), Fishwild *et al.* (1996).

Kirin has also demonstrated the generation of human antibodies from mice in which, through microcell fusion, large pieces of chromosomes, or entire chromosomes, have been introduced. See European Patent Application Nos. 773 288 and 843 961. Xenerex Biosciences is developing a technology for the potential generation of human antibodies. In this technology, SCID mice are reconstituted with human lymphatic cells, e.g., B and/or T cells. Mice are then immunized with an antigen and can generate an immune response against the antigen. See U.S. Pat. Nos. 5,476,996; 5,698,767; and 5,958,765.

Human anti-mouse antibody (HAMA) responses have led the industry to prepare chimeric or otherwise humanized antibodies. It is however expected that certain human anti-chimeric antibody (HACA) responses will be observed, particularly in chronic or multi-dose utilizations of the antibody. Thus, it would be desirable to provide antibody constructs comprising a human binding domain against MSLN and a human binding domain against CD3 in order to vitiate concerns and/or effects of HAMA or HACA response.

The terms “(specifically) binds to”, (specifically) recognizes", “is (specifically) directed to”, and “(specifically) reacts with” mean in accordance with this invention that a binding domain interacts or specifically interacts with a given epitope or a given target site on the target molecules (antigens), here: MSLN and CD3, respectively.

The term “epitope” refers to a site on an antigen to which a binding domain, such as an antibody or immunoglobulin, or a derivative, fragment or variant of an antibody or an immunoglobulin, specifically binds. An “epitope” is antigenic and thus the term epitope is sometimes also referred to herein as “antigenic structure” or “antigenic determinant”. Thus, the binding domain is an “antigen interaction site”. Said binding/interaction is also understood to define a “specific recognition”.

“Epitopes” can be formed both by contiguous amino acids or non-contiguous amino acids juxtaposed by tertiary folding of a protein. A “linear epitope” is an epitope where an amino acid primary sequence comprises the recognized epitope. A linear epitope typically includes at least

3 or at least 4, and more usually, at least 5 or at least 6 or at least 7, for example, about 8 to about 10 amino acids in a unique sequence.

A "conformational epitope", in contrast to a linear epitope, is an epitope wherein the primary sequence of the amino acids comprising the epitope is not the sole defining component of the epitope recognized (*e.g.*, an epitope wherein the primary sequence of amino acids is not necessarily recognized by the binding domain). Typically a conformational epitope comprises an increased number of amino acids relative to a linear epitope. With regard to recognition of conformational epitopes, the binding domain recognizes a three-dimensional structure of the antigen, preferably a peptide or protein or fragment thereof (in the context of the present invention, the antigenic structure for one of the binding domains is comprised within the MSLN protein). For example, when a protein molecule folds to form a three-dimensional structure, certain amino acids and/or the polypeptide backbone forming the conformational epitope become juxtaposed enabling the antibody to recognize the epitope. Methods of determining the conformation of epitopes include, but are not limited to, x-ray crystallography, two-dimensional nuclear magnetic resonance (2D-NMR) spectroscopy and site-directed spin labelling and electron paramagnetic resonance (EPR) spectroscopy.

A method for epitope mapping is described in the following: When a region (a contiguous amino acid stretch) in the human MSLN protein is exchanged / replaced with its corresponding region of a non-human and non-primate MSLN antigen (e.g., mouse MSLN, but others like chicken, rat, hamster, rabbit etc. might also be conceivable), a decrease in the binding of the binding domain is expected to occur, unless the binding domain is cross-reactive for the non-human, non-primate MSLN used. Said decrease is preferably at least 10%, 20%, 30%, 40%, or 50%; more preferably at least 60%, 70%, or 80%, and most preferably 90%, 95% or even 100% in comparison to the binding to the respective region in the human MSLN protein, whereby binding to the respective region in the human MSLN protein is set to be 100%. It is envisaged that the aforementioned human MSLN / non-human MSLN chimeras are expressed in CHO cells. The human MSLN / non-human MSLN chimeras may also be fused with a transmembrane domain and/or cytoplasmic domain of a different membrane-bound protein such as EpCAM, although such technique was not necessary for the method described in Examples 1 and 2.

In an alternative or additional method for epitope mapping, several truncated versions of the human MSLN extracellular domain can be generated in order to determine a specific region that is recognized by a binding domain. In these truncated versions, the different extracellular MSLN

domains / sub-domains or regions are stepwise deleted, starting from the N-terminus. The truncated MSLN versions that may be expressed in CHO cells. It is also envisaged that the truncated MSLN versions may be fused with a transmembrane domain and/or cytoplasmic domain of a different membrane-bound protein such as EpCAM. It is also envisaged that the truncated MSLN versions may encompass a signal peptide domain at their N-terminus, for example a signal peptide derived from mouse IgG heavy chain signal peptide. It is furtherore envisaged that the truncated MSLN versions may encompass a v5 domain at their N-terminus (following the signal peptide) which allows verifying their correct expression on the cell surface. A decrease or a loss of binding is expected to occur with those truncated MSLN versions which do not encompass any more the MSLN region that is recognized by the binding domain. The decrease of binding is preferably at least 10%, 20%, 30%, 40%, 50%; more preferably at least 60%, 70%, 80%, and most preferably 90%, 95% or even 100%, whereby binding to the entire human MSLN protein (or its extracellular region or domain) is set to be 100%.

A further method to determine the contribution of a specific residue of a target antigen to the recognition by a antibody construct or binding domain is alanine scanning (see e.g. Morrison KL & Weiss GA. Cur Opin Chem Biol. 2001 Jun;5(3):302-7), where each residue to be analyzed is replaced by alanine, e.g. via site-directed mutagenesis. Alanine is used because of its non-bulky, chemically inert, methyl functional group that nevertheless mimics the secondary structure references that many of the other amino acids possess. Sometimes bulky amino acids such as valine or leucine can be used in cases where conservation of the size of mutated residues is desired. Alanine scanning is a mature technology which has been used for a long period of time.

The interaction between the binding domain and the epitope or the region comprising the epitope implies that a binding domain exhibits appreciable affinity for the epitope / the region comprising the epitope on a particular protein or antigen (here: MSLN and CD3, respectively) and, generally, does not exhibit significant reactivity with proteins or antigens other than MSLN or CD3. “Appreciable affinity” includes binding with an affinity of about 10^{-6} M (KD) or stronger. Preferably, binding is considered specific when the binding affinity is about 10^{-12} to 10^{-8} M, 10^{-12} to 10^{-9} M, 10^{-12} to 10^{-10} M, 10^{-11} to 10^{-8} M, preferably of about 10^{-11} to 10^{-9} M. Whether a binding domain specifically reacts with or binds to a target can be tested readily by, *inter alia*, comparing the reaction of said binding domain with a target protein or antigen with the reaction of said binding domain with proteins or antigens other than MSLN or CD3. Preferably, a binding domain of the invention does not essentially or substantially bind to proteins or antigens other than

MSLN or CD3 (*i.e.*, the first binding domain is not capable of binding to proteins other than MSLN and the second binding domain is not capable of binding to proteins other than CD3).

The term "does not essentially / substantially bind" or "is not capable of binding" means that a binding domain of the present invention does not bind a protein or antigen other than MSLN or CD3, *i.e.*, does not show reactivity of more than 30%, preferably not more than 20%, more preferably not more than 10%, particularly preferably not more than 9%, 8%, 7%, 6% or 5% with proteins or antigens other than MSLN or CD3, whereby binding to MSLN or CD3, respectively, is set to be 100%.

Specific binding is believed to be effected by specific motifs in the amino acid sequence of the binding domain and the antigen. Thus, binding is achieved as a result of their primary, secondary and/or tertiary structure as well as the result of secondary modifications of said structures. The specific interaction of the antigen-interaction-site with its specific antigen may result in a simple binding of said site to the antigen. Moreover, the specific interaction of the antigen-interaction-site with its specific antigen may alternatively or additionally result in the initiation of a signal, *e.g.* due to the induction of a change of the conformation of the antigen, an oligomerization of the antigen, etc.

It is also preferred in one embodiement of the invention that the second binding domain binds to human CD3 epsilon and to *Callithrix jacchus, Saguinus Oedipus* or *Saimiri sciureus* CD3 epsilon.

In another aspect, the present invention provides a bispecific antibody construct comprising a first binding domain which binds to human MSLN on the surface of a target cell and a second binding domain which binds to human CD3 on the surface of a T cell, wherein the first binding domain binds to an epitope of MSLN which is comprised within the region of the human MSLN having a sequence as depicted in SEQ ID NO selected form the group consisting of SEQ ID NO: 244 (cluster 1+2), SEQ ID NO: 245 (cluster 2+3) and SEQ ID NO: 241 (cluster 4).

Preferably, the first binding domain of the bispecific antibody construct of the invention comprises a VH region comprising CDR-H1, CDR-H2 and CDR-H3 and a VL region comprising CDR-L1, CDR-L2 and CDR-L3 selected from the group consisting of:

a) CDR-H1 as depicted in SEQ ID NO: 151, CDR-H2 as depicted in SEQ ID NO: 152, CDR-H3 as depicted in SEQ ID NO: 153, CDR-L1 as depicted in SEQ ID NO: 154, CDR-L2 as depicted in SEQ ID NO: 155 and CDR-L3 as depicted in SEQ ID NO: 156;
b) CDR-H1 as depicted in SEQ ID NO: 161, CDR-H2 as depicted in SEQ ID NO: 162, CDR-H3 as depicted in SEQ ID NO: 163, CDR-L1 as depicted in SEQ ID NO: 164, CDR-L2 as depicted in SEQ ID NO: 165 and CDR-L3 as depicted in SEQ ID NO: 166;
c) CDR-H1 as depicted in SEQ ID NO: 171, CDR-H2 as depicted in SEQ ID NO: 172, CDR-H3 as depicted in SEQ ID NO: 173, CDR-L1 as depicted in SEQ ID NO: 174, CDR-L2 as depicted in SEQ ID NO: 175 and CDR-L3 as depicted in SEQ ID NO: 176;
d) CDR-H1 as depicted in SEQ ID NO: 181, CDR-H2 as depicted in SEQ ID NO: 182, CDR-H3 as depicted in SEQ ID NO: 183, CDR-L1 as depicted in SEQ ID NO: 184, CDR-L2 as depicted in SEQ ID NO: 185 and CDR-L3 as depicted in SEQ ID NO: 186;
e) CDR-H1 as depicted in SEQ ID NO: 191, CDR-H2 as depicted in SEQ ID NO: 192, CDR-H3 as depicted in SEQ ID NO: 193, CDR-L1 as depicted in SEQ ID NO: 194, CDR-L2 as depicted in SEQ ID NO: 195 and CDR-L3 as depicted in SEQ ID NO: 196;
f) CDR-H1 as depicted in SEQ ID NO: 201, CDR-H2 as depicted in SEQ ID NO: 202, CDR-H3 as depicted in SEQ ID NO: 203, CDR-L1 as depicted in SEQ ID NO: 204, CDR-L2 as depicted in SEQ ID NO: 205 and CDR-L3 as depicted in SEQ ID NO: 206;
g) CDR-H1 as depicted in SEQ ID NO: 211, CDR-H2 as depicted in SEQ ID NO: 212, CDR-H3 as depicted in SEQ ID NO: 213, CDR-L1 as depicted in SEQ ID NO: 214, CDR-L2 as depicted in SEQ ID NO: 215 and CDR-L3 as depicted in SEQ ID NO: 216; and
h) CDR-H1 as depicted in SEQ ID NO: 221, CDR-H2 as depicted in SEQ ID NO: 222, CDR-H3 as depicted in SEQ ID NO: 223, CDR-L1 as depicted in SEQ ID NO: 224, CDR-L2 as depicted in SEQ ID NO: 225 and CDR-L3 as depicted in SEQ ID NO: 226.

The term “variable” refers to the portions of the antibody or immunoglobulin domains that exhibit variability in their sequence and that are involved in determining the specificity and binding affinity of a particular antibody (i.e., the “variable domain(s)”). The pairing of a variable heavy chain (VH) and a variable light chain (VL) together forms a single antigen-binding site.

Variability is not evenly distributed throughout the variable domains of antibodies; it is concentrated in sub-domains of each of the heavy and light chain variable regions. These sub-domains are called “hypervariable regions” or "complementarity determining regions" (CDRs). The more conserved (i.e., non-hypervariable) portions of the variable domains are called the “framework” regions (FRM or FR) and provide a scaffold for the six CDRs in three dimensional

space to form an antigen-binding surface. The variable domains of naturally occurring heavy and light chains each comprise four FRM regions (FR1, FR2, FR3, and FR4), largely adopting a β-sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the β-sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRM and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site (see Kabat *et al.*, *loc. cit.*).

The terms “CDR”, and its plural “CDRs”, refer to the complementarity determining region of which three make up the binding character of a light chain variable region (CDR-L1, CDR-L2 and CDR-L3) and three make up the binding character of a heavy chain variable region (CDR-H1, CDR-H2 and CDR-H3). CDRs contain most of the residues responsible for specific interactions of the antibody with the antigen and hence contribute to the functional activity of an antibody molecule: they are the main determinants of antigen specificity.

The exact definitional CDR boundaries and lengths are subject to different classification and numbering systems. CDRs may therefore be referred to by Kabat, Chothia, contact or any other boundary definitions, including the numbering system described herein. Despite differing boundaries, each of these systems has some degree of overlap in what constitutes the so called “hypervariable regions” within the variable sequences. CDR definitions according to these systems may therefore differ in length and boundary areas with respect to the adjacent framework region. See for example Kabat (an approach based on cross-species sequence variability), Chothia (an approach based on crystallographic studies of antigen-antibody complexes), and/or MacCallum (Kabat *et al.*, *loc. cit.*; Chothia *et al.*, J. Mol. Biol, 1987, 196: 901-917; and MacCallum *et al.*, J. Mol. Biol, 1996, 262: 732). Still another standard for characterizing the antigen binding site is the AbM definition used by Oxford Molecular's AbM antibody modeling software. See, *e.g.*, Protein Sequence and Structure Analysis of Antibody Variable Domains. In: Antibody Engineering Lab Manual (Ed.: Duebel, S. and Kontermann, R., Springer-Verlag, Heidelberg). To the extent that two residue identification techniques define regions of overlapping, but not identical regions, they can be combined to define a hybrid CDR. However, the numbering in accordance with the so-called Kabat system is preferred.

Typically, CDRs form a loop structure that can be classified as a canonical structure. The term “canonical structure” refers to the main chain conformation that is adopted by the antigen binding (CDR) loops. From comparative structural studies, it has been found that five of the six antigen binding loops have only a limited repertoire of available conformations. Each canonical

structure can be characterized by the torsion angles of the polypeptide backbone. Correspondent loops between antibodies may, therefore, have very similar three dimensional structures, despite high amino acid sequence variability in most parts of the loops (Chothia and Lesk, J. Mol. Biol., 1987, 196: 901; Chothia *et al.*, Nature, 1989, 342: 877; Martin and Thornton, J. Mol. Biol, 1996, 263: 800). Furthermore, there is a relationship between the adopted loop structure and the amino acid sequences surrounding it. The conformation of a particular canonical class is determined by the length of the loop and the amino acid residues residing at key positions within the loop, as well as within the conserved framework (*i.e.*, outside of the loop). Assignment to a particular canonical class can therefore be made based on the presence of these key amino acid residues.

The term “canonical structure” may also include considerations as to the linear sequence of the antibody, for example, as catalogued by Kabat (Kabat *et al.*, loc. cit.). The Kabat numbering scheme (system) is a widely adopted standard for numbering the amino acid residues of an antibody variable domain in a consistent manner and is the preferred scheme applied in the present invention as also mentioned elsewhere herein. Additional structural considerations can also be used to determine the canonical structure of an antibody. For example, those differences not fully reflected by Kabat numbering can be described by the numbering system of Chothia *et al.* and/or revealed by other techniques, for example, crystallography and two- or three-dimensional computational modeling. Accordingly, a given antibody sequence may be placed into a canonical class which allows for, among other things, identifying appropriate chassis sequences (*e.g.*, based on a desire to include a variety of canonical structures in a library). Kabat numbering of antibody amino acid sequences and structural considerations as described by Chothia *et al.*, *loc. cit.* and their implications for construing canonical aspects of antibody structure, are described in the literature. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known in the art. For a review of the antibody structure, see Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, eds. Harlow *et al.*, 1988.

The CDR3 of the light chain and, particularly, the CDR3 of the heavy chain may constitute the most important determinants in antigen binding within the light and heavy chain variable regions. In some antibody constructs, the heavy chain CDR3 appears to constitute the major area of contact between the antigen and the antibody. *In vitro* selection schemes in which CDR3 alone is varied can be used to vary the binding properties of an antibody or determine which residues contribute to the binding of an antigen. Hence, CDR3 is typically the greatest

source of molecular diversity within the antibody-binding site. H3, for example, can be as short as two amino acid residues or greater than 26 amino acids.

In a classical full-length antibody or immunoglobulin, each light (L) chain is linked to a heavy (H) chain by one covalent disulfide bond, while the two H chains are linked to each other by one or more disulfide bonds depending on the H chain isotype. The CH domain most proximal to VH is usually designated as CH1. The constant ("C") domains are not directly involved in antigen binding, but exhibit various effector functions, such as antibody-dependent, cell-mediated cytotoxicity and complement activation.The Fc region of an antibody is comprised within the heavy chain constant domains and is for example able to interact with cell surface located Fc receptors.

The sequence of antibody genes after assembly and somatic mutation is highly varied, and these varied genes are estimated to encode 10^{10} different antibody molecules (Immunoglobulin Genes, 2nd ed., eds. Jonio et al., Academic Press, San Diego, CA, 1995). Accordingly, the immune system provides a repertoire of immunoglobulins. The term "repertoire" refers to at least one nucleotide sequence derived wholly or partially from at least one sequence encoding at least one immunoglobulin. The sequence(s) may be generated by rearrangement *in vivo* of the V, D, and J segments of heavy chains, and the V and J segments of light chains. Alternatively, the sequence(s) can be generated from a cell in response to which rearrangement occurs, e.g., *in vitro* stimulation. Alternatively, part or all of the sequence(s) may be obtained by DNA splicing, nucleotide synthesis, mutagenesis, and other methods, see, e.g., U.S. Patent 5,565,332. A repertoire may include only one sequence or may include a plurality of sequences, including ones in a genetically diverse collection.

A preferred antibody construct according to the invention can also be defined as a bispecific antibody construct comprising a first (preferably human) binding domain which binds to human MSLN on the surface of a target cell and a second binding domain which binds to human CD3 on the surface of a T cell, wherein the first binding domain binds to the same epitope of MSLN as an antibody selected from the group consisting of MS_1 to MS_8, *i.e.*, an antibody comprising a VH region comprising CDR-H1, CDR-H2 and CDR-H3 and a VL region comprising CDR-L1, CDR-L2 and CDR-L3 selected from the group consisting of:

a) CDR-H1 as depicted in SEQ ID NO: 151, CDR-H2 as depicted in SEQ ID NO: 152, CDR-H3 as depicted in SEQ ID NO: 153, CDR-L1 as depicted in SEQ ID NO: 154, CDR-L2 as depicted in SEQ ID NO: 155 and CDR-L3 as depicted in SEQ ID NO: 156;

b) CDR-H1 as depicted in SEQ ID NO: 161, CDR-H2 as depicted in SEQ ID NO: 162, CDR-H3 as depicted in SEQ ID NO: 163, CDR-L1 as depicted in SEQ ID NO: 164, CDR-L2 as depicted in SEQ ID NO: 165 and CDR-L3 as depicted in SEQ ID NO: 166;
c) CDR-H1 as depicted in SEQ ID NO: 171, CDR-H2 as depicted in SEQ ID NO: 172, CDR-H3 as depicted in SEQ ID NO: 173, CDR-L1 as depicted in SEQ ID NO: 174, CDR-L2 as depicted in SEQ ID NO: 175 and CDR-L3 as depicted in SEQ ID NO: 176;
d) CDR-H1 as depicted in SEQ ID NO: 181, CDR-H2 as depicted in SEQ ID NO: 182, CDR-H3 as depicted in SEQ ID NO: 183, CDR-L1 as depicted in SEQ ID NO: 184, CDR-L2 as depicted in SEQ ID NO: 185 and CDR-L3 as depicted in SEQ ID NO: 186;
e) CDR-H1 as depicted in SEQ ID NO: 191, CDR-H2 as depicted in SEQ ID NO: 192, CDR-H3 as depicted in SEQ ID NO: 193, CDR-L1 as depicted in SEQ ID NO: 194, CDR-L2 as depicted in SEQ ID NO: 195 and CDR-L3 as depicted in SEQ ID NO: 196;
f) CDR-H1 as depicted in SEQ ID NO: 201, CDR-H2 as depicted in SEQ ID NO: 202, CDR-H3 as depicted in SEQ ID NO: 203, CDR-L1 as depicted in SEQ ID NO: 204, CDR-L2 as depicted in SEQ ID NO: 205 and CDR-L3 as depicted in SEQ ID NO: 206;
g) CDR-H1 as depicted in SEQ ID NO: 211, CDR-H2 as depicted in SEQ ID NO: 212, CDR-H3 as depicted in SEQ ID NO: 213, CDR-L1 as depicted in SEQ ID NO: 214, CDR-L2 as depicted in SEQ ID NO: 215 and CDR-L3 as depicted in SEQ ID NO: 216; and
h) CDR-H1 as depicted in SEQ ID NO: 221, CDR-H2 as depicted in SEQ ID NO: 222, CDR-H3 as depicted in SEQ ID NO: 223, CDR-L1 as depicted in SEQ ID NO: 224, CDR-L2 as depicted in SEQ ID NO: 225 and CDR-L3 as depicted in SEQ ID NO: 226.

Whether or not an antibody construct binds to the same epitope of MSLN as another given antibody construct can be measured *e.g.* by epitope mapping with chimeric or truncated target molecules, *e.g.* as described herein above and in in the appended Examples 1 and 2.

A preferred antibody construct according to the invention can also be defined as a bispecific antibody construct comprising a first (preferably human) binding domain which binds to human MSLN on the surface of a target cell and a second binding domain which binds to human CD3 on the surface of a T cell, wherein the first binding domain competes for binding with an antibody selected from the group consisting of MS_1 to MS_8, *i.e.*, an antibody comprising a VH region comprising CDR-H1, CDR-H2 and CDR-H3 and a VL region comprising CDR-L1, CDR-L2 and CDR-L3 selected from the group consisting of those described above.

Whether or not an antibody construct competes for binding with another given antibody construct can be measured in a competition assay such as a competitive ELISA or a cell-based competition assay. Avidin-coupled microparticles (beads) can also be used. Similar to an avidin-coated ELISA plate, when reacted with a biotinylated protein, each of these beads can be used as a substrate on which an assay can be performed. Antigen is coated onto a bead and then precoated with the first antibody. The second antibody is added and any additional binding is determined. Possible means for the read-out includes flow cytometry.

In one embodiment, the first binding domain of the antibody construct of the invention comprises a VH region selected from the group consisting of those depicted in SEQ ID NO: 157, SEQ ID NO: 167, SEQ ID NO: 177, SEQ ID NO: 187, SEQ ID NO: 197, SEQ ID NO: 207, SEQ ID NO: 217, and SEQ ID NO: 227.

In a further embodiment, the first binding domain of the antibody construct of the invention comprises a VL region selected from the group consisting of those depicted in SEQ ID NO: 158, SEQ ID NO: 168, SEQ ID NO: 178, SEQ ID NO: 188, SEQ ID NO: 198, SEQ ID NO: 208, SEQ ID NO: 218, and SEQ ID NO: 228.

In another embodiment, the first binding domain of the antibody construct of the invention comprises a VH region and a VL region selected from the group consisting of pairs of a VH region and a VL region as depicted in SEQ ID NO: 157+158, SEQ ID NO: 167+168, SEQ ID NO: 177+178, SEQ ID NO: 187+188, SEQ ID NO: 197+198, SEQ ID NO: 207+208, SEQ ID NO: 217+218, and SEQ ID NO: 227+228..

In yet a further embodiment, the first binding domain of the antibody construct of the invention comprises a polypeptide selected from the group consisting of those depicted in SEQ ID NO: 159, SEQ ID NO: 169, SEQ ID NO: 179, SEQ ID NO: 189, SEQ ID NO: 199, SEQ ID NO: 209, SEQ ID NO: 219, and SEQ ID NO: 229.

The above first binding domains (which are specified by their CDRs, VH region and VL region and combinations thereof) characterize as binding domains which bind to an epitope of MSLN as depicted in SEQ ID NOs: 231, 232, and 233.

The term “bispecific” as used herein refers to an antibody construct which is “at least bispecific”, *i.e.*, it comprises at least a first binding domain and a second binding domain, wherein the first

binding domain binds to one antigen or target (here: MSLN), and the second binding domain binds to another antigen or target (here: CD3). Accordingly, antibody constructs according to the invention comprise specificities for at least two different antigens or targets. The term "bispecific antibody construct" of the invention also encompasses multispecific antibody constructs such as trispecific antibody constructs, the latter ones including three binding domains, or constructs having more than three (e.g. four, five…) specificites.

Given that the antibody constructs according to the invention are (at least) bispecific, they do not occur naturally and they are markedly different from naturally occurring products. A "bispecific" antibody construct or immunoglobulin is hence an artificial hybrid antibody or immunoglobulin having at least two distinct binding sites with different specificities. Bispecific antibody constructs can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. See, *e.g.*, Songsivilai & Lachmann, Clin. Exp. Immunol. 79:315-321 (1990).

The at least two binding domains and the variable domains of the antibody construct of the present invention may or may not comprise peptide linkers (spacer peptides). The term "peptide linker" comprises in accordance with the present invention an amino acid sequence by which the amino acid sequences of one (variable and/or binding) domain and another (variable and/or binding) domain of the antibody construct of the invention are linked with each other. An essential technical feature of such peptide linker is that it does not comprise any polymerization activity. Among the suitable peptide linkers are those described in U.S. Patents 4,751,180 and 4,935,233 or WO 88/09344. The peptide linkers can also be used to attach other domains or modules or regions (such as half-life extending domains) to the antibody construct of the invention.

In the event that a linker is used, this linker is preferably of a length and sequence sufficient to ensure that each of the first and second domains can, independently from one another, retain their differential binding specificities. For peptide linkers which connect the at least two binding domains (or two variable domains) in the antibody construct of the invention, those peptide linkers are preferred which comprise only a few number of amino acid residues, *e.g.* 12 amino acid residues or less. Thus, peptide linkers of 12, 11, 10, 9, 8, 7, 6 or 5 amino acid residues are preferred. An envisaged peptide linker with less than 5 amino acids comprises 4, 3, 2 or one amino acid(s), wherein Gly-rich linkers are preferred. A particularly preferred "single" amino acid in the context of said "peptide linker" is Gly. Accordingly, said peptide linker may consist of the

single amino acid Gly. Another preferred embodiment of a peptide linker is characterized by the amino acid sequence Gly-Gly-Gly-Gly-Ser, i.e. Gly_4Ser (SEQ ID NO: 1), or polymers thereof, i.e. $(Gly_4Ser)x$, where x is an integer of 1 or greater (e.g. 2 or 3). Preferred linkers are depicted in SEQ ID NOs: 1-9. The characteristics of said peptide linker, which comprise the absence of the promotion of secondary structures, are known in the art and are described *e.g.* in Dall'Acqua et al. (Biochem. (1998) 37, 9266-9273), Cheadle et al. (Mol Immunol (1992) 29, 21-30) and Raag and Whitlow (FASEB (1995) 9(1), 73-80). Peptide linkers which furthermore do not promote any secondary structures are preferred. The linkage of said domains to each other can be provided, *e.g.*, by genetic engineering, as described in the examples. Methods for preparing fused and operatively linked bispecific single chain constructs and expressing them in mammalian cells or bacteria are well-known in the art (*e.g.* WO 99/54440 or Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 2001).

As described herein above, the invention provides a preferred embodiment wherein the antibody construct is in a format selected from the group consisting of $(scFv)_2$, scFv-single domain mAb, diabodies and oligomers of any of the those formats.

According to a particularly preferred embodiment, and as documented in the appended examples, the antibody construct of the invention is a "bispecific single chain antibody construct", more prefereably a bispecific "single chain Fv" (scFv). Although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker – as described hereinbefore – that enables them to be made as a single protein chain in which the VL and VH regions pair to form a monovalent molecule; see *e.g.*, Huston et al. (1988) Proc. Natl. Acad. Sci USA 85:5879-5883). These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are evaluated for function in the same manner as are whole or full-length antibodies. A single-chain variable fragment (scFv) is hence a fusion protein of the variable region of the heavy chain (VH) and of the light chain (VL) of immunoglobulins, usually connected with a short linker peptide of about ten to about 25 amino acids, preferably about 15 to 20 amino acids. The linker is usually rich in glycine for flexibility, as well as serine or threonine for solubility, and can either connect the N-terminus of the VH with the C-terminus of the VL, or *vice versa*. This protein retains the specificity of the original immunoglobulin, despite removal of the constant regions and introduction of the linker.

Bispecific single chain molecules are known in the art and are described in WO 99/54440, Mack, J. Immunol. (1997), 158, 3965-3970, Mack, PNAS, (1995), 92, 7021-7025, Kufer, Cancer Immunol. Immunother., (1997), 45, 193-197, Löffler, Blood, (2000), 95, 6, 2098-2103, Brühl, Immunol., (2001), 166, 2420-2426, Kipriyanov, J. Mol. Biol., (1999), 293, 41-56. Techniques described for the production of single chain antibodies (see, *inter alia*, US Patent 4,946,778, Kontermann and Dübel (2010), *loc. cit.* and Little (2009), *loc. cit.*) can be adapted to produce single chain antibody constructs specifically recognizing (an) elected target(s).

Bivalent (also called divalent) or bispecific single-chain variable fragments (bi-scFvs or di-scFvs having the format $(scFv)_2$ can be engineered by linking two scFv molecules (*e.g.* with linkers as described hereinbefore). If these two scFv molecules have the same binding specificity, the resulting $(scFv)_2$ molecule will preferably be called bivalent (*i.e.* it has two valences for the same target epitope). If the two scFv molecules have different binding specificities, the resulting $(scFv)_2$ molecule will preferably be called bispecific. The linking can be done by producing a single peptide chain with two VH regions and two VL regions, yielding tandem scFvs (see *e.g.* Kufer P. *et al.*, (2004) Trends in Biotechnology 22(5):238-244). Another possibility is the creation of scFv molecules with linker peptides that are too short for the two variable regions to fold together (*e.g.* about five amino acids), forcing the scFvs to dimerize. This type is known as diabodies (see *e.g.* Hollinger, Philipp *et al.*, (July 1993) Proceedings of the National Academy of Sciences of the United States of America 90 (14): 6444-8.).

Accorcing to an also preferred embodiment of the antibody construct of the invention the heavy chain (VH) and of the light chain (VL) of a binding domain binding either to the targe antigen MSLN or CD3 are not directly connected via an above described peptide linker but the binding domain is formed due to the formation of a bispecifc molecule as described for the diabody. Thus, the VH chain of the CD3 binding domain may be fused to the VL of the MSLN binding domain via such peptide linker, while the VH chain of the MSLN binding domain is fused to the VL of the CD3 binding domain via such peptide linker.

Single domain antibodies comprise merely one (monomeric) antibody variable domain which is able to bind selectively to a specific antigen, independently of other V regions or domains. The first single domain antibodies were engineered from havy chain antibodies found in camelids, and these are called V_HH fragments. Cartilaginous fishes also have heavy chain antibodies (IgNAR) from which single domain antibodies called V_{NAR} fragments can be obtained. An alternative approach is to split the dimeric variable domains from common immunoglobulins *e.g.*

from humans or rodents into monomers, hence obtaining VH or VL as a single domain Ab. Although most research into single domain antibodies is currently based on heavy chain variable domains, nanobodies derived from light chains have also been shown to bind specifically to target epitopes. Examples of single domain antibodies are called sdAb, nanobodies or single variable domain antibodies.

A (single domain mAb)$_2$ is hence a monoclonal antibody construct composed of (at least) two single domain monoclonal antibodies, which are individually selected from the group comprising VH, VL, V_HH and V_{NAR}. The linker is preferably in the form of a peptide linker. Similarly, an "scFv-single domain mAb" is a monoclonal antibody construct composed of at least one single domain antibody as described above and one scFv molecule as described above. Again, the linker is preferably in the form of a peptide linker.

It is furthermore envisaged that the present invention provides a bispecific antibody construct comprising a first binding domain which binds to human MSLN on the surface of a target cell and a second binding domain which binds to human CD3 on the surface of a T cell, wherein the first binding domain binds to an epitope of MSLN which is comprised within the region as depicted in SEQ ID NO: 245 (cluster 2+3).

Accordingly, in a further aspect of the invention, the first binding domain of the bispecific antibody construct comprises a VH region comprising CDR-H1, CDR-H2 and CDR-H3 and a VL region comprising CDR-L1, CDR-L2 and CDR-L3 selected from the group consisting of:

a) CDR-H1 as depicted in SEQ ID NO: 161, CDR-H2 as depicted in SEQ ID NO: 162, CDR-H3 as depicted in SEQ ID NO: 163, CDR-L1 as depicted in SEQ ID NO: 164, CDR-L2 as depicted in SEQ ID NO: 165 and CDR-L3 as depicted in SEQ ID NO: 166;
b) CDR-H1 as depicted in SEQ ID NO: 171, CDR-H2 as depicted in SEQ ID NO: 172, CDR-H3 as depicted in SEQ ID NO: 173, CDR-L1 as depicted in SEQ ID NO: 174, CDR-L2 as depicted in SEQ ID NO: 175 and CDR-L3 as depicted in SEQ ID NO: 176;
c) CDR-H1 as depicted in SEQ ID NO: 181, CDR-H2 as depicted in SEQ ID NO: 182, CDR-H3 as depicted in SEQ ID NO: 183, CDR-L1 as depicted in SEQ ID NO: 184, CDR-L2 as depicted in SEQ ID NO: 185 and CDR-L3 as depicted in SEQ ID NO: 186;
d) CDR-H1 as depicted in SEQ ID NO: 191, CDR-H2 as depicted in SEQ ID NO: 192, CDR-H3 as depicted in SEQ ID NO: 193, CDR-L1 as depicted in SEQ ID NO: 194, CDR-L2 as depicted in SEQ ID NO: 195 and CDR-L3 as depicted in SEQ ID NO: 196;

e) CDR-H1 as depicted in SEQ ID NO: 201, CDR-H2 as depicted in SEQ ID NO: 202, CDR-H3 as depicted in SEQ ID NO: 203, CDR-L1 as depicted in SEQ ID NO: 204, CDR-L2 as depicted in SEQ ID NO: 205 and CDR-L3 as depicted in SEQ ID NO: 206.

In one embodiment, the first binding domain of the antibody construct of the invention comprises a VH region selected from the group consisting of those depicted in SEQ ID NO: 167, SEQ ID NO: 177, SEQ ID NO: 187, SEQ ID NO: 197, and SEQ ID NO: 207.

In a further embodiment, the first binding domain of the antibody construct of the invention comprises a VL region selected from the group consisting of those depicted in SEQ ID NO: 168, SEQ ID NO: 178, SEQ ID NO: 188, SEQ ID NO: 198, and SEQ ID NO: 208.

In another embodiment, the first binding domain of the antibody construct of the invention comprises a VH region and a VL region selected from the group consisting of pairs of a VH region and a VL region as depicted in SEQ ID NO: 167+168, SEQ ID NO: 177+178, SEQ ID NO: 187+188, SEQ ID NO: 197+198, and SEQ ID NO: 207+208.

In a further embodiment, the first binding domain of the antibody construct of the invention comprises a polypeptide selected from the group consisting of those depicted in SEQ ID NO: 169, SEQ ID NO: 179, SEQ ID NO: 189, SEQ ID NO: 199, and SEQ ID NO: 209.

It is also envisaged that the present invention provides a bispecific antibody construct comprising a first binding domain which binds to human MSLN on the surface of a target cell and a second binding domain which binds to human CD3 on the surface of a T cell, wherein the first binding domain binds to an epitope of MSLN which is comprised within the region as depicted in SEQ ID NO: 244 (cluster 1+2).

Accordingly, in a further aspect of the invention, the first binding domain of the bispecific antibody construct comprises a VH region comprising CDR-H1, CDR-H2 and CDR-H3 and a VL region comprising CDR-L1, CDR-L2 and CDR-L3 as follows:

(a) CDR-H1 as depicted in SEQ ID NO: 151, CDR-H2 as depicted in SEQ ID NO: 152, CDR-H3 as depicted in SEQ ID NO: 153, CDR-L1 as depicted in SEQ ID NO: 154, CDR-L2 as depicted in SEQ ID NO: 155 and CDR-L3 as depicted in SEQ ID NO: 156; or

(b) CDR-H1 as depicted in SEQ ID NO: 221, CDR-H2 as depicted in SEQ ID NO: 222, CDR-H3 as depicted in SEQ ID NO: 223, CDR-L1 as depicted in SEQ ID NO: 224, CDR-L2 as depicted in SEQ ID NO: 225 and CDR-L3 as depicted in SEQ ID NO: 226.

In one embodiment, the first binding domain of the antibody construct of the invention comprises a VH region depicted in SEQ ID NO: 157 or SEQ ID NO: 227.

In a further embodiment, the first binding domain of the antibody construct of the invention comprises a VL region depicted in SEQ ID NO: 158, and SEQ ID NO: 228.

In another embodiment, the first binding domain of the antibody construct of the invention comprises a VH region and a VL region selected from the group consisting of pairs of a VH region and a VL region as depicted in SEQ ID NO: 157+158, and SEQ ID NO: 227+228.

In a further embodiment, the first binding domain of the antibody construct of the invention comprises a polypeptide selected from the group consisting of those depicted in SEQ ID NO: 159, and SEQ ID NO: 229.

It is also envisaged that the present invention provides a bispecific antibody construct comprising a first binding domain which binds to human MSLN on the surface of a target cell and a second binding domain which binds to human CD3 on the surface of a T cell, wherein the first binding domain binds to an epitope of MSLN which is comprised within the region as depicted in SEQ ID NO: 241 (cluster 4).

Accordingly, in a further aspect of the invention, the first binding domain of the bispecific antibody construct comprises a VH region comprising CDR-H1 as depicted in SEQ ID NO: 211, CDR-H2 as depicted in SEQ ID NO: 212, CDR-H3 as depicted in SEQ ID NO: 213, CDR-L1 as depicted in SEQ ID NO: 214, CDR-L2 as depicted in SEQ ID NO: 215 and CDR-L3 as depicted in SEQ ID NO: 216.

In one embodiment, the first binding domain of the antibody construct of the invention comprises a VH region depicted in SEQ ID NO: 217.

In a further embodiment, the first binding domain of the antibody construct of the invention comprises a VL region depicted in SEQ ID NO: 218.

In another embodiment, the first binding domain of the antibody construct of the invention comprises a VH region and a VL region as depicted in SEQ ID NO: 217+218.

In a further embodiment, the first binding domain of the antibody construct of the invention comprises a polypeptide as depicted in SEQ ID NO: 219.

Another preferred antibody construct according to the invention can also be defined as a bispecific antibody construct comprising a first (preferably human) binding domain which binds to human MSLN on the surface of a target cell and a second binding domain which binds to human CD3 on the surface of a T cell, wherein the first binding domain competes for binding with an antibody selected from the group consisting of MS-3, MS-4 and MS-5, *i.e.*, an antibody comprising a VH region comprising CDR-H1, CDR-H2 and CDR-H3 and a VL region comprising CDR-L1, CDR-L2 and CDR-L3 selected from the group consisting of those described above.

T cells or T lymphocytes are a type of lymphocyte (itself a type of white blood cell) that play a central role in cell-mediated immunity. There are several subsets of T cells, each with a distinct function. T cells can be distinguished from other lymphocytes, such as B cells and NK cells, by the presence of a T cell receptor (TCR) on the cell surface. The TCR is responsible for recognizing antigens bound to major histocompatibility complex (MHC) molecules and is composed of two different protein chains. In 95% of the T cells, the TCR consists of an alpha (α) and beta (β) chain. When the TCR engages with antigenic peptide and MHC (peptide / MHC complex), the T lymphocyte is activated through a series of biochemical events mediated by associated enzymes, co-receptors, specialized adaptor molecules, and activated or released transcription factors

The CD3 receptor complex is a protein complex and is composed of four chains. In mammals, the complex contains a CD3γ (gamma) chain, a CD3δ (delta) chain, and two CD3ε (epsilon) chains. These chains associate with the T cell receptor (TCR) and the so-called ζ (zeta) chain to form the T cell receptor CD3 complex and to generate an activation signal in T lymphocytes. The CD3γ (gamma), CD3δ (delta), and CD3ε (epsilon) chains are highly related cell-surface proteins of the immunoglobulin superfamily containing a single extracellular immunoglobulin domain. The intracellular tails of the CD3 molecules contain a single conserved motif known as an immunoreceptor tyrosine-based activation motif or ITAM for short, which is essential for the signaling capacity of the TCR. The CD3 epsilon molecule is a polypeptide which in humans is

encoded by the *CD3E* gene which resides on chromosome 11. The most preferred epitope of CD3 epsilon is comprised within amino acid residues 1-27 of the human CD3 epsilon extracellular domain.

The redirected lysis of target cells via the recruitment of T cells by a multispecific, at least bispecific, antibody construct involves cytolytic synapse formation and delivery of perforin and granzymes. The engaged T cells are capable of serial target cell lysis, and are not affected by immune escape mechanisms interfering with peptide antigen processing and presentation, or clonal T cell differentiation; see, for example, WO 2007/042261.

Cytotoxicity mediated by MSLNxCD3 bispecific antibody constructs can be measured in various ways. See Examples 5. Effector cells can be e.g. stimulated enriched (human) CD8 positive T cells or unstimulated (human) peripheral blood mononuclear cells (PBMC). If the target cells are of macaque origin or express or are transfected with macaque MSLN, the effector cells should also be of macaque origin such as a macaque T cell line, e.g. 4119LnPx. The target cells should express (at least the extracellular domain of) MSLN, e.g. human or macaque MSLN. Target cells can be a cell line (such as CHO) which is stably or transiently transfected with MSLN, e.g. human or macaque MSLN. Alternatively, the target cells can be a MSLN positive natural expresser cell line, such as the human cell line OVCAR-8. Usually EC50 values are expected to be lower with target cell lines expressing higher levels of MSLN on the cell surface. The effector to target cell (E:T) ratio is usually about 10:1, but can also vary. Cytotoxic activity of MSLNxCD3 bispecific antibody constructs can be measured in a 51-chromium release assay (incubation time of about 18 hours) or in a in a FACS-based cytotoxicity assay (incubation time of about 48 hours). Modifications of the assay incubation time (cytotoxic reaction) are also possible. Other methods of measuring cytotoxicity are well-known to the skilled person and comprise MTT or MTS assays, ATP-based assays including bioluminescent assays, the sulforhodamine B (SRB) assay, WST assay, clonogenic assay and the ECIS technology.

The cytotoxic activity mediated by MSLNxCD3 bispecific antibody constructs of the present invention is preferably measured in a cell-based cytotoxicity assay. It may also be measured in a 51-chromium release assay. It is represented by the EC_{50} value, which corresponds to the half maximal effective concentration (concentration of the antibody construct which induces a cytotoxic response halfway between the baseline and maximum). Preferably, the EC_{50} value of the MSLNxCD3 bispecific antibody constructs is ≤5000 pM or ≤4000 pM, more preferably

≤3000 pM or ≤2000 pM, even more preferably ≤1000 pM or ≤500 pM, even more preferably ≤400 pM or ≤300 pM, even more preferably ≤200 pM, even more preferably ≤100 pM, even more preferably ≤50 pM, even more preferably ≤20 pM or ≤10 pM, and most preferably ≤5 pM.

The above given EC_{50} values can be measured in different assays. The skilled person is aware that an EC_{50} value can be expected to be lower when stimulated / enriched CD8+ T cells are used as effector cells, compared with unstimulated PBMC. It can furthermore be expected that the EC_{50} values are lower when the target cells express a high number of the target antigen compared with a low target expression rat. For example, when stimulated / enriched human CD8+ T cells are used as effector cells (and either MSLN transfected cells such as CHO cells or a MSLN positive human cell line OVCAR-8 are used as target cells), the EC_{50} value of the MSLN xCD3 bispecific antibody construct is preferably ≤1000 pM, more preferably ≤500 pM, even more preferably ≤250 pM, even more preferably ≤100 pM, even more preferably ≤50 pM, even more preferably ≤10 pM, and most preferably ≤5 pM. When human PBMCs are used as effector cells, the EC_{50} value of the MSLNxCD3 bispecific antibody construct is preferably ≤5000 pM or ≤4000 pM (in particular when the target cells are a MSLN positive human cell line OVCAR-8), more preferably ≤2000 pM (in particular when the target cells are MSLN transfected cells such as CHO cells), more preferably ≤1000 pM or ≤500 pM, even more preferably ≤200 pM, even more preferably ≤150 pM, even more preferably ≤100 pM, and most preferably ≤50 pM, or lower. When a macaque T cell line such as LnPx4119 is used as effector cells, and a macaque MSLN transfected cell line such as CHO cells is used as target cell line, the EC_{50} value of the MSLN xCD3 bispecific antibody construct is preferably ≤2000 pM or ≤1500 pM, more preferably ≤1000 pM or ≤500 pM, even more preferably ≤300 pM or ≤250 pM, even more preferably ≤100 pM, and most preferably ≤50 pM.

Preferably, the MSLNxCD3 bispecific antibody constructs of the present invention do not induce / mediate lysis or do not essentially induce / mediate lysis of MSLN negative cells such as CHO cells. The term “do not induce lysis”, “do not essentially induce lysis”, “do not mediate lysis” or “do not essentially mediate lysis” means that an antibody construct of the present invention does not induce or mediate lysis of more than 30%, preferably not more than 20%, more preferably not more than 10%, particularly preferably not more than 9%, 8%, 7%, 6% or 5% of MSLN negative cells, whereby lysis of a MSLN positive human cell line OVCAR-8 (see above) is set to be 100%. This usually applies for concentrations of the antibody construct of up to 500 nM. The skilled person knows how to measure cell lysis without further ado. Moreover, the present specification teaches specific instructions how to measure cell lysis.

The difference in cytotoxic activity between the monomeric and the dimeric isoform of individual MSLN xCD3 bispecific antibody constructs is referred to as "potency gap". This potency gap can *e.g.* be calculated as ratio between EC_{50} values of the molecule's monomeric and dimeric form, see Example 5.8. Potency gaps of the MSLNxCD3 bispecific antibody constructs of the present invention are preferably ≤ 5, more preferably ≤ 4, even more preferably ≤ 3, even more preferably ≤ 2, furthermore preferably ≤ 1, and most preferably ≤ 0.3.

The first and/or the second (or any further) binding domain(s) of the antibody construct of the invention is/are preferably cross-species specific for members of the mammalian order of primates. Cross-species specific CD3 binding domains are, for example, described in WO 2008/119567. According to one embodiment, the first and/or second binding domain, in addition to binding to human **MSLN** and human CD3, respectively, will also bind to **MSLN** / CD3 of primates including (but not limited to) new world primates (such as *Callithrix jacchus*, *Saguinus Oedipus* or *Saimiri sciureus*), old world primates (such baboons and macaques), gibbons, orangutans, and non-human homininae. It is envisaged that the first binding domain of the antibody construct of the invention which binds to human MSLN on the surface of a target cell also binds at least to macaque MSLN, and/or the second binding domain which binds to human CD3 on the surface of a T cell also binds at least to macaque CD3. A preferred macaque is *Macaca fascicularis*. *Macaca mulatta* (Rhesus) is also envisaged.

In one aspect of the invention, the first binding domain binds to human MSLN and further binds to macaque MSLN, such as MSLN of *Macaca fascicularis*, and more preferably, to macaque MSLN expressed on the surface macaque cells. A preferred *Macaca fascicularis* MSLN is depicted in SEQ ID NO: 234. The affinity of the first binding domain for macaque MSLN is preferably ≤15 nM, more preferably ≤10 nM, even more preferably ≤5 nM, even more preferably ≤1 nM, even more preferably ≤0.5 nM, even more preferably ≤0.1 nM, and most preferably ≤0.05 nM or even ≤0.01 nM.

Preferably the affinity gap of the antibody constructs according to the invention for binding macaque MSLN versus human MSLN [ma MSLN:hu MSLN] (as determined *e.g.* by BiaCore or by Scatchard analysis) is <100, preferably <20, more preferably <15, further preferably <10, even more preferably<8, more preferably <6 and most preferably <2. Preferred ranges for the affinity gap of the antibody constructs according to the invention for binding macaque MSLN versus human MSLN are between 0.1 and 20, more preferably between 0.2 and 10, even more

preferably between 0.3 and 6, even more preferably between 0.5 and 3 or between 0.5 and 2.5, and most preferably between 0.5 and 2 or between 0.6 and 2. See Examples 3.
Accordingly, in line with this invention antibody construct comprising a MSLN binder for the epitope cluster 2+3 are preferred, which all are shown to have an affinity gap ≤15. Further preferred are antibody construct comprising a MSLN binder for the epitope cluster 2+3 having an affinity gap ≤6, such as MS-3, MS-4 or MS-5 based bispecific antibody constructs.

In one embodiment of the antibody construct of the invention, the second binding domain binds to human CD3 epsilon and to *Callithrix jacchus*, *Saguinus Oedipus* or *Saimiri sciureus* CD3 epsilon. Preferably, the second binding domain binds to an extracellular epitope of these CD3 epsilon chains. It is also envisaged that the second binding domain binds to an extracellular epitope of the human and the *Macaca* CD3 epsilon chain. The most preferred epitope of CD3 epsilon is comprised within amino acid residues 1-27 of the human CD3 epsilon extracellular domain. Even more specifically, the epitope comprises at least the amino acid sequence Gln-Asp-Gly-Asn-Glu. *Callithrix jacchus and Saguinus oedipus* are both new world primate belonging to the family of *Callitrichidae*, while *Saimiri sciureus* is a new world primate belonging to the family of *Cebidae*.

It is particularly preferred for the antibody construct of the present invention that the second binding domain which binds to human CD3 on the surface of a T cell comprises a VL region comprising CDR-L1, CDR-L2 and CDR-L3 selected from:

(a) CDR-L1 as depicted in SEQ ID NO: 27 of WO 2008/119567, CDR-L2 as depicted in SEQ ID NO: 28 of WO 2008/119567 and CDR-L3 as depicted in SEQ ID NO: 29 of WO 2008/119567;

(b) CDR-L1 as depicted in SEQ ID NO: 117 of WO 2008/119567, CDR-L2 as depicted in SEQ ID NO: 118 of WO 2008/119567 and CDR-L3 as depicted in SEQ ID NO: 119 of WO 2008/119567; and

(c) CDR-L1 as depicted in SEQ ID NO: 153 of WO 2008/119567, CDR-L2 as depicted in SEQ ID NO: 154 of WO 2008/119567 and CDR-L3 as depicted in SEQ ID NO: 155 of WO 2008/119567.

In an alternatively preferred embodiment of the antibody construct of the present invention, the second binding domain which binds to human CD3 on the surface of a T cell comprises a VH region comprising CDR-H 1, CDR-H2 and CDR-H3 selected from:

(a) CDR-H1 as depicted in SEQ ID NO: 12 of WO 2008/119567, CDR-H2 as depicted in SEQ ID NO: 13 of WO 2008/119567 and CDR-H3 as depicted in SEQ ID NO: 14 of WO 2008/119567;

(b) CDR-H1 as depicted in SEQ ID NO: 30 of WO 2008/119567, CDR-H2 as depicted in SEQ ID NO: 31 of WO 2008/119567 and CDR-H3 as depicted in SEQ ID NO: 32 of WO 2008/119567;

(c) CDR-H1 as depicted in SEQ ID NO: 48 of WO 2008/119567, CDR-H2 as depicted in SEQ ID NO: 49 of WO 2008/119567 and CDR-H3 as depicted in SEQ ID NO: 50 of WO 2008/119567;

(d) CDR-H1 as depicted in SEQ ID NO: 66 of WO 2008/119567, CDR-H2 as depicted in SEQ ID NO: 67 of WO 2008/119567 and CDR-H3 as depicted in SEQ ID NO: 68 of WO 2008/119567;

(e) CDR-H1 as depicted in SEQ ID NO: 84 of WO 2008/119567, CDR-H2 as depicted in SEQ ID NO: 85 of WO 2008/119567 and CDR-H3 as depicted in SEQ ID NO: 86 of WO 2008/119567;

(f) CDR-H1 as depicted in SEQ ID NO: 102 of WO 2008/119567, CDR-H2 as depicted in SEQ ID NO: 103 of WO 2008/119567 and CDR-H3 as depicted in SEQ ID NO: 104 of WO 2008/119567;

(g) CDR-H1 as depicted in SEQ ID NO: 120 of WO 2008/119567, CDR-H2 as depicted in SEQ ID NO: 121 of WO 2008/119567 and CDR-H3 as depicted in SEQ ID NO: 122 of WO 2008/119567;

(h) CDR-H1 as depicted in SEQ ID NO: 138 of WO 2008/119567, CDR-H2 as depicted in SEQ ID NO: 139 of WO 2008/119567 and CDR-H3 as depicted in SEQ ID NO: 140 of WO 2008/119567;

(i) CDR-H1 as depicted in SEQ ID NO: 156 of WO 2008/119567, CDR-H2 as depicted in SEQ ID NO: 157 of WO 2008/119567 and CDR-H3 as depicted in SEQ ID NO: 158 of WO 2008/119567; and

(j) CDR-H1 as depicted in SEQ ID NO: 174 of WO 2008/119567, CDR-H2 as depicted in SEQ ID NO: 175 of WO 2008/119567 and CDR-H3 as depicted in SEQ ID NO: 176 of WO 2008/119567.

It is further preferred for the antibody construct of the present invention that the second binding domain which binds to human CD3 on the surface of a T cell comprises a VL region selected from the group consisting of a VL region as depicted in SEQ ID NO: 18, SEQ ID NO: 27, SEQ ID NO: 36, SEQ ID NO: 45, SEQ ID NO: 54, SEQ ID NO: 63, SEQ ID NO: 72, SEQ ID

NO: 81, SEQ ID NO: 90, SEQ ID NO: 99, and SEQ ID NO: 102 (see also SEQ ID NO: 35, 39, 125, 129, 161 or 165 of WO 2008/119567).

It is alternatively preferred that the second binding domain which binds to human CD3 on the surface of a T cell comprises a VH region selected from the group consisting of a VH region as depicted in SEQ ID NO: 17, SEQ ID NO: 26, SEQ ID NO: 35, SEQ ID NO: 44, SEQ ID NO: 53, SEQ ID NO: 62, SEQ ID NO: 71, SEQ ID NO: 80, SEQ ID NO: 89, SEQ ID NO: 98, and SEQ ID NO: 101 (see also SEQ ID NO: 15, 19, 33, 37, 51, 55, 69, 73, 87, 91, 105, 109, 123, 127, 141, 145, 159, 163, 177 or 181 of WO 2008/119567).

More preferably, the antibody construct of the present invention is characterized by the second binding domain which binds to human CD3 on the surface of a T cell comprising a VL region and a VH region selected from the group consisting of:

(a) a VL region as depicted in SEQ ID NO: 17 or 21 of WO 2008/119567 and a VH region as depicted in SEQ ID NO: 15 or 19 of WO 2008/119567;
(b) a VL region as depicted in SEQ ID NO: 35 or 39 of WO 2008/119567 and a VH region as depicted in SEQ ID NO: 33 or 37 of WO 2008/119567;
(c) a VL region as depicted in SEQ ID NO: 53 or 57 of WO 2008/119567 and a VH region as depicted in SEQ ID NO: 51 or 55 of WO 2008/119567;
(d) a VL region as depicted in SEQ ID NO: 71 or 75 of WO 2008/119567 and a VH region as depicted in SEQ ID NO: 69 or 73 of WO 2008/119567;
(e) a VL region as depicted in SEQ ID NO: 89 or 93 of WO 2008/119567 and a VH region as depicted in SEQ ID NO: 87 or 91 of WO 2008/119567;
(f) a VL region as depicted in SEQ ID NO: 107 or 111 of WO 2008/119567 and a VH region as depicted in SEQ ID NO: 105 or 109 of WO 2008/119567;
(g) a VL region as depicted in SEQ ID NO: 125 or 129 of WO 2008/119567 and a VH region as depicted in SEQ ID NO: 123 or 127 of WO 2008/119567;
(h) a VL region as depicted in SEQ ID NO: 143 or 147 of WO 2008/119567 and a VH region as depicted in SEQ ID NO: 141 or 145 of WO 2008/119567;
(i) a VL region as depicted in SEQ ID NO: 161 or 165 of WO 2008/119567 and a VH region as depicted in SEQ ID NO: 159 or 163 of WO 2008/119567; and
(j) a VL region as depicted in SEQ ID NO: 179 or 183 of WO 2008/119567 and a VH region as depicted in SEQ ID NO: 177 or 181 of WO 2008/119567.

Also preferred in connection with the antibody construct of the present invention is a second binding domain which binds to human CD3 on the surface of a T cell comprising a VL region as depicted in SEQ ID NO: 102 and a VH region as depicted in SEQ ID NO: 101.

According to a preferred embodiment of the antibody construct of the present invention, the binding domains and in particular the second binding domain (which binds to human CD3 on the surface of a T cell) have the following format: The pairs of VH regions and VL regions are in the format of a single chain antibody (scFv). The VH and VL regions are arranged in the order VH-VL or VL-VH. It is preferred that the VH-region is positioned N-terminally of a linker sequence, and the VL-region is positioned C-terminally of the linker sequence.

A preferred embodiment of the above described antibody construct of the present invention is characterized by the second binding domain which binds to human CD3 on the surface of a T cell comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 28, SEQ ID NO: 37, SEQ ID NO: 46, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 73, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 100, and SEQ ID NO: 103 (see also SEQ ID NOs: 23, 25, 41, 43, 59, 61, 77, 79, 95, 97, 113, 115, 131, 133, 149, 151, 167, 169, 185 or 187 of WO 2008/119567).

It is also envisaged that the antibody construct of the invention has, in addition to its function to bind to the target molecules MSLN and CD3, a further function. In this format, the antibody construct is a trifunctional or multifunctional antibody construct by targeting target cells through binding to MSLN, mediating cytotoxic T cell activity through CD3 binding and providing a further function such as a fully functional Fc constant domain mediating antibody-dependent cellular cytotoxicity through recruitment of effector cells like NK cells, a label (fluorescent etc.), a therapeutic agent such as a toxin or radionuclide, and/or means to enhance serum half-life, etc.

Examples for means to extend serum half-life of the antibody constructs of the invention include peptides, proteins or domains of proteins, which are fused or otherwise attached to the antibody constructs. The group of peptides, proteins or protein domains includes peptides binding to other proteins with preferred pharmacokinetic profile in the human body such as serum albumin (see WO 2009/127691). An alternative concept of such half-life extending peptides includes peptides binding to the neonatal Fc receptor (FcRn, see WO 2007/098420), which can also be used in the constructs of the present invention. The concept of attaching larger domains of proteins or complete proteins includes *e.g.* the fusion of human serum albumin, variants or

mutants of human serum albumin (see WO 2011/051489, WO 2012/059486, WO 2012/150319, WO 2013/135896, WO 2014/072481, WO 2013/075066) or domains thereof as well as the fusion of constant region of immunoglobulins (Fc domains) and variants thereof. Such variants of Fc domains may be optimized / modified in order to allow the desired pairing of dimers or mulimers, to abolish Fc receptor binding (e.g. the Fcγ receptor) or for other reasons. A further concept known in the art to extend the half-life of small protein compounds in the human body is the pegylation of those compounds such as the antibody construct of the present invention.

In a preferred embodiment, the antibody construct of the invention is described as follows:

(a) a polypeptide comprising in the following order starting from the N-terminus:
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 159, SEQ ID NO: 169, SEQ ID NO: 179, SEQ ID NO: 189, SEQ ID NO: 199, SEQ ID NO: 209, SEQ ID NO: 219, and SEQ ID NO: 229
- a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-9; and
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 28, SEQ ID NO: 37, SEQ ID NO: 46, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 73, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 100, and SEQ ID NO: 103; and
- optionally a His-tag, such as the one depicted in SEQ ID NO 10;

(b) a polypeptide comprising in following order starting from the N-terminus:
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 159, SEQ ID NO: 169, SEQ ID NO: 179, SEQ ID NO: 189, SEQ ID NO: 199, SEQ ID NO: 209, SEQ ID NO: 219, and SEQ ID NO: 229
- a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-9;
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 28, SEQ ID NO: 37, SEQ ID NO: 46, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 73, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 100, and SEQ ID NO: 103;
- optionally a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-9;
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NOs: 104-134; and
- optionally a His-tag, such as the one depicted in SEQ ID NO 10;

(c) a polypeptide comprising in the following order starting from the N-terminus:

- a polypeptide having the amino acid sequence QRFVTGHFGGLX$_1$PANG (SEQ ID NO: 135) whereas X_1 is Y or H; and
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 159, SEQ ID NO: 169, SEQ ID NO: 179, SEQ ID NO: 189, SEQ ID NO: 199, SEQ ID NO: 209, SEQ ID NO: 219, and SEQ ID NO: 229;
- a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-9;
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 28, SEQ ID NO: 37, SEQ ID NO: 46, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 73, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 100, and SEQ ID NO: 103;
- a polypeptide having the amino acid sequence QRFVTGHFGGLHPANG (SEQ ID NO: 137) or QRFCTGHFGGLHPCNG (SEQ ID NO: 139); and
- optionally a His-tag, such as the one depicted in SEQ ID NO 10;

(d) a polypeptide comprising in the following order starting from the N-terminus

- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 17, SEQ ID NO: 26, SEQ ID NO: 35, SEQ ID NO: 44, SEQ ID NO: 53, SEQ ID NO: 62, SEQ ID NO: 71, SEQ ID NO: 80, SEQ ID NO: 89, SEQ ID NO: 98, and SEQ ID NO: 101;
- a peptide linker having the amino acid sequence depicted in SEQ ID NO: 8;
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 158, SEQ ID NO: 168, SEQ ID NO: 178, SEQ ID NO: 188, SEQ ID NO: 198, SEQ ID NO: 208, SEQ ID NO: 218, and SEQ ID NO: 228 and a serine residue at the C-terminus;
- a polypeptide having the amino acid sequence depicted in SEQ ID NO: 140;and

a polypeptide comprising in the following order starting from the N-terminus:

- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 157, SEQ ID NO: 167, SEQ ID NO: 177, SEQ ID NO: 187, SEQ ID NO: 197, SEQ ID NO: 207, SEQ ID NO: 217, and SEQ ID NO: 227;
- a peptide linker having the amino acid sequence depicted in SEQ ID NO: 8;
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 18, SEQ ID NO: 27, SEQ ID NO: 36, SEQ ID NO: 45, SEQ ID NO: 54, SEQ ID NO: 63, SEQ ID NO: 72, SEQ ID NO: 81, SEQ ID NO: 90, SEQ ID NO: 99, and SEQ ID NO: 102 and a serine residue at the C-terminus;

- a polypeptide having the amino acid sequence depicted in SEQ ID NO: 141;

(e) a polypeptide comprising in the following order starting from the N-terminus:

- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 17, SEQ ID NO: 26, SEQ ID NO: 35, SEQ ID NO: 44, SEQ ID NO: 53, SEQ ID NO: 62, SEQ ID NO: 71, SEQ ID NO: 80, SEQ ID NO: 89, SEQ ID NO: 98, and SEQ ID NO: 101;
- a peptide linker having the amino acid sequence depicted in SEQ ID NO: 8;
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 158, SEQ ID NO: 168, SEQ ID NO: 178, SEQ ID NO: 188, SEQ ID NO: 198, SEQ ID NO: 208, SEQ ID NO: 218, and SEQ ID NO: 228;
- a polypeptide having the amino acid sequence depicted in SEQ ID NO: 142;and

a polypeptide comprising in the following order starting from the N-terminus:

- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 157, SEQ ID NO: 167, SEQ ID NO: 177, SEQ ID NO: 187, SEQ ID NO: 197, SEQ ID NO: 207, SEQ ID NO: 217, and SEQ ID NO: 227;
- a peptide linker having an amino acid sequence depicted in SEQ ID NO: 8;
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 18, SEQ ID NO: 27, SEQ ID NO: 36, SEQ ID NO: 45, SEQ ID NO: 54, SEQ ID NO: 63, SEQ ID NO: 72, SEQ ID NO: 81, SEQ ID NO: 90, SEQ ID NO: 99, and SEQ ID NO: 102 and a serine residue at the C-terminus;
- a polypeptide having the amino acid sequence depicted in SEQ ID NO: 143;

(f) a polypeptide comprising in the following order starting from the N-terminus:

- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 159, SEQ ID NO: 169, SEQ ID NO: 179, SEQ ID NO: 189, SEQ ID NO: 199, SEQ ID NO: 209, SEQ ID NO: 219, and SEQ ID NO: 229;
- a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-9; and
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 28, SEQ ID NO: 37, SEQ ID NO: 46, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 73, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 100, and SEQ ID NO: 103; and
- a polypeptide having the amino acid sequence depicted in SEQ ID NO: 144; and

a polypeptide having the amino acid sequence depicted in SEQ ID NO: 145;

(g) a polypeptide comprising in the following order starting from the N-terminus:

- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 159, SEQ ID NO: 169, SEQ ID NO: 179, SEQ ID NO: 189, SEQ ID NO: 199, SEQ ID NO: 209, SEQ ID NO: 219, and SEQ ID NO: 229; and
- a polypeptide having the amino acid sequence depicted in SEQ ID NO: 146;and

a polypeptide comprising in the following order starting from the N-terminus:

- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 28, SEQ ID NO: 37, SEQ ID NO: 46, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 73, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 100, and SEQ ID NO: 103; and
- a polypeptide having the amino acid sequence depicted in SEQ ID NO: 147;

(h) a polypeptide comprising in the following order starting from the N-terminus:

- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 159, SEQ ID NO: 169, SEQ ID NO: 179, SEQ ID NO: 189, SEQ ID NO: 199, SEQ ID NO: 209, SEQ ID NO: 219, and SEQ ID NO: 229; and
- a polypeptide having the amino acid sequence depicted in SEQ ID NO: 148;and

a polypeptide comprising in the following order starting from the N-terminus:

- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 28, SEQ ID NO: 37, SEQ ID NO: 46, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 73, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 100, and SEQ ID NO: 103; and
- a polypeptide having the amino acid sequence depicted in SEQ ID NO: 149; or

(i) a polypeptide comprising in the following order starting from the N-terminus:

- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 159, SEQ ID NO: 169, SEQ ID NO: 179, SEQ ID NO: 189, SEQ ID NO: 199, SEQ ID NO: 209, SEQ ID NO: 219, and SEQ ID NO: 229;
- a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-9; and
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 28, SEQ ID NO: 37, SEQ ID NO: 46, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 73, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 100, and SEQ ID NO: 103; and
- a polypeptide having the amino acid sequence depicted in SEQ ID NO: 150.

As described above, several preferred antibody constructs of the invention are modified by fusion with another moiety such as albumin or albumin variants. If these fusion constructs are

characterized for their properties, in particular target affinity or cytotoxic activity, the skilled person will be aware that similar fusion constructs or unmodified bispecific antibody constructs can be expected to have similar (or even better) properties. For example, if a bispecific antibody construct fused with albumin has an appreciable or desirable cytotoxic activity or target affinity, it can be expected that the same / similar or even a higher cytotoxic activity / target affinity will be observed for the construct w/o albumin.

According to another preferred embodiment, the bispecific antibody construct of the invention comprises (in addition to the two binding domains) a third domain which comprises two polypeptide monomers, each comprising a hinge, a CH2 and a CH3 domain, wherein said two polypeptides (or polypeptide monomers) are fused to each other via a peptide linker. Preferably, said third domain comprises in an N- to C-terminal order: hinge-CH2-CH3-linker-hinge-CH2-CH3. Preferred amino acid sequences for said third domain are depicted in SEQ ID NOs: 260-267. Each of said two polypeptide monomers preferably has an amino acid sequence that is selected from the group consisting of SEQ ID NOs: 252-259, or that is at least 90% identical to those sequences. In another preferred embodiment, the first and second binding domains of the bispecific antibody construct of the invention are fused to the third domain via a peptide linker which is for example selected from the group consisting of SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8 and 9.

In line with the present invention, a “hinge” is an IgG hinge region. This region can be identified by analogy using the Kabat numbering, see Kabat positions 223-243. In line with the above, the minimal requirement for a “hinge” are the amino acid residues corresponding to the IgG_1 sequence stretch of D231 to P243 according to the Kabat numbering. The terms CH2 and CH3 refer to the immunoglobulin heavy chain constant regions 2 and 3. These regions can as well be identified by analogy using the Kabat numbering, see Kabat positions 244-360 for CH2 and Kabat positions 361-478 for CH3. Is is understood that there is some variation between the immunoglobulins in terms of their IgG_1 Fc region, IgG_2 Fc region, IgG_3 Fc region, IgG_4 Fc region, IgM Fc region, IgA Fc region, IgD Fc region and IgE Fc region (see, *e.g.,* Padlan, Molecular Immunology, 31(3), 169-217 (1993)). The term Fc monomer refers to the last two heavy chain constant regions of IgA, IgD, and IgG, and the last three heavy chain constant regions of IgE and IgM. The Fc monomer can also include the flexible hinge N-terminal to these domains. For IgA and IgM, the Fc monomer may include the J chain. For IgG, the Fc portion comprises immunoglobulin domains CH2 and CH3 and the hinge between the first two domains and CH2. Although the boundaries of the Fc portion of an immunoglobulin may vary, an

example for a human IgG heavy chain Fc portion comprising a functional hinge, CH2 and CH3 domain can be defined e.g. to comprise residues D231 (of the hinge domain) to P476 (of the C-terminus of the CH3 domain), or D231 to L476, respectively, for IgG_4, wherein the numbering is according to Kabat.

The antibody construct of the invention may hence comprise in an N- to C-terminal order:

(a) the first binding domain;
(b) a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 8 and 9;
(c) the second binding domain;
(d) a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 2, 4, 5, 6, 8 and 9;
(e) the first polypeptide monomer of the third domain (comprising a hinge, a CH2 and a CH3 domain);
(f) a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 301, 302, 303 and 304; and
(g) the second polypeptide monomer of the third domain (comprising a hinge, a CH2 and a CH3 domain).

It is also preferred that the antibody construct of the invention comprises in an N- to C-terminal order:

- the first binding domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 159, SEQ ID NO: 169, SEQ ID NO: 179, SEQ ID NO: 189, SEQ ID NO: 199, SEQ ID NO: 209, SEQ ID NO: 219, and SEQ ID NO: 229;
- a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 8 and 9;
- the second binding domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 28, SEQ ID NO: 37, SEQ ID NO: 46, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 73, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 100, and SEQ ID NO: 103 (see also SEQ ID NOs: 23, 25, 41, 43, 59, 61, 77, 79, 95, 97, 113, 115, 131, 133, 149, 151, 167, 169, 185 or 187 of WO 2008/119567);
- a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 2, 4, 5, 6, 8 and 9; and
- the third domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 260-267.

Hence, in a preferred embodiment, the antibody construct of the present invention comprises or consists of a polypeptide selected from the group consisting of those depicted in SEQ ID NOs: 268 to 299.

It is also prefereably in one embodiment of the invention that the antibody construct of the present invention comprises or consists of a polypeptide selected from the group consisting of those depicted in SEQ ID NOs: 276 to 287.

Also in a preferred embodiment of the invention that the antibody construct of the present invention comprises or consists of a polypeptide selected from the group consisting of those depicted in SEQ ID NOs: 276, 280 and 284, more preferably comprises or consists of a polypeptide as depicted in SEQ ID NO: 280.

Covalent modifications of the antibody constructs are also included within the scope of this invention, and are generally, but not always, done post-translationally. For example, several types of covalent modifications of the antibody construct are introduced into the molecule by reacting specific amino acid residues of the antibody construct with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C-terminal residues.

Cysteinyl residues most commonly are reacted with α-haloacetates (and corresponding amines), such as chloroacetic acid or chloroacetamide, to give carboxymethyl or carboxyamidomethyl derivatives. Cysteinyl residues also are derivatized by reaction with bromotrifluoroacetone, α-bromo-β-(5-imidozoyl)propionic acid, chloroacetyl phosphate, N-alkylmaleimides, 3-nitro-2-pyridyl disulfide, methyl 2-pyridyl disulfide, p-chloromercuribenzoate, 2-chloromercuri-4-nitrophenol, or chloro-7-nitrobenzo-2-oxa-1,3-diazole.

Histidyl residues are derivatized by reaction with diethylpyrocarbonate at pH 5.5-7.0 because this agent is relatively specific for the histidyl side chain. Para-bromophenacyl bromide also is useful; the reaction is preferably performed in 0.1 M sodium cacodylate at pH 6.0. Lysinyl and amino terminal residues are reacted with succinic or other carboxylic acid anhydrides. Derivatization with these agents has the effect of reversing the charge of the lysinyl residues. Other suitable reagents for derivatizing alpha-amino-containing residues include imidoesters such as methyl picolinimidate; pyridoxal phosphate; pyridoxal; chloroborohydride;

trinitrobenzenesulfonic acid; O-methylisourea; 2,4-pentanedione; and transaminase-catalyzed reaction with glyoxylate.

Arginyl residues are modified by reaction with one or several conventional reagents, among them phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, and ninhydrin. Derivatization of arginine residues requires that the reaction be performed in alkaline conditions because of the high pKa of the guanidine functional group. Furthermore, these reagents may react with the groups of lysine as well as the arginine epsilon-amino group.

The specific modification of tyrosyl residues may be made, with particular interest in introducing spectral labels into tyrosyl residues by reaction with aromatic diazonium compounds or tetranitromethane. Most commonly, N-acetylimidizole and tetranitromethane are used to form O-acetyl tyrosyl species and 3-nitro derivatives, respectively. Tyrosyl residues are iodinated using ^{125}I or ^{131}I to prepare labeled proteins for use in radioimmunoassay, the chloramine T method described above being suitable.

Carboxyl side groups (aspartyl or glutamyl) are selectively modified by reaction with carbodiimides (R'—N=C=N--R'), where R and R' are optionally different alkyl groups, such as 1-cyclohexyl-3-(2-morpholinyl-4-ethyl) carbodiimide or 1-ethyl-3-(4-azonia-4,4-dimethylpentyl) carbodiimide. Furthermore, aspartyl and glutamyl residues are converted to asparaginyl and glutaminyl residues by reaction with ammonium ions.

Derivatization with bifunctional agents is useful for crosslinking the antibody constructs of the present invention to a water-insoluble support matrix or surface for use in a variety of methods. Commonly used crosslinking agents include, *e.g.*, 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), and bifunctional maleimides such as bis-N-maleimido-1,8-octane. Derivatizing agents such as methyl-3-[(p-azidophenyl)dithio]propioimidate yield photoactivatable intermediates that are capable of forming crosslinks in the presence of light. Alternatively, reactive water-insoluble matrices such as cyanogen bromide-activated carbohydrates and the reactive substrates as described in U.S. Pat. Nos. 3,969,287; 3,691,016; 4,195,128; 4,247,642; 4,229,537; and 4,330,440 are employed for protein immobilization.

Glutaminyl and asparaginyl residues are frequently deamidated to the corresponding glutamyl and aspartyl residues, respectively. Alternatively, these residues are deamidated under mildly acidic conditions. Either form of these residues falls within the scope of this invention.

Other modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the α-amino groups of lysine, arginine, and histidine side chains (T. E. Creighton, Proteins: Structure and Molecular Properties, W. H. Freeman & Co., San Francisco, 1983, pp. 79-86), acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification of the antibody constructs included within the scope of this invention comprises altering the glycosylation pattern of the protein. As is known in the art, glycosylation patterns can depend on both the sequence of the protein (*e.g.*, the presence or absence of particular glycosylation amino acid residues, discussed below), or the host cell or organism in which the protein is produced. Particular expression systems are discussed below.

Glycosylation of polypeptides is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tri-peptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tri-peptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-acetylgalactosamine, galactose, or xylose, to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.

Addition of glycosylation sites to the antibody construct is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tri-peptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the starting sequence (for O-linked glycosylation sites). For ease, the amino acid sequence of an antibody construct is preferably altered through changes at the DNA level, particularly by mutating the DNA encoding the polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

Another means of increasing the number of carbohydrate moieties on the antibody construct is by chemical or enzymatic coupling of glycosides to the protein. These procedures are advantageous in that they do not require production of the protein in a host cell that has glycosylation capabilities for N- and O-linked glycosylation. Depending on the coupling mode used, the sugar(s) may be attached to (a) arginine and histidine, (b) free carboxyl groups, (c) free sulfhydryl groups such as those of cysteine, (d) free hydroxyl groups such as those of serine, threonine, or hydroxyproline, (e) aromatic residues such as those of phenylalanine, tyrosine, or tryptophan, or (f) the amide group of glutamine. These methods are described in WO 87/05330, and in Aplin and Wriston, 1981, CRC Crit. Rev. Biochem., pp. 259-306.

Removal of carbohydrate moieties present on the starting antibody construct may be accomplished chemically or enzymatically. Chemical deglycosylation requires exposure of the protein to the compound trifluoromethanesulfonic acid, or an equivalent compound. This treatment results in the cleavage of most or all sugars except the linking sugar (N-acetylglucosamine or N-acetylgalactosamine), while leaving the polypeptide intact. Chemical deglycosylation is described by Hakimuddin *et al.*, 1987, *Arch. Biochem. Biophys.* 259:52 and by Edge *et al.*, 1981, *Anal. Biochem.* 118:131. Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura *et al.*, 1987, Meth. Enzymol. 138:350. Glycosylation at potential glycosylation sites may be prevented by the use of the compound tunicamycin as described by Duskin *et al.*, 1982, J. Biol. Chem. 257:3105. Tunicamycin blocks the formation of protein-N-glycoside linkages.

Other modifications of the antibody construct are also contemplated herein. For example, another type of covalent modification of the antibody construct comprises linking the antibody construct to various non-proteinaceous polymers, including, but not limited to, various polyols such as polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol and polypropylene glycol, in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337. In addition, as is known in the art, amino acid substitutions may be made in various positions within the antibody construct, e.g. in order to facilitate the addition of polymers such as PEG.

In some embodiments, the covalent modification of the antibody constructs of the invention comprises the addition of one or more labels. The labelling group may be coupled to the antibody construct *via* spacer arms of various lengths to reduce potential steric hindrance.

Various methods for labelling proteins are known in the art and can be used in performing the present invention. The term “label” or “labelling group” refers to any detectable label. In general, labels fall into a variety of classes, depending on the assay in which they are to be detected – the following examples include, but are not limited to:

a) isotopic labels, which may be radioactive or heavy isotopes, such as radioisotopes or radionuclides (*e.g.*, ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{89}Zr, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I)
b) magnetic labels (*e.g.,* magnetic particles)
c) redox active moieties
d) optical dyes (including, but not limited to, chromophores, phosphors and fluorophores) such as fluorescent groups (*e.g.*, FITC, rhodamine, lanthanide phosphors), chemiluminescent groups, and fluorophores which can be either “small molecule” fluores or proteinaceous fluores
e) enzymatic groups (*e.g.* horseradish peroxidase, β-galactosidase, luciferase, alkaline phosphatase)
f) biotinylated groups
g) predetermined polypeptide epitopes recognized by a secondary reporter (*e.g.*, leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags, etc.)

By “fluorescent label” is meant any molecule that may be detected *via* its inherent fluorescent properties. Suitable fluorescent labels include, but are not limited to, fluorescein, rhodamine, tetramethylrhodamine, eosin, erythrosin, coumarin, methyl-coumarins, pyrene, Malacite green, stilbene, Lucifer Yellow, Cascade BlueJ, Texas Red, IAEDANS, EDANS, BODIPY FL, LC Red 640, Cy 5, Cy 5.5, LC Red 705, Oregon green, the Alexa-Fluor dyes (Alexa Fluor 350, Alexa Fluor 430, Alexa Fluor 488, Alexa Fluor 546, Alexa Fluor 568, Alexa Fluor 594, Alexa Fluor 633, Alexa Fluor 660, Alexa Fluor 680), Cascade Blue, Cascade Yellow and R-phycoerythrin (PE) (Molecular Probes, Eugene, OR), FITC, Rhodamine, and Texas Red (Pierce, Rockford, IL), Cy5, Cy5.5, Cy7 (Amersham Life Science, Pittsburgh, PA). Suitable optical dyes, including fluorophores, are described in Molecular Probes Handbook by Richard P. Haugland.

Suitable proteinaceous fluorescent labels also include, but are not limited to, green fluorescent protein, including a Renilla, Ptilosarcus, or Aequorea species of GFP (Chalfie *et al.*, 1994, *Science* 263:802-805), EGFP (Clontech Laboratories, Inc., Genbank Accession Number U55762), blue fluorescent protein (BFP, Quantum Biotechnologies, Inc. 1801 de Maisonneuve

Blvd. West, 8th Floor, Montreal, Quebec, Canada H3H 1J9; Stauber, 1998, *Biotechniques* 24:462-471; Heim *et al.*, 1996, *Curr. Biol.* 6:178-182), enhanced yellow fluorescent protein (EYFP, Clontech Laboratories, Inc.), luciferase (Ichiki *et al.*, 1993, *J. Immunol.* 150:5408-5417), β galactosidase (Nolan *et al.*, 1988, *Proc. Natl. Acad. Sci. U.S.A.* 85:2603-2607) and Renilla (WO92/15673, WO95/07463, WO98/14605, WO98/26277, WO99/49019, U.S. Patent Nos. 5,292,658; 5,418,155; 5,683,888; 5,741,668; 5,777,079; 5,804,387; 5,874,304; 5,876,995; 5,925,558).

Leucine zipper domains are peptides that promote oligomerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz *et al.*, 1988, *Science* 240:1759), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble oligomeric proteins are described in PCT application WO 94/10308, and the leucine zipper derived from lung surfactant protein D (SPD) described in Hoppe *et al.*, 1994, *FEBS Letters* 344:191. The use of a modified leucine zipper that allows for stable trimerization of a heterologous protein fused thereto is described in Fanslow *et al.*, 1994, Semin. Immunol. 6:267-78. In one approach, recombinant fusion proteins comprising a MSLN antibody fragment or derivative fused to a leucine zipper peptide are expressed in suitable host cells, and the soluble oligomeric MSLN antibody fragments or derivatives that form are recovered from the culture supernatant.

The antibody construct of the invention may also comprise additional domains, which are *e.g.* helpful in the isolation of the molecule or relate to an adapted pharmacokinetic profile of the molecule. Domains helpful for the isolation of an antibody construct may be selected from peptide motives or secondarily introduced moieties, which can be captured in an isolation method, e.g. an isolation column. Non-limiting embodiments of such additional domains comprise peptide motives known as Myc-tag, HAT-tag, HA-tag, TAP-tag, GST-tag, chitin binding domain (CBD-tag), maltose binding protein (MBP-tag), Flag-tag, Strep-tag and variants thereof (e.g. StrepII-tag) and His-tag. All herein disclosed antibody constructs characterized by the identified CDRs are preferred to comprise a His-tag domain, which is generally known as a repeat of consecutive His residues in the amino acid sequence of a molecule, preferably of five, and more preferably of six His residues (hexa-histidine). The His-tag may be located *e.g.* at the N- or C-terminus of the antibody construct, preferably it is located at the C-terminus. Most

preferably, a hexa-histidine tag (HHHHHH) (SEQ ID NO:10) is linked via peptide bond to the C-terminus of the antibody construct according to the invention.

The first binding domain of the antibody construct of the present invention binds to human MSLN on the surface of a target cell. The preferred amino acid sequence of human MSLN is represented by NOs: 231, 232, and 233. The first binding domain according to the invention hence preferably binds to MSLN when it is expressed by naturally expressing cells or cell lines, and/or by cells or cell lines transformed or (stably / transiently) transfected with MSLN. In a preferred embodiment the first binding domain also binds to MSLN when MSLN is used as a "target" or "ligand" molecule in an *in vitro* binding assay such as BIAcore or Scatchard. The "target cell" can be any prokaryotic or eukaryotic cell expressing MSLN on its surface; preferably the target cell is a cell that is part of the human or animal body, such as a ovarian cancer cell, pancreatic cancer cell, mesothelioma cell, lung cancer cell, gastric cancer cell and triple negative breast cancer cell.

The affinity of the first binding domain for human MSLN is preferably ≤20 nM, more preferably ≤10 nM, even more preferably ≤5 nM, even more preferably ≤2 nM, even more preferably ≤1 nM, even more preferably ≤0.6 nM, even more preferably ≤0.5 nM, and most preferably ≤0.4 nM. The affinity can be measured for example in a BIAcore assay or in a Scatchard assay, *e.g.* as described in the Examples. Other methods of determining the affinity are also well-known to the skilled person; see e.g. appended Example 3.

Amino acid sequence modifications of the antibody constructs described herein are also contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the antibody construct. Amino acid sequence variants of the antibody constructs are prepared by introducing appropriate nucleotide changes into the antibody constructs nucleic acid, or by peptide synthesis. All of the below described amino acd sequence modifications should result in an antibody construct which still retains the desired biological activity (binding to MSLN and to CD3) of the unmodified parental molecule.

The term "amino acid" or "amino acid residue" typically refers to an amino acid having its art recognized definition such as an amino acid selected from the group consisting of: alanine (Ala or A); arginine (Arg or R); asparagine (Asn or N); aspartic acid (Asp or D); cysteine (Cys or C); glutamine (Gln or Q); glutamic acid (Glu or E); glycine (Gly or G); histidine (His or H); isoleucine (He or I): leucine (Leu or L); lysine (Lys or K); methionine (Met or M); phenylalanine (Phe or F);

pro line (Pro or P); serine (Ser or S); threonine (Thr or T); tryptophan (Trp or W); tyrosine (Tyr or Y); and valine (Val or V), although modified, synthetic, or rare amino acids may be used as desired. Generally, amino acids can be grouped as having a nonpolar side chain (e.g., Ala, Cys, He, Leu, Met, Phe, Pro, Val); a negatively charged side chain (e.g., Asp, Glu); a positively charged sidechain (e.g., Arg, His, Lys); or an uncharged polar side chain (e.g., Asn, Cys, Gln, Gly, His, Met, Phe, Ser, Thr, Trp, and Tyr).

Amino acid modifications include, for example, deletions from, and/or insertions into, and/or substitutions of, residues within the amino acid sequences of the antibody constructs. Any combination of deletion, insertion, and substitution is made to arrive at the final construct, provided that the final construct possesses the desired characteristics. The amino acid changes also may alter post-translational processes of the antibody constructs, such as changing the number or position of glycosylation sites.

For example, 1, 2, 3, 4, 5, or 6 amino acids may be inserted or deleted in each of the CDRs (of course, dependent on their length), while 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 25 amino acids may be inserted or deleted in each of the FRs. Preferably, amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 residues to polypeptides containing a hundred or more residues, as well as intra-sequence insertions of single or multiple amino acid residues. An insertional variant of the antibody construct of the invention includes the fusion to the N-terminus or to the C-terminus of the antibody construct of an enzyme or the fusion to a polypeptide which increases the serum half-life of the antibody construct.

The sites of greatest interest for substitutional mutagenesis include the CDRs of the heavy and/or light chain, in particular the hypervariable regions, but FR alterations in the heavy and/or light chain are also contemplated. The substitutions are preferably conservative substitutions as described herein. Preferably, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids may be substituted in a CDR, while 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 25 amino acids may be substituted in the framework regions (FRs), depending on the length of the CDR or FR. For example, if a CDR sequence encompasses 6 amino acids, it is envisaged that one, two or three of these amino acids are substituted. Similarly, if a CDR sequence encompasses 15 amino acids it is envisaged that one, two, three, four, five or six of these amino acids are substituted.

A useful method for identification of certain residues or regions of the antibody constructs that are preferred locations for mutagenesis is called “alanine scanning mutagenesis” as described by Cunningham and Wells in Science, 244: 1081-1085 (1989). Here, a residue or group of target residues within the antibody construct is/are identified (*e.g.* charged residues such as arg, asp, his, lys, and glu) and replaced by a neutral or negatively charged amino acid (most preferably alanine or polyalanine) to affect the interaction of the amino acids with the epitope.

Those amino acid locations demonstrating functional sensitivity to the substitutions are then refined by introducing further or other variants at, or for, the sites of substitution. Thus, while the site or region for introducing an amino acid sequence variation is predetermined, the nature of the mutation *per se* needs not to be predetermined. For example, to analyze or optimize the performance of a mutation at a given site, alanine scanning or random mutagenesis may be conducted at a target codon or region, and the expressed antibody construct variants are screened for the optimal combination of desired activity. Techniques for making substitution mutations at predetermined sites in the DNA having a known sequence are well known, for example, M13 primer mutagenesis and PCR mutagenesis. Screening of the mutants is done using assays of antigen binding activities, such as MSLN or CD3 binding.

Generally, if amino acids are substituted in one or more or all of the CDRs of the heavy and/or light chain, it is preferred that the then-obtained “substituted” sequence is at least 60% or 65%, more preferably 70% or 75%, even more preferably 80% or 85%, and particularly preferably 90% or 95% identical to the “original” CDR sequence. This means that it is dependent of the length of the CDR to which degree it is identical to the “substituted” sequence. For example, a CDR having 5 amino acids is preferably 80% identical to its substituted sequence in order to have at least one amino acid substituted. Accordingly, the CDRs of the antibody construct may have different degrees of identity to their substituted sequences, e.g., CDRL1 may have 80%, while CDRL3 may have 90%.

Preferred substitutions (or replacements) are conservative substitutions. However, any substitution (including non-conservative substitution or one or more from the “exemplary substitutions” listed in Table 1, below) is envisaged as long as the antibody construct retains its capability to bind to MSLN via the first binding domain and to CD3 or CD3 epsilon via the second binding domain and/or its CDRs have an identity to the then substituted sequence (at least 60% or 65%, more preferably 70% or 75%, even more preferably 80% or 85%, and particularly preferably 90% or 95% identical to the “original” CDR sequence).

Conservative substitutions are shown in Table 1 under the heading of "preferred substitutions". If such substitutions result in a change in biological activity, then more substantial changes, denominated "exemplary substitutions" in Table 1, or as further described below in reference to amino acid classes, may be introduced and the products screened for a desired characteristic.

Table 1: Amino acid substitutions

Original	Exemplary Substitutions	Preferred Substitutions
Ala (A)	val, leu, ile	val
Arg (R)	lys, gln, asn	lys
Asn (N)	gln, his, asp, lys, arg	gln
Asp (D)	glu, asn	glu
Cys (C)	ser, ala	ser
Gln (Q)	asn, glu	asn
Glu (E)	asp, gln	asp
Gly (G)	Ala	ala
His (H)	asn, gln, lys, arg	arg
Ile (I)	leu, val, met, ala, phe	leu
Leu (L)	norleucine, ile, val, met, ala	ile
Lys (K)	arg, gln, asn	arg
Met (M)	leu, phe, ile	leu
Phe (F)	leu, val, ile, ala, tyr	tyr
Pro (P)	Ala	ala
Ser (S)	Thr	thr
Thr (T)	Ser	ser
Trp (W)	tyr, phe	tyr
Tyr (Y)	trp, phe, thr, ser	phe
Val (V)	ile, leu, met, phe, ala	leu

Substantial modifications in the biological properties of the antibody construct of the present invention are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties: (1) hydrophobic: norleucine, met, ala, val, leu,

ile; (2) neutral hydrophilic: cys, ser, thr; (3) acidic: asp, glu; (4) basic: asn, gin, his, lys, arg; (5) residues that influence chain orientation: gly, pro; and (6) aromatic : trp, tyr, phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another class. Any cysteine residue not involved in maintaining the proper conformation of the antibody construct may be substituted, generally with serine, to improve the oxidative stability of the molecule and prevent aberrant crosslinking. Conversely, cysteine bond(s) may be added to the antibody to improve its stability (particularly where the antibody is an antibody fragment such as an Fv fragment).

For amino acid sequences, sequence identity and/or similarity is determined by using standard techniques known in the art, including, but not limited to, the local sequence identity algorithm of Smith and Waterman, 1981, *Adv. Appl. Math.* 2:482, the sequence identity alignment algorithm of Needleman and Wunsch, 1970, *J. Mol. Biol.* 48:443, the search for similarity method of Pearson and Lipman, 1988, *Proc. Nat. Acad. Sci. U.S.A.* 85:2444, computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Drive, Madison, Wis.), the Best Fit sequence program described by Devereux *et al.*, 1984, *Nucl. Acid Res.* 12:387-395, preferably using the default settings, or by inspection. Preferably, percent identity is calculated by FastDB based upon the following parameters: mismatch penalty of 1; gap penalty of 1; gap size penalty of 0.33; and joining penalty of 30, "Current Methods in Sequence Comparison and Analysis," Macromolecule Sequencing and Synthesis, Selected Methods and Applications, pp 127-149 (1988), Alan R. Liss, Inc.

An example of a useful algorithm is PILEUP. PILEUP creates a multiple sequence alignment from a group of related sequences using progressive, pairwise alignments. It can also plot a tree showing the clustering relationships used to create the alignment. PILEUP uses a simplification of the progressive alignment method of Feng & Doolittle, 1987, *J. Mol. Evol.* 35:351-360; the method is similar to that described by Higgins and Sharp, 1989, *CABIOS* 5:151-153. Useful PILEUP parameters including a default gap weight of 3.00, a default gap length weight of 0.10, and weighted end gaps.

Another example of a useful algorithm is the BLAST algorithm, described in: Altschul *et al.*, 1990, *J. Mol. Biol.* 215:403-410; Altschul *et al.*, 1997, *Nucleic Acids Res.* 25:3389-3402; and Karin *et al.*, 1993, *Proc. Natl. Acad. Sci. U.S.A.* 90:5873-5787. A particularly useful BLAST

program is the WU-BLAST-2 program which was obtained from Altschul *et al.*, 1996, *Methods in Enzymology* 266:460-480. WU-BLAST-2 uses several search parameters, most of which are set to the default values. The adjustable parameters are set with the following values: overlap span=1, overlap fraction=0.125, word threshold (T)=II. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched; however, the values may be adjusted to increase sensitivity.

An additional useful algorithm is gapped BLAST as reported by Altschul *et al.*, 1993, *Nucl. Acids Res.* 25:3389-3402. Gapped BLAST uses BLOSUM-62 substitution scores; threshold T parameter set to 9; the two-hit method to trigger ungapped extensions, charges gap lengths of k a cost of 10+k; Xu set to 16, and Xg set to 40 for database search stage and to 67 for the output stage of the algorithms. Gapped alignments are triggered by a score corresponding to about 22 bits.

Generally, the amino acid homology, similarity, or identity between individual variant CDRs are at least 60% to the sequences depicted herein, and more typically with preferably increasing homologies or identities of at least 65% or 70%, more preferably at least 75% or 80%, even more preferably at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, and almost 100%. In a similar manner, “percent (%) nucleic acid sequence identity” with respect to the nucleic acid sequence of the binding proteins identified herein is defined as the percentage of nucleotide residues in a candidate sequence that are identical with the nucleotide residues in the coding sequence of the antibody construct. A specific method utilizes the BLASTN module of WU-BLAST-2 set to the default parameters, with overlap span and overlap fraction set to 1 and 0.125, respectively.

Generally, the nucleic acid sequence homology, similarity, or identity between the nucleotide sequences encoding individual variant CDRs and the nucleotide sequences depicted herein are at least 60%, and more typically with preferably increasing homologies or identities of at least 65%, 70%, 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%, and almost 100%. Thus, a “variant CDR” is one with the specified homology, similarity, or identity to the parent CDR of the invention, and shares biological function, including, but not limited to, at least 60%, 65%, 70%, 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% of the specificity and/or activity of the parent CDR.

In one embodiment, the percentage of identity to human germline of the antibody constructs according to the invention is ≥ 70% or ≥ 75%, more preferably ≥ 80% or ≥ 85%, even more preferably ≥ 90%, and most preferably ≥ 91%, ≥ 92%, ≥ 93%, ≥ 94%, ≥ 95% or even ≥ 96%. Identity to human antibody germline gene products is thought to be an important feature to reduce the risk of therapeutic proteins to elicit an immune response against the drug in the patient during treatment. Hwang & Foote ("Immunogenicity of engineered antibodies"; Methods 36 (2005) 3-10) demonstrate that the reduction of non-human portions of drug antibody constructs leads to a decrease of risk to induce anti-drug antibodies in the patients during treatment. By comparing an exhaustive number of clinically evaluated antibody drugs and the respective immunogenicity data, the trend is shown that humanization of the V-regions of antibodies makes the protein less immunogenic (average 5.1 % of patients) than antibodies carrying unaltered non-human V regions (average 23.59 % of patients). A higher degree of identity to human sequences is hence desirable for V-region based protein therapeutics in the form of antibody constructs. For this purpose of determining the germline identity, the V-regions of VL can be aligned with the amino acid sequences of human germline V segments and J segments (http://vbase.mrc-cpe.cam.ac.uk/) using Vector NTI software and the amino acid sequence calculated by dividing the identical amino acid residues by the total number of amino acid residues of the VL in percent. The same can be for the VH segments (http://vbase.mrc-cpe.cam.ac.uk/) with the exception that the VH CDR3 may be excluded due to its high diversity and a lack of existing human germline VH CDR3 alignment partners. Recombinant techniques can then be used to increase sequence identity to human antibody germline genes.

In a further embodiment, the bispecific antibody constructs of the present invention exhibit high monomer yields under standard research scale conditions, *e.g.,* in a standard two-step purification process. Preferably the monomer yield of the antibody constructs according to the invention is ≥ 0.25 mg/L supernatant, more preferably ≥ 0.5 mg/L, even more preferably ≥ 1 mg/L, and most preferably ≥ 3 mg/L supernatant.

Likewise, the yield of the dimeric antibody construct isoforms and hence the monomer percentage (*i.e.*, monomer : (monomer+dimer)) of the antibody constructs can be determined. The productivity of monomeric and dimeric antibody constructs and the calculated monomer percentage can *e.g.* be obtained in the SEC purification step of culture supernatant from standardized research-scale production in roller bottles. In one embodiment, the monomer

percentage of the antibody constructs is ≥ 80%, more preferably ≥ 85%, even more preferably ≥ 90%, and most preferably ≥ 95%.

In one embodiment, the antibody constructs have a preferred plasma stability (ratio of EC50 with plasma to EC50 w/o plasma) of ≤ 5 or ≤ 4, more preferably ≤ 3.5 or ≤ 3, even more preferably ≤ 2.5 or ≤ 2, and most preferably ≤ 1.5 or ≤ 1. The plasma stability of an antibody construct can be tested by incubation of the construct in human plasma at 37°C for 24 hours followed by EC50 determination in a 51-chromium release cytotoxicity assay. The effector cells in the cytotoxicity assay can be stimulated enriched human CD8 positive T cells. Target cells can *e.g.* be CHO cells transfected with human **MSLN**. The effector to target cell (E:T) ratio can be chosen as 10:1. The human plasma pool used for this purpose is derived from the blood of healthy donors collected by EDTA coated syringes. Cellular components are removed by centrifugation and the upper plasma phase is collected and subsequently pooled. As control, antibody constructs are diluted immediately prior to the cytotoxicity assay in RPMI-1640 medium. The plasma stability is calculated as ratio of EC50 (after plasma incubation) to EC50 (control). See Example 6.

It is furthermore preferred that the monomer to dimer conversion of antibody constructs of the invention is low. The conversion can be measured under different conditions and analyzed by high performance size exclusion chromatography. See Example 9. For example, incubation of the monomeric isoforms of the antibody constructs can be carried out for 7 days at 37°C and concentrations of *e.g.* 100 µg/ml or 250 µg/ml in an incubator. Under these conditions, it is preferred that the antibody constructs of the invention show a dimer percentage that is ≤5%, more preferably ≤4%, even more preferably ≤3%, even more preferably ≤2.5%, even more preferably ≤2%, even more preferably ≤1.5%, and most preferably ≤1% or ≤0.5% or even 0%.

It is also preferred that the bispecific antibody constructs of the present invention present with very low dimer conversion after a number of freeze/thaw cycles. For example, the antibody construct monomer is adjusted to a concentration of 250 µg/ml *e.g.* in generic formulation buffer and subjected to three freeze/thaw cycles (freezing at -80°C for 30 min followed by thawing for 30 min at room temperature), followed by high performance SEC to determine the percentage of initially monomeric antibody construct, which had been converted into dimeric antibody construct. Preferably the dimer percentages of the bispecific antibody constructs are ≤5%, more preferably ≤4%, even more preferably ≤3%, even more preferably ≤2.5%, even more preferably

≤2%, even more preferably ≤1.5%, and most preferably ≤1% or even ≤0.5%, for example after three freeze/thaw cycles.

The bispecific antibody constructs of the present invention preferably show a favorable thermostability with aggregation temperatures ≥45°C or ≥50°C, more preferably ≥51°C, ≥52°C, ≥53°C or ≥54°C, even more preferably ≥56°C or ≥57°C, and most preferably ≥58°C or ≥59°C. The thermostability parameter can be determined in terms of antibody aggregation temperature as follows: Antibody solution at a concentration 250 µg/ml is transferred into a single use cuvette and placed in a Dynamic Light Scattering (DLS) device. The sample is heated from 40°C to 70°C at a heating rate of 0.5°C/min with constant acquisition of the measured radius. Increase of radius indicating melting of the protein and aggregation is used to calculate the aggregation temperature of the antibody. See Example 10.

Alternatively, temperature melting curves can be determined by Differential Scanning Calorimetry (DSC) to determine intrinsic biophysical protein stabilities of the antibody constructs. These experiments are performed using a MicroCal LLC (Northampton, MA, U.S.A) VP-DSC device. The energy uptake of a sample containing an antibody construct is recorded from 20°C to 90°C compared to a sample containing only the formulation buffer. The antibody constructs are adjusted to a final concentration of 250 µg/ml *e.g.* in SEC running buffer. For recording of the respective melting curve, the overall sample temperature is increased stepwise. At each temperature T energy uptake of the sample and the formulation buffer reference is recorded. The difference in energy uptake Cp (kcal/mole/°C) of the sample minus the reference is plotted against the respective temperature. The melting temperature is defined as the temperature at the first maximum of energy uptake.

The MSLN xCD3 bispecific antibody constructs of the invention are also envisaged to have a turbidity (as measured by OD340 after concentration of purified monomeric antibody construct to 2.5 mg/ml and over night incubation) of ≤ 0.2, preferably of ≤ 0.15, more preferably of ≤ 0.12, even more preferably of ≤ 0.1 or even ≥0.09, and most preferably of ≤ 0.08 or ≥0.07. See Example 11.

In a further embodiment the antibody construct according to the invention is stable at acidic pH. The more tolerant the antibody construct behaves at unphysiologic pH such as pH 5.5 (a pH which is required to run e.g. a cation exchange chromatography), the higher is the recovery of the antibody construct eluted from an ion exchange column relative to the total amount of

loaded protein. Recovery of the antibody construct from an ion (*e.g.*, cation) exchange column at pH 5.5 is preferably ≥ 30%, more preferably ≥ 40%, more preferably ≥ 50%, even more preferably ≥ 60%, even more preferably ≥ 70%, even more preferably ≥ 80%, even more preferably ≥ 90%, even more preferably ≥ 95%, and most preferably ≥ 99%. See Example 7.

It is furthermore envisaged that the bispecific antibody constructs of the present invention exhibit therapeutic efficacy or anti-tumor activity. This can *e.g.* be assessed in a study as disclosed in the following example of an advanced stage human tumor xenograft model:

On day 1 of the study, $5x10^6$ cells of a human MSLN positive cancer cell line (e.g. OVCAR-8) are subcutaneously injected in the right dorsal flank of female NOD/SCID mice. When the mean tumor volume reaches about 100 mm^3, in vitro expanded human CD3 positive T cells are transplanted into the mice by injection of about $2x10^7$ cells into the peritoneal cavity of the animals. Mice of vehicle control group 1 do not receive effector cells and are used as an untransplanted control for comparison with vehicle control group 2 (receiving effector cells) to monitor the impact of T cells alone on tumor growth. The antibody treatment starts when the mean tumor volume reaches about 200 mm^3. The mean tumor size of each treatment group on the day of treatment start should not be statistically different from any other group (analysis of variance). Mice are treated with 0.5 mg/kg/day of a MSLN xCD3 bispecifc antibody construct by intravenous bolus injection for about 15 to 20 days. Tumors are measured by caliper during the study and progress evaluated by intergroup comparison of tumor volumes (TV). The tumor growth inhibition T/C [%] is determined by calculating TV as T/C% = 100 x (median TV of analyzed group) / (median TV of control group 2).

The skilled person knows how to modify or adapt certain parameters of this study, such as the number of injected tumor cells, the site of injection, the number of transplanted human T cells, the amount of bispecific antibody constructs to be administered, and the timelines, while still arriving at a meaningful and reproducible result. Preferably, the tumor growth inhibition T/C [%] is ≤ 70 or ≤ 60, more preferably ≤ 50 or ≤ 40, even more preferably ≤ 30 or ≤ 20 and most preferably ≤ 10 or ≤ 5 or even ≤ 2.5.

The invention further provides a polynucleotide / nucleic acid molecule encoding an antibody construct of the invention.

A polynucleotide is a biopolymer composed of 13 or more nucleotide monomers covalently bonded in a chain. DNA (such as cDNA) and RNA (such as mRNA) are examples of polynucleotides with distinct biological function. Nucleotides are organic molecules that serve as the monomers or subunits of nucleic acid molecules like DNA or RNA. The nucleic acid molecule or polynucleotide can be double stranded and single stranded, linear and circular. It is preferably comprised in a vector which is preferably comprised in a host cell. Said host cell is, *e.g.* after transformation or transfection with the vector or the polynucleotide of the invention, capable of expressing the antibody construct. For that purpose the polynucleotide or nucleic acid molecule is operatively linked with control sequences.

The genetic code is the set of rules by which information encoded within genetic material (nucleic acids) is translated into proteins. Biological decoding in living cells is accomplished by the ribosome which links amino acids in an order specified by mRNA, using tRNA molecules to carry amino acids and to read the mRNA three nucleotides at a time. The code defines how sequences of these nucleotide triplets, called codons, specify which amino acid will be added next during protein synthesis. With some exceptions, a three-nucleotide codon in a nucleic acid sequence specifies a single amino acid. Because the vast majority of genes are encoded with exactly the same code, this particular code is often referred to as the canonical or standard genetic code. While the genetic code determines the protein sequence for a given coding region, other genomic regions can influence when and where these proteins are produced.

Furthermore, the invention provides a vector comprising a polynucleotide / nucleic acid molecule of the invention.

A vector is a nucleic acid molecule used as a vehicle to transfer (foreign) genetic material into a cell. The term “vector” encompasses – but is not restricted to – plasmids, viruses, cosmids and artificial chromosomes. In general, engineered vectors comprise an origin of replication, a multicloning site and a selectable marker. The vector itself is generally a nucleotide sequence, commonly a DNA sequence, that comprises an insert (transgene) and a larger sequence that serves as the “backbone” of the vector. Modern vectors may encompass additional features besides the transgene insert and a backbone: promoter, genetic marker, antibiotic resistance, reporter gene, targeting sequence, protein purification tag. Vectors called expression vectors (expression constructs) specifically are for the expression of the transgene in the target cell, and generally have control sequences.

The term “control sequences” refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

A nucleic acid is “operably linked” when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, “operably linked” means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

“Transfection” is the process of deliberately introducing nucleic acid molecules or polynucleotides (including vectors) into target cells. The term is mostly used for non-viral methods in eukaryotic cells. Transduction is often used to describe virus-mediated transfer of nucleic acid molecules or polynucleotides. Transfection of animal cells typically involves opening transient pores or “holes” in the cell membrane, to allow the uptake of material. Transfection can be carried out using calcium phosphate, by electroporation, by cell squeezing or by mixing a cationic lipid with the material to produce liposomes, which fuse with the cell membrane and deposit their cargo inside.

The term “transformation” is used to describe non-viral transfer of nucleic acid molecules or polynucleotides (including vectors) into bacteria, and also into non-animal eukaryotic cells, including plant cells. Transformation is hence the genetic alteration of a bacterial or non-animal eukaryotic cell resulting from the direct uptake through the cell membrane(s) from its surroundings and subsequent incorporation of exogenous genetic material (nucleic acid molecules). Transformation can be effected by artificial means. For transformation to happen, cells or bacteria must be in a state of competence, which might occur as a time-limited response to environmental conditions such as starvation and cell density.

Moreover, the invention provides a host cell transformed or transfected with the polynucleotide / nucleic acid molecule or with the vector of the invention.

As used herein, the terms “host cell” or “recipient cell” are intended to include any individual cell or cell culture that can be or has/have been recipients of vectors, exogenous nucleic acid molecules, and polynucleotides encoding the antibody construct of the present invention; and/or recipients of the antibody construct itself. The introduction of the respective material into the cell is carried out by way of transformation, transfection and the like. The term “host cell” is also intended to include progeny or potential progeny of a single cell. Because certain modifications may occur in succeeding generations due to either natural, accidental, or deliberate mutation or due to environmental influences, such progeny may not, in fact, be completely identical (in morphology or in genomic or total DNA complement) to the parent cell, but is still included within the scope of the term as used herein. Suitable host cells include prokaryotic or eukaryotic cells, and also include but are not limited to bacteria, yeast cells, fungi cells, plant cells, and animal cells such as insect cells and mammalian cells, e.g., murine, rat, macaque or human.

The antibody construct of the invention can be produced in bacteria. After expression, the antibody construct of the invention is isolated from the *E. coli* cell paste in a soluble fraction and can be purified through, e.g., affinity chromatography and/or size exclusion. Final purification can be carried out similar to the process for purifying antibody expressed *e.g.*, in CHO cells.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for the antibody construct of the invention. *Saccharomyces cerevisiae*, or common baker's yeast, is the most commonly used among lower eukaryotic host microorganisms. However, a number of other genera, species, and strains are commonly available and useful herein, such as *Schizosaccharomyces pombe*, Kluyveromyces hosts such as *K. lactis, K. fragilis* (ATCC 12424), *K. bulgaricus* (ATCC 16045), *K. wickeramii* (ATCC 24178), *K. waltii* (ATCC 56500), *K. drosophilarum* (ATCC 36906), *K. thermotolerans*, and *K. marxianus*; yarrowia (EP 402 226); *Pichia pastoris* (EP 183 070); Candida; *Trichoderma reesia* (EP 244 234); *Neurospora crassa*; Schwanniomyces such as *Schwanniomyces occidentalis*; and filamentous fungi such as Neurospora, Penicillium, Tolypocladium, and Aspergillus hosts such as *A. nidulans* and *A. niger*.

Suitable host cells for the expression of glycosylated antibody construct of the invention are derived from multicellular organisms. Examples of invertebrate cells include plant and insect

cells. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts such as *Spodoptera frugiperda* (caterpillar), *Aedes aegypti* (mosquito), *Aedes albopictus* (mosquito), *Drosophila melanogaster* (fruit fly), and *Bombyx mori* have been identified. A variety of viral strains for transfection are publicly available, *e.g.*, the L-1 variant of *Autographa californica* NPV and the Bm-5 strain of *Bombyx mori* NPV, and such viruses may be used as the virus herein according to the present invention, particularly for transfection of *Spodoptera frugiperda* cells.

Plant cell cultures of cotton, corn, potato, soybean, petunia, tomato, Arabidopsis and tobacco can also be used as hosts. Cloning and expression vectors useful in the production of proteins in plant cell culture are known to those of skill in the art. See *e.g.* Hiatt *et al.*, Nature (1989) 342: 76-78, Owen *et al.* (1992) Bio/Technology 10: 790-794, Artsaenko *et al.* (1995) The Plant J 8: 745-750, and Fecker *et al.* (1996) Plant Mol Biol 32: 979-986.

However, interest has been greatest in vertebrate cells, and propagation of vertebrate cells in culture (tissue culture) has become a routine procedure. Examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al. , J. Gen Virol. 36 : 59 (1977)); baby hamster kidney cells (BHK, ATCC CCL 10); Chinese hamster ovary cells/-DHFR (CHO, Urlaub *et al.*, Proc. Natl. Acad. Sci. USA 77: 4216 (1980)); mouse sertoli cells (TM4, Mather, Biol. Reprod. 23: 243-251 (1980)); monkey kidney cells (CVI ATCC CCL 70); African green monkey kidney cells (VERO-76, ATCC CRL1587); human cervical carcinoma cells (HELA, ATCC CCL 2); canine kidney cells (MDCK, ATCC CCL 34); buffalo rat liver cells (BRL 3A, ATCC CRL 1442); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2,1413 8065); mouse mammary tumor (MMT 060562, ATCC CCL5 1); TRI cells (Mather *et al.*, Annals N. Y Acad. Sci. (1982) 383: 44-68); MRC 5 cells; FS4 cells; and a human hepatoma line (Hep G2).

In a further embodiment the invention provides a process for the production of an antibody construct of the invention, said process comprising culturing a host cell of the invention under conditions allowing the expression of the antibody construct of the invention and recovering the produced antibody construct from the culture.

As used herein, the term “culturing” refers to the *in vitro* maintenance, differentiation, growth, proliferation and/or propagation of cells under suitable conditions in a medium. The term

"expression" includes any step involved in the production of an antibody construct of the invention including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and secretion.

When using recombinant techniques, the antibody construct can be produced intracellularly, in the periplasmic space, or directly secreted into the medium. If the antibody construct is produced intracellularly, as a first step, the particulate debris, either host cells or lysed fragments, are removed, for example, by centrifugation or ultrafiltration. Carter *et al.*, Bio/Technology 10: 163-167 (1992) describe a procedure for isolating antibodies which are secreted to the periplasmic space of *E. coli*. Briefly, cell paste is thawed in the presence of sodium acetate (pH 3.5), EDTA, and phenylmethylsulfonylfluoride (PMSF) over about 30 min. Cell debris can be removed by centrifugation. Where the antibody is secreted into the medium, supernatants from such expression systems are generally first concentrated using a commercially available protein concentration filter, for example, an Amicon or Millipore Pellicon ultrafiltration unit. A protease inhibitor such as PMSF may be included in any of the foregoing steps to inhibit proteolysis and antibiotics may be included to prevent the growth of adventitious contaminants.

The antibody construct of the invention prepared from the host cells can be recovered or purified using, for example, hydroxylapatite chromatography, gel electrophoresis, dialysis, and affinity chromatography. Other techniques for protein purification such as fractionation on an ion-exchange column, ethanol precipitation, Reverse Phase HPLC, chromatography on silica, chromatography on heparin SEPHAROSE^{TM}, chromatography on an anion or cation exchange resin (such as a polyaspartic acid column), chromato-focusing, SDS-PAGE, and ammonium sulfate precipitation are also available depending on the antibody to be recovered. Where the antibody construct of the invention comprises a CH3 domain, the Bakerbond ABX resin (J.T. Baker, Phillipsburg, NJ) is useful for purification.

Affinity chromatography is a preferred purification technique. The matrix to which the affinity ligand is attached is most often agarose, but other matrices are available. Mechanically stable matrices such as controlled pore glass or poly (styrenedivinyl) benzene allow for faster flow rates and shorter processing times than can be achieved with agarose.

Moreover, the invention provides a pharmaceutical composition comprising an antibody construct of the invention or an antibody construct produced according to the process of the

invention. It is preferred for the pharmaceutical composition of the invention that the homogeneity of the antibody construct is ≥ 80%, more preferably ≥ 81%,≥ 82%,≥ 83%,≥ 84%, or ≥ 85%, further preferably ≥ 86%,≥ 87%,≥ 88%,≥ 89%, or ≥ 90%, still further preferably, ≥ 91%,≥ 92%,≥ 93%,≥ 94%, or ≥ 95% and most preferably ≥ 96%,≥ 97%,≥ 98% or ≥ 99%.

As used herein, the term "pharmaceutical composition" relates to a composition which is suitable for administration to a patient, preferably a human patient. The particularly preferred pharmaceutical composition of this invention comprises one or a plurality of the antibody construct(s) of the invention, preferably in a therapeutically effective amount. Preferably, the pharmaceutical composition further comprises suitable formulations of one or more (pharmaceutically effective) carriers, stabilizers, excipients, diluents, solubilizers, surfactants, emulsifiers, preservatives and/or adjuvants. Acceptable constituents of the composition are preferably nontoxic to recipients at the dosages and concentrations employed. Pharmaceutical compositions of the invention include, but are not limited to, liquid, frozen, and lyophilized compositions.

The inventive compositions may comprise a pharmaceutically acceptable carrier. In general, as used herein, "pharmaceutically acceptable carrier" means any and all aqueous and non-aqueous solutions, sterile solutions, solvents, buffers, e.g. phosphate buffered saline (PBS) solutions, water, suspensions, emulsions, such as oil/water emulsions, various types of wetting agents, liposomes, dispersion media and coatings, which are compatible with pharmaceutical administration, in particular with parenteral administration. The use of such media and agents in pharmaceutical compositions is well known in the art, and the compositions comprising such carriers can be formulated by well-known conventional methods.

Certain embodiments provide pharmaceutical compositions comprising the antibody construct of the invention and further one or more excipients such as those illustratively described in this section and elsewhere herein. Excipients can be used in the invention in this regard for a wide variety of purposes, such as adjusting physical, chemical, or biological properties of formulations, such as adjustment of viscosity, and or processes of the invention to improve effectiveness and or to stabilize such formulations and processes against degradation and spoilage due to, for instance, stresses that occur during manufacturing, shipping, storage, pre-use preparation, administration, and thereafter.

In certain embodiments, the pharmaceutical composition may contain formulation materials for the purpose of modifying, maintaining or preserving, *e.g.*, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition (see, REMINGTON'S PHARMACEUTICAL SCIENCES, 18" Edition, (A.R. Genrmo, ed.), 1990, Mack Publishing Company). In such embodiments, suitable formulation materials may include, but are not limited to:

- amino acids such as glycine, alanine, glutamine, asparagine, threonine, proline, 2-phenylalanine, including charged amino acids, preferably lysine, lysine acetate, arginine, glutamate and/or histidine
- antimicrobials such as antibacterial and antifungal agents
- antioxidants such as ascorbic acid, methionine, sodium sulfite or sodium hydrogen-sulfite;
- buffers, buffer systems and buffering agents which are used to maintain the composition at physiological pH or at a slightly lower pH, typically within a pH range of from about 5 to about 8 or 9; examples of buffers are borate, bicarbonate, Tris-HCl, citrates, phosphates or other organic acids, succinate, phosphate, histidine and acetate; for example Tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5;
- non-aqueous solvents such as propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate;
- aqueous carriers including water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media;
- biodegradable polymers such as polyesters;
- bulking agents such as mannitol or glycine;
- chelating agents such as ethylenediamine tetraacetic acid (EDTA);
- isotonic and absorption delaying agents;
- complexing agents such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin)
- fillers;
- monosaccharides; disaccharides; and other carbohydrates (such as glucose, mannose or dextrins); carbohydrates may be non-reducing sugars, preferably trehalose, sucrose, octasulfate, sorbitol or xylitol;
- (low molecular weight) proteins, polypeptides or proteinaceous carriers such as human or bovine serum albumin, gelatin or immunoglobulins, preferably of human origin;
- coloring and flavouring agents;

- sulfur containing reducing agents, such as glutathione, thioctic acid, sodium thioglycolate, thioglycerol, [alpha]-monothioglycerol, and sodium thio sulfate
- diluting agents;
- emulsifying agents;
- hydrophilic polymers such as polyvinylpyrrolidone)
- salt-forming counter-ions such as sodium;
- preservatives such as antimicrobials, anti-oxidants, chelating agents, inert gases and the like; examples are: benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide);
- metal complexes such as Zn-protein complexes;
- solvents and co-solvents (such as glycerin, propylene glycol or polyethylene glycol);
- sugars and sugar alcohols, such as trehalose, sucrose, octasulfate, mannitol, sorbitol or xylitol stachyose, mannose, sorbose, xylose, ribose, myoinisitose, galactose, lactitol, ribitol, myoinisitol, galactitol, glycerol, cyclitols (e.g., inositol), polyethylene glycol; and polyhydric sugar alcohols;
- suspending agents;
- surfactants or wetting agents such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate, triton, tromethamine, lecithin, cholesterol, tyloxapal; surfactants may be detergents, preferably with a molecular weight of >1.2 KD and/or a polyether, preferably with a molecular weight of >3 KD; non-limiting examples for preferred detergents are Tween 20, Tween 40, Tween 60, Tween 80 and Tween 85; non-limiting examples for preferred polyethers are PEG 3000, PEG 3350, PEG 4000 and PEG 5000;
- stability enhancing agents such as sucrose or sorbitol;
- tonicity enhancing agents such as alkali metal halides, preferably sodium or potassium chloride, mannitol sorbitol;
- parenteral delivery vehicles including sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils;
- intravenous delivery vehicles including fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose).

It is evident to those skilled in the art that the different constituents of the pharmaceutical composition (*e.g.*, those listed above) can have different effects, for example, and amino acid can act as a buffer, a stabilizer and/or an antioxidant; mannitol can act as a bulking agent

and/or a tonicity enhancing agent; sodium chloride can act as delivery vehicle and/or tonicity enhancing agent; etc.

It is envisaged that the composition of the invention might comprise, in addition to the polypeptide of the invention defined herein, further biologically active agents, depending on the intended use of the composition. Such agents might be drugs acting on the gastro-intestinal system, drugs acting as cytostatica, drugs preventing hyperurikemia, drugs inhibiting immunoreactions (e.g. corticosteroids), drugs modulating the inflammatory response, drugs acting on the circulatory system and/or agents such as cytokines known in the art. It is also envisaged that the antibody construct of the present invention is applied in a co-therapy, *i.e.*, in combination with another anti-cancer medicament.

In certain embodiments, the optimal pharmaceutical composition will be determined by one skilled in the art depending upon, for example, the intended route of administration, delivery format and desired dosage. See, for example, REMINGTON'S PHARMACEUTICAL SCIENCES, *supra*. In certain embodiments, such compositions may influence the physical state, stability, rate of *in vivo* release and rate of *in vivo* clearance of the antibody construct of the invention. In certain embodiments, the primary vehicle or carrier in a pharmaceutical composition may be either aqueous or non-aqueous in nature. For example, a suitable vehicle or carrier may be water for injection, physiological saline solution or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. In certain embodiments, the antibody construct of the invention compositions may be prepared for storage by mixing the selected composition having the desired degree of purity with optional formulation agents (REMINGTON'S PHARMACEUTICAL SCIENCES, *supra*) in the form of a lyophilized cake or an aqueous solution. Further, in certain embodiments, the antibody construct of the invention may be formulated as a lyophilizate using appropriate excipients such as sucrose.

When parenteral administration is contemplated, the therapeutic compositions for use in this invention may be provided in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising the desired antibody construct of the invention in a pharmaceutically acceptable vehicle. A particularly suitable vehicle for parenteral injection is sterile distilled water in which the antibody construct of the invention is formulated as a sterile, isotonic solution, properly preserved. In certain embodiments, the preparation can involve the formulation of the

desired molecule with an agent, such as injectable microspheres, bio-erodible particles, polymeric compounds (such as polylactic acid or polyglycolic acid), beads or liposomes, that may provide controlled or sustained release of the product which can be delivered via depot injection. In certain embodiments, hyaluronic acid may also be used, having the effect of promoting sustained duration in the circulation. In certain embodiments, implantable drug delivery devices may be used to introduce the desired antibody construct.

Additional pharmaceutical compositions will be evident to those skilled in the art, including formulations involving the antibody construct of the invention in sustained- or controlled-delivery / release formulations. Techniques for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art. See, for example, International Patent Application No. PCT/US93/00829, which describes controlled release of porous polymeric microparticles for delivery of pharmaceutical compositions. Sustained-release preparations may include semipermeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Sustained release matrices may include polyesters, hydrogels, polylactides (as disclosed in U.S. Pat. No. 3,773,919 and European Patent Application Publication No. EP 058481), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman et al., 1983, Biopolymers 2:547-556), poly (2-hydroxyethyl-methacrylate) (Langer *et al.*, 1981, J. Biomed. Mater. Res. 15:167-277 and Langer, 1982, Chem. Tech. 12:98-105), ethylene vinyl acetate (Langer et al., 1981, supra) or poly-D(-)-3-hydroxybutyric acid (European Patent Application Publication No. EP 133,988). Sustained release compositions may also include liposomes that can be prepared by any of several methods known in the art. See, *e.g.*, Eppstein et al., 1985, Proc. Natl. Acad. Sci. U.S.A. 82:3688-3692; European Patent Application Publication Nos. EP 036,676; EP 088,046 and EP 143,949.

The antibody construct may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization (for example, hydroxymethylcellulose or gelatine-microcapsules and poly (methylmethacylate) microcapsules, respectively), in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nanoparticles and nanocapsules), or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, 16th edition, Oslo, A., Ed., (1980).

Pharmaceutical compositions used for *in vivo* administration are typically provided as sterile preparations. Sterilization can be accomplished by filtration through sterile filtration membranes.

When the composition is lyophilized, sterilization using this method may be conducted either prior to or following lyophilization and reconstitution. Compositions for parenteral administration can be stored in lyophilized form or in a solution. Parenteral compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Another aspect of the invention includes self-buffering antibody construct of the invention formulations, which can be used as pharmaceutical compositions, as described in international patent application WO 06138181A2 (PCT/US2006/022599). A variety of expositions are available on protein stabilization and formulation materials and methods useful in this regard, such as Arakawa et al., "Solvent interactions in pharmaceutical formulations," Pharm Res. 8(3): 285-91 (1991); Kendrick et al., "Physical stabilization of proteins in aqueous solution" in: RATIONAL DESIGN OF STABLE PROTEIN FORMULATIONS: THEORY AND PRACTICE, Carpenter and Manning, eds. Pharmaceutical Biotechnology. 13: 61-84 (2002), and Randolph et al., "Surfactant-protein interactions", Pharm Biotechnol. 13: 159-75 (2002), see particularly the parts pertinent to excipients and processes of the same for self-buffering protein formulations in accordance with the current invention, especially as to protein pharmaceutical products and processes for veterinary and/or human medical uses.

Salts may be used in accordance with certain embodiments of the invention to, for example, adjust the ionic strength and/or the isotonicity of a formulation and/or to improve the solubility and/or physical stability of a protein or other ingredient of a composition in accordance with the invention. As is well known, ions can stabilize the native state of proteins by binding to charged residues on the protein's surface and by shielding charged and polar groups in the protein and reducing the strength of their electrostatic interactions, attractive, and repulsive interactions. Ions also can stabilize the denatured state of a protein by binding to, in particular, the denatured peptide linkages (--CONH) of the protein. Furthermore, ionic interaction with charged and polar groups in a protein also can reduce intermolecular electrostatic interactions and, thereby, prevent or reduce protein aggregation and insolubility.

Ionic species differ significantly in their effects on proteins. A number of categorical rankings of ions and their effects on proteins have been developed that can be used in formulating pharmaceutical compositions in accordance with the invention. One example is the Hofmeister series, which ranks ionic and polar non-ionic solutes by their effect on the conformational stability of proteins in solution. Stabilizing solutes are referred to as "kosmotropic". Destabilizing

solutes are referred to as “chaotropic”. Kosmotropes commonly are used at high concentrations (e.g., >1 molar ammonium sulfate) to precipitate proteins from solution (“salting-out”). Chaotropes commonly are used to denture and/or to solubilize proteins (“salting-in”). The relative effectiveness of ions to “salt-in” and “salt-out” defines their position in the Hofmeister series.

Free amino acids can be used in the antibody construct of the invention formulations in accordance with various embodiments of the invention as bulking agents, stabilizers, and antioxidants, as well as other standard uses. Lysine, proline, serine, and alanine can be used for stabilizing proteins in a formulation. Glycine is useful in lyophilization to ensure correct cake structure and properties. Arginine may be useful to inhibit protein aggregation, in both liquid and lyophilized formulations. Methionine is useful as an antioxidant.

Polyols include sugars, e.g., mannitol, sucrose, and sorbitol and polyhydric alcohols such as, for instance, glycerol and propylene glycol, and, for purposes of discussion herein, polyethylene glycol (PEG) and related substances. Polyols are kosmotropic. They are useful stabilizing agents in both liquid and lyophilized formulations to protect proteins from physical and chemical degradation processes. Polyols also are useful for adjusting the tonicity of formulations. Among polyols useful in select embodiments of the invention is mannitol, commonly used to ensure structural stability of the cake in lyophilized formulations. It ensures structural stability to the cake. It is generally used with a lyoprotectant, e.g., sucrose. Sorbitol and sucrose are among preferred agents for adjusting tonicity and as stabilizers to protect against freeze-thaw stresses during transport or the preparation of bulks during the manufacturing process. Reducing sugars (which contain free aldehyde or ketone groups), such as glucose and lactose, can glycate surface lysine and arginine residues. Therefore, they generally are not among preferred polyols for use in accordance with the invention. In addition, sugars that form such reactive species, such as sucrose, which is hydrolyzed to fructose and glucose under acidic conditions, and consequently engenders glycation, also is not among preferred polyols of the invention in this regard. PEG is useful to stabilize proteins and as a cryoprotectant and can be used in the invention in this regard.

Embodiments of the antibody construct of the invention formulations further comprise surfactants. Protein molecules may be susceptible to adsorption on surfaces and to denaturation and consequent aggregation at air-liquid, solid-liquid, and liquid-liquid interfaces. These effects generally scale inversely with protein concentration. These deleterious

interactions generally scale inversely with protein concentration and typically are exacerbated by physical agitation, such as that generated during the shipping and handling of a product. Surfactants routinely are used to prevent, minimize, or reduce surface adsorption. Useful surfactants in the invention in this regard include polysorbate 20, polysorbate 80, other fatty acid esters of sorbitan polyethoxylates, and poloxamer 188. Surfactants also are commonly used to control protein conformational stability. The use of surfactants in this regard is protein-specific since, any given surfactant typically will stabilize some proteins and destabilize others.

Polysorbates are susceptible to oxidative degradation and often, as supplied, contain sufficient quantities of peroxides to cause oxidation of protein residue side-chains, especially methionine. Consequently, polysorbates should be used carefully, and when used, should be employed at their lowest effective concentration. In this regard, polysorbates exemplify the general rule that excipients should be used in their lowest effective concentrations.

Embodiments of the antibody construct of the invention formulations further comprise one or more antioxidants. To some extent deleterious oxidation of proteins can be prevented in pharmaceutical formulations by maintaining proper levels of ambient oxygen and temperature and by avoiding exposure to light. Antioxidant excipients can be used as well to prevent oxidative degradation of proteins. Among useful antioxidants in this regard are reducing agents, oxygen/free-radical scavengers, and chelating agents. Antioxidants for use in therapeutic protein formulations in accordance with the invention preferably are water-soluble and maintain their activity throughout the shelf life of a product. EDTA is a preferred antioxidant in accordance with the invention in this regard. Antioxidants can damage proteins. For instance, reducing agents, such as glutathione in particular, can disrupt intramolecular disulfide linkages. Thus, antioxidants for use in the invention are selected to, among other things, eliminate or sufficiently reduce the possibility of themselves damaging proteins in the formulation.

Formulations in accordance with the invention may include metal ions that are protein co-factors and that are necessary to form protein coordination complexes, such as zinc necessary to form certain insulin suspensions. Metal ions also can inhibit some processes that degrade proteins. However, metal ions also catalyze physical and chemical processes that degrade proteins. Magnesium ions (10-120 mM) can be used to inhibit isomerization of aspartic acid to isoaspartic acid. Ca^{+2} ions (up to 100 mM) can increase the stability of human deoxyribonuclease. Mg^{+2}, Mn^{+2}, and Zn^{+2}, however, can destabilize rhDNase. Similarly, Ca^{+2} and Sr^{+2} can stabilize Factor

VIII, it can be destabilized by Mg^{+2}, Mn^{+2} and Zn^{+2}, Cu^{+2} and Fe^{+2}, and its aggregation can be increased by Al^{+3} ions.

Embodiments of the antibody construct of the invention formulations further comprise one or more preservatives. Preservatives are necessary when developing multi-dose parenteral formulations that involve more than one extraction from the same container. Their primary function is to inhibit microbial growth and ensure product sterility throughout the shelf-life or term of use of the drug product. Commonly used preservatives include benzyl alcohol, phenol and m-cresol. Although preservatives have a long history of use with small-molecule parenterals, the development of protein formulations that includes preservatives can be challenging. Preservatives almost always have a destabilizing effect (aggregation) on proteins, and this has become a major factor in limiting their use in multi-dose protein formulations. To date, most protein drugs have been formulated for single-use only. However, when multi-dose formulations are possible, they have the added advantage of enabling patient convenience, and increased marketability. A good example is that of human growth hormone (hGH) where the development of preserved formulations has led to commercialization of more convenient, multi-use injection pen presentations. At least four such pen devices containing preserved formulations of hGH are currently available on the market. Norditropin (liquid, Novo Nordisk), Nutropin AQ (liquid, Genentech) & Genotropin (lyophilized--dual chamber cartridge, Pharmacia & Upjohn) contain phenol while Somatrope (Eli Lilly) is formulated with m-cresol. Several aspects need to be considered during the formulation and development of preserved dosage forms. The effective preservative concentration in the drug product must be optimized. This requires testing a given preservative in the dosage form with concentration ranges that confer anti-microbial effectiveness without compromising protein stability.

As might be expected, development of liquid formulations containing preservatives are more challenging than lyophilized formulations. Freeze-dried products can be lyophilized without the preservative and reconstituted with a preservative containing diluent at the time of use. This shortens the time for which a preservative is in contact with the protein, significantly minimizing the associated stability risks. With liquid formulations, preservative effectiveness and stability should be maintained over the entire product shelf-life (about 18 to 24 months). An important point to note is that preservative effectiveness should be demonstrated in the final formulation containing the active drug and all excipient components.

The antibody constructs disclosed herein may also be formulated as immuno-liposomes. A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes. Liposomes containing the antibody construct are prepared by methods known in the art, such as described in Epstein *et al.*, Proc. Natl. Acad. Sci. USA, 82: 3688 (1985); Hwang *et al.* , Proc. Natl Acad. Sci. USA, 77: 4030 (1980); US Pat. Nos. 4,485,045 and 4,544,545; and W0 97/38731. Liposomes with enhanced circulation time are disclosed in US Patent No. 5,013, 556. Particularly useful liposomes can be generated by the reverse phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody construct of the present invention can be conjugated to the liposomes as described in Martin *et al.* J. Biol. Chem. 257: 286-288 (1982) via a disulfide interchange reaction. A chemotherapeutic agent is optionally contained within the liposome. See Gabizon *et al.* J. National Cancer Inst. 81 (19) 1484 (1989).

Once the pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, crystal, or as a dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form or in a form (*e.g.*, lyophilized) that is reconstituted prior to administration.

The biological activity of the pharmaceutical composition defined herein can be determined for instance by cytotoxicity assays, as described in the following examples, in WO 99/54440 or by Schlereth *et al.* (Cancer Immunol. Immunother. 20 (2005), 1-12). "Efficacy" or "*in vivo* efficacy" as used herein refers to the response to therapy by the pharmaceutical composition of the invention, using e.g. standardized NCI response criteria. The success or *in vivo* efficacy of the therapy using a pharmaceutical composition of the invention refers to the effectiveness of the composition for its intended purpose, *i.e.* the ability of the composition to cause its desired effect, i.e. depletion of pathologic cells, e.g. tumor cells. The *in vivo* efficacy may be monitored by established standard methods for the respective disease entities including, but not limited to white blood cell counts, differentials, Fluorescence Activated Cell Sorting, bone marrow aspiration. In addition, various disease specific clinical chemistry parameters and other established standard methods may be used. Furthermore, computer-aided tomography, X-ray, nuclear magnetic resonance tomography (e.g. for National Cancer Institute-criteria based

response assessment [Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, Lister TA, Vose J, Grillo-Lopez A, Hagenbeek A, Cabanillas F, Klippensten D, Hiddemann W, Castellino R, Harris NL, Armitage JO, Carter W, Hoppe R, Canellos GP. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol. 1999 Apr;17(4):1244]), positron-emission tomography scanning, white blood cell counts, differentials, Fluorescence Activated Cell Sorting, bone marrow aspiration, lymph node biopsies/histologies, and various lymphoma specific clinical chemistry parameters (e.g. lactate dehydrogenase) and other established standard methods may be used.

Another major challenge in the development of drugs such as the pharmaceutical composition of the invention is the predictable modulation of pharmacokinetic properties. To this end, a pharmacokinetic profile of the drug candidate, i.e. a profile of the pharmacokinetic parameters that affect the ability of a particular drug to treat a given condition, can be established. Pharmacokinetic parameters of the drug influencing the ability of a drug for treating a certain disease entity include, but are not limited to: half-life, volume of distribution, hepatic first-pass metabolism and the degree of blood serum binding. The efficacy of a given drug agent can be influenced by each of the parameters mentioned above.

“Half-life" means the time where 50% of an administered drug are eliminated through biological processes, e.g. metabolism, excretion, etc. By "hepatic first-pass metabolism" is meant the propensity of a drug to be metabolized upon first contact with the liver, i.e. during its first pass through the liver. “Volume of distribution" means the degree of retention of a drug throughout the various compartments of the body, like e.g. intracellular and extracellular spaces, tissues and organs, etc. and the distribution of the drug within these compartments. “Degree of blood serum binding" means the propensity of a drug to interact with and bind to blood serum proteins, such as albumin, leading to a reduction or loss of biological activity of the drug.

Pharmacokinetic parameters also include bioavailability, lag time (Tlag), Tmax, absorption rates, more onset and/or Cmax for a given amount of drug administered. “Bioavailability” means the amount of a drug in the blood compartment. “Lag time" means the time delay between the administration of the drug and its detection and measurability in blood or plasma. “Tmax” is the time after which maximal blood concentration of the drug is reached, and “Cmax” is the blood concentration maximally obtained with a given drug. The time to reach a blood or tissue concentration of the drug which is required for its biological effect is influenced by all

parameters. Pharmacokinetic parameters of bispecific antibody constructs exhibiting cross-species specificity, which may be determined in preclinical animal testing in non-chimpanzee primates as outlined above, are also set forth e.g. in the publication by Schlereth *et al.* (Cancer Immunol. Immunother. 20 (2005), 1-12).

One embodiment provides the antibody construct of the invention or the antibody construct produced according to the process of the invention for use in the prevention, treatment or amelioration of a tumor or cancer disease or of a metastatic cancer disease.

According to a preferred embodiment of the invention said tumor or cancer disease is a solid tumor disease.

The formulations described herein are useful as pharmaceutical compositions in the treatment, amelioration and/or prevention of the pathological medical condition as described herein in a patient in need thereof. The term "treatment" refers to both therapeutic treatment and prophylactic or preventative measures. Treatment includes the application or administration of the formulation to the body, an isolated tissue, or cell from a patient who has a disease/disorder, a symptom of a disease/disorder, or a predisposition toward a disease/disorder, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect the disease, the symptom of the disease, or the predisposition toward the disease.

The term “amelioration” as used herein refers to any improvement of the disease state of a patient having a tumor or cancer or a metastatic cancer as specified herein below, by the administration of an antibody construct according to the invention to a subject in need thereof. Such an improvement may also be seen as a slowing or stopping of the p progression of the tumor or cancer or metastatic cancer of the patient. The term “prevention” as used herein means the avoidance of the occurrence or re-occurrence of a patient having a tumor or cancer or a metastatic cancer as specified herein below, by the administration of an antibody construct according to the invention to a subject in need thereof.

The term “disease” refers to any condition that would benefit from treatment with the antibody construct or the pharmaceutic composition described herein. This includes chronic and acute disorders or diseases including those pathological conditions that predispose the mammal to the disease in question.

A “neoplasm” is is an abnormal growth of tissue, usually but not always forming a mass. When also forming a mass, it is commonly referred to as a “tumor”. Neoplasms or tumors or can be benign, potentially malignant (pre-cancerous), or malignant. Malignant neoplasms are commonly called cancer. They usually invade and destroy the surrounding tissue and may form metastases, i.e., they spread to other parts, tissues or organs of the body. Hence, the term “metatstatic cancer” encompasses metastases to other tissues or organs than the one of the original tumor. Lymphomas and leukemias are lymphoid neoplasms. For the purposes of the present invention, they are also encompassed by the terms “tumor” or “cancer”.

In a preferred embodiment of the invention, the tumor or cancer disease is a solid tumor disease and the metastatic cancer disease can be derived from any of the foregoing.

Preferred tumor or cancer diseases in conncetion with this invention are selected from a group consisting of breast cancer, Carcinoid, cervical cancer, colorectal cancer, endometrial cancer, gastric cancer, head and neck cancer, mesothelioma, liver cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, skin cancer, renal cancer and stomach cancer. More prefereably, the tumor or cancer disease, which is prefereably a solid tumor disease, can be selected from the group consisting of ovarian cancer, pancreatic cancer, mesothelioma, lung cancer, gastric cancer and triple negative breast cancer. The metastatic cancer disease can be derived from any of the foregoing.

The invention also provides a method for the treatment or amelioration of tumor or cancer disease or a metastatic cancer disease, comprising the step of administering to a subject in need thereof the antibody construct of the invention or the antibody construct produced according to the process of the invention.

The terms “subject in need” or those “in need of treatment" includes those already with the disorder, as well as those in which the disorder is to be prevented. The subject in need or "patient" includes human and other mammalian subjects that receive either prophylactic or therapeutic treatment.

The antibody construct of the invention will generally be designed for specific routes and methods of administration, for specific dosages and frequencies of administration, for specific treatments of specific diseases, with ranges of bio-availability and persistence, among other

things. The materials of the composition are preferably formulated in concentrations that are acceptable for the site of administration.

Formulations and compositions thus may be designed in accordance with the invention for delivery by any suitable route of administration. In the context of the present invention, the routes of administration include, but are not limited to

- topical routes (such as epicutaneous, inhalational, nasal, opthalmic, auricular / aural, vaginal, mucosal);
- enteral routes (such as oral, gastrointestinal, sublingual, sublabial, buccal, rectal); and
- parenteral routes (such as intravenous, intraarterial, intraosseous, intramuscular, intracerebral, intracerebroventricular, epidural, intrathecal, subcutaneous, intraperitoneal, extra-amniotic, intraarticular, intracardiac, intradermal, intralesional, intrauterine, intravesical, intravitreal, transdermal, intranasal, transmucosal, intrasynovial, intraluminal).

The pharmaceutical compositions and the antibody construct of this invention are particularly useful for parenteral administration, e.g., subcutaneous or intravenous delivery, for example by injection such as bolus injection, or by infusion such as continuous infusion. Pharmaceutical compositions may be administered using a medical device. Examples of medical devices for administering pharmaceutical compositions are described in U.S. Patent Nos. 4,475,196; 4,439,196; 4,447,224; 4,447, 233; 4,486,194; 4,487,603; 4,596,556; 4,790,824; 4,941,880; 5,064,413; 5,312,335; 5,312,335; 5,383,851; and 5,399,163.

In particular, the present invention provides for an uninterrupted administration of the suitable composition. As a non-limiting example, uninterrupted or substantially uninterrupted, *i.e.* continuous administration may be realized by a small pump system worn by the patient for metering the influx of therapeutic agent into the body of the patient. The pharmaceutical composition comprising the antibody construct of the invention can be administered by using said pump systems. Such pump systems are generally known in the art, and commonly rely on periodic exchange of cartridges containing the therapeutic agent to be infused. When exchanging the cartridge in such a pump system, a temporary interruption of the otherwise uninterrupted flow of therapeutic agent into the body of the patient may ensue. In such a case, the phase of administration prior to cartridge replacement and the phase of administration following cartridge replacement would still be considered within the meaning of the

pharmaceutical means and methods of the invention together make up one “uninterrupted administration” of such therapeutic agent.

The continuous or uninterrupted administration of the antibody constructs of the invention may be intravenous or subcutaneous by way of a fluid delivery device or small pump system including a fluid driving mechanism for driving fluid out of a reservoir and an actuating mechanism for actuating the driving mechanism. Pump systems for subcutaneous administration may include a needle or a cannula for penetrating the skin of a patient and delivering the suitable composition into the patient’s body. Said pump systems may be directly fixed or attached to the skin of the patient independently of a vein, artery or blood vessel, thereby allowing a direct contact between the pump system and the skin of the patient. The pump system can be attached to the skin of the patient for 24 hours up to several days. The pump system may be of small size with a reservoir for small volumes. As a non-limiting example, the volume of the reservoir for the suitable pharmaceutical composition to be administered can be between 0.1 and 50 ml.

The continuous administration may also be transdermal by way of a patch worn on the skin and replaced at intervals. One of skill in the art is aware of patch systems for drug delivery suitable for this purpose. It is of note that transdermal administration is especially amenable to uninterrupted administration, as exchange of a first exhausted patch can advantageously be accomplished simultaneously with the placement of a new, second patch, for example on the surface of the skin immediately adjacent to the first exhausted patch and immediately prior to removal of the first exhausted patch. Issues of flow interruption or power cell failure do not arise.

If the pharmaceutical composition has been lyophilized, the lyophilized material is first reconstituted in an appropriate liquid prior to administration. The lyophilized material may be reconstituted in, e.g., bacteriostatic water for injection (BWFI), physiological saline, phosphate buffered saline (PBS), or the same formulation the protein had been in prior to lyophilization.

The compositions of the present invention can be administered to the subject at a suitable dose which can be determined e.g. by dose escalating studies by administration of increasing doses of the antibody construct of the invention exhibiting cross-species specificity described herein to non-chimpanzee primates, for instance macaques. As set forth above, the antibody construct of the invention exhibiting cross-species specificity described herein can be advantageously used in identical form in preclinical testing in non-chimpanzee primates and as drug in humans. The

dosage regimen will be determined by the attending physician and clinical factors. As is well known in the medical arts, dosages for any one patient depend upon many factors, including the patient's size, body surface area, age, the particular compound to be administered, sex, time and route of administration, general health, and other drugs being administered concurrently.

The term “effective dose” or “effective dosage” is defined as an amount sufficient to achieve or at least partially achieve the desired effect. The term “therapeutically effective dose” is defined as an amount sufficient to cure or at least partially arrest the disease and its complications in a patient already suffering from the disease. Amounts or doses effective for this use will depend on the condition to be treated (the indication), the delivered antibody construct, the therapeutic context and objectives, the severity of the disease, prior therapy, the patient's clinical history and response to the therapeutic agent, the route of administration, the size (body weight, body surface or organ size) and/or condition (the age and general health) of the patient, and the general state of the patient's own immune system. The proper dose can be adjusted according to the judgment of the attending physician such that it can be administered to the patient once or over a series of administrations, and in order to obtain the optimal therapeutic effect.

A typical dosage may range from about 0.1 µg/kg to up to about 30 mg/kg or more, depending on the factors mentioned above. In specific embodiments, the dosage may range from 1.0 µg/kg up to about 20 mg/kg, optionally from 10 µg/kg up to about 10 mg/kg or from 100 µg/kg up to about 5 mg/kg.

A therapeutic effective amount of an antibody construct of the invention preferably results in a decrease in severity of disease symptoms, an increase in frequency or duration of disease symptom-free periods or a prevention of impairment or disability due to the disease affliction. For treating MSLN-expressing tumors, a therapeutically effective amount of the antibody construct of the invention, e.g. an anti- MSLN /anti-CD3 antibody construct, preferably inhibits cell growth or tumor growth by at least about 20%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% relative to untreated patients. The ability of a compound to inhibit tumor growth may be evaluated in an animal model predictive of efficacy in human tumors.

The pharmaceutical composition can be administered as a sole therapeutic or in combination with additional therapies such as anti-cancer therapies as needed, e.g. other proteinaceous and non-proteinaceous drugs. These drugs may be administered simultaneously with the

composition comprising the antibody construct of the invention as defined herein or separately before or after administration of said antibody construct in timely defined intervals and doses.

The term “effective and non-toxic dose” as used herein refers to a tolerable dose of an inventive antibody construct which is high enough to cause depletion of pathologic cells, tumor elimination, tumor shrinkage or stabilization of disease without or essentially without major toxic effects. Such effective and non-toxic doses may be determined *e.g.* by dose escalation studies described in the art and should be below the dose inducing severe adverse side events (dose limiting toxicity, DLT).

The term “toxicity” as used herein refers to the toxic effects of a drug manifested in adverse events or severe adverse events. These side events might refer to a lack of tolerability of the drug in general and/or a lack of local tolerance after administration. Toxicity could also include teratogenic or carcinogenic effects caused by the drug.

The term “safety”, “*in vivo* safety” or “tolerability” as used herein defines the administration of a drug without inducing severe adverse events directly after administration (local tolerance) and during a longer period of application of the drug. “Safety”, “*in vivo* safety” or “tolerability” can be evaluated e.g. at regular intervals during the treatment and follow-up period. Measurements include clinical evaluation, e.g. organ manifestations, and screening of laboratory abnormalities. Clinical evaluation may be carried out and deviations to normal findings recorded/coded according to NCI-CTC and/or MedDRA standards. Organ manifestations may include criteria such as allergy/immunology, blood/bone marrow, cardiac arrhythmia, coagulation and the like, as set forth *e.g.* in the Common Terminology Criteria for adverse events v3.0 (CTCAE). Laboratory parameters which may be tested include for instance hematology, clinical chemistry, coagulation profile and urine analysis and examination of other body fluids such as serum, plasma, lymphoid or spinal fluid, liquor and the like. Safety can thus be assessed e.g. by physical examination, imaging techniques (i.e. ultrasound, x-ray, CT scans, Magnetic Resonance Imaging (MRI), other measures with technical devices (i.e. electrocardiogram), vital signs, by measuring laboratory parameters and recording adverse events. For example, adverse events in non-chimpanzee primates in the uses and methods according to the invention may be examined by histopathological and/or histochemical methods.

The above terms are also referred to *e.g.* in the Preclinical safety evaluation of biotechnology-derived pharmaceuticals S6; ICH Harmonised Tripartite Guideline; ICH Steering Committee meeting on July 16, 1997.

In a further embodiment, the invention provides a kit comprising an antibody construct of the invention, an antibody construct produced according to the process of the invention, a polynucleotide of the invention, a vector of the invention, and/or a host cell of the invention.

In the context of the present invention, the term "kit" means two or more components – one of which corresponding to the antibody construct, the pharmaceutical composition, the vector or the host cell of the invention – packaged together in a container, recipient or otherwise. A kit can hence be described as a set of products and/or utensils that are sufficient to achieve a certain goal, which can be marketed as a single unit.

The kit may comprise one or more recipients (such as vials, ampoules, containers, syringes, bottles, bags) of any appropriate shape, size and material (preferably waterproof, *e.g.* plastic or glass) containing the antibody construct or the pharmaceutical composition of the present invention in an appropriate dosage for administration (see above). The kit may additionally contain directions for use (*e.g.* in the form of a leaflet or instruction manual), means for administering the antibody construct of the present invention such as a syringe, pump, infuser or the like, means for reconstituting the antibody construct of the invention and/or means for diluting the antibody construct of the invention.

The invention also provides kits for a single-dose administration unit. The kit of the invention may also contain a first recipient comprising a dried / lyophilized antibody construct and a second recipient comprising an aqueous formulation. In certain embodiments of this invention, kits containing single-chambered and multi-chambered pre-filled syringes (*e.g.*, liquid syringes and lyosyringes) are provided.

The Figures show:

Figure 1:

Schematic representation of the human-mouse MSLN chimera. The MSLN chimera were generated with 6 distinct sequence stretch exchanges from human to mouse MSLN. Respective variants were expressed on the surface of CHO cell clones (E1-E6). See Example 1.

Figure 2

Cross-Reactivity of anti-MSLN antibody constructs as detected by flow cytometry: binding to human and macaque MSLN and CD3. See Example 4.

Figure 3

Analysis of anti-MSLN antibody constructs by flow cytometry: binding to human variants v2 and v6. See Example 4.

Figure 4

The potency of MSLNxCD3 bispecific antibody constructs in redirecting stimulated human CD8+ effector T cells against human MSLN-transfected CHO cells was measured in an 18 hour ^{51}Cr release assay(Effector target ration 10:1).

Figure 5

The potency of MSLNxCD3 bispecific antibody constructs in redirecting stimulated human CD8+ effector T cells against the MSLN positive OVCAR-8 was measured in an 18 hour ^{51}Cr release assay(Effector target ration 10:1).

Figure 6

The potency of MSLNxCD3 bispecific antibody constructs in redirecting the T cells in unstimulated human PBMC ($CD14^-/CD56^-$) against human MSLN-transfected CHO cells in the absence and presence of soluble MSLN was measured in a 48 hour FACS-based cytotoxicity assay (Effector target ration 10:1).

Figure 7

The potency of MSLNxCD3 bispecific antibody constructs in redirecting the T cells in unstimulated human PBMC ($CD14^-/CD56^-$) against the MSLN-positive human cell line OVCAR-8 was measured in a 48 hour FACS-based cytotoxicity assay.

Figure 8

Confirmation of the cross-reactive MSLNxCD3 bispecific antibody constructs are capable of redirecting macaque T cells against macaque MSLN-transfected CHO cells, a 48 hour FACS-based cytotoxicity assay was performed with a macaque T cell line LnPx4119 as effector T cells(Effector target ration 10:1).

Figure 9

Potency gap between the monomeric and the dimeric isoforms of MSLNxCD3 bispecific antibody constructs in redirecting the T cells in stimulated human CD8+ effector T cells against human MSLN-transfected CHO cells was measured in an 18 hour ^{51}Cr release assay(Effector target ration 10:1).

Figure 10

Stability of MSLNxCD3 bispecific antibody constructs after incubation for 96 hours in human plasma. 18-hour ^{51}Cr based assay. Effector cells: stimulated enriched human CD8 T cells.

Target cells: hu MSLN transfected CHO cells. Effector to target cell (E:T) ratio: 10:1. BiTE protein as indicated.

Figure 11

The protein homogeneity of the antibody constructs of the invention analyzed High Resolution Cation Exchange Chromatography CIEX

Figure 12

The surface hydrophobicity of bispecific antibody constructs of the invention tested in Hydrophobic Interaction Chromatography HIC in flow-through mode

Figure 13

Monomer to dimer conversion after three freeze/thaw cycles.

Figure 14

Monomer to dimer conversion after 7 days of incubation at 250 µg/ml

Figure 15: Evaluation of Target-independent T Cell Activation by Mesothelin (MS) HLE BiTE® antibody constructs. 2(a) antibody construct of the invention in 48 h activation assay with human PBMC (3x); HLE BiTE®serial dilutions (start 20 nM; 1:5, 7x+blank); w/o or with FcR blocking [10 mg/mL huIgG (Kiovog, Baxter)]; FACS measurement of CD69 and CD25 [not shown] expression on $CD4^+$, $CD8^+$ T cells. 2(b) Hetero-Fc antibody construct in 48 h activation assay with human PBMC and $CD14^+/CD33^+$ cell depleted PBMC (3x); HLE BiTE® serial dilutions (start 20 nM; 1:5, 7x+blank); FACS measurement of CD69 and CD25 [not shown] expression on $CD4^+$, $CD8^+$ T cells.

Figure 16: Evaluation of Target-independent T Cell Activation by CDH19 HLE BiTE® antibody constructs. 3(a) antibody construct of the invention in 48 h activation assay with human PBMC (3x); HLE BiTE® serial dilutions (start 20 nM; 1:5, 7x+blank); w/o or with FcR blocking [10 mg/mL huIgG (Kiovog, Baxter)]; FACS measurement of CD69 and CD25 [not shown] expression on $CD4^+$, $CD8^+$ T cells. 3(b) Hetero-Fc antibody construct in 48 h activation assay with human PBMC and $CD14^+/CD33^+$ cell depleted PBMC (3x); HLE BiTE® serial dilutions (start 20 nM; 1:5, 7x+blank); FACS measurement of CD69 and CD25 [not shown] expression on $CD4^+$, $CD8^+$ T cells. 3(c) X-body construct in 48 h activation assay with human PBMC and $CD14^+/CD33^+$ cell depleted PBMC (3x); HLE BiTE® serial dilutions (start 20 nM; 1:5, 7x+blank); FACS measurement of CD69 and CD25 [not shown] expression on $CD4^+$, $CD8^+$ T cells.

Figure 17: Complement C1q Binding of BiTE® Fc fusion antibody constructs. BiTE® Fc fusion antibody constructs (BiTE® single chain Fc (triangle), BiTE® hetero Fc (squares), canonical BiTE® (circle)) were coated on a Maxisorp plate (in dilution series), prior to incubation with pooled human serum and incubation with polyclonal anti human CC1q murine antibody, visualized by goat anti-mouse Fc-AP conjugate.

Figure 18: Mean PK profiles of four pairs of BiTE®-HLE fusion proteins after single dose administration in cynomolgus monkeys. For reasons of comparability, serum concentrations were dose-normalized to 15 µg/kg and indicated in nmol.

Figure 19: Mean PK profiles of five different BiTE® antibody constructs, each fused to a scFc half-life extending moiety. For reasons of comparability, serum concentrations were dose-normalized to 15 µg/kg and indicated in nmol.

Examples:

The following examples illustrate the invention. These examples should not be construed as to limit the scope of this invention. The present invention is limited only by the claims.

Example 1

Generation of CHO cells expressing wild type and chimeric MSLN

The MSLN antigen can be subdivided into six different sub-domains or regions that are defined, for the purposes of Examples 1 and 2. The aa sequence of those six sub-domains is depicted in SEQ ID NOs: 238-243.

The following molecules were generated; see also Figure 1:

- hu orl MSLN-E1 mu SEQ ID NO: 246
- hu orl MSLN-E2 mu SEQ ID NO: 247
- hu orl MSLN-E3 mu SEQ ID NO: 248
- hu orl MSLN-E4 mu SEQ ID NO: 249
- hu orl MSLN-E5 mu SEQ ID NO: 250
- hu orl MSLN-E6 mu SEQ ID NO: 251
- hu orl MSLN- full human SEQ ID NO: 231

For the generation of CHO cells expressing human, cynomolgus macaque ("cyno") and truncated human N-terminal V5 tagged MSLN, the respective coding sequences for human MSLN (SEQ ID NO: 231; see also GeneBank accession number NM_005823), cyno MSLN (SEQ ID NO: 234, see LMR C52457) and the six cimeric human/murine MSLN versions (see above) were cloned into a plasmid designated pEF-DHFR (pEF-DHFR is described in Raum *et al.* Cancer Immunol Immunother 50 (2001) 141-150). For cell surface expression of human and cyno MSLN the original signal peptide was used. All cloning procedures were carried out according to standard protocols (Sambrook, Molecular Cloning; A Laboratory Manual, 3rd edition, Cold Spring Harbour Laboratory Press, Cold Spring Harbour, New York (2001)). For

each construct, a corresponding plasmid was transfected into DHFR deficient CHO cells for eukaryotic expression, as described by Kaufman R.J. (1990) Methods Enzymol. 185, 537-566. The expression of human, chimeric and cyno MSLN on CHO cells was verified in a FACS assay using a monoclonal mouse IgG2b anti-human MSLN antibody. As negative control, cells were incubated with isotype control antibody instead of the first antibody. The samples were measured by flow cytometry.

Example 2

Epitope mapping of anti-MSLN antibody constructs

Cells transfected with human MSLN and with the chimeric human MSLN molecules (see Example 1) were stained with crude, undiluted periplasmic extract containing bispecific MSLNxCD3 antibody constructs (with the CD3 binding domain being denominated I2C) fused to a human albumin (variant 1), in PBS/1,5%FCS. Bound molecules were detected with an in-house mouse monoclonal anti-CD3 binding domain antibody (50 µl) followed by an anti-mouse IgG Fc-gamma-PE (1:100, 50 µl; Jackson Immunoresearch # 115-116-071) All antibodies were diluted in PBS / 1.5% FCS. As negative control, cells were incubated with PBS / 2% FCS instead of the periplasmic extract. The samples were measured by flow cytometry.

The regions that were recognized by the respective MSLN binding domains are indicated in the sequence table (Table 2). Loss of the FACS signal in the respective chimeric MSLN constructs comprising the murine epitope cluster was the read out for the relevance of the respective cluster for the binding. In case the FACS signal was negatively impacted for more than one, respectively two, chimeric MSLN clone, it was concluded that both cluster are relevant.

Table 2: Mapping of the epitope clusters for MS-1 to MS-8

Epitope cluster	Binder
E 1+2	MS-1
E 2+3	MS-2
E 2+3	MS-3
E 2+3	MS-4
E 2+3	MS-5
E 2+3	MS-6
E 4	MS-7
E 1+2	MS-8

Example 3

Scatchard-based analysis of MSLNxCD3 bispecific antibody construct affinity to human and macaque MSLN on target antigen positive cells and determination of the interspecies affinity gap

The affinities of MSLNxCD3 bispecific antibody constructs to CHO cells transfected with human or macaque MSLN were also determined by Scatchard analysis as the most reliable method for measuring potential affinity gaps between human and macaque MSLN. For the Scatchard analysis, saturation binding experiments are performed using a monovalent detection system to precisely determine monovalent binding of the MSLNxCD3 bispecific antibody constructs to the respective cell line.

2 x 10^4 cells of the respective cell line (recombinantly human MSLN-expressing CHO cell line, recombinantly macaque MSLN-expressing CHO cell line) were incubated each with 50 µl of a triplet dilution series (twelve dilutions at 1:2) of the respective MSLNxCD3 bispecific antibody construct (until saturation is reached) starting at 10-20 nM followed by 16 h incubation at 4°C under agitation and one residual washing step. Then, the cells were incubated for another hour with 30 µl of a CD3xALEXA488 conjugate solution. After one washing step, the cells were resuspended in 150 µl FACS buffer containing 3.5 % formaldehyde, incubated for further 15 min, centrifuged, resuspended in FACS buffer and analyzed using a FACS CantoII machine and FACS Diva software. Data were generated from two independent sets of experiments, each using triplicates. Respective Scatchard analysis was calculated to extrapolate maximal binding (Bmax). The concentrations of MSLNxCD3 bispecific antibody constructs at half-maximal binding were determined reflecting the respective KDs. Values of triplicate measurements were plotted as hyperbolic curves and as S-shaped curves to demonstrate proper concentration ranges from minimal to optimal binding.

Values depicted in Table 3 were derived from two independent experiments per MSLNxCD3 bispecific antibody construct. Cell based Scatchard analysis confirmed that the MSLNxCD3 bispecific antibody constructs of the invention are subnanomolar in affinity to human MSLN and to mac MSLN and present with a small cyno/human interspecies affinity gap of around 1.

Table 3: Affinities (KD) of MSLNxCD3 bispecific antibody constructs as determined in cell based Scatchard analysis with the calculated affinity gap KD macaque MSLN / KD human MSLN. Antibody constructs were measured in two independent experiments, each using triplicates.

BiTE antibody MS x I2C-HALB	**Cell based affinity hu MSLN* [nM]**	**Cell based affinity mac MSLN* [nM]**	**Affinity gap KD^{mac}/ KD^{hu} MSLN**
MS-1	**1.25** ± 0.8	**13.86** ± 2.9	**11.08**
MS-8	**4.68** ± 0.4	**85.86** ± 16.7	**18.35**
MS-2	**1.40** ± 0.9	**10.16** ± 3.5	**7.28**
MS-3	**0.74** ± 0.8	**0.82** ± 0.5	**1.12**
MS-4	**0.91** ± 1.0	**0.77** ± 0.7	**0.85**

MS-5	**0.39** ± 0.3	**2.31** ± 3.7	**5.91**
MS-6	**0.60** ± 0.3	**9.03** ± 3.7	**15.04**
MS-7	**1.06** ± 0.5	**4.07** ± 1.0	**3.86**

Example 4

Bispecific binding and interspecies cross-reactivity

For confirmation of binding to human MSLN and CD3 and to cyno MSLN and CD3, bispecific antibody constructs of the invention were tested by flow cytometry using

- CHO cells transfected with human MSLN, with human MSLN isoform (NM_013404=SEQ ID NO:232 and AY743922=SEQ ID NO:233), and with macaque MSLN, respectively,
- the human MSLN positive human cell line OVCAR-8,
- CD3-expressing human T cell leukemia cell line HPB-all (DSMZ, Braunschweig, ACC483), and
- the cynomolgus CD3-expressing T cell line LnPx 4119

For flow cytometry 200,000 cells of the respective cell lines were incubated for 60 min at 4°C with 50 µl of purified bispecific antibody construct at a concentration of 5 µg/ml. The cells were washed twice in PBS/2% FCS and then incubated with an in-house mouse antibody (2 µg/ml) specific for the CD3 binding part of the bispecific antibody constructs for 30 min at 4°C. After washing, bound mouse antibodies were detected with a goat anti-mouse Fcγ-PE (1:100) for 30 min at 4°C. Samples were measured by flow cytometry. Non-transfected CHO cells were used as negative control.

The results are shown in Figures 2 and 3. The MSLNxCD3 bispecific antibody constructs of the invention stained CHO cells transfected with human MSLN, the artificial MSLN isoform and with cyno MSLN, and they also stained the human MSLN positive human cell line OVCAR-8 (natural expresser). Human and cyno T cell lines expressing CD3 were also recognized by the bispecific antibody constructs. Moreover, there was no staining of the negative control cells (non-transfected CHO).

Example 5

Cytotoxic activity

The potency of MSLNxCD3 bispecific antibody constructs of the invention in redirecting effector T cells against MSLN-expressing target cells was analyzed in five *in vitro* cytotoxicity assays:

- The potency of MSLNxCD3 bispecific antibody constructs in redirecting stimulated human CD8+ effector T cells against human MSLN-transfected CHO cells was

measured in an 18 hour ^{51}Cr release assay(Effector target ration 10:1). Figure 4 and Table 4

- The potency of MSLNxCD3 bispecific antibody constructs in redirecting stimulated human CD8+ effector T cells against the MSLN positive cell line OVCAR-8 was measured in an 18 hour ^{51}Cr release assay(Effector target ration 10:1). Figure 5 Table 5
- The potency of MSLNxCD3 bispecific antibody constructs in redirecting the T cells in unstimulated human PBMC ($CD14^-/CD56^-$) against human MSLN-transfected CHO cells in the absence and presence of soluble MSLN was measured in a 48 hour FACS-based cytotoxicity assay (Effector target ration 10:1). Figure 6 and Table 6
- The potency of MSLNxCD3 bispecific antibody constructs in redirecting the T cells in unstimulated human PBMC ($CD14^-/CD56^-$) against the MSLN-positive human cell line OVCAR-8 was measured in a 48 hour FACS-based cytotoxicity assay. Figure 7
- For confirmation that the cross-reactive MSLNxCD3 bispecific antibody constructs are capable of redirecting macaque T cells against macaque MSLN-transfected CHO cells, a 48 hour FACS-based cytotoxicity assay was performed with a macaque T cell line LnPx4119 as effector T cells(Effector target ration 10:1). Figure 8
- Potency gap between the monomeric and the dimeric isoforms of MSLNxCD3 bispecific antibody constructs in redirecting the T cells in stimulated human CD8+ effector T cells against human MSLN-transfected CHO cells was measured in an 18 hour ^{51}Cr release assay(Effector target ration 10:1). Figure 9

Example 5.1

Chromium release assay with stimulated human T cells

Stimulated T cells enriched for $CD8^+$ T cells were obtained as described in the following. A petri dish (145 mm diameter, Greiner bio-one GmbH, Kremsmünster) was coated with a commercially available anti-CD3 specific antibody (OKT3, Orthoclone) in a final concentration of 1 µg/ml for 1 hour at 37°C. Unbound protein was removed by one washing step with PBS. 3 – 5 x 10^7 human PBMC were added to the precoated petri dish in 120 ml of RPMI 1640 with stabilized glutamine / 10% FCS / IL-2 20 U/ml (Proleukin®, Chiron) and stimulated for 2 days. On the third day, the cells were collected and washed once with RPMI 1640. IL-2 was added to a final concentration of 20 U/ml and the cells were cultured again for one day in the same cell culture medium as above. $CD8^+$ cytotoxic T lymphocytes (CTLs) were enriched by depletion of $CD4^+$ T cells and $CD56^+$ NK cells using Dynal-Beads according to the manufacturer's protocol.

Cyno MSLN- or human MSLN-transfected CHO target cells were washed twice with PBS and labeled with 11.1 MBq ^{51}Cr in a final volume of 100 µl RPMI with 50% FCS for 60 minutes at

37°C. Subsequently, the labeled target cells were washed 3 times with 5 ml RPMI and then used in the cytotoxicity assay. The assay was performed in a 96-well plate in a total volume of 200 µl supplemented RPMI with an E:T ratio of 10:1. A starting concentration of 0.01 – 1 µg/ml of purified bispecific antibody construct and threefold dilutions thereof were used. Incubation time for the assay was 18 hours. Cytotoxicity was determined as relative values of released chromium in the supernatant relative to the difference of maximum lysis (addition of Triton-X) and spontaneous lysis (without effector cells). All measurements were carried out in quadruplicates. Measurement of chromium activity in the supernatants was performed in a Wizard 3'' gamma counter (Perkin Elmer Life Sciences GmbH, Köln, Germany). Analysis of the results was carried out with Prism 5 for Windows (version 5.0, GraphPad Software Inc., San Diego, California, USA). EC50 values calculated by the analysis program from the sigmoidal dose response curves were used for comparison of cytotoxic activity.

Example 5.2

Potency of redirecting stimulated human effector T cells against human MSLN-transfected CHO cells

The cytotoxic activity of MSLNxCD3 bispecific antibody constructs according to the invention was analyzed in a 51-chromium (^{51}Cr) release cytotoxicity assay using CHO cells transfected with human MSLN as target cells, and stimulated human CD8+ T cells as effector cells. The experiment was carried out as described in Example 8.1.

The results are shown in Table 4. The MSLNxCD3 bispecific antibody constructs showed very potent cytotoxic activity against human MSLN transfected CHO cells in the 1-digit picomolar range.

Table 4: EC50 values [pM] of MSLNxCD3 bispecific antibody constructs analyzed in a 51-chromium (^{51}Cr) release cytotoxicity assay using CHO cells transfected with human MSLN as target cells, and stimulated human CD8 T cells as effector cells.

BiTE x I2C-HALB	EC50 [pM]
MS 1	1.5
MS 8	6.5
MS 2	2.0
MS 3	0.2
MS 4	0.1

MS 5	0.2
MS 6	0.5
MS 7	6.0

Example 5.3

Potency of redirecting stimulated human effector T cells against the MSLN positive human cell line OVCAR-8

The cytotoxic activity of MSLNxCD3 bispecific antibody constructs was analyzed in a 51-chromium (^{51}Cr) release cytotoxicity assay using the MSLN-positive human cell line OVCAR-8 as source of target cells, and stimulated human CD8+ T cells as effector cells. The assay was carried out as described in Example 8.1.

In accordance with the results of the 51-chromium release assays with stimulated enriched human CD8+ T lymphocytes as effector cells and human MSLN-transfected CHO cells as target cells, MSLNxCD3 bispecific antibody constructs of the present invention are also potent in cytotoxic activity against natural expresser target cells (see Table 5).

Table 5: EC50 values [pM] of MSLNxCD3 bispecific antibody constructs analyzed in an 18-hour 51-chromium (^{51}Cr) release cytotoxicity assay with the MSLN-positive human cell line OVCAR-8 as source of target cells, and stimulated enriched human CD8 T cells as effector cells.

BiTE x I2C-HALB	EC50 [pM]
MS 1	0.2
MS 8	1.3
MS 2	0.8
MS 3	0.1
MS 4	0.1
MS 5	0.3
MS 6	0.2
MS 7	0.5

Example 5.4

FACS-based cytotoxicity assay with unstimulated human PBMC

Isolation of effector cells

Human peripheral blood mononuclear cells (PBMC) were prepared by Ficoll density gradient centrifugation from enriched lymphocyte preparations (buffy coats), a side product of blood banks collecting blood for transfusions. Buffy coats were supplied by a local blood bank and PBMC were prepared on the same day of blood collection. After Ficoll density centrifugation and extensive washes with Dulbecco's PBS (Gibco), remaining erythrocytes were removed from PBMC via incubation with erythrocyte lysis buffer (155 mM NH_4Cl, 10 mM $KHCO_3$, 100 µM EDTA). Platelets were removed via the supernatant upon centrifugation of PBMC at 100 x g. Remaining lymphocytes mainly encompass B and T lymphocytes, NK cells and monocytes. PBMC were kept in culture at 37°C/5% CO_2 in RPMI medium (Gibco) with 10% FCS (Gibco).

Depletion of $CD14^+$ and $CD56^+$ cells

For depletion of $CD14^+$ cells, human CD14 MicroBeads (Milteny Biotec, MACS, #130-050-201) were used, for depletion of NK cells human CD56 MicroBeads (MACS, #130-050-401). PBMC were counted and centrifuged for 10 min at room temperature with 300 x g. The supernatant was discarded and the cell pellet resuspended in MACS isolation buffer [80 µL/ 10^7 cells; PBS (Invitrogen, #20012-043), 0.5% (v/v) FBS (Gibco, #10270-106), 2 mM EDTA (Sigma-Aldrich, #E-6511)]. CD14 MicroBeads and CD56 MicroBeads (20 µL/10^7 cells) were added and incubated for 15 min at 4 - 8°C. The cells were washed with MACS isolation buffer (1 - 2 mL/10^7 cells). After centrifugation (see above), supernatant was discarded and cells resuspended in MACS isolation buffer (500 µL/10^8 cells). CD14/CD56 negative cells were then isolated using LS Columns (Miltenyi Biotec, #130-042-401). PBMC w/o CD14+/CD56+ cells were cultured in RPMI complete medium i.e. RPMI1640 (Biochrom AG, #FG1215) supplemented with 10% FBS (Biochrom AG, #S0115), 1x non-essential amino acids (Biochrom AG, #K0293), 10 mM Hepes buffer (Biochrom AG, #L1613), 1 mM sodium pyruvate (Biochrom AG, #L0473) and 100 U/mL penicillin/streptomycin (Biochrom AG, #A2213) at 37°C in an incubator until needed.

Target cell labeling

For the analysis of cell lysis in flow cytometry assays, the fluorescent membrane dye $DiOC_{18}$ (DiO) (Molecular Probes, #V22886) was used to label human MSLN- or macaque MSLN-transfected CHO cells as target cells and distinguish them from effector cells. Briefly, cells were harvested, washed once with PBS and adjusted to 10^6 cell/mL in PBS containing 2 % (v/v) FBS and the membrane dye DiO (5 µL/10^6 cells). After incubation for 3 min at 37°C, cells were washed twice in complete RPMI medium and the cell number adjusted to 1.25 x 10^5 cells/mL. The vitality of cells was determined using 0.5 % (v/v) isotonic EosinG solution (Roth, #45380).

Flow cytometry based analysis

This assay was designed to quantify the lysis of cyno or human MSLN-transfected CHO cells in the presence of serial dilutions of MSLN bispecific antibody constructs. Equal volumes of DiO-

labeled target cells and effector cells (i.e., PBMC w/o $CD14^+$ cells) were mixed, resulting in an E:T cell ratio of 10:1. 160 µl of this suspension were transferred to each well of a 96-well plate. 40 µL of serial dilutions of the MSLNxCD3 bispecific antibody constructs and a negative control bispecific (a CD3-based bispecific antibody construct recognizing an irrelevant target antigen) or RPMI complete medium as an additional negative control were added. The bispecific antibody-mediated cytotoxic reaction proceeded for 48 hours in a 7% CO_2 humidified incubator. Then cells were transferred to a new 96-well plate and loss of target cell membrane integrity was monitored by adding propidium iodide (PI) at a final concentration of 1 µg/mL. PI is a membrane impermeable dye that normally is excluded from viable cells, whereas dead cells take it up and become identifiable by fluorescent emission.

Samples were measured by flow cytometry on a FACSCanto II instrument and analyzed by FACSDiva software (both from Becton Dickinson). Target cells were identified as DiO-positive cells. PI-negative target cells were classified as living target cells. Percentage of cytotoxicity was calculated according to the following formula:

$$\text{Cytotoxicity}[\%] = \frac{n_{\text{dead target cells}}}{n_{\text{target cells}}} \times 100$$

n = number of events

Using GraphPad Prism 5 software (Graph Pad Software, San Diego), the percentage of cytotoxicity was plotted against the corresponding bispecific antibody construct concentrations. Dose response curves were analyzed with the four parametric logistic regression models for evaluation of sigmoid dose response curves with fixed hill slope and EC50 values were calculated.

Example 5.5

Potency of redirecting unstimulated human PBMC against human MSLN-transfected CHO cells in absence and presence of soluble MSLN

The cytotoxic activity of MSLNxCD3 bispecific antibody constructs was analyzed in a FACS-based cytotoxicity assay using CHO cells transfected with human MSLN as target cells, and unstimulated human PBMC as effector cells. The assay was carried out as described in Example 8.4 above.

The results of the FACS-based cytotoxicity assays with unstimulated human PBMC as effector cells and human MSLN-transfected CHO cells as targets are shown in Table 7.

Table 6: Cytotoxic Activity of Unstimulated Human PBMC Against Human MSLN-transfected CHO Cells in absence and presence of soluble MSLN

	w/o sMSLN	with 50 ng/ml sMSLN	with 400 ng/ml sMSLN
BiTE x I2C-HALB	**EC50 [pM]**	**EC50 [pM]**	**EC50 [pM]**
MS-1	12	53	215
MS-8	3.4	8.3	39
MS-2	2.4	2.9	6.3
MS-3	1.2	3.0	16
MS-4	1.5	3.9	11
MS-5	1.0	2.2	11
MS-6	1.1	2.6	12
MS-7	8.1	28	166

Expectedly, EC50 values were generally higher in cytotoxicity assays with unstimulated PBMC as effector cells compared with cytotoxicity assays using stimulated human CD8+ T cells (see Example 8.2).

Example 5.6

Potency of redirecting unstimulated human PBMC against the MSLN-positive cell line OVCAR-8 cells

The cytotoxic activity of MSLNxCD3 bispecific antibody constructs was furthermore analyzed in a FACS-based cytotoxicity assay using the MSLN-positive human cell line OVCAR-8 as a source of target cells and unstimulated human PBMC as effector cells. The assay was carried out as described in Example 8.4 above. The results are shown in Table 7.

Table 7: EC50 values [pM] of MSLNxCD3 bispecific antibody constructs as measured in a 48-hour FACS-based cytotoxicity assay with unstimulated human PBMC as effector cells and the human cell line OVCAR-8 as source of target cells.

BiTE x I2C-HALB	EC50 [pM]
MS 1	5.9
MS 8	13
MS 2	18
MS 3	1.5

MS 4	2.0
MS 5	1.9
MS 6	2.3
MS 7	9.7

Example 5.7

Potency of redirecting macaque T cells against macaque MSLN-expressing CHO cells

The cytotoxic activity of MSLNxCD3 bispecific antibody constructs was analyzed in a FACS-based cytotoxicity assay using CHO cells transfected with macaque (cyno) MSLN as target cells, and the macaque T cell line 4119LnPx (Knappe et al. Blood 95:3256-61 (2000)) as source of effector cells. Target cell labeling of macaque MSLN-transfected CHO cells and flow cytometry based analysis of cytotoxic activity was performed as described above.

Results are shown in Table 8. Macaque T cells from cell line 4119LnPx were induced to efficiently kill macaque MSLN-transfected CHO cells by MSLNxCD3 bispecific antibody constructs of the invention.

Table 8: EC50 values [pM] of MSLNxCD3 bispecific as measured in a 48-hour FACS-based cytotoxicity assay with macaque T cell line 4119LnPx as effector cells and CHO cells transfected with macaque MSLN as target cells.

BiTE x I2C-HALB	EC50 [pM]
MS 1	434
MS 8	1589
MS 2	583
MS 3	56
MS 4	67
MS 5	85
MS 6	100
MS 7	1791

Example 5.8

Potency gap between the monomeric and the dimeric isoform of bispecific antibody constructs

In order to determine the difference in cytotoxic activity between the monomeric and the dimeric isoform of individual MSLNxCD3 bispecific antibody constructs (referred to as potency gap), an 18 hour 51-chromium release cytotoxicity assay was carried out as described hereinabove (Example 8.1) with purified bispecific antibody construct monomer and dimer. Effector cells were stimulated enriched human CD8+ T cells. Target cells were hu MSLN transfected CHO cells. Effector to target cell (E:T) ratio was 10:1. The potency gap was calculated as ratio between EC50 values.

The results of the assays with stimulated enriched human CD^+ T cells as effector cells and human MSLN-transfected CHO cells as targets are shown in Table 9.

Table 9: Cytotoxic Activity of Unstimulated Human PBMC Against Human MSLN-transfected CHO Cells using monomeric and dimeric MSLNxCD3 bispecific antibody constructs

BiTE x I2C-HALB	***EC_{50} [pM] Monomer Dimer***		***Monomer to dimer ratio (EC_{50} Monomer /EC_{50} Dimer)***
MS 1	1.5	1.7	0.9
MS 8	6.5	9.5	0.7
MS 2	2.0	2.0	1.0
MS 3	0.2	0.7	0.3
MS 4	0.1	0.9	0.1
MS 5	0.2	1.1	0.2
MS 6	0.5	3.4	0.1
MS 7	6.0	21	0.3

Example 6

Stability after incubation for 24 hours in human plasma

Purified bispecific antibody constructs were incubated at a ratio of 1:5 in a human plasma pool at 37°C for 96 hours at a final concentration of 2-20 µg/ml. After plasma incubation the antibody constructs were compared in a 51-chromium release assay with stimulated enriched human CD8+ T cells and human MSLN-transfected CHO cells at a starting concentration of 0.01-0.1 µg/ml and with an effector to target cell (E:T) ratio of 10:1 (assay as described in Example 8.1). Non-incubated, freshly thawed bispecific antibody constructs were included as controls.

The results are shown in Table 10 below; All tested antibody constructs had a very favourable plasma stability (EC_{50} plasma / EC_{50} control) of ≤ 4,.

Table 10: EC50 values of the antibody constructs with and without plasma incubation and calculated plasma / control value

BiTE x I2C-HALB	***EC_{50} [pM]***		***Plasma to Control Ratio (EC_{50} Plasma /EC_{50} Control)***
	w/ Plasma	***w/o Plasma***	
MS 1	3.0	1.5	2.0
MS 8	4.8	6.5	0.7
MS 2	6.7	2.0	3.4
MS 3	0.3	0.2	1.5
MS 4	0.4	0.1	4
MS 5	0.3	0.2	1.5
MS 6	0.6	0.5	1.2
MS 7	11.4	6.0	1.9

Example 7

Protein Homogeneity by high resolution cation exchange chromatography

The protein homogeneity the antibody constructs of the invention was analyzed by high resolution cation exchange chromatography CIEX.

50 µg of antibody construct monomer were diluted with 50 ml binding buffer A (20 mM sodium dihydrogen phosphate, 30 mM NaCl, 0.01% sodium octanate, pH 5.5), and 40 ml of this solution were applied to a 1 ml BioPro SP-F column (YMC, Germany) connected to an Äkta Micro FPLC device (GE Healthcare, Germany). After sample binding, a wash step with further binding buffer was carried out. For protein elution, a linear increasing salt gradient using buffer B (20 mM sodium dihydrogen phosphate, 1000 mM NaCl, 0.01% sodium octanate, pH 5.5) up to 50% percent buffer B was applied over 10 column volumes. The whole run was monitored at 280, 254 and 210 nm optical absorbance. Analysis was done by peak integration of the 280 nm signal recorded in the Äkta Unicorn software run evaluation sheet.

The results are shown in Table 11 below. Almost all tested antibody constructs have a very favourable homogeneity of ≥ 80% (area under the curve (= AUC) of the main peak). The only exception is MS-2xCD3-HALB bispecific construct with merely 67 % homogeneity.

Table 11: Protein homogeneity of the antibody constructs (% AUC of main peak)

MSLN HALB BiTE	AUC of Main Peak [%]
MS 1	100
MS 8	93
MS 2	67
MS 3	87
MS 4	80
MS 5	89
MS 6	81
MS 7	100

Example 8

Surface hydrophobicity as measured by HIC Butyl

The surface hydrophobicity of bispecific antibody constructs of the invention was tested in Hydrophobic Interaction Chromatography HIC in flow-through mode.

50 µg of antibody construct monomer were diluted with generic formulation buffer to a final volume of 500 µl (10 mM citric acid, 75 mM lysine HCl, 4% trehalose, pH 7.0) and applied to a 1 ml Butyl Sepharose FF column (GE Healthcare, Germany) connected to a Äkta Purifier FPLC system (GE Healthcare, Germany). The whole run was monitored at 280, 254 and 210 nm optical absorbance. Analysis was done by peak integration of the 280 nm signal recorded in the Äkta Unicorn software run evaluation sheet. Elution behavior was evaluated by comparing area and velocity of rise and decline of protein signal thereby indicating the strength of interaction of the BiTE albumin fusion with the matrix.

The antibody constructs had a good elution behaviour, which was mostly rapid and complete; see Table 12.

Table 12: The surface hydrophobicity of bispecific antibody constructs

MSLN HALB BiTE	HIC Butyl Elution behavior
MS 1	1
MS 8	1
MS 2	1
MS 3	1
MS 4	1

MS 5	1
MS 6	1
MS 7	1

Example 9

Monomer to dimer conversion after (i) three freeze/thaw cycles and (ii) 7 days of incubation at 250 µg/ml

Bispecific MSLNxCD3 antibody monomeric construct were subjected to different stress conditions followed by high performance SEC to determine the percentage of initially monomeric antibody construct, which had been converted into dimeric antibody construct.

(i) 25 µg of monomeric antibody construct were adjusted to a concentration of 250 µg/ml with generic formulation buffer and then frozen at -80°C for 30 min followed by thawing for 30 min at room temperature. After three freeze/thaw cycles the dimer content was determined by HP-SEC.

(ii) 25 µg of monomeric antibody construct were adjusted to a concentration of 250 µg/ml with generic formulation buffer followed by incubation at 37°C for 7 days. The dimer content was determined by HP-SEC.

A high resolution SEC Column TSK Gel G3000 SWXL (Tosoh, Tokyo-Japan) was connected to an Äkta Purifier 10 FPLC (GE Lifesciences) equipped with an A905 Autosampler. Column equilibration and running buffer consisted of 100 mM KH2PO4 – 200 mM Na2SO4 adjusted to pH 6.6. The antibody solution (25 µg protein) was applied to the equilibrated column and elution was carried out at a flow rate of 0.75 ml/min at a maximum pressure of 7 MPa. The whole run was monitored at 280, 254 and 210 nm optical absorbance. Analysis was done by peak integration of the 210 nm signal recorded in the Äkta Unicorn software run evaluation sheet. Dimer content was calculated by dividing the area of the dimer peak by the total area of monomer plus dimer peak.

The results are shown in Table 13 below. The MSLNxCD3 bispecific antibody constructs of the invention presented with dimer percentages of 0.0% after three freeze/thaw cycles, and with dimer percentages of ≤ 2,2% after 7 days of incubation at 37°C.

Table 13: Percentage of monomeric versus dimeric MSLNxCD3 bispecific antibody constructs as determined by High Performance Size Exclusion Chromatography (HP-SEC).

MSLN HALB BiTE	**BiTE Dimer Conversion [%]**
MS 1	0.2

MS 8	1.6
MS 2	0.0
MS 3	1.7
MS 4	0.3
MS 5	1.2
MS 6	0.4
MS 7	2.2

Example 10

Thermostability

Antibody aggregation temperature was determined as follows: 40 µl of antibody construct solution at 250 µg/ml were transferred into a single use cuvette and placed in a Wyatt Dynamic Light Scattering device DynaPro Nanostar (Wyatt). The sample was heated from 40°C to 70°C at a heating rate of 0.5°C/min with constant acquisition of the measured radius. Increase of radius indicating melting of the protein and aggregation was used by the software package delivered with the DLS device to calculate the aggregation temperature of the antibody construct.

All tested MSLNxCD3 bispecific antibody constructs of the invention showed thermal stability with aggregation temperatures ≥49°C, as shown in Table 14 below. The group of antibody constructs binding to epitope cluster 2+3 even had a thermal stability of ≥51° and up to more than 56°C.

Table 14: Thermostability of the bispecific antibody constructs as determined by DLS (dynamic light scattering)

MSLN HALB BiTE	Thermal Stability DLS T_A [°C]
MS 1	49.3
MS 8	51.0
MS 2	53.1
MS 3	51.6
MS 4	56.5
MS 5	54.4
MS 6	53.9
MS 7	51.4

Example 11

Turbidity at 2500 µg/ml antibody concentration

1 ml of purified antibody construct solution of a concentration of 250 µg/ml was concentrated by spin concentration units to 2500 µg/ml. After 16h storage at 5°C the turbidity of the antibody solution was determined by OD340 nm optical absorption measurement against the generic formulation buffer.

The results are shown in Table 15 below. All tested antibody constructs have a very favourable turbidity of ≤ 0.09.

Table 15: Turbidity of the antibody constructs after concentration to 2.5 mg/ml over night

MSLN HALB BiTE	Turbidity after 16h @ 2500 µg/ml [OD340]
MS 1	0.080
MS 8	0.079
MS 2	0.070
MS 3	0.087
MS 4	0.076
MS 5	0.071
MS 6	0.070
MS 7	0.066

Example 12: BiTE® induced CD69 Expression on T Cells in Absence of Target Cells

Isolated PBMC from healthy human donors were cultured with increasing CDH19/CD3 or MSLN/CD3 HLE bispecific antibody constructs for 48 h. The expression of the activation marker CD69 on T cells was determined by immunostaining and flow cytometry and antigen specific conjugates mAb.

Target-independent T cell activation in terms of CD69 upregulation was observed for all anti-CDH 19 constructs but was most pronounced for heteroFc and crossbody molecules. Upregulation of CD69 by antiCDH19-scFc occurred at higher concentrations and the amplitude was in part lower compared to the other two Fc-based constructs.

For the anti-MSLN almost no target-independent T cell activation was observed for the scFc-containing molecule, while the heteroFc construct induced a strong upregulation of CD69 on the cell surface T cells in the absence of target cells.

Target-independent T cell activation induced by BiTE® constructs containing a single chain-Fc, or hetero-Fc fusion at the C-terminus was evaluated for the following constructs:
BiTE® constructs (serial dilutions: 0.1 pM – 2 µM)

a. MSLN scFc; 1.14 mg/mL;
b. MSLN Hetero Fc; 1.02 mg/

Human PBMC effector cells (3 donors; #065, #823, #836 (scFc) #401, #415, #433 (heteroFc); #590, #595, 598, #605 (X-body)).

48 h incubation time.

Determination of CD69 expression on CD4+ and CD8+ T cells with flow cytometer and antigen-specific conjugates mAb. Results see Figure 15.

Target-independent T cell activation induced by BiTE® antibody constructs containing a single chain-Fc, hetero-Fc or crossbody fusion at the C-terminus was evaluated for the following constructs:
BiTE® constructs (serial dilutions: 0.1 pM – 2 µM)

c. CDH19 scFc; 245.3 µg/mL (
d. CDH-19 Hetero Fc; 1 mg/mL
e. CDH19 Xbody; 6.3 mg/mL

Human PBMC effector cells (3 to 4 donors; #386, #392, #401 (scFc) #282, #284, #287 (heteroFc)).

48 h incubation time.

Determination of CD69 expression on CD4+ and CD8+ T cells with flow cytometer and antigen-specific conjugates mAb. Results see Figure 16.

Example 13:

Purified BiTE® antibody constructs were coated on a Maxisorb Plate in decreasing concentration (100nM, 1:4 dilutions). After 3x washing with PBS-T and blocking with PBS/3% (w/v) BSA (60 min, 37°C), pooled human plasma was incubated for 60 min, 80 rpm at room temperature. After 3x washing a mouse monoclonal antibody specific for human C1q subunit A (CC1q) was added (Thermo MA1-83963, 1:500) for 60 min, 80 rpm, room temperature, after described washing

steps a goat anti mouse Fc-POX mAb (1:5,000) was incubated for 60 min, 80 rpm, room temperature. After additional washing, TMB substrate was incubated and stopped after colorimetric reaction by addition of H_2SO_4. The absorption was determined at 450 nm.

Result: As shown in figure 17 at high concentrations, the BiTE® hetero Fc construct (squares) showed higher binding signals for human CC1q compared to a BiTE® single chain Fc construct (triangle). As a negative control a canonical BiTE® (circle) was used, which showed no significant CC1q binding.

Example 14: Pharmacokinetics of BiTE® antibody constructs fused to single-chain Fc- (scFc) and hetero-Fc (hetFc) proteins

Various target binding BiTE® antibodies were fused to two different half-life extending moieties. The two different HLE-variants per BiTE® antibody, subsequently named as BiTE®-scFc and BiTE®-hetFc, were tested in the cynomolgus monkey in the context of pharmacokinetic (PK) studies. The corresponding nomenclature of these molecules is briefly summarized in Table 16 below.

Table 16 Compound nomenclature of nine single dosed BiTE® HLE antibody constructs

compound synonym	test compound name
Compound 1a	CD33cc-scFc
Compound 1b	CD33cc-hetFc
Compound 2a	MSLN-scFc
Compound 2b	MSLN-hetFc
Compound 3a	CDH19-scFc
Compound 3b	CH19-hetFc
Compound 4	CD20-scFc
Compound 5a	DLL3-scFc
Compound 5b	DLL3-hetFc

The BiTE® HLE antibody construct were administered as intravenous bolus (compounds 1b-5b) and intravenous infusion (compound 1a, 30 min) at 6 µg/kg (compound 2b), 12 µg/kg

(compounds 2a and 3a-5b) and 15 µg/kg (compounds 1a and 1b), respectively. For each of the above named compounds a group of at least two to three animals was used. Blood samples were collected and serum was prepared for determination of serum concentrations. Serum BiTE® antibody construct levels were measured using an immunoassay. The assay is performed by capturing the BiTE® via its target moiety, while an antibody directed against the CD3-binding part of the construct was used for detection. The serum concentration-time profiles were used to determine PK parameters. Blood sampling time points are listed in Table 17 below.

Table 17 Blood sampling time points during the PK study

blood sampling time points cmpd. 1a [h]	blood sampling time points cmpd. 1b [h]	blood sampling time points cmpd. 2a-5b [h]
0.085	0.085	0.05
4.00	1	0.25
24.00	4	0.5
48.00	12	1
72.00	24	4
96.00	48	8
120.00	72	24
144.00	96	48
168	144	72
	168	168
		240
		336

The pharmacokinetics of four BiTE®-HLE antibody construct pairs are shown exemplarily in Figure 18. Each pair stands for the same BiTE® protein fused to either a scFc- or a hetFc extension. For all proteins serum levels were quantifiable for all time points in all animals after BiTE®-HLE administration. The PK profiles describe a biphasic, exponential decline after each of the single test item administrations.

The pharmacokinetic parameters were determined using standard non-compartmental analysis (NCA) methods. Using non compartmental analysis, the following PK parameters were estimated: AUCinf (Area under the serum concentration- time curve), Vss (volume of distribution at steady state), CL (systemic clearance) and terminal t1/2 (terminal half-life).

The PK parameter for each tested compound are summarized as mean of n=2 and n=3, respectively in Table 18 below.

Table 18 Pharmacokinetic parameter of scFc- and heteroFc-variants from different BiTE®-target binders in cynomolgus monkeys.

test item	terminal $t_{1/2}$ [h]	AUC_{inf} [h*ng/mL]	Cl [mL/h/kg]	Vss [mL/kg]
Compound 1a	167	6645	1.4	256
Compound 1b	95	4955	2.6	261
Compound 2a	213	12072	0.73	179
Compound 2b	116	6971	0.8	78
Compound 3a	61	3293	3.6	129
Compound 3b	59	3633	3.3	79
Compound 4	97	6266	1.9	180
Compound 5a	234	24769	0.48	144
Compound 5b	173	14639	0.82	166

Overall, the AUCinf for the different BiTE®-HLE pairs of target binders fused to either –scFc and –hetFc moiety, respectively, ranged between 3293 h*ng/mL and 24769 h*ng/mL, depending on the BiTE® target context. All analyzed HLE fusions achieved systemic clearance values of 0.48 to 3.6 mL/h/kg. The corresponding volumes of distribution ranged between 78 and 261 mL/kg.

Example 15:

Preformulated drug substances containing purified MSLN-hALB, MSLN-hFc, and MSLN-scFc respectively were buffer exchanged via ultrafiltration / diafiltration using membranes with a molecular weight cut-off (MWCO) of 10 kDa. Final formulation was achieved by adding concentrated stock solutions. Resulting formulations for each construct are listed in Table 19 and comprise K60RTrT composed of 20 mM potassium phosphate, 150 mM L-arginine hydrochloride, 6% (w/V) trehalose dihydrate, 0.01% (w/V) polysorbate 80 at pH 6.0 and G40MSuT composed of 10 mM glutamate, 4% (w/V) mannitol, 2% (w/V) sucrose, 0.01% (w/V) polysorbate 80 at pH 4.0. The target protein concentration was 1.0 mg/mL. Formulated MSLN contructs were filled to 1 mL in type I glass vials which were stoppered with butyl rubber stoppers and crimped with aluminum seals. Filled vials were incubated at -20, 5, 25 and 37°C. One vial of each version was subjected to five freeze and thaw (F/T) cycles. Target freezing

temperature was -29°C. Target thawing temperature was 2°C. The ramp rate was approximately 0.3 K/min.

Visual particles were assessed in accordance to the method described by Ph Eur 2.9.20 by trained operators. Visual particle counts per vial are depicted in Table 7. The number of visual (larger than 125 µm) proteinaceous particles was higher for MSLN-hFc if compared to both MSLN-hALB and MSLN-scFc.

Table 19: Number of visual proteinaceous particles per vial for stressed and unstressed (T0) samples containing different half-life extended anti-Mesothelin (MSLN) BiTE® constructs. K60RTrT denotes for a formulation containing 20 mM potassium phosphate, 150 mM L-arginine hydrochloride, 6% (w/V) trehalose dihydrate, 0.01% (w/V) polysorbate 80, pH 6.0. G40MSuT denotes for a formulation containing 10 mM glutamate, 4% (w/V) mannitol, 2% (w/V) sucrose, 0.01% (w/V) polysorbate 80, pH 4.0

Construct	hALB	hFc		scFc	
Formulation	K60RTrT	K60RTrT	G40MSuT	K60RTrT	G40MSuT
Number of visible (>125 µm) proteinaceous particles per vial					
T0	0	0	1	0	0
5 F/T cycles	0	2	2	0	1
2w 5°C	0	2	2	0	0
2w 25°C	0	2	1	0	0
2w 37°C	0	2	2	0	0
4w -20°C	0	2	1	0	0
4w 5°C	0	1	2	0	0
4w 25°C	0	2	2	0	0
4w 37°C	0	2	2	0	0

The samples described above were also analyzed by size exclusion ultra-high performance chromatography (SE-UPLC) in order to quantify the percentaged content of high molecular weight species (HMWS). SE-UPLC was performed on an AcquityH-Class UPLC system (Waters) using an Acquity UPLC BEH200 SEC 150 mm column (Waters). Column temperature was set to 25°C. Separation of size variants was achieved by applying an isocratic method with a flow rate of 0.4 mL/min. The mobile phase was composed of 100 mM sodium phosphate, 250 mM NaCl at pH 6.8. The run time totals 6.0 minutes. Samples were held at 8°C within the autosampler until analysis. A total amount of 3 µg protein was injected. In order to avoid carry over an intermediate injection with 40% acetonitrile was performed after each sample. Detection was based on fluorescence emission (excitation at 280 nm, emission at 325 nm). Peak integration was performed using Empower® software. Relative area under the curve of HMWS was reported (Table 20).

Fc based constructs exhibited lower HMWS contents in the formulation variant G40MSuT than in K60RTrT independent on the stress condition. It became evident that MSLN-scFc contained less HMWS than MSLN-hFc in both G40MSuT as well as K60RTrT preparations. MSLN-scFc in its preferred formulation (G40MSuT) was less prone to HMWS formation than MSLN-hALB formulated in K60RTrT. In previous experiments this buffer showed improved stabilizing potential for hALB based constructs if compared to formulations with more acidic pH values.

Table 20: Overview on HMWS contents in stressed and unstressed (T0) MSLN-hALB, -hFc, and -scFc preparations determined via SE-UPLC

Construct	hALB	hFc		scFc	
Formulation	K60RTrT	K60RTrT	G40MSuT	K60RTrT	G40MSuT
%HMWS					
T0	1.8	6.7	3.3	2.5	1.3
5 F/T cycles	2.0	7.2	4.1	3.0	1.5
2w 5°C	n.t.	n.t.	n.t.	2.9	1.1
2w 25°C	n.t.	6.6	2.7	2.4	0.5
2w 37°C	2.6	6.3	2.1	2.7	0.3
4w -20°C	5.9	8.7	1.6	6.6	0.3
4w 5°C	2.0	8.2	2.8	3.6	0.6
4w 25°C	2.2	6.8	2.6	2.7	0.4
4w 37°C	3.5	7.6	1.9	4.3	0.3

n.t. = not tested

The abundance of chemical modifications upon heat stress (incubation at 37°C) was monitored by peptide mapping. Protein samples were enzymatically digested and the resulting peptides were separated using reversed phase chromatography. The column eluate was directly injected into the ion source of a mass spectrometer for identification and quantitation of the peptides.

In order to achieve maximum coverage, two separate enzyme digests were performed: once with trypsin and once with chymotrypsin. In each case, the proteins were denatured with guanidinum chloride and then reduced with dithiothreitol (DTT). After incubation in DTT, free cysteine residues were alkylated by the addition of iodoacetic acid. Samples were then buffer exchanged into 50 mM Tris pH 7.8 for digestion. Trypsin and chymotrypsin were added to separate reaction tubes at a ratio of 1:10 (sample:enzyme) each. Samples were digested for 30 min at 37°C and the reaction was quenched by adding trifluoroacetic acid.

A load of 5 µg of each digest was separately injected onto a Zorbax SB-C18 (Agilent #859700-902) reversed phase column equilibrated in 0.1% (V/V) formic acid (FA). A 156 minutes gradient of up to 90% acetonitrile containing 0.1% FA was used to elute the peptides directly into the electrospray ion source of a Q-Exactive Plus mass spectrometer (Thermo Scientific). Data was

collected in data dependent mode using a top 12 method in which a full scan (resolution 70 000; scan range 200-2000 m/z) was followed by high energy collision dissociation (HCD) of the 12 most abundant ions (resolution 17 500).

Peptides were identified based on accurate mass and tandem mass spectrum using in-house software. Identifications were manually verified. Relative quantities of modified and unmodified peptides were calculated based on ion abundance using Pinpoint software (Thermo Scientific).

Percentages of chemical modifications of the complement determining regions (CDRs) and of the half-life extending portion (either hALB or Fc) detected in MSLN-hALB, -hFc, and -scFc preparations are given by Table 21. When comparing similar formulation conditions, it became obvious that overall, chemical modifications were least abundant in scFc constructs.

Table 21: Overview on chemical modifications in stressed and unstressed (T0) MSLN-hALB, -hFc, and -scFc preparations determined via peptide mapping

Construct	hALB	hFc		scFc	
Formulation	K60RTrT	K60RTrT	G40MSuT	K60RTrT	G40MSuT
%N101 deamidation (CDR)					
T0	0.1	0.2	0.2	0.2	0.2
2w 37°C	0.7	0.8	3.0	0.7	3.2
4w 37°C	1.3	n.t.	8.5	n.t.	6.4
%N162 deamidation (CDR)					
T0	3.0	1.7	1.9	2.3	2.5
2w 37°C	15.9	11.6	2.7	15.0	3.3
4w 37°C	26.8	n.t.	3.7	n.t.	4.1
%M279 oxidation (CDR)					
T0	0.6	1.4	1.6	0.6	1.0
2w 37°C	1.2	0.8	0.8	0.6	1.0
4w 37°C	0.9	n.t.	0.8	n.t.	0.6
%N348 deamidation (CDR)					
T0	0.5	3.2	3.3	0.5	0.9
2w 37°C	20.5	21.6	1.9	9.4	1.3
4w 37°C	22.8	n.t.	2.0	n.t.	2.9
%N351 deamidation (CDR)					
T0	0.2	2.9	2.6	0.5	1.0
2w 37°C	6.6	12.7	0.9	3.8	0.4
4w 37°C	8.7	n.t.	0.8	n.t.	0.8
%M530 oxidation (Fc)					
T0	n.a.	3.9	4.1	2.6	3.2
2w 37°C	n.a.	9.0	3.1	4.0	4.3
4w 37°C	n.a.	n.t.	3.4	n.t.	3.5
% N603 deamidation (Fc)					
T0	n.a.	1.3	1.9	1.3	1.4
2w 37°C	n.a.	7.9	4.6	7.0	5.6
4w 37°C	n.a.	n.t.	6.9	n.t.	8.1
%M706 oxidation (Fc)					

Construct	hALB	hFc		scFc	
Formulation	K60RTrT	K60RTrT	G40MSuT	K60RTrT	G40MSuT
T0	n.a.	3.2	3.6	1.5	2.1
2w 37°C	n.a.	6.0	2.8	2.1	2.5
4w 37°C	n.a.	n.t.	2.6	n.t.	2.0
%M587 oxidation (hALB)					
T0	1.0	n.a.	n.a.	n.a.	n.a.
2w 37°C	2.2	n.a.	n.a.	n.a.	n.a.
4w 37°C	2.3	n.a.	n.a.	n.a.	n.a.
%M623 oxidation (hALB)					
T0	1.9	n.a.	n.a.	n.a.	n.a.
2w 37°C	2.4	n.a.	n.a.	n.a.	n.a.
4w 37°C	3.0	n.a.	n.a.	n.a.	n.a.
%M798 oxidation (hALB)					
T0	1.4	n.a.	n.a.	n.a.	n.a.
2w 37°C	3.3	n.a.	n.a.	n.a.	n.a.
4w 37°C	3.5	n.a.	n.a.	n.a.	n.a.
%M829 oxidation (hALB)					
T0	8.9	n.a.	n.a.	n.a.	n.a.
2w 37°C	42.9	n.a.	n.a.	n.a.	n.a.
4w 37°C	44.1	n.a.	n.a.	n.a.	n.a.

n.a. = not applicable; n.t. = not tested

Example 16:

MSLN-hALB, -hFc, -scFc formulated as described under Example 15 were subjected to a pH jump experiment. The concentration of the starting materials was 1.0 mg/mL. A volume of 0.38 mL of each starting material was filled in a glass vial. After preconditioning at 37°C the solutions were spiked with 20 fold phosphate buffered saline (PBS) which was composed of 0.090 M potassium phosphate, 0.480 M sodium phosphate (both dibasic), 0.052 M potassium chloride and 2.76 M NaCl. The spiked samples were incubated at 37°C for two weeks. After incubation they were analyzed by SE-UPLC using the method described under Example 15 and the percentaged content of HMWS was reported (Table 22). When comparing all constructs formulated in K60RTrT the HMWS content increased in the following order: hALB < scFc < hFc. MSLN-scFc also showed a lower HMWS content than MSLN-hFc when formulated in G40MSuT.

Table 22: Overview on HMWS contents in stressed (pH jump + 2w 37°C) MSLN-hALB, -hFc, and -scFc preparations determined via SE-UPLC

Construct	hALB	hFc		scFc	
Formulation	K60RTrT	K60RTrT	G40MSuT	K60RTrT	G40MSuT
%HMWS					

2w 37°C	1.5	8.3	7.1	5.4	5.1

Example 17:

MSLN-hALB, -hFc, and -scFc formulated as described under Example 15 were subjected to agitation stress. The concentration of the starting materials was 1.0 mg/mL. A volume of 0.5 mL of each solution was filtered through an appropriate 0.22 µm filter and filled into 3cc glass vials. The vials were placed in a plastic box ensuring that the vials were not displaced within the box during agitation. The box was placed onto an orbital shaker. The samples were agitated at 500 rpm for 65 hours. Visual particles were assessed in accordance to the method described by Ph Eur 2.9.20. The method was conducted by trained operators. Visual particle counts per vial are depicted in Table 23. Visible proteinaceous particles were only observed in MSLN-hFc preparations.

Table 23: Number of visual proteinaceous particles per vial in agitated samples

Construct	hALB	hFc		scFc	
Formulation	**K60RTrT**	**K60RTrT**	**G40MSuT**	**K60RTrT**	**G40MSuT**
Number of visible (>125 µm) proteinaceous particles per vial					
65h, 500 rpm	0	1	1	0	0

Above samples were also analyzed by size exclusion ultra-high performance chromatography (SE-UPLC) in order to quantify the percentaged content of high molecular weight species (HMWS). The same method as described in Example 15 was applied. The HMWS contents of agitated samples are outlined by Table 24. The formation of HMWS was most pronounced in MSLN-hFc when comparing K60RTrT preparations. For Fc based constructs the HMWS contents could be reduced by lowering the formulation pH (G40MSuT). But again HMWS were more abundant in MSLN-hFc than in MLSN-scFc.

Table 24: Overview on HMWS contents in stressed (pH jump + 2w 37°C) MSLN-hALB, -hFc, and -scFc preparations determined via SE-UPLC

Construct	hALB	hFc		scFc	
Formulation	**K60RTrT**	**K60RTrT**	**G40MSuT**	**K60RTrT**	**G40MSuT**
%HMWS					
65h, 500 rpm	1.8	5.8	2.4	1.8	0.3

Example 17:

MSLN-hALB, -hFc, and -scFc formulated as described under Example 15 were exposed to visible and UVA light (photo stress). Protein concentration totaled 1 mg/mL in all preparations.

Protein solutions were filtered through a filter with 0.22 µm pore size and filled to 0.5 mL in type I glass vials. MSLN-hALB and -scFc were subjected to two different tests including 0.2 MLux visible light / 25 W*h/m^2 UVA light and 1.2MLux visible light / 173 W*h/m^2 respectively. MSLN-hFc was subjected to two different tests including 0.2 MLux visible light without UVA light and 1.2 MLux visible light / 30 W*h/m^2 UVA light respectively. Chamber temperatures were adjusted to 25°C. After light exposure samples were analyzed by visible inspection (Table 25), SE-UPLC (Table 26) and peptide map (Table 27). Aforementioned methods were performed according to the procedures described under Example 15. Although MSLN-hALB, and -scFc were exposed to higher doses of UVA light, no visible proteinaceous particles was observed whereas MSLN-hFc samples exhibited one visible proteinaceous particle per vial for both tests irrespective of the formulation.

Table 25: Overview on the number of visible proteinaceous particles per vial in MSLN-hALB, -hFc, and -scFc preparations determined after light exposure

Construct	hALB	hFc		scFc	
Formulation	K60RTrT	K60RTrT	G40MSuT	K60RTrT	G40MSuT
Number of visible (>125 µm) proteinaceous particles per vial					
T0	0	0	1	0	0
Test 1	0[1)]	1[2)]	1[2)]	0[1)]	0[1)]
Test 2	0[3)]	1[4)]	1[4)]	0[3)]	0[3)]

[1)] 0.2 MLux visible light / 25 W*h/m^2 UVA light, [2)] 0.2 MLux visible light without UVA light, [3)] 1.2 MLux visible light / 173 W*h/m^2, [4)] 1.2 MLux visible light / 30 W*h/m^2

HMWS increased in the following order MSLN-hALB < -scFc < -hFc when the protein was formulated in K60RTrT. HMWS could be reduced for Fc based constructs when formulated in G40MSuT. However HMWS were again less pronounced for MSLN-scFc. MSLN-hFc revealed to be especially sensitive towards UVA light exposure.

Table 26: Overview on HMWS contents in MSLN-hALB, -hFc, and -scFc preparations determined after light exposure via SE-UPLC

Construct	hALB	hFc		scFc	
Formulation	K60RTrT	K60RTrT	G40MSuT	K60RTrT	G40MSuT
%HMWS					
T0	1.8	6.7	3.3	2.5	1.3
Test 1	1.8[1)]	6.3[2)]	2.5[2)]	2.1[1)]	0.4[1)]
Test 2	2.0[3)]	11.0[4)]	2.1[4)]	2.4[3)]	0.3[3)]

[1)] 0.2 MLux visible light / 25 W*h/m^2 UVA light, [2)] 0.2 MLux visible light without UVA light, [3)] 1.2 MLux visible light / 173 W*h/m^2, [4)] 1.2 MLux visible light / 30 W*h/m^2

Percentages of chemical modifications of the complement determining regions (CDRs) and of the half-life extending portion (either hALB or Fc) detected in MSLN-hALB, -hFc, and -scFc

preparations are given by Table 27. When comparing similar formulation conditions, it became obvious that overall, chemical modifications were least abundant in scFc constructs.

Table 27: Overview on chemical modifications in MSLN-hALB, -hFc, and -scFc preparations determined after light exposure via peptide mapping

Construct	hALB	hFc		scFc	
Formulation	K60RTrT	K60RTrT	G40MSuT	K60RTrT	G40MSuT
%N101 deamidation (CDR)					
T0	0.1	0.2	0.2	0.2	0.2
Test 1	0.2[1)]	n.t.	0.3[2)]	n.t.	0.5[1)]
Test 2	0.2[3)]	n.t.	0.6[4)]	n.t.	0.7[3)]
%N162 deamidation (CDR)					
T0	3.0	1.7	1.9	2.3	2.5
Test 1	3.0[1)]	n.t.	2.1[2)]	n.t.	2.7[1)]
Test 2	3.6[3)]	n.t.	3.1[4)]	n.t.	2.8[3)]
%M279 oxidation (CDR)					
T0	0.6	1.4	1.6	0.6	1.0
Test 1	0.8[1)]	n.t.	2.6[2)]	n.t.	0.6[1)]
Test 2	1.0[3)]	n.t.	6.3[4)]	n.t.	0.7[3)]
%N348 deamidation (CDR)					
T0	0.5	3.2	3.3	0.5	0.9
Test 1	0.4[1)]	n.t.	2.7[2)]	n.t.	0.2[1)]
Test 2	0.9[3)]	n.t.	3.9[4)]	n.t.	0.2[3)]
%N351 deamidation (CDR)					
T0	0.2	2.9	2.6	0.5	1.0
Test 1	0.4[1)]	n.t.	2.0[2)]	n.t.	0.3[1)]
Test 2	0.5[3)]	n.t.	2.6[4)]	n.t.	0.3[3)]
%M530 oxidation (Fc)					
T0	n.a.	3.9	4.1	2.6	3.2
Test 1	n.a.	n.t.	7.6[2)]	n.t.	3.1[1)]
Test 2	n.a.	n.t.	21.8[4)]	n.t.	4.1[3)]
%M706 oxidation (Fc)					
T0	n.a.	3.2	3.6	1.5	2.1
Test 1	n.a.	n.t.	6.5[2)]	n.t.	1.8[1)]
Test 2	n.a.	n.t.	17.8[4)]	n.t.	2.7[3)]
%M587 oxidation (hALB)					
T0	1.0	n.a.	n.a.	n.a.	n.a.
Test 1	1.5	n.a.	n.a.	n.a.	n.a.
Test 2	2.4	n.a.	n.a.	n.a.	n.a.
%M623 oxidation (hALB)					
T0	1.9	n.a.	n.a.	n.a.	n.a.
Test 1	4.0	n.a.	n.a.	n.a.	n.a.
Test 2	4.1	n.a.	n.a.	n.a.	n.a.
%M798 oxidation (hALB)					
T0	1.4	n.a.	n.a.	n.a.	n.a.
Test 1	2.1	n.a.	n.a.	n.a.	n.a.
Test 2	3.1	n.a.	n.a.	n.a.	n.a.
%M829 oxidation (hALB)					
T0	8.9	n.a.	n.a.	n.a.	n.a.

Construct	hALB	hFc		scFc	
Formulation	K60RTrT	K60RTrT	G40MSuT	K60RTrT	G40MSuT
Test 1	31.0	n.a.	n.a.	n.a.	n.a.
Test 2	25.2	n.a.	n.a.	n.a.	n.a.

n.a. = not applicable; n.t. = not tested

Example 18:

MSLN-hALB was formulated in K60RTrT and MSLN-scFc was formulated in G40MSuT according to the procedure described in Example 15. Protein concentrations totaled 0.05 mg/mL. Glass (borosilicate, type I, 13 mm 3cc vial from West, Art. No. 68000375) and polypropylene test containers (2 mL with O-ring, e.g. from Sarstedt, Art No. 72.694.005) are filled with 500 µL of the test solution. The test solution was left for five minutes in the first test container. Then a 150 µL aliquot was sampled for analysis. The remaining test solution (350 µL) was transferred sequentially from one test container to the next (five containers in total). In each vial, the solution was left for five minutes before the next transfer. The same pipette tip was used for each transfer step. The same test was performed using 30 mL polycarbonate bottles (Nalgene, PCS-000295 with closure, PP/20-415/ZTPE). For this container type the first container was filled with 5 mL. After a 150 µL aliquot was sampled, the residual volume was transferred from one test container to the next (according to the procedure described above). Samples pulled from container #1 and #5 were analyzed by SE-UPLC (method as described under Example 15). In addition protein detection was carried out with a PDA detector (280 nm) in order to determine protein concentrations. Percentaged protein recovery from each test container is given by Table 28. It was shown that protein recovery was more pronounced for MSLN-scFc than for MSLN-hALB irrespective of the container type.

Table 28: Protein recovery from different container types for MSLN-hALB, and -scFc determined by SE-UPLC

Construct	hALB	scFc
Formulation	K60RTrT	G40MSuT
%Protein recovery (from nominal)		
Type I glass	80.0	92.0
Polypropylene	87.0	97.3
Polycarbonate	87.0	96.0

Example 19:

MSLN-hALB was formulated in K60RTrT and MSLN-scFc was formulated in K60RTrT and G40MSuT according to the procedure described in Example 15. The protein concentration totaled 1.0 mg/mL. 1950 µL of each test solution was spiked with 50 µL of a 1000 ppm silicon

standard solution (Specpure from AlfaAesar, Art.No. 38717) resulting in a 25 ppm spike. An unspiked test solution served as control sample. The spiked test solution as well as the control sample were filled into 3cc type I glass vials and were incubated at 37°C for 24 hours. All samples were analyzed by SE-UPLC according to the method described in Example 15 in order to quantify the amount of HMWS (Table 29). When formulated in K60RTrT, MSLN-hALB and -scFc showed similar increases in HMWS upon silicon spiking. For the scFc construct it could be shown that this increase could be reduced by lowering the formulation pH to 4.0. According to preliminary experiments, this approach was not feasible for MLSN-hALB since it revealed to undergo fragmentation at formulation pH values of 5.0 and below.

Table 29: Overview on HMWS contents in MSLN-hALB, and -scFc preparations determined via SE-UPLC after spiking with 25 ppm silicon

Construct	**hALB**	**scFc**	
Formulation	**K60RTrT**	**K60RTrT**	**G40MSuT**
Δ %HMWS (compared to unspiked control)			
25 ppm spike	1.0	1.0	0.2

Table 30: Sequence Listing

SEQ ID NO:	Description	Source	Sequence
1.	Peptide linker	artificial	GGGG
2.	Peptide linker	artificial	GGGGS
3.	Peptide linker	artificial	GGGGQ
4.	Peptide linker	artificial	PGGGGS
5.	Peptide linker	artificial	PGGDGS
6.	Peptide linker	artificial	SGGGGS
7.	Peptide linker	artificial	GGGGSGGGS
8.	Peptide linker	artificial	GGGGSGGGGS
9.	Peptide linker	artificial	GGGGSGGGGSGGGGS
10.	Hexa-histidine	artificial	HHHHHH
11.	CDR-L1 of F6A	artificial	GSSTGAVTSGYYPN
12.	CDR-L2 of F6A	artificial	GTKFLAP
13.	CDR-L3 of F6A	artificial	ALWYSNRWV
14.	CDR-H1 of F6A	artificial	IYAMN

15.	CDR-H2 of F6A	artificial	RIRSKYNNYATYYADSVKS
16.	CDR-H3 of F6A	artificial	HGNFGNSYVSFFAY
17.	VH of F6A	artificial	EVQLVESGGGLVQPGGSLKLSCAASGFTFNIYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKSRFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHGNFGNSYVSFFAYWGQGTLVTVSS
18.	VL of F6A	artificial	QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGV QPEDEAEYYCALWYSNRWVFGGGTKLTVL
19.	VH-VL of F6A	artificial	EVQLVESGGGLVQPGGSLKLSCAASGFTFNIYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKSRFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHGNFGNSYVSFFAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGGTVTL TCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNRWVF GGGTKLTVL
20.	CDR-L1 of H2C	artificial	GSSTGAVTSGYYPN
21.	CDR-L2 of H2C	artificial	GTKFLAP
22.	CDR-L3 of H2C	artificial	ALWYSNRWV
23.	CDR-H1 of H2C	artificial	KYAMN
24.	CDR-H2 of H2C	artificial	RIRSKYNNYATYYADSVKD
25.	CDR-H3 of H2C	artificial	HGNFGNSYISYWAY
26.	VH of H2C	artificial	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSS
27.	VL of H2C	artificial	QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGV QPEDEAEYYCALWYSNRWVFGGGTKLTVL
28.	VH-VL of H2C	artificial	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGGTVTL TCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNRWVF GGGTKLTVL
29.	CDR-L1 of H1E	artificial	GSSTGAVTSGYYPN
30.	CDR-L2 of H1E	artificial	GTKFLAP

31.	CDR-L3 of H1E	artificial	ALWYSNRWV
32.	CDR-H1 of H1E	artificial	SYAMN
33.	CDR-H2 of H1E	artificial	RIRSKYNNYATYYADSVKG
34.	CDR-H3 of H1E	artificial	HGNFGNSYLSFWAY
35.	VH of H1E	artificial	EVQLVESGGGLEQPGGSLKLSCAASGFTFNSYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKGRFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHGNFGNSYLSFWAYWGQGTLVTVSS
36.	VL of H1E	artificial	QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGV QPEDEAEYYCALWYSNRWVFGGGTKLTVL
37.	VH-VL of H1E	artificial	EVQLVESGGGLEQPGGSLKLSCAASGFTFNSYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKGRFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHGNFGNSYLSFWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGGTVTL TCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNRWVF GGGTKLTVL
38.	CDR-L1 of G4H	artificial	GSSTGAVTSGYYPN
39.	CDR-L2 of G4H	artificial	GTKFLAP
40.	CDR-L3 of G4H	artificial	ALWYSNRWV
41.	CDR-H1 of G4H	artificial	RYAMN
42.	CDR-H2 of G4H	artificial	RIRSKYNNYATYYADSVKG
43.	CDR-H3 of G4H	artificial	HGNFGNSYLSYFAY
44.	VH of G4H	artificial	EVQLVESGGGLVQPGGSLKLSCAASGFTFNRYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKGRFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHGNFGNSYLSYFAYWGQGTLVTVSS
45.	VL of G4H	artificial	QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGV QPEDEAEYYCALWYSNRWVFGGGTKLTVL
46.	VH-VL of G4H	artificial	EVQLVESGGGLVQPGGSLKLSCAASGFTFNRYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKGRFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHGNFGNSYLSYFAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGGTVTL TCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNRWVF GGGTKLTVL

47.	CDR-L1 of A2J	artificial	RSSTGAVTSGYYPN
48.	CDR-L2 of A2J	artificial	ATDMRPS
49.	CDR-L3 of A2J	artificial	ALWYSNRWV
50.	CDR-H1 of A2J	artificial	VYAMN
51.	CDR-H2 of A2J	artificial	RIRSKYNNYATYYADSVKK
52.	CDR-H3 of A2J	artificial	HGNFGNSYLSWWAY
53.	VH of A2J	artificial	EVQLVESGGGLVQPGGSLKLSCAASGFTFNVYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKKRFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHGNFGNSYLSWWAYWGQGTLVTVSS
54.	VL of A2J	artificial	QTVVTQEPSLTVSPGGTVTLTCRSSTGAVTSGYYPNWVQQKPGQAPRGLIGATDMRPSGTPARFSGSLLGGKAALTLSGV QPEDEAEYYCALWYSNRWVFGGGTKLTVL
55.	VH-VL of A2J	artificial	EVQLVESGGGLVQPGGSLKLSCAASGFTFNVYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKKRFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHGNFGNSYLSWWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGGTVTL TCRSSTGAVTSGYYPNWVQQKPGQAPRGLIGATDMRPSGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNRWVF GGGTKLTVL
56.	CDR-L1 of E1L	artificial	GSSTGAVTSGYYPN
57.	CDR-L2 of E1L	artificial	GTKFLAP
58.	CDR-L3 of E1L	artificial	ALWYSNRWV
59.	CDR-H1 of E1L	artificial	KYAMN
60.	CDR-H2 of E1L	artificial	RIRSKYNNYATYYADSVKS
61.	CDR-H3 of E1L	artificial	HGNFGNSYTSYYAY
62.	VH of E1L	artificial	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKSRFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHGNFGNSYTSYYAYWGQGTLVTVSS
63.	VL of E1L	artificial	QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGV

			QPEDEAEYYCALWYSNRWVFGGGTKLTVL
64.	VH-VL of E1L	artificial	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKSRFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHGNFGNSYTSYYAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGGTVTL TCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNRWVF GGGTKLTVL
65.	CDR-L1 of E2M	artificial	RSSTGAVTSGYYPN
66.	CDR-L2 of E2M	artificial	ATDMRPS
67.	CDR-L3 of E2M	artificial	ALWYSNRWV
68.	CDR-H1 of E2M	artificial	GYAMN
69.	CDR-H2 of E2M	artificial	RIRSKYNNYATYYADSVKE
70.	CDR-H3 of E2M	artificial	HRNFGNSYLSWFAY
71.	VH of E2M	artificial	EVQLVESGGGLVQPGGSLKLSCAASGFTFNGYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKERFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHRNFGNSYLSWFAYWGQGTLVTVSS
72.	VL of E2M	artificial	QTVVTQEPSLTVSPGGTVTLTCRSSTGAVTSGYYPNWVQQKPGQAPRGLIGATDMRPSGTPARFSGSLLGGKAALTLSGV QPEDEAEYYCALWYSNRWVFGGGTKLTVL
73.	VH-VL of E2M	artificial	EVQLVESGGGLVQPGGSLKLSCAASGFTFNGYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKERFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHRNFGNSYLSWFAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGGTVTL TCRSSTGAVTSGYYPNWVQQKPGQAPRGLIGATDMRPSGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNRWVF GGGTKLTVL
74.	CDR-L1 of F7O	artificial	GSSTGAVTSGYYPN
75.	CDR-L2 of F7O	artificial	GTKFLAP
76.	CDR-L3 of F7O	artificial	ALWYSNRWV
77.	CDR-H1 of F7O	artificial	VYAMN
78.	CDR-H2 of F7O	artificial	RIRSKYNNYATYYADSVKK

79.	CDR-H3 of F7O	artificial	HGNFGNSYISWWAY
80.	VH of F7O	artificial	EVQLVESGGGLVQPGGSLKLSCAASGFTFNVYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKKRFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHGNFGNSYISWWAYWGQGTLVTVSS
81.	VL of F7O	artificial	QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGV QPEDEAEYYCALWYSNRWVFGGGTKLTVL
82.	VH-VL of F7O	artificial	EVQLVESGGGLVQPGGSLKLSCAASGFTFNVYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKKRFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHGNFGNSYISWWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGGTVTL TCGSSTGAVTSGYYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNRWVF GGGTKLTVL
83.	CDR-L1 of F12Q	artificial	GSSTGAVTSGNYPN
84.	CDR-L2 of F12Q	artificial	GTKFLAP
85.	CDR-L3 of F12Q	artificial	VLWYSNRWV
86.	CDR-H1 of F12Q	artificial	SYAMN
87.	CDR-H2 of F12Q	artificial	RIRSKYNNYATYYADSVKG
88.	CDR-H3 of F12Q	artificial	HGNFGNSYVSWWAY
89.	VH of F12Q	artificial	EVQLVESGGGLVQPGGSLKLSCAASGFTFNSYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKGRFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHGNFGNSYVSWWAYWGQGTLVTVSS
90.	VL of F12Q	artificial	QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGV QPEDEAEYYCVLWYSNRWVFGGGTKLTVL
91.	VH-VL of F12Q	artificial	EVQLVESGGGLVQPGGSLKLSCAASGFTFNSYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKGRFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHGNFGNSYVSWWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGGTVTL TCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVF GGGTKLTVL
92.	CDR-L1 of I2C	artificial	GSSTGAVTSGNYPN
93.	CDR-L2 of I2C	artificial	GTKFLAP
94.	CDR-L3 of	artificial	VLWYSNRWV

	I2C		
95.	CDR-H1 of I2C	artificial	KYAMN
96.	CDR-H2 of I2C	artificial	RIRSKYNNYATYYADSVKD
97.	CDR-H3 of I2C	artificial	HGNFGNSYISYWAY
98.	VH of I2C	artificial	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSS
99.	VL of I2C	artificial	QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGV QPEDEAEYYCVLWYSNRWVFGGGTKLTVL
100.	VH-VL of I2C	artificial	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGGTVTL TCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVF GGGTKLTVL
101.	VH of F12q	artificial	EVQLVESGGGLVQPGGSLRLSCAASGFTFNSYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKGRFTISRDDSKNT AYLQMNSLKTEDTAVYYCVRHGNFGNSYVSWWAYWGQGTLVTVSS
102.	VL of F12q	artificial	QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGV QPEDEAEYYCVLWYSNRWVFGGGTKLTVL
103.	F12q	scFv	EVQLVESGGGLVQPGGSLRLSCAASGFTFNSYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKGRFTISRDDSKNT AYLQMNSLKTEDTAVYYCVRHGNFGNSYVSWWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGGTVTL TCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVF GGGTKLTVL
104.	HALB	human	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCK ADDKETCFAEEGKKLVAASQAALGL
105.	HALB7	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALEVDETYVPKEFNAGTFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAAMDDFAAFVEKCCK ADDKETCFAEEGKKLVAASQAALGL

106.	HALB098	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCK ADDKETCFAEEGPKLVAASQAALGL
107.	HALB114	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALDVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCK ADDKETCFAEEGPHLVAASKAALGL
108.	HALB254	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALGVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCCK ADDKETCFAEEGPKLVAASQAALGL
109.	HALB253	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALDVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCCK ADDKETCFAEEGPKLVAASQAALGL
110.	HALB131	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCCK ADDKETCFAEEGPHLVAASQAALGL

111.	HALB135	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCK ADDKETCFAEEGPHLVAASKAALGL
112.	HALB133	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCCK ADDKETCFAEEGPKLVAASKAALGL
113.	HALB234	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALDVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCK ADDKETCFAEEGPKLVAASKAALGL
114.	HALB C34S	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCK ADDKETCFAEEGKKLVAASQAALGL
115.	HALB7 C34S	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALEVDETYVPKEFNAGTFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAAMDDFAAFVEKCCK ADDKETCFAEEGKKLVAASQAALGL

116.	HALB098 C34S	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCK ADDKETCFAEEGPKLVAASQAALGL
117.	HALB114 C34S	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALDVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCK ADDKETCFAEEGPHLVAASQAALGL
118.	HALB254 C34S	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALGVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCCK ADDKETCFAEEGPKLVAASQAALGL
119.	HALB253 C34S	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALDVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCCK ADDKETCFAEEGPKLVAASQAALGL
120.	HALB131 C34S	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCCK ADDKETCFAEEGPHLVAASQAALGL

121.	HALB135 C34S	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCK ADDKETCFAEEGPHLVAASKAALGL
122.	HALB133 C34S	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCCK ADDKETCFAEEGPKLVAASKAALGL
123.	HALB234 C34S	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQSPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALDVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCK ADDKETCFAEEGPKLVAASKAALGL
124.	HALB C34A	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQAPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCK ADDKETCFAEEGKKLVAASQAALGL
125.	HALB7 C34A	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQAPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALEVDETYVPKEFNAGTFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAAMDDFAAFVEKCCK ADDKETCFAEEGKKLVAASQAALGL

126.	HALB098 C34A	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQAPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCK ADDKETCFAEEGPKLVAASQAALGL
127.	HALB114 C34A	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQAPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALDVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCK ADDKETCFAEEGPHLVAASKAALGL
128.	HALB254 C34A	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQAPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALGVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCCK ADDKETCFAEEGPKLVAASQAALGL
129.	HALB253 C34A	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQAPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALDVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCCK ADDKETCFAEEGPKLVAASQAALGL
130.	HALB131 C34A	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQAPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCCK ADDKETCFAEEGPHLVAASQAALGL

131.	HALB135 C34A	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQAPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCK ADDKETCFAEEGPHLVAASKAALGL
132.	HALB133 C34A	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQAPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDKFAAFVEKCCK ADDKETCFAEEGPKLVAASKAALGL
133.	HALB234 C34A	artificial	DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQAPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATL RETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYFYAPELLFFAKR YKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTK VHTECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA EAKDVFLGMFLYEYARRHPDYSVVLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGE YKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVTKCCTES LVNRRPCFSALDVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCCK ADDKETCFAEEGPKLVAASKAALGL
134.	Ab156	artificial	RDWNDFDVFGGGTPVGG
135.	linear FcRn binding peptide	artificial	QRFVTGHFGGLXPANG
136.	linear FcRn binding peptide Y	artificial	QRFVTGHFGGLYPANG
137.	linear FcRn binding peptide H	artificial	QRFVTGHFGGLHPANG
138.	core FcRn binding peptide H	artificial	TGHFGGLHP

139.	cyclic FcRn binding peptide H	artificial	QRFCTGHFGGLHPCNG
140.	Cross body 1 HC		ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
141.	Cross body 1 LC		GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWK SHRSYSCQVTHEGSTVEKTVAPTECSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS RKEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGK
142.	Cross body 2 HC		ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQT YTCNVDHKPSNTKVDKTVEPKSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
143.	Cross body 2 LC		GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWK SHRSYSCQVTHEGSTVEKTVAPTECSEPKSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY TLPPSRKEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK
144.	Hetero-Fc binder Fc		DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTY RCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRKEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
145.	Hetero-Fc partner Fc		DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTY RCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
146.	Maxibody 1 target Fc		EPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQ YGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
147.	Maxibody 1 CD3 Fc		EPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQ YGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
148.	Maxibody 2 target Fc		EPKSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
149.	Maxibody 2		EPKSSDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPS

	CD3 Fc		DIAVEWESNGQPENNYDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
150.	Mono Fc		APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVTTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YDTTPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
151.	MS_1	VH CDR1	SSSYYWG
152.	MS_1	VH CDR2	SIYYSGITNYNPSLKS
153.	MS_1	VH CDR3	PSNYDAFDI
154.	MS_1	VL CDR1	TGSSSNIGAGYDVH
155.	MS_1	VL CDR2	GNSKRPS
156.	MS_1	VL CDR3	QSYDSSLGGWV
157.	MS_1	VH	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIGSIYYSGITNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARPSNYDAFDIWGQGTMVTVSS
158.	MS_1	VL	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQVPGTAPKLLIYGNSKRPSGVPDRFSGSKSGTSASLAITGL QAEDEADYYCQSYDSSLGGWVFGGGTKLTVL
159.	MS_1	scFv	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIGSIYYSGITNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARPSNYDAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSQSVLTQPPSVSGAPGQRVTISCTGSS SNIGAGYDVHWYQQVPGTAPKLLIYGNSKRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDSSLGGWVFGGGT KLTVL
160.	MS_1	bispecificmolecule	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIGSIYYSGITNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARPSNYDAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSQSVLTQPPSVSGAPGQRVTISCTGSS SNIGAGYDVHWYQQVPGTAPKLLIYGNSKRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDSSLGGWVFGGGT KLTVLSGGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDR FTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPS LTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYY CVLWYSNRWVFGGGTKLTVL
161.	MS_2	VH CDR1	DHYMS
162.	MS_2	VH CDR2	YISSSGSTIYYADSVKG
163.	MS_2	VH	DLGPSFDY

		CDR3	
164.	MS_2	VL CDR1	RASQGISSWLA
165.	MS_2	VL CDR2	AASRLQS
166.	MS_2	VL CDR3	QQANSFPRT
167.	MS_2	VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSDHYMSWIRQTPGKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDLGPSFDYWGQGSLVTVSS
168.	MS_2	VL	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIDAASRLQSGVPSRFSGSGSGTDFTLTISSLQP EDFATYYCQQANSFPRTFGQGTKVEIK
169.	MS_2	scFv	QVQLVESGGGVVQPGRSLRLSCAASGFTFSDHYMSWIRQTPGKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDLGPSFDYWGQGSLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQG ISSWLAWYQQKPGKAPKLLIDAASRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPRTFGQGTKVEIK
170.	MS_2	bispecifi c molecule	QVQLVESGGGVVQPGRSLRLSCAASGFTFSDHYMSWIRQTPGKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDLGPSFDYWGQGSLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQG ISSWLAWYQQKPGKAPKLLIDAASRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPRTFGQGTKVEIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPG GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVL
171.	MS_3	VH CDR1	DYYMT
172.	MS_3	VH CDR2	YISSSGSTIYYADSVKG
173.	MS_3	VH CDR3	DRNSHFDY
174.	MS_3	VL CDR1	RASQGITRWLA
175.	MS_3	VL CDR2	AASVLQS
176.	MS_3	VL CDR3	QQSNSFPRT
177.	MS_3	VH	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWIRQAPGKGLEWISYISSSGSTIYYADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDRNSHFDYWGQGTLVTVSS
178.	MS_3	VL	DIQMTQSPSSVSASVGDRVTITCRASQGITRWLAWYQQKPGKAPKLLIYAASVLQSGVPSRFSGSGSGTDFTLTISSLQP

			EDFATYYCQQSNSFPRTFGQGTKVEIK
179.	MS_3	scFv	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWIRQAPGKGLEWISYISSSGSTIYYADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDRNSHFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQG ITRWLAWYQQKPGKAPKLLIYAASVLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSNSFPRTFGQGTKVEIK
180.	MS_3	bispecific molecule	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWIRQAPGKGLEWISYISSSGSTIYYADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDRNSHFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQG ITRWLAWYQQKPGKAPKLLIYAASVLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSNSFPRTFGQGTKVEIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPG GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVL
181.	MS_4	VH CDR1	DYYMT
182.	MS_4	VH CDR2	YISSSGSTIYYADSVKG
183.	MS_4	VH CDR3	DRNSHFDY
184.	MS_4	VL CDR1	RASQGINTWLA
185.	MS_4	VL CDR2	GASGLQS
186.	MS_4	VL CDR3	QQAKSFPRT
187.	MS_4	VH	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWIRQAPGKGLEWLSYISSSGSTIYYADSVKGRFTISRDNAKNSLF LQMNSLRAEDTAVYYCARDRNSHFDYWGQGTLVTVSS
188.	MS_4	VL	DIQMTQSPSSVSASVGDRVTITCRASQGINTWLAWYQQKPGKAPKLLIYGASGLQSGVPSRFSGSGSGTDFTLTISSLQP EDFATYYCQQAKSFPRTFGQGTKVEIK
189.	MS_4	scFv	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWIRQAPGKGLEWLSYISSSGSTIYYADSVKGRFTISRDNAKNSLF LQMNSLRAEDTAVYYCARDRNSHFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQG INTWLAWYQQKPGKAPKLLIYGASGLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAKSFPRTFGQGTKVEIK
190.	MS_4	bispecific molecule	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWIRQAPGKGLEWLSYISSSGSTIYYADSVKGRFTISRDNAKNSLF LQMNSLRAEDTAVYYCARDRNSHFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQG INTWLAWYQQKPGKAPKLLIYGASGLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAKSFPRTFGQGTKVEIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPG GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVL

191.	MS_5	VH CDR1	DHYMS
192.	MS_5	VH CDR2	YISSSGGIIYYADSVKG
193.	MS_5	VH CDR3	DVGSHFDY
194.	MS_5	VL CDR1	RASQDISRWLA
195.	MS_5	VL CDR2	AASRLQS
196.	MS_5	VL CDR3	QQAKSFPRT
197.	MS_5	VH	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDHYMSWIRQAPGKGLEWFSYISSSGGIIYYADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDVGSHFDYWGQGTLVTVSS
198.	MS_5	VL	DIQMTQSPSSVSASVGDRVTITCRASQDISRWLAWYQQKPGKAPKLLISAASRLQSGVPSRFSGSGSGTDFTLTISSLQP EDFAIYYCQQAKSFPRTFGQGTKVEIK
199.	MS_5	scFv	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDHYMSWIRQAPGKGLEWFSYISSSGGIIYYADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDVGSHFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQD ISRWLAWYQQKPGKAPKLLISAASRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFAIYYCQQAKSFPRTFGQGTKVEIK
200.	MS_5	bispecific molecule	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDHYMSWIRQAPGKGLEWFSYISSSGGIIYYADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDVGSHFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQD ISRWLAWYQQKPGKAPKLLISAASRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFAIYYCQQAKSFPRTFGQGTKVEIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPG GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVL
201.	MS_6	VH CDR1	DHYMS
202.	MS_6	VH CDR2	YISNSGSIIYYVDSVKG
203.	MS_6	VH CDR3	DVRTAFDY
204.	MS_6	VL CDR1	RASQSIGSWLA
205.	MS_6	VL	AASSLQS

		CDR2	
206.	MS_6	VL CDR3	QQANSFPRT
207.	MS_6	VH	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDHYMSWIRQAPGKGLEWISYISNSGSIIYYVDSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDVRTAFDYWGQGTLVTVSS
208.	MS_6	VL	DIQMTQSPSSVSASVGDRVTITCRASQSIGSWLAWYQQKPGKAPNLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQP EDFATYYCQQANSFPRTFGQGTKVDIK
209.	MS_6	scFv	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDHYMSWIRQAPGKGLEWISYISNSGSIIYYVDSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDVRTAFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQS IGSWLAWYQQKPGKAPNLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPRTFGQGTKVDIK
210.	MS_6	bispecific molecule	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDHYMSWIRQAPGKGLEWISYISNSGSIIYYVDSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDVRTAFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQS IGSWLAWYQQKPGKAPNLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPRTFGQGTKVDIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPG GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVL
211.	MS_7	VH CDR1	SKFMT
212.	MS_7	VH CDR2	VIYSGGKTYYADSVKG
213.	MS_7	VH CDR3	DSGGWGYFDY
214.	MS_7	VL CDR1	KSSQSVLYSSNNKNYLA
215.	MS_7	VL CDR2	WASTRES
216.	MS_7	VL CDR3	QQYYSTPPT
217.	MS_7	VH	EVQLVESGGGLIQPGGSLRLSCAVSGFTVSSKFMTWVRQAPGKGLEWVSVIYSGGKTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCARDSGGWGYFDYWGQGTLVTVSS
218.	MS_7	VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLT ISSLQAEDVAVYYCQQYYSTPPTFGQGTKVEIK
219.	MS_7	scFv	EVQLVESGGGLIQPGGSLRLSCAVSGFTVSSKFMTWVRQAPGKGLEWVSVIYSGGKTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCARDSGGWGYFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIVMTQSPDSLAVSLGERATINCKSSQ SVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTPPTFGQG TKVEIK

220.	MS_7	bispecific molecule	EVQLVESGGGLIQPGGSLRLSCAVSGFTVSSKFMTWVRQAPGKGLEWVSVIYSGGKTYYADSVKGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCARDSGGWGYFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIVMTQSPDSLAVSLGERATINCKSSQ SVLYSSNNKNYLAWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTPPTFGQG TKVEIKSGGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKD RFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEP SLTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEY YCVLWYSNRWVFGGGTKLTVL
221.	MS_8	VH CDR1	SYYWN
222.	MS_8	VH CDR2	RIYYNGNTYYNPSLKS
223.	MS_8	VH CDR3	PKLGIDAFDI
224.	MS_8	VL CDR1	TGSSSNIGAGYDVH
225.	MS_8	VL CDR2	GNSNRPS
226.	MS_8	VL CDR3	QSYDSSLSGWV
227.	MS_8	VH	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWNWIRQPPGKGLEWIGRIYYNGNTYYNPSLKSRVTISGDTSKNQFSL KLSSVTAADTAVYYCARPKLGIDAFDIWGQGTMVTVSS
228.	MS_8	VL	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAITGL QAEDEADYYCQSYDSSLSGWVFGGGTKLTVL
229.	MS_8	scFv	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWNWIRQPPGKGLEWIGRIYYNGNTYYNPSLKSRVTISGDTSKNQFSL KLSSVTAADTAVYYCARPKLGIDAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSQSVLTQPPSVSGAPGQRVTISCTGSSS NIGAGYDVHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDSSLSGWVFGGGTK LTVL
230.	MS_8	bispecific molecule	QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWNWIRQPPGKGLEWIGRIYYNGNTYYNPSLKSRVTISGDTSKNQFSL KLSSVTAADTAVYYCARPKLGIDAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSQSVLTQPPSVSGAPGQRVTISCTGSSS NIGAGYDVHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDSSLSGWVFGGGTK LTVLSGGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRF TISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSL TVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYC VLWYSNRWVFGGGTKLTVL
231.	Human MSLN v1 NM_005823	human	MALPTARPLLGSCGTPALGSLLFLLFSLGWVQPSRTLAGETGQEAAPLDGVLANPPNISSLSPRQLLGFPCAEVSGLSTE RVRELAVALAQKNVKLSTEQLRCLAHRLSEPPEDLDALPLDLLLFLNPDAFSGPQACTRFFSRITKANVDLLPRGAPERQ RLLPAALACWGVRGSLLSEADVRALGGLACDLPGRFVAESAEVLLPRLVSCPGPLDQDQQEAARAALQGGGPPYGPPSTW SVSTMDALRGLLPVLGQPIIRSIPQGIVAAWRQRSSRDPSWRQPERTILRPRFREVEKTACPSGKKAREIDESLIFYKK

			WELEACVDAALLATQMDRVNAIPFTYEQLDVLKHKLDELYPQGYPESVIQHLGYLFLKMSPEDIRKWNVTSLETLKALLE VNKGHEMSPQVATLIDRFVKGRGQLDKDTLDTLTAFYPGYLCSLSPEELSSVPPSSIWAVRPQDLDTCDPRQLDVLYPKA RLAFQNMNGSEYFVKIQSFLGGAPTEDLKALSQQNVSMDLATFMKLRTDAVLPLTVAEVQKLLGPHVEGLKAEERHRPVR DWILRQRQDDLDTLGLGLQGGIPNGYLVLDLSMQEALSGTPCLLGPGPVLTVLALLLASTLA
232.	Human MSLN v2 NM_013404	human	MALPTARPLLGSCGTPALGSLLFLLFSLGWVQPSRTLAGETGQEAAPLDGVLANPPNISSLSPRQLLGFPCAEVSGLSTE RVRELAVALAQKNVKLSTEQLRCLAHRLSEPPEDLDALPLDLLLFLNPDAFSGPQACTRFFSRITKANVDLLPRGAPERQ RLLPAALACWGVRGSLLSEADVRALGGLACDLPGRFVAESAEVLLPRLVSCPGPLDQDQQEAARAALQGGGPPYGPPSTW SVSTMDALRGLLPVLGQPIIRSIPQGIVAAWRQRSSRDPSWRQPERTILRPRFRREVEKTACPSGKKAREIDESLIFYKK WELEACVDAALLATQMDRVNAIPFTYEQLDVLKHKLDELYPQGYPESVIQHLGYLFLKMSPEDIRKWNVTSLETLKALLE VNKGHEMSPQAPRRPLPQVATLIDRFVKGRGQLDKDTLDTLTAFYPGYLCSLSPEELSSVPPSSIWAVRPQDLDTCDPRQ LDVLYPKARLAFQNMNGSEYFVKIQSFLGGAPTEDLKALSQQNVSMDLATFMKLRTDAVLPLTVAEVQKLLGPHVEGLKA EERHRPVRDWILRQRQDDLDTLGLGLQGGIPNGYLVLDLSMQEALSGTPCLLGPGPVLTVLALLLASTLA
233.	Human MSLN v6 AY743922	human	MALPTARPLLGSCGTPALGSLLFLLFSLGWVQPSRTLAGETGQEAAPLDGVLANPPNISSLSPRQLLGFPCAEVSGLSTE RVRELAVALAQKNVKLSTEQLRCLAHRLSEPPEDLDALPLDLLLFLNPDAFSGPQACTHFFSRITKANVDLLPRGAPERQ RLLPAALACWGVRGSLLSEADVRALGGLACDLPGRFVAESAEVLLPRLVSCPGPLDQDQQEAARAALQGGGPPYGPPSTW SVSTMDALRGLLPVLGQPIIRSIPQGIVAAWRQRSSRDPSWRQPERTILRPRFRREVEKTACPSGKKAREIDESLIFYKK WELEACVDAALLATQMDRVNAIPFTYEQLDVLKHKLDELYPQGYPESVIQHLGYLFLKMSPEDIRKWNVTSLETLKALLE VNKGHEMSPQVATLIDRFVKGRGQLDKDTLDTLTAFYPGYLCSLSPEELSSVPPSSIWAVRPQDLDTCDPRQLDVLYPKA RLAFQNMNGSEYFVKIQSFLGGAPTEDLKALSQQNVSMDLATFMKLRTDAVLPLTVAEVQKLLGPHVEGLKAEERHRPVR DWILRQRQDDLDTLGLGLQGGIPNGYLVLDLSVQEALSGTPCLLGPGPVLTVLALLLASTLA
234.	cyno MSLN v1 LMR C52457	macaque	MALPMARPLSGSCGTPALGSLLFLLFSLGWVQPSRVLAGETRQEAAPLDGILTNAPDIASLSPRQLLGFTCVEVSGLSTE LVQELAVALGQKNVKLSAEQLRCLAHRLSEPPEDLDALPLDLLLFLNPDAFSGPQACTHFFSRVAKANVDLLPRGAPERQ RLLPAALTCWGVRGSLLSEADVRALGGLACDLPGRFVAESAEVVLPRLVRCLGPLDQDQQEAARAALQRGGPPYGPPSTW SISTLDDLQSLLPVLGQPVIHSIPQGILAAWRQRSSRDPSWQQPEQTVLRPRFRRDVERTTCPPEKEVHEIDENLIFYKK RELEACVDAALLAAQMDRVDAIPFTYEQLDVLKHKLDELYPQGYPESVIRHLGHLFLKMSPEDIRKWNVTSLETLKALLK VSKGHEMSAQVATLIDRVVVGRGQLDKDTADTLTAFCPGCLCSLSPERLSSVPPSVIGAVRPQDLDTCGPRQLDVLYPKA RLAFQNMSGSEYFVKIRPFLGGAPTEDLKALSQQNVSMDLATFMKLRREAVLPLTVAEVQKLLGPHVEGLKVEEQHSPVR DWILKQRQDDLDTLGLGLQGGIPNGYLILDLSVREALSGTPCLLGPGPVLTILALLLASTLA
235.	Megakaryocyte-potentiating factor NM_005823	human	MALPTARPLLGSCGTPALGSLLFLLFSLGWVQPSRTLAGETGQEAAPLDGVLANPPNISSLSPRQLLGFPCAEVSGLSTE RVRELAVALAQKNVKLSTEQLRCLAHRLSEPPEDLDALPLDLLLFLNPDAFSGPQACTRFFSRITKANVDLLPRGAPERQ RLLPAALACWGVRGSLLSEADVRALGGLACDLPGRFVAESAEVLLPRLVSCPGPLDQDQQEAARAALQGGGPPYGPPSTW SVSTMDALRGLLPVLGQPIIRSIPQGIVAAWRQRSSRDPSWRQPER
236.	MSLN, cleaved form NM_005823	human	EVEKTACPSGKKAREIDESLIFYKKWELEACVDAALLATQMDRVNAIPFTYEQLDVLKHKLDELYPQGYPESVIQHLGYL FLKMSPEDIRKWNVTSLETLKALLEVNKGHEMSPQVATLIDRFVKGRGQLDKDTLDTLTAFYPGYLCSLSPEELSSVPPS SIWAVRPQDLDTCDPRQLDVLYPKARLAFQNMNGSEYFVKIQSFLGGAPTEDLKALSQQNVSMDLATFMKLRTDAVLPLT VAEVQKLLGPHVEGLKAEERHRPVRDWILRQRQDDLDTLGLGLQGGIPNGYLVLDLSMQEALS
237.	C-terminal cleavage NM_005823	human	GTPCLLGPGPVLTVLALLLASTLA
238.	MSLN-E 1	human	EVEKTACPSGKKAREIDESLIFYKKWELEACVDAALLATQMDRVNAIPFTY

239.	MSLN-E 2	human	EQLDVLKHKLDELYPQGYPESVIQHLGYLFLKMSPEDI
240.	MSLN-E 3	human	RKWNVTSLETLKALLEVNKGHEMSPQVATLIDRFVKGRGQLDKDTLDTLTAFYPGYLCSLSPEELSSVP
241.	MSLN-E 4	human	PSSIWAVRPQDLDTCDPRQLDVLYPKARLAFQNMNGSEYFVKIQSFLG
242.	MSLN-E 5	human	GAPTEDLKALSQQNVSMDLATFMKLRTDAVLPLTVAEVQKLLGP
243.	MSLN-E 6	human	HVEGLKAEERHRPVRDWILRQRQDDLDTLGLGLQGGIPNGYLVLDLSMQEAL
244.	MSLN-E 1+2	human	EVEKTACPSGKKAREIDESLIFYKKWELEACVDAALLATQMDRVNAIPFTYEQLDVLKHKLDELYPQGYPESVIQHLGYL FLKMSPEDI
245.	MSLN-E 2+3	human	EQLDVLKHKLDELYPQGYPESVIQHLGYLFLKMSPEDIRKWNVTSLETLKALLEVNKGHEMSPQVATLIDRFVKGRGQLD KDTLDTLTAFYPGYLCSLSPEELSSVP
246.	hu orl MSLN-E1 mu	artificial	MALPTARPLLGSCGTPALGSLLFLLFSLGWVQPSRTLAGETGQEAAPLDGVLANPPNISSLSPRQLLGFPCAEVSGLSTE RVRELAVALAQKNVKLSTEQLRCLAHRLSEPPEDLDALPLDLLLFLNPDAFSGPQACTRFFSRITKANVDLLPRGAPERQ RLLPAALACWGVRGSLLSEADVRALGGLACDLPGRFVAESAEVLLPRLVSCPGPLDQDQQEAARAALQGGGPPYGPPSTW SVSTMDALRGLLPVLGQPIIRSIPQGIVAAWRQRSSRDPSWRQPERTILRPRFRRDAEQKACPPGKEPYKVDEDLIFYQN WELEACVDGTMLARQMDLVNEIPFTYEQLDVLKHKLDELYPQGYPESVIQHLGYLFLKMSPEDIRKWNVTSLETLKALLE VNKGHEMSPQVATLIDRFVKGRGQLDKDTLDTLTAFYPGYLCSLSPEELSSVPPSSIWAVRPQDLDTCDPRQLDVLYPKA RLAFQNMNGSEYFVKIQSFLGGAPTEDLKALSQQNVSMDLATFMKLRTDAVLPLTVAEVQKLLGPHVEGLKAEERHRPVR DWILRQRQDDLDTLGLGLQGGIPNGYLVLDLSMQEALSGTPCLLGPGPVLTVLALLLASTLA
247.	hu orl MSLN-E2 mu	artificial	MALPTARPLLGSCGTPALGSLLFLLFSLGWVQPSRTLAGETGQEAAPLDGVLANPPNISSLSPRQLLGFPCAEVSGLSTE RVRELAVALAQKNVKLSTEQLRCLAHRLSEPPEDLDALPLDLLLFLNPDAFSGPQACTRFFSRITKANVDLLPRGAPERQ RLLPAALACWGVRGSLLSEADVRALGGLACDLPGRFVAESAEVLLPRLVSCPGPLDQDQQEAARAALQGGGPPYGPPSTW SVSTMDALRGLLPVLGQPIIRSIPQGIVAAWRQRSSRDPSWRQPERTILRPRFRREVEKTACPSGKKAREIDESLIFYKK WELEACVDAALLATQMDRVNAIPFTYEQLSIFKHKLDKTYPQGYPESLIQQLGHFFRYVSPEDIRKWNVTSLETLKALLE VNKGHEMSPQVATLIDRFVKGRGQLDKDTLDTLTAFYPGYLCSLSPEELSSVPPSSIWAVRPQDLDTCDPRQLDVLYPKA RLAFQNMNGSEYFVKIQSFLGGAPTEDLKALSQQNVSMDLATFMKLRTDAVLPLTVAEVQKLLGPHVEGLKAEERHRPVR DWILRQRQDDLDTLGLGLQGGIPNGYLVLDLSMQEALSGTPCLLGPGPVLTVLALLLASTLA
248.	hu orl MSLN-E3 mu	artificial	MALPTARPLLGSCGTPALGSLLFLLFSLGWVQPSRTLAGETGQEAAPLDGVLANPPNISSLSPRQLLGFPCAEVSGLSTE RVRELAVALAQKNVKLSTEQLRCLAHRLSEPPEDLDALPLDLLLFLNPDAFSGPQACTRFFSRITKANVDLLPRGAPERQ RLLPAALACWGVRGSLLSEADVRALGGLACDLPGRFVAESAEVLLPRLVSCPGPLDQDQQEAARAALQGGGPPYGPPSTW SVSTMDALRGLLPVLGQPIIRSIPQGIVAAWRQRSSRDPSWRQPERTILRPRFRREVEKTACPSGKKAREIDESLIFYKK WELEACVDAALLATQMDRVNAIPFTYEQLDVLKHKLDELYPQGYPESVIQHLGYLFLKMSPEDIHQWNVTSPDTVKTLLK VSKGQKMNAQAIALVACYLRGGGQLDEDMVKALGDIPLSYLCDFSPQDLHSVPPSSIWAVRPQDLDTCDPRQLDVLYPKA RLAFQNMNGSEYFVKIQSFLGGAPTEDLKALSQQNVSMDLATFMKLRTDAVLPLTVAEVQKLLGPHVEGLKAEERHRPVR DWILRQRQDDLDTLGLGLQGGIPNGYLVLDLSMQEALSGTPCLLGPGPVLTVLALLLASTLA
249.	hu orl MSLN-E4 mu	artificial	MALPTARPLLGSCGTPALGSLLFLLFSLGWVQPSRTLAGETGQEAAPLDGVLANPPNISSLSPRQLLGFPCAEVSGLSTE RVRELAVALAQKNVKLSTEQLRCLAHRLSEPPEDLDALPLDLLLFLNPDAFSGPQACTRFFSRITKANVDLLPRGAPERQ RLLPAALACWGVRGSLLSEADVRALGGLACDLPGRFVAESAEVLLPRLVSCPGPLDQDQQEAARAALQGGGPPYGPPSTW SVSTMDALRGLLPVLGQPIIRSIPQGIVAAWRQRSSRDPSWRQPERTILRPRFRREVEKTACPSGKKAREIDESLIFYKK WELEACVDAALLATQMDRVNAIPFTYEQLDVLKHKLDELYPQGYPESVIQHLGYLFLKMSPEDIRKWNVTSLETLKALLE

			VNKGHEMSPQVATLIDRFVKGRGQLDKDTLDTLTAFYPGYLCSLSPEELSSVPSSVMWLVGPQDLDKCSQRHLGLLYQKA CSAFQNVSGLEYFEKIKTFLGGAPTEDLKALSQQNVSMDLATFMKLRTDAVLPLTVAEVQKLLGPHVEGLKAEERHRPVR DWILRQRQDDLDTLGLGLQGGIPNGYLVLDLSMQEALSGTPCLLGPGPVLTVLALLLASTLA
250.	hu orl MSLN-E5 mu	artificial	MALPTARPLLGSCGTPALGSLLFLLFSLGWVQPSRTLAGETGQEAAPLDGVLANPPNISSLSPRQLLGFPCAEVSGLSTE RVRELAVALAQKNVKLSTEQLRCLAHRLSEPPEDLDALPLDLLLFLNPDAFSGPQACTRFFSRITKANVDLLPRGAPERQ RLLPAALACWGVRGSLLSEADVRALGGLACDLPGRFVAESAEVLLPRLVSCPGPLDQDQQEAARAALQGGGPPYGPPSTW SVSTMDALRGLLPVLGQPIIRSIPQGIVAAWRQRSSRDPSWRQPERTILRPRFRREVEKTACPSGKKAREIDESLIFYKK WELEACVDAALLATQMDRVNAIPFTYEQLDVLKHKLDELYPQGYPESVIQHLGYLFLKMSPEDIRKWNVTSLETLKALLE VNKGHEMSPQVATLIDRFVKGRGQLDKDTLDTLTAFYPGYLCSLSPEELSSVPPSSIWAVRPQDLDTCDPRQLDVLYPKA RLAFQNMNGSEYFVKIQSFLGGASVKDLRALSQHNVSMDIATFKRLQVDSLVGLSVAEVQKLLGPHVEGLKAEERHRPVR DWILRQRQDDLDTLGLGLQGGIPNGYLVLDLSMQEALSGTPCLLGPGPVLTVLALLLASTLA
251.	hu orl MSLN-E6 mu	artificial	MALPTARPLLGSCGTPALGSLLFLLFSLGWVQPSRTLAGETGQEAAPLDGVLANPPNISSLSPRQLLGFPCAEVSGLSTE RVRELAVALAQKNVKLSTEQLRCLAHRLSEPPEDLDALPLDLLLFLNPDAFSGPQACTRFFSRITKANVDLLPRGAPERQ RLLPAALACWGVRGSLLSEADVRALGGLACDLPGRFVAESAEVLLPRLVSCPGPLDQDQQEAARAALQGGGPPYGPPSTW SVSTMDALRGLLPVLGQPIIRSIPQGIVAAWRQRSSRDPSWRQPERTILRPRFRREVEKTACPSGKKAREIDESLIFYKK WELEACVDAALLATQMDRVNAIPFTYEQLDVLKHKLDELYPQGYPESVIQHLGYLFLKMSPEDIRKWNVTSLETLKALLE VNKGHEMSPQVATLIDRFVKGRGQLDKDTLDTLTAFYPGYLCSLSPEELSSVPPSSIWAVRPQDLDTCDPRQLDVLYPKA RLAFQNMNGSEYFVKIQSFLGGAPTEDLKALSQQNVSMDLATFMKLRTDAVLPLTVAEVQKLLGPNIVDLKTEEDKSPVR DWLFRQHQKDLDRLGLGLQGGIPNGYLVLDLFNVREAFSGTPCLLGPGPVLTVLALLLASTLA
252.	Fc monomer-1 +c/-g		DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTY RCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
253.	Fc monomer-2 +c/- g/delGK		DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTY RCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
254.	Fc monomer-3 -c/+g		DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
255.	Fc monomer-4 - c/+g/delGK		DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
256.	Fc monomer-5 -c/-g		DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

257.	Fc monomer-6 -c/-g/delGK		DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
258.	Fc monomer-7 +c/+g		DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYNSTY RCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
259.	Fc monomer-8 +c/+g/delGK		DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYNSTY RCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
260.	scFc-1		DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTY RCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGG GSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK
261.	scFc-2		DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTY RCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGGGSGGGGSGGGS GGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
262.	scFc-3		DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGG GSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK
263.	scFc-4		DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGGGSGGGGSGGGS GGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
264.	scFc-5		DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE

			WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGG GSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK
265.	scFc-6		DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYGSTY RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGGSGGGGSGGGS GGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
266.	scFc-7		DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYNSTY RCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGG GSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE VHNAKTKPCEEQYNSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK
267.	scFc-8		DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYNSTY RCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGGSGGGGSGGGS GGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPCEEQYNSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL TCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP
268.	MS_1xCD3-scFc	Bispecific HLE molecule	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIGSIYYSGITNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARPSNYDAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSQSVLTQPPSVSGAPGQRVTISCTGSS SNIGAGYDVHWYQQVPGTAPKLLIYGNSKRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDSSLGGWVFGGGT KLTVLSGGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDR FTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPS LTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYY CVLWYSNRWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGKGGGGSGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK
269.	MS_1xCD3-scFc_delGK	Bispecific HLE molecule	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIGSIYYSGITNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARPSNYDAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSQSVLTQPPSVSGAPGQRVTISCTGSS SNIGAGYDVHWYQQVPGTAPKLLIYGNSKRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDSSLGGWVFGGGT

			KLTVLSGGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDR FTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPS LTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYY CVLWYSNRWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGGGSGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK
270.	MS_1_CCx CD3-scFc	Bispecifi c HLE molecule	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKCLEWIGSIYYSGITNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARPSNYDAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSQSVLTQPPSVSGAPGQRVTISCTGSS SNIGAGYDVHWYQQVPGTAPKLLIYGNSKRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDSSLGGWVFGCGT KLTVLSGGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDR FTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPS LTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYY CVLWYSNRWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGKGGGGSGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK
271.	MS_1_CCx CD3-scFc_delGK	Bispecifi c HLE molecule	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKCLEWIGSIYYSGITNYNPSLKSRVTISVDTSKNQF SLKLSSVTAADTAVYYCARPSNYDAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSQSVLTQPPSVSGAPGQRVTISCTGSS SNIGAGYDVHWYQQVPGTAPKLLIYGNSKRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDSSLGGWVFGCGT KLTVLSGGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDR FTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPS LTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYY CVLWYSNRWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGGGSGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGK
272.	MS_2xCD3 -scFc	Bispecifi c HLE molecule	QVQLVESGGGVVQPGRSLRLSCAASGFTFSDHYMSWIRQTPGKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDLGPSFDYWGQGSLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQG ISSWLAWYQQKPGKAPKLLIDAASRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPRTFGQGTKVEIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPG

			GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGKGGGGSGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK
273.	MS_2xCD3 - scFc_delGK	Bispecifi c HLE molecule	QVQLVESGGGVVQPGRSLRLSCAASGFTFSDHYMSWIRQTPGKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDLGPSFDYWGQGSLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQG ISSWLAWYQQKPGKAPKLLIDAASRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPRTFGQGTKVEIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPG GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGKGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK
274.	MS_2_CCx CD3-scFc	Bispecifi c HLE molecule	QVQLVESGGGVVQPGRSLRLSCAASGFTFSDHYMSWIRQTPGKCLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDLGPSFDYWGQGSLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQG ISSWLAWYQQKPGKAPKLLIDAASRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPRTFGCGTKVEIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPG GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS LSPGKGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK
275.	MS_2_CCx CD3-scFc_delGK	Bispecifi c HLE molecule	QVQLVESGGGVVQPGRSLRLSCAASGFTFSDHYMSWIRQTPGKCLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDLGPSFDYWGQGSLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQG ISSWLAWYQQKPGKAPKLLIDAASRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPRTFGCGTKVEIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPG GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV

			EVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGGGGSGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK
276.	MS_3xCD3-scFc	Bispecifi c HLE molecule	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWIRQAPGKGLEWISYISSSGSTIYYADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDRNSHFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQG ITRWLAWYQQKPGKAPKLLIYAASVLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSNSFPRTFGQGTKVEIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPG GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGKGGGGSGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
277.	MS_3xCD3-scFc_delGK	Bispecifi c HLE molecule	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWIRQAPGKGLEWISYISSSGSTIYYADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDRNSHFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQG ITRWLAWYQQKPGKAPKLLIYAASVLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSNSFPRTFGQGTKVEIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQG GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGGGGSGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK
278.	MS_3_CCx CD3-scFc	Bispecifi c HLE molecule	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWIRQAPGKCLEWISYISSSGSTIYYADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDRNSHFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQG ITRWLAWYQQKPGKAPKLLIYAASVLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSNSFPRTFGCGTKVEIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPG GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS

			LSPGKGGGGSGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK
279.	MS_3_CCx CD3-scFc_delGK	Bispecifi c HLE molecule	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWIRQAPGKCLEWISYISSSGSTIYYADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDRNSHFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQG ITRWLAWYQQKPGKAPKLLIYAASVLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSNSFPRTFGCGTKVEIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPG GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK
280.	MS_4xCD3 -scFc	Bispecifi c HLE molecule	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWIRQAPGKGLEWLSYISSSGSTIYYADSVKGRFTISRDNAKNSLF LQMNSLRAEDTAVYYCARDRNSHFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQG INTWLAWYQQKPGKAPKLLIYGASGLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAKSFPRTFGQGTKVEIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPG GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGKGGGGSGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK
281.	MS_4xCD3 - scFc_delGK	Bispecifi c HLE molecule	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWIRQAPGKGLEWLSYISSSGSTIYYADSVKGRFTISRDNAKNSLF LQMNSLRAEDTAVYYCARDRNSHFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQG INTWLAWYQQKPGKAPKLLIYGASGLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAKSFPRTFGQGTKVEIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPG GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGKGGGGSGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ

			VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK
282.	MS_4_CCx CD3-scFc	Bispecifi c HLE molecule	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWIRQAPGKCLEWLSYISSSGSTIYYADSVKGRFTISRDNAKNSLF LQMNSLRAEDTAVYYCARDRNSHFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQG INTWLAWYQQKPGKAPKLLIYGASGLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAKSFPRTFGCGTKVEIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPG GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK
283.	MS_4_CCx CD3-scFc_delGK	Bispecifi c HLE molecule	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMTWIRQAPGKCLEWLSYISSSGSTIYYADSVKGRFTISRDNAKNSLF LQMNSLRAEDTAVYYCARDRNSHFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQG INTWLAWYQQKPGKAPKLLIYGASGLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQAKSFPRTFGCGTKVEIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPG GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK LSPGKGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK
284.	MS_5xCD3 -scFc	Bispecifi c HLE molecule	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDHYMSWIRQAPGKGLEWFSYISSSGGIIYYADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDVGSHFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQD ISRWLAWYQQKPGKAPKLLISAASRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFAIYYCQQAKSFPRTFGQGTKVEIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPG GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK LSPGKGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK

285.	MS_5xCD3 - scFc_delGK	Bispecifi c HLE molecule	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDHYMSWIRQAPGKGLEWFSYISSSGGIIYYADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDVGSHFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQD ISRWLAWYQQKPGKAPKLLISAASRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFAIYYCQQAKSFPRTFGQGTKVEIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPG GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGGGGSGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK
286.	MS_5_CCx CD3-scFc	Bispecifi c HLE molecule	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDHYMSWIRQAPGKCLEWFSYISSSGGIIYYADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDVGSHFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQD ISRWLAWYQQKPGKAPKLLISAASRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFAIYYCQQAKSFPRTFGCGTKVEIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPG GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGKGGGGSGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK
287.	MS_5_CCx CD3-scFc_delGK	Bispecifi c HLE molecule	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDHYMSWIRQAPGKCLEWFSYISSSGGIIYYADSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDVGSHFDYWGQGTLVTVSSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQD ISRWLAWYQQKPGKAPKLLISAASRLQSGVPSRFSGSGSGTDFTLTISSLQPEDFAIYYCQQAKSFPRTFGCGTKVEIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPG GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGGGGSGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK
288.	MS_6xCD3	Bispecifi	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDHYMSWIRQAPGKGLEWISYISNSGSIIYYVDSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDVRTAFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQS

	-scFc	c HLE molecule	IGSWLAWYQQKPGKAPNLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPRTFGQGTKVDIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPG GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGKGGGGSGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK
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290.	MS_6_CCx CD3-scFc	Bispecifi c HLE molecule	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDHYMSWIRQAPGKCLEWISYISNSGSIIYYVDSVKGRFTISRDNAKNSLY LQMNSLRAEDTAVYYCARDVRTAFDYWGQGTLVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSVSASVGDRVTITCRASQS IGSWLAWYQQKPGKAPNLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPRTFGCGTKVDIKS GGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRD DSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPG GTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYS NRWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGKGGGGSGGGGSGGGGSGGGGSGGGGSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK
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<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 11

Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
1 5 10

<210> 12
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 12

Gly Thr Lys Phe Leu Ala Pro
1 5

<210> 13
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 13

Ala Leu Trp Tyr Ser Asn Arg Trp Val
1 5

<210> 14
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 14

Ile Tyr Ala Met Asn
1 5

<210> 15

<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 15

Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Ser

<210> 16
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 16

His Gly Asn Phe Gly Asn Ser Tyr Val Ser Phe Phe Ala Tyr
1 5 10

<210> 17
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 17

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

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ile Tyr
20 25 30

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

Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp

```
    50                  55                  60

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

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

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Phe Phe
            100                 105                 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125
```

<210> 18
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 18

```
Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1               5                   10                  15

Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly
            20                  25                  30

Tyr Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45

Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe
    50                  55                  60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65                  70                  75                  80

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95

Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
```

100 105

<210> 19
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 19

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

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ile Tyr
20 25 30

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

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

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

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

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Phe Phe
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
130 135 140

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145 150 155 160

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn

```
                165                 170                 175

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
            180                 185                 190

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
        195                 200                 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
    210                 215                 220

Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Arg Trp Val Phe
225                 230                 235                 240

Gly Gly Gly Thr Lys Leu Thr Val Leu
                245
```

<210> 20
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 20

```
Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
1               5                   10
```

<210> 21
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 21

```
Gly Thr Lys Phe Leu Ala Pro
1               5
```

<210> 22
<211> 9
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 22

Ala Leu Trp Tyr Ser Asn Arg Trp Val
1 5

<210> 23
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 23

Lys Tyr Ala Met Asn
1 5

<210> 24
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 24

Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Asp

<210> 25
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 25

His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr

1 5 10

<210> 26
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 26

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

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
20 25 30

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

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

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

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

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 27
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 27

```
Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly
1               5                   10                  15


Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly
            20                  25                  30


Tyr Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45


Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe
    50                  55                  60


Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65                  70                  75                  80


Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95


Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105


<210>  28
<211>  249
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  28

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


Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
            20                  25                  30


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


Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50                  55                  60
```

```
Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65                  70                  75                  80

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

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
            100                 105                 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
    130                 135                 140

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145                 150                 155                 160

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
                165                 170                 175

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
            180                 185                 190

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
        195                 200                 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
    210                 215                 220

Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Arg Trp Val Phe
225                 230                 235                 240

Gly Gly Gly Thr Lys Leu Thr Val Leu
                245
```

<210> 29
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 29

Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
1   5   10

<210> 30
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 30

Gly Thr Lys Phe Leu Ala Pro
1   5

<210> 31
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 31

Ala Leu Trp Tyr Ser Asn Arg Trp Val
1   5

<210> 32
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 32

Ser Tyr Ala Met Asn
1   5

<210> 33
<211> 19
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 33

Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Gly

<210> 34
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 34

His Gly Asn Phe Gly Asn Ser Tyr Leu Ser Phe Trp Ala Tyr
1 5 10

<210> 35
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 35

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

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

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

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

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


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


Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Leu Ser Phe Trp
            100                 105                 110


Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125


<210>  36
<211>  109
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  36

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


Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly
            20                  25                  30


Tyr Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45


Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe
    50                  55                  60


Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65                  70                  75                  80


Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95


Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105
```

<210> 37
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 37

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


Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30


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


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


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


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


Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Leu Ser Phe Trp
            100                 105                 110


Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
    130                 135                 140


Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145                 150                 155                 160


Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
                165                 170                 175
```

```
Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
            180                 185                 190


Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
        195                 200                 205


Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
    210                 215                 220


Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Arg Trp Val Phe
225                 230                 235                 240


Gly Gly Gly Thr Lys Leu Thr Val Leu
                245
```

<210> 38
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 38

```
Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
1               5                   10
```

<210> 39
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 39

```
Gly Thr Lys Phe Leu Ala Pro
1               5
```

<210> 40
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 40

Ala Leu Trp Tyr Ser Asn Arg Trp Val
1   5

<210> 41
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 41

Arg Tyr Ala Met Asn
1   5

<210> 42
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 42

Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser
1   5   10   15

Val Lys Gly

<210> 43
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 43

His Gly Asn Phe Gly Asn Ser Tyr Leu Ser Tyr Phe Ala Tyr
1   5   10

<210> 44
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 44

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

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Arg Tyr
20 25 30

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

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

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

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

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Leu Ser Tyr Phe
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 45
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 45

Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly

```
1               5                   10                  15

Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly
            20                  25                  30

Tyr Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45

Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe
    50                  55                  60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65                  70                  75                  80

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95

Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105


<210>  46
<211>  249
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  46

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

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Arg Tyr
            20                  25                  30

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

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

Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
```

65 70 75 80

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

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Leu Ser Tyr Phe
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
130 135 140

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145 150 155 160

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
165 170 175

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
180 185 190

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
195 200 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
210 215 220

Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Arg Trp Val Phe
225 230 235 240

Gly Gly Gly Thr Lys Leu Thr Val Leu
245

<210> 47
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 47

Arg Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
1 5 10

<210> 48
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 48

Ala Thr Asp Met Arg Pro Ser
1 5

<210> 49
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 49

Ala Leu Trp Tyr Ser Asn Arg Trp Val
1 5

<210> 50
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 50

Val Tyr Ala Met Asn
1 5

<210> 51
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 51

Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser
1   5   10   15

Val Lys Lys

<210> 52
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 52

His Gly Asn Phe Gly Asn Ser Tyr Leu Ser Trp Trp Ala Tyr
1   5   10

<210> 53
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 53

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

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Val Tyr
            20   25   30

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

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

Ser Val Lys Lys Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr

65 70 75 80

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

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Leu Ser Trp Trp
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 54
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 54

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

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

Tyr Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
35 40 45

Leu Ile Gly Ala Thr Asp Met Arg Pro Ser Gly Thr Pro Ala Arg Phe
50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65 70 75 80

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
85 90 95

Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 55

<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 55

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


Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Val Tyr
            20                  25                  30


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


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


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


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


Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Leu Ser Trp Trp
            100                 105                 110


Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
    130                 135                 140


Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145                 150                 155                 160


Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
                165                 170                 175


Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Ala
```

```
            180                 185                 190

Thr Asp Met Arg Pro Ser Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
        195                 200                 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
    210                 215                 220

Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Arg Trp Val Phe
225                 230                 235                 240

Gly Gly Gly Thr Lys Leu Thr Val Leu
                245
```

<210> 56
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 56

```
Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
1               5                   10
```

<210> 57
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 57

```
Gly Thr Lys Phe Leu Ala Pro
1               5
```

<210> 58
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 58

Ala Leu Trp Tyr Ser Asn Arg Trp Val
1 5

<210> 59
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 59

Lys Tyr Ala Met Asn
1 5

<210> 60
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 60

Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Ser

<210> 61
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 61

His Gly Asn Phe Gly Asn Ser Tyr Thr Ser Tyr Tyr Ala Tyr
1 5 10

<210> 62

<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 62

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

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
20 25 30

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

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

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

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

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Thr Ser Tyr Tyr
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 63
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 63

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

```
Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly
            20                  25                  30

Tyr Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45

Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe
    50                  55                  60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65                  70                  75                  80

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95

Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105
```

<210> 64
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 64

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

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
            20                  25                  30

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

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

Ser Val Lys Ser Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65                  70                  75                  80
```

```
Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Thr Ser Tyr Tyr
            100                 105                 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
    130                 135                 140

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145                 150                 155                 160

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
                165                 170                 175

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
            180                 185                 190

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
        195                 200                 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
    210                 215                 220

Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Arg Trp Val Phe
225                 230                 235                 240

Gly Gly Gly Thr Lys Leu Thr Val Leu
                245
```

<210> 65
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 65

Arg Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
1 5 10

<210> 66
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 66

Ala Thr Asp Met Arg Pro Ser
1 5

<210> 67
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 67

Ala Leu Trp Tyr Ser Asn Arg Trp Val
1 5

<210> 68
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 68

Gly Tyr Ala Met Asn
1 5

<210> 69
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 69

Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Glu

<210> 70
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 70

His Arg Asn Phe Gly Asn Ser Tyr Leu Ser Trp Phe Ala Tyr
1 5 10

<210> 71
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 71

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

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Gly Tyr
20 25 30

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

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

Ser Val Lys Glu Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

```
Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95


Tyr Cys Val Arg His Arg Asn Phe Gly Asn Ser Tyr Leu Ser Trp Phe
            100                 105                 110


Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125


<210>  72
<211>  109
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  72

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


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


Tyr Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45


Leu Ile Gly Ala Thr Asp Met Arg Pro Ser Gly Thr Pro Ala Arg Phe
    50                  55                  60


Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65                  70                  75                  80


Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95


Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105


<210>  73
<211>  249
<212>  PRT
```

<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 73

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

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Gly Tyr
20 25 30

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

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

Ser Val Lys Glu Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

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

Tyr Cys Val Arg His Arg Asn Phe Gly Asn Ser Tyr Leu Ser Trp Phe
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
130 135 140

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145 150 155 160

Thr Cys Arg Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
165 170 175

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Ala
180 185 190

Thr Asp Met Arg Pro Ser Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
195 200 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
210 215 220

Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Arg Trp Val Phe
225 230 235 240

Gly Gly Gly Thr Lys Leu Thr Val Leu
245

<210> 74
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 74

Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
1 5 10

<210> 75
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 75

Gly Thr Lys Phe Leu Ala Pro
1 5

<210> 76
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 76

Ala Leu Trp Tyr Ser Asn Arg Trp Val
1 5

<210> 77
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 77

Val Tyr Ala Met Asn
1 5

<210> 78
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 78

Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Lys

<210> 79
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 79

His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Trp Trp Ala Tyr
1 5 10

<210> 80
<211> 125
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 80

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

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Val Tyr
20 25 30

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

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

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

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

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Trp Trp
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 81
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 81

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

Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly

```
            20                  25                  30

Tyr Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45

Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe
    50                  55                  60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65                  70                  75                  80

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn
                85                  90                  95

Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105


<210>  82
<211>  249
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  82

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

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Val Tyr
            20                  25                  30

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

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

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

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
```

```
                85                  90                  95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Trp Trp
            100                 105                 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
    130                 135                 140

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145                 150                 155                 160

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Tyr Tyr Pro Asn
                165                 170                 175

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
            180                 185                 190

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
        195                 200                 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
    210                 215                 220

Glu Ala Glu Tyr Tyr Cys Ala Leu Trp Tyr Ser Asn Arg Trp Val Phe
225                 230                 235                 240

Gly Gly Gly Thr Lys Leu Thr Val Leu
                245
```

<210> 83
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 83

```
Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
```

1 5 10

<210> 84
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 84

Gly Thr Lys Phe Leu Ala Pro
1 5

<210> 85
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 85

Val Leu Trp Tyr Ser Asn Arg Trp Val
1 5

<210> 86
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 86

Ser Tyr Ala Met Asn
1 5

<210> 87
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 87

```
Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser
1               5                   10                  15


Val Lys Gly



<210>  88
<211>  14
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  88

His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Trp Ala Tyr
1               5                   10


<210>  89
<211>  125
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  89

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


Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30


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


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


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


Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
```

85 90 95

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Trp
100 105 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 90
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 90

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

Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly
20 25 30

Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
35 40 45

Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe
50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65 70 75 80

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn
85 90 95

Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> 91
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 91

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


Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
            20                  25                  30


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


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


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


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


Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Trp
            100                 105                 110


Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125


Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
    130                 135                 140


Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145                 150                 155                 160


Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
                165                 170                 175


Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
            180                 185                 190


Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
```

195 200 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
210 215 220

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
225 230 235 240

Gly Gly Gly Thr Lys Leu Thr Val Leu
245

<210> 92
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 92

Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
1 5 10

<210> 93
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 93

Gly Thr Lys Phe Leu Ala Pro
1 5

<210> 94
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 94

Val Leu Trp Tyr Ser Asn Arg Trp Val

1 5

<210> 95
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 95

Lys Tyr Ala Met Asn
1 5

<210> 96
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 96

Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Asp

<210> 97
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 97

His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr
1 5 10

<210> 98
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 98

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

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
            20   25   30

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

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

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

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

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
            100   105   110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120   125

<210> 99
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 99

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

Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly
            20   25   30

```
Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35                  40                  45

Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe
    50                  55                  60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65                  70                  75                  80

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn
                85                  90                  95

Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105
```

<210> 100
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 100

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

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr
            20                  25                  30

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

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

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

Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95
```

```
Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp
            100                 105                 110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
    130                 135                 140

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145                 150                 155                 160

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
                165                 170                 175

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
            180                 185                 190

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
        195                 200                 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
    210                 215                 220

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
225                 230                 235                 240

Gly Gly Gly Thr Lys Leu Thr Val Leu
                245
```

<210> 101
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 101

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

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

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

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

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

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

Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Trp
            100   105   110

Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115   120   125

<210> 102
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 102

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

Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly
            20   25   30

Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly
        35   40   45

Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe
    50   55   60

```
Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val
65                  70                  75                  80


Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn
                85                  90                  95


Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105


<210>  103
<211>  249
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  103

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


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


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


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


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


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


Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser Tyr Val Ser Trp Trp
            100                 105                 110


Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
```

```
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val
    130                 135                 140

Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu
145                 150                 155                 160

Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn
                165                 170                 175

Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly
            180                 185                 190

Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu
        195                 200                 205

Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp
    210                 215                 220

Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe
225                 230                 235                 240

Gly Gly Gly Thr Lys Leu Thr Val Leu
                245
```

<210> 104
<211> 585
<212> PRT
<213> Homo sapiens

<400> 104

```
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>  105
<211>  585
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  105

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 Gly 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 Ala 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> 106
<211> 585
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 106

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


Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585


<210>  107
<211>  585
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  107

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 Asp 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 His Leu Val
                565                 570                 575


Ala Ala Ser Lys Ala Ala Leu Gly Leu
            580                 585


<210>  108
<211>  585
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  108

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 Gly 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 Lys 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>  109
<211>  585
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  109

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 Asp 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 Lys 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>  110
<211>  585
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  110

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 Lys 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 His Leu Val
                565                 570                 575

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

<210> 111
<211> 585
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 111

```
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 His Leu Val
                565                 570                 575


Ala Ala Ser Lys Ala Ala Leu Gly Leu
            580                 585
```

<210> 112
<211> 585

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 112

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 Lys 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 Lys Ala Ala Leu Gly Leu
            580                 585
```

<210> 113
<211> 585
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic peptide

<400> 113

```
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 Asp 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 Lys Ala Ala Leu Gly Leu
            580                 585
```

<210> 114
<211> 585
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 114

```
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 Ser 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>  115
<211>  585
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  115

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 Ser 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 Gly 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 Ala 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> 116
<211> 585
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 116

```
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 Ser 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


Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585


<210>  117
<211>  585
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  117

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 Ser 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 Asp 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 His Leu Val
                565                 570                 575


Ala Ala Ser Lys Ala Ala Leu Gly Leu
            580                 585


<210>  118
<211>  585
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  118

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 Ser 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 Gly 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 Lys 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> 119
<211> 585
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 119

```
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 Ser 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 Asp 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 Lys 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> 120
<211> 585
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 120

```
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 Ser 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 Lys 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 His Leu Val
                565                 570                 575

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

<210> 121
<211> 585
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 121

```
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 Ser 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 His Leu Val
                565                 570                 575


Ala Ala Ser Lys Ala Ala Leu Gly Leu
            580                 585


<210>  122
<211>  585
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  122

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 Ser 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 Lys 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 Lys Ala Ala Leu Gly Leu
            580                 585


<210>  123
<211>  585
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  123

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 Ser 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 Asp 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 Lys Ala Ala Leu Gly Leu
580 585

<210> 124
<211> 585
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 124

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 Ala 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> 125
<211> 585
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 125

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 Ala 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 Gly 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 Ala 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
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<210> 126
<211> 585
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 126

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 Ala 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

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

<210> 127
<211> 585
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 127

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 Ala 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 Asp 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 His Leu Val
                565                 570                 575


Ala Ala Ser Lys Ala Ala Leu Gly Leu
            580                 585


<210>  128
<211>  585
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  128

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 Ala 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 Gly 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 Lys 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>  129
<211>  585
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  129

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 Ala 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 Asp 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 Lys 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>  130
<211>  585
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  130

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 Ala 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 Lys 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 His Leu Val
                565                 570                 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
            580                 585


<210>  131
<211>  585
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  131

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 Ala 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 His Leu Val
                565                 570                 575

Ala Ala Ser Lys Ala Ala Leu Gly Leu
            580                 585


<210>  132
<211>  585
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  132

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 Ala 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 Lys 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 Lys Ala Ala Leu Gly Leu
580 585

<210> 133
<211> 585
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 133

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 Ala 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 Asp 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 Lys Ala Ala Leu Gly Leu
580 585

<210> 134
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 134

Arg Asp Trp Asp Phe Asp Val Phe Gly Gly Gly Thr Pro Val Gly Gly
1 5 10 15

<210> 135
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<220>
<221> misc_feature
<222> (12)..(12)
<223> Xaa can be any naturally occurring amino acid

<400> 135

Gln Arg Phe Val Thr Gly His Phe Gly Gly Leu Xaa Pro Ala Asn Gly
1 5 10 15

<210> 136
<211> 16

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 136

Gln Arg Phe Val Thr Gly His Phe Gly Gly Leu Tyr Pro Ala Asn Gly
1 5 10 15

<210> 137
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 137

Gln Arg Phe Val Thr Gly His Phe Gly Gly Leu His Pro Ala Asn Gly
1 5 10 15

<210> 138
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 138

Thr Gly His Phe Gly Gly Leu His Pro
1 5

<210> 139
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 139

Gln Arg Phe Cys Thr Gly His Phe Gly Gly Leu His Pro Cys Asn Gly
1 5 10 15

<210> 140
<211> 330
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 140

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
165 170 175

```
Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285

Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330
```

<210> 141
<211> 333
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 141

```
Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
1               5                   10                  15
```

```
Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
            20                  25                  30

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
        35                  40                  45

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
    50                  55                  60

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65                  70                  75                  80

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
                85                  90                  95

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser Asp Lys Thr His Thr Cys
            100                 105                 110

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
        115                 120                 125

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
    130                 135                 140

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
145                 150                 155                 160

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

Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu
            180                 185                 190

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
        195                 200                 205

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
    210                 215                 220

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
225                 230                 235                 240
```

```
Arg Lys Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
                245                 250                 255


Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
            260                 265                 270


Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly
        275                 280                 285


Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
    290                 295                 300


Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
305                 310                 315                 320


His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330


<210>  142
<211>  330
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  142

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15


Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30


Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45


Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60


Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
65                  70                  75                  80
```

```
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Thr Val Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
225                 230                 235                 240

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

Asn Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285
```

```
Leu Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330
```

<210> 143
<211> 338
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 143

```
Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser
1               5                   10                  15

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
            20                  25                  30

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
        35                  40                  45

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
    50                  55                  60

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65                  70                  75                  80

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
                85                  90                  95

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser Glu Pro Lys Ser Ser Asp
            100                 105                 110

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly
        115                 120                 125
```

```
Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
    130                 135                 140

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
145                 150                 155                 160

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
                165                 170                 175

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
            180                 185                 190

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
        195                 200                 205

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
    210                 215                 220

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
225                 230                 235                 240

Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val Ser Leu
                245                 250                 255

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
            260                 265                 270

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
        275                 280                 285

Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
    290                 295                 300

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
305                 310                 315                 320

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
                325                 330                 335

Gly Lys
```

<210> 144
<211> 227
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 144

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr
65 70 75 80

Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
100 105 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115 120 125

Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met Thr Lys Asn Gln Val Ser
130 135 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145 150 155 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
165 170 175

```
Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220


Pro Gly Lys
225


<210>  145
<211>  227
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  145

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                   10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr
65                  70                  75                  80


Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110
```

```
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    130                 135                 140


Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160


Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Thr Pro Pro
                165                 170                 175


Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val
            180                 185                 190


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220


Pro Gly Lys
225


<210>  146
<211>  232
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  146

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1               5                   10                  15


Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            20                  25                  30


Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        35                  40                  45
```

```
Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
    50                  55                  60

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln
65                  70                  75                  80

Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln
                85                  90                  95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
            100                 105                 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        115                 120                 125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met Thr
    130                 135                 140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145                 150                 155                 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                165                 170                 175

Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr
            180                 185                 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        195                 200                 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    210                 215                 220

Ser Leu Ser Leu Ser Pro Gly Lys
225                 230


<210>  147
<211>  232
<212>  PRT
<213>  Artificial Sequence
```

<220>
<223> Synthetic peptide

<400> 147

```
Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1               5                  10                  15


Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            20                  25                  30


Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        35                  40                  45


Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
    50                  55                  60


Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln
65                  70                  75                  80


Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln
                85                  90                  95


Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
            100                 105                 110


Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        115                 120                 125


Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
    130                 135                 140


Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145                 150                 155                 160


Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                165                 170                 175


Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            180                 185                 190
```

```
Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        195                 200                 205


Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    210                 215                 220


Ser Leu Ser Leu Ser Pro Gly Lys
225                 230


<210>  148
<211>  232
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  148

Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1               5                   10                  15


Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            20                  25                  30


Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        35                  40                  45


Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
    50                  55                  60


Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65                  70                  75                  80


Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
                85                  90                  95


Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
            100                 105                 110


Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        115                 120                 125
```

```
Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Lys Glu Met Thr
    130                 135                 140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145                 150                 155                 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                165                 170                 175

Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Phe Leu Tyr
            180                 185                 190

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        195                 200                 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    210                 215                 220

Ser Leu Ser Leu Ser Pro Gly Lys
225                 230
```

<210> 149
<211> 232
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 149

```
Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
1               5                   10                  15

Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
            20                  25                  30

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
        35                  40                  45

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
    50                  55                  60
```

```
Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
65                  70                  75                  80

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
                85                  90                  95

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
            100                 105                 110

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
        115                 120                 125

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
    130                 135                 140

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
145                 150                 155                 160

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
                165                 170                 175

Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
            180                 185                 190

Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
        195                 200                 205

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
    210                 215                 220

Ser Leu Ser Leu Ser Pro Gly Lys
225                 230
```

<210> 150
<211> 217
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 150

```
Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
1               5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            20                  25                  30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        35                  40                  45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    50                  55                  60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
65                  70                  75                  80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            100                 105                 110

Pro Arg Glu Pro Gln Val Thr Thr Leu Pro Pro Ser Arg Glu Glu Met
        115                 120                 125

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    130                 135                 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
145                 150                 155                 160

Tyr Asp Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                165                 170                 175

Tyr Ser Asp Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            180                 185                 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        195                 200                 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys
    210                 215
```

<210> 151
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 151

Ser Ser Ser Tyr Tyr Trp Gly
1 5

<210> 152
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 152

Ser Ile Tyr Tyr Ser Gly Ile Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 153
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 153

Pro Ser Asn Tyr Asp Ala Phe Asp Ile
1 5

<210> 154
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 154

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Asp Val His
1   5   10

<210> 155
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 155

Gly Asn Ser Lys Arg Pro Ser
1   5

<210> 156
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 156

Gln Ser Tyr Asp Ser Ser Leu Gly Gly Trp Val
1   5   10

<210> 157
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 157

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
            20   25   30

Ser Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
        35   40   45

```
Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ile Thr Asn Tyr Asn Pro Ser
    50                  55                  60

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

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Arg Pro Ser Asn Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110

Thr Met Val Thr Val Ser Ser
        115
```

<210> 158
<211> 111
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 158

```
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30

Tyr Asp Val His Trp Tyr Gln Gln Val Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Gly Asn Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
                85                  90                  95
```

```
Leu Gly Gly Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110


<210>  159
<211>  245
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  159

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


Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30


Ser Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
        35                  40                  45


Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ile Thr Asn Tyr Asn Pro Ser
    50                  55                  60


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


Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95


Cys Ala Arg Pro Ser Asn Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110


Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125


Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro Ser Val
    130                 135                 140


Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr Gly Ser Ser
145                 150                 155                 160
```

```
Ser Asn Ile Gly Ala Gly Tyr Asp Val His Trp Tyr Gln Gln Val Pro
                165                 170                 175


Gly Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asn Ser Lys Arg Pro Ser
            180                 185                 190


Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser
        195                 200                 205


Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys
    210                 215                 220


Gln Ser Tyr Asp Ser Ser Leu Gly Gly Trp Val Phe Gly Gly Gly Thr
225                 230                 235                 240


Lys Leu Thr Val Leu
                245


<210>  160
<211>  500
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  160

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


Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30


Ser Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
        35                  40                  45


Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ile Thr Asn Tyr Asn Pro Ser
    50                  55                  60


Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65                  70                  75                  80
```

```
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Arg Pro Ser Asn Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110

Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro Ser Val
    130                 135                 140

Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr Gly Ser Ser
145                 150                 155                 160

Ser Asn Ile Gly Ala Gly Tyr Asp Val His Trp Tyr Gln Gln Val Pro
                165                 170                 175

Gly Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asn Ser Lys Arg Pro Ser
            180                 185                 190

Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser
        195                 200                 205

Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys
    210                 215                 220

Gln Ser Tyr Asp Ser Ser Leu Gly Gly Trp Val Phe Gly Gly Gly Thr
225                 230                 235                 240

Lys Leu Thr Val Leu Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val
                245                 250                 255

Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser
            260                 265                 270

Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val
        275                 280                 285

Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser
    290                 295                 300
```

```
Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg
305                 310                 315                 320

Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met
                325                 330                 335

Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His
            340                 345                 350

Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln
        355                 360                 365

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    370                 375                 380

Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser
385                 390                 395                 400

Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser
                405                 410                 415

Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys
            420                 425                 430

Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala
        435                 440                 445

Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala
    450                 455                 460

Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr
465                 470                 475                 480

Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys
                485                 490                 495

Leu Thr Val Leu
            500
```

<210> 161
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 161

Asp His Tyr Met Ser
1 5

<210> 162
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 162

Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 163
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 163

Asp Leu Gly Pro Ser Phe Asp Tyr
1 5

<210> 164
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 164

Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala
1 5 10

<210> 165
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 165

Ala Ala Ser Arg Leu Gln Ser
1 5

<210> 166
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 166

Gln Gln Ala Asn Ser Phe Pro Arg Thr
1 5

<210> 167
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 167

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

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

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

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

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

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

Ala Arg Asp Leu Gly Pro Ser Phe Asp Tyr Trp Gly Gln Gly Ser Leu
            100                 105                 110

Val Thr Val Ser Ser
        115
```

<210> 168
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 168

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Asp Ala Ala Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Arg
                85                  90                  95
```

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 169
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 169

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

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

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

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

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

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

Ala Arg Asp Leu Gly Pro Ser Phe Asp Tyr Trp Gly Gln Gly Ser Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
145 150 155 160

```
Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175


Lys Leu Leu Ile Asp Ala Ala Ser Arg Leu Gln Ser Gly Val Pro Ser
            180                 185                 190


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205


Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn
    210                 215                 220


Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
225                 230                 235


<210>  170
<211>  494
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  170

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


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


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


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


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


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

```
Ala Arg Asp Leu Gly Pro Ser Phe Asp Tyr Trp Gly Gln Gly Ser Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
145                 150                 155                 160

Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Lys Leu Leu Ile Asp Ala Ala Ser Arg Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300
```

```
Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
                405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430

Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
    450                 455                 460

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

Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                485                 490
```

<210> 171
<211> 5
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic peptide

<400> 171

Asp Tyr Tyr Met Thr
1   5

<210> 172
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 172

Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val Lys
1   5   10   15

Gly

<210> 173
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 173

Asp Arg Asn Ser His Phe Asp Tyr
1   5

<210> 174
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 174

Arg Ala Ser Gln Gly Ile Thr Arg Trp Leu Ala
1   5   10

<210> 175
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 175

Ala Ala Ser Val Leu Gln Ser
1 5

<210> 176
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 176

Gln Gln Ser Asn Ser Phe Pro Arg Thr
1 5

<210> 177
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 177

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

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

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

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

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


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


Ala Arg Asp Arg Asn Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ser
        115


<210>  178
<211>  107
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  178

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Thr Arg Trp
            20                  25                  30


Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Val Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60


Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80


Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Asn Ser Phe Pro Arg
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 179
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 179

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15


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


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


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


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


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


Ala Arg Asp Arg Asn Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125


Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140


Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
145                 150                 155                 160


Ile Thr Arg Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175
```

```
Lys Leu Leu Ile Tyr Ala Ala Ser Val Leu Gln Ser Gly Val Pro Ser
            180                 185                 190


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205


Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
    210                 215                 220


Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
225                 230                 235


<210>  180
<211>  494
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  180

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


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


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


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


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


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


Ala Arg Asp Arg Asn Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110
```

```
Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
145                 150                 155                 160

Ile Thr Arg Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Lys Leu Leu Ile Tyr Ala Ala Ser Val Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335
```

```
Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
                405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430

Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
    450                 455                 460

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

Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                485                 490
```

<210> 181
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 181

```
Asp Tyr Tyr Met Thr
1               5
```

<210> 182
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 182

Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 183
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 183

Asp Arg Asn Ser His Phe Asp Tyr
1 5

<210> 184
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 184

Arg Ala Ser Gln Gly Ile Asn Thr Trp Leu Ala
1 5 10

<210> 185
<211> 7
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic peptide

<400> 185

Gly Ala Ser Gly Leu Gln Ser
1 5

<210> 186
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 186

Gln Gln Ala Lys Ser Phe Pro Arg Thr
1 5

<210> 187
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 187

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

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

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

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

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

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

Ala Arg Asp Arg Asn Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 188
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 188

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Asn Thr Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Gly Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Lys Ser Phe Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 189
<211> 239
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic peptide

<400> 189

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                  10                  15


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


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


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


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


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


Ala Arg Asp Arg Asn Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125


Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140


Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
145                 150                 155                 160


Ile Asn Thr Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175


Lys Leu Leu Ile Tyr Gly Ala Ser Gly Leu Gln Ser Gly Val Pro Ser
            180                 185                 190


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205
```

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Lys
210 215 220

Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
225 230 235

<210> 190
<211> 494
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 190

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

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

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

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

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

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

Ala Arg Asp Arg Asn Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
130 135 140

```
Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
145                 150                 155                 160


Ile Asn Thr Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175


Lys Leu Leu Ile Tyr Gly Ala Ser Gly Leu Gln Ser Gly Val Pro Ser
            180                 185                 190


Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205


Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Lys
    210                 215                 220


Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Ser
225                 230                 235                 240


Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255


Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270


Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285


Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300


Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320


Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335


Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350
```

```
Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
                405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430

Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
    450                 455                 460

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

Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                485                 490


<210>  191
<211>  5
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  191

Asp His Tyr Met Ser
1               5


<210>  192
<211>  17
<212>  PRT
<213>  Artificial Sequence
```

<220>
<223> Synthetic peptide

<400> 192

Tyr Ile Ser Ser Ser Gly Gly Ile Ile Tyr Tyr Ala Asp Ser Val Lys
1   5   10   15

Gly

<210> 193
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 193

Asp Val Gly Ser His Phe Asp Tyr
1   5

<210> 194
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 194

Arg Ala Ser Gln Asp Ile Ser Arg Trp Leu Ala
1   5   10

<210> 195
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 195

Ala Ala Ser Arg Leu Gln Ser
1   5

<210> 196
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 196

Gln Gln Ala Lys Ser Phe Pro Arg Thr
1 5

<210> 197
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 197

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

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

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Phe
35 40 45

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

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

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

Ala Arg Asp Val Gly Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
        115

<210> 198
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 198

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1   5   10   15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Arg Trp
            20   25   30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35   40   45

Ser Ala Ala Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Ile Tyr Tyr Cys Gln Gln Ala Lys Ser Phe Pro Arg
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> 199
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 199

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

```
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp His
            20                  25                  30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Phe
        35                  40                  45

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

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

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

Ala Arg Asp Val Gly Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp
145                 150                 155                 160

Ile Ser Arg Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Lys Leu Leu Ile Ser Ala Ala Ser Arg Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Ile Tyr Tyr Cys Gln Gln Ala Lys
    210                 215                 220
```

Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
225 230 235

<210> 200
<211> 494
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 200

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

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

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Phe
35 40 45

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

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

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

Ala Arg Asp Val Gly Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp
145 150 155 160

```
Ile Ser Arg Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Lys Leu Leu Ile Ser Ala Ala Ser Arg Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Ile Tyr Tyr Cys Gln Gln Ala Lys
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380
```

```
Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400


Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
                405                 410                 415


Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430


Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445


Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
    450                 455                 460


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


Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                485                 490


<210>  201
<211>  5
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  201

Asp His Tyr Met Ser
1               5


<210>  202
<211>  17
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  202
```

Tyr Ile Ser Asn Ser Gly Ser Ile Ile Tyr Tyr Val Asp Ser Val Lys
1   5   10   15

Gly

<210> 203
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 203

Asp Val Arg Thr Ala Phe Asp Tyr
1   5

<210> 204
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 204

Arg Ala Ser Gln Ser Ile Gly Ser Trp Leu Ala
1   5   10

<210> 205
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 205

Ala Ala Ser Ser Leu Gln Ser
1   5

<210> 206
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 206

Gln Gln Ala Asn Ser Phe Pro Arg Thr
1   5

<210> 207
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 207

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

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

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

Ser Tyr Ile Ser Asn Ser Gly Ser Ile Ile Tyr Tyr Val Asp Ser Val
    50   55   60

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

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

Ala Arg Asp Val Arg Thr Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100   105   110

Val Thr Val Ser Ser
        115

<210> 208
<211> 107

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 208

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Gly Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Arg
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys
100 105

<210> 209
<211> 239
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 209

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

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

```
Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Ser Tyr Ile Ser Asn Ser Gly Ser Ile Ile Tyr Tyr Val Asp Ser Val
    50                  55                  60

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

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

Ala Arg Asp Val Arg Thr Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser
145                 150                 155                 160

Ile Gly Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Asn Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys
225                 230                 235

<210>  210
<211>  494
```

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 210

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                  10                  15


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


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


Ser Tyr Ile Ser Asn Ser Gly Ser Ile Ile Tyr Tyr Val Asp Ser Val
    50                  55                  60


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


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


Ala Arg Asp Val Arg Thr Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125


Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140


Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser
145                 150                 155                 160


Ile Gly Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175


Asn Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser
            180                 185                 190
```

```
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400
```

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
405 410 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
420 425 430

Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
435 440 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
450 455 460

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

Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
485 490

<210> 211
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 211

Ser Lys Phe Met Thr
1 5

<210> 212
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 212

Val Ile Tyr Ser Gly Gly Lys Thr Tyr Tyr Ala Asp Ser Val Lys Gly
1 5 10 15

<210> 213
<211> 10

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 213

Asp Ser Gly Gly Trp Gly Tyr Phe Asp Tyr
1   5   10

<210> 214
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 214

Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr Leu
1   5   10   15

Ala

<210> 215
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 215

Trp Ala Ser Thr Arg Glu Ser
1   5

<210> 216
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 216

Gln Gln Tyr Tyr Ser Thr Pro Pro Thr
1   5

<210> 217
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 217

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

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

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

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

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

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

Arg Asp Ser Gly Gly Trp Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
            100   105   110

Leu Val Thr Val Ser Ser
        115

<210> 218
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 218

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Ser Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> 219
<211> 246
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 219

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

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

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

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

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

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

Arg Asp Ser Gly Gly Trp Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125

Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu
    130                 135                 140

Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln
145                 150                 155                 160

Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln
                165                 170                 175

Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr
            180                 185                 190

Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
        195                 200                 205

Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val
    210                 215                 220

Tyr Tyr Cys Gln Gln Tyr Tyr Ser Thr Pro Pro Thr Phe Gly Gln Gly
225                 230                 235                 240

Thr Lys Val Glu Ile Lys
                245
```

<210> 220
<211> 501
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 220

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Ile Gln Pro Gly Gly
1               5                   10                  15


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


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


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


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


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


Arg Asp Ser Gly Gly Trp Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125


Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu
    130                 135                 140


Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln
145                 150                 155                 160


Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln
                165                 170                 175
```

```
Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr
            180                 185                 190

Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
        195                 200                 205

Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val
    210                 215                 220

Tyr Tyr Cys Gln Gln Tyr Tyr Ser Thr Pro Pro Thr Phe Gly Gln Gly
225                 230                 235                 240

Thr Lys Val Glu Ile Lys Ser Gly Gly Gly Gly Ser Glu Val Gln Leu
                245                 250                 255

Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu
            260                 265                 270

Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp
        275                 280                 285

Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg
    290                 295                 300

Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp
305                 310                 315                 320

Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln
                325                 330                 335

Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg
            340                 345                 350

His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly
        355                 360                 365

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
    370                 375                 380

Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro
385                 390                 395                 400
```

Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser
405 410 415

Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln
420 425 430

Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu
435 440 445

Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys
450 455 460

Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr
465 470 475 480

Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr
485 490 495

Lys Leu Thr Val Leu
500

<210> 221
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 221

Ser Tyr Tyr Trp Asn
1 5

<210> 222
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 222

Arg Ile Tyr Tyr Asn Gly Asn Thr Tyr Tyr Asn Pro Ser Leu Lys Ser
1   5   10   15

<210> 223
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 223

Pro Lys Leu Gly Ile Asp Ala Phe Asp Ile
1   5   10

<210> 224
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 224

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Asp Val His
1   5   10

<210> 225
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 225

Gly Asn Ser Asn Arg Pro Ser
1   5

<210> 226
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 226

Gln Ser Tyr Asp Ser Ser Leu Ser Gly Trp Val
1 5 10

<210> 227
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 227

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
20 25 30

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

Gly Arg Ile Tyr Tyr Asn Gly Asn Thr Tyr Tyr Asn Pro Ser Leu Lys
50 55 60

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Pro Lys Leu Gly Ile Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
100 105 110

Met Val Thr Val Ser Ser
115

<210> 228
<211> 111
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic peptide

<400> 228

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
85 90 95

Leu Ser Gly Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 229
<211> 244
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 229

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
20 25 30

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

```
Gly Arg Ile Tyr Tyr Asn Gly Asn Thr Tyr Tyr Asn Pro Ser Leu Lys
    50                  55                  60

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Arg Pro Lys Leu Gly Ile Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
            100                 105                 110

Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125

Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser
    130                 135                 140

Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser
145                 150                 155                 160

Asn Ile Gly Ala Gly Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly
                165                 170                 175

Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly
            180                 185                 190

Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu
        195                 200                 205

Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln
    210                 215                 220

Ser Tyr Asp Ser Ser Leu Ser Gly Trp Val Phe Gly Gly Gly Thr Lys
225                 230                 235                 240

Leu Thr Val Leu
```

<210> 230
<211> 499

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 230

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
20 25 30

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

Gly Arg Ile Tyr Tyr Asn Gly Asn Thr Tyr Tyr Asn Pro Ser Leu Lys
50 55 60

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Pro Lys Leu Gly Ile Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
100 105 110

Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
115 120 125

Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser
130 135 140

Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser
145 150 155 160

Asn Ile Gly Ala Gly Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly
165 170 175

Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly
180 185 190

```
Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu
        195                 200                 205

Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln
    210                 215                 220

Ser Tyr Asp Ser Ser Leu Ser Gly Trp Val Phe Gly Gly Gly Thr Lys
225                 230                 235                 240

Leu Thr Val Leu Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu
                245                 250                 255

Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys
            260                 265                 270

Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg
        275                 280                 285

Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys
    290                 295                 300

Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe
305                 310                 315                 320

Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn
                325                 330                 335

Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly
            340                 345                 350

Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly
        355                 360                 365

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu
385                 390                 395                 400
```

```
Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr
                405                 410                 415


Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro
            420                 425                 430


Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro
        435                 440                 445


Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala
    450                 455                 460


Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys
465                 470                 475                 480


Val Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu
                485                 490                 495


Thr Val Leu
```

<210> 231
<211> 622
<212> PRT
<213> Homo sapiens

<400> 231

```
Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro
1               5                   10                  15


Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
            20                  25                  30


Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
        35                  40                  45


Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
    50                  55                  60


Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65                  70                  75                  80
```

```
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
                85                  90                  95

Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
            100                 105                 110

Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
        115                 120                 125

Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
    130                 135                 140

Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145                 150                 155                 160

Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
                165                 170                 175

Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
            180                 185                 190

Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
        195                 200                 205

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

Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225                 230                 235                 240

Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
                245                 250                 255

Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
            260                 265                 270

Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile
        275                 280                 285

Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
```

```
    290                 295                 300

Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
305                 310                 315                 320

Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
                325                 330                 335

Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
            340                 345                 350

Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
        355                 360                 365

Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
    370                 375                 380

Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
385                 390                 395                 400

Val Asn Lys Gly His Glu Met Ser Pro Gln Val Ala Thr Leu Ile Asp
                405                 410                 415

Arg Phe Val Lys Gly Arg Gly Gln Leu Asp Lys Asp Thr Leu Asp Thr
            420                 425                 430

Leu Thr Ala Phe Tyr Pro Gly Tyr Leu Cys Ser Leu Ser Pro Glu Glu
        435                 440                 445

Leu Ser Ser Val Pro Pro Ser Ser Ile Trp Ala Val Arg Pro Gln Asp
    450                 455                 460

Leu Asp Thr Cys Asp Pro Arg Gln Leu Asp Val Leu Tyr Pro Lys Ala
465                 470                 475                 480

Arg Leu Ala Phe Gln Asn Met Asn Gly Ser Glu Tyr Phe Val Lys Ile
                485                 490                 495

Gln Ser Phe Leu Gly Gly Ala Pro Thr Glu Asp Leu Lys Ala Leu Ser
            500                 505                 510
```

```
Gln Gln Asn Val Ser Met Asp Leu Ala Thr Phe Met Lys Leu Arg Thr
        515                 520                 525

Asp Ala Val Leu Pro Leu Thr Val Ala Glu Val Gln Lys Leu Leu Gly
    530                 535                 540

Pro His Val Glu Gly Leu Lys Ala Glu Glu Arg His Arg Pro Val Arg
545                 550                 555                 560

Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu
                565                 570                 575

Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Val Leu Asp Leu Ser
            580                 585                 590

Met Gln Glu Ala Leu Ser Gly Thr Pro Cys Leu Leu Gly Pro Gly Pro
        595                 600                 605

Val Leu Thr Val Leu Ala Leu Leu Leu Ala Ser Thr Leu Ala
    610                 615                 620
```

<210> 232
<211> 630
<212> PRT
<213> Homo sapiens

<400> 232

```
Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro
1               5                   10                  15

Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
            20                  25                  30

Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
        35                  40                  45

Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
    50                  55                  60

Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65                  70                  75                  80
```

```
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
                85                  90                  95

Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
            100                 105                 110

Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
        115                 120                 125

Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
    130                 135                 140

Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145                 150                 155                 160

Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
                165                 170                 175

Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
            180                 185                 190

Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
        195                 200                 205

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

Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225                 230                 235                 240

Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
                245                 250                 255

Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
            260                 265                 270

Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile
        275                 280                 285
```

```
Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
    290                 295                 300

Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
305                 310                 315                 320

Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
                325                 330                 335

Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
            340                 345                 350

Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
        355                 360                 365

Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
    370                 375                 380

Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
385                 390                 395                 400

Val Asn Lys Gly His Glu Met Ser Pro Gln Ala Pro Arg Arg Pro Leu
                405                 410                 415

Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln
            420                 425                 430

Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr
        435                 440                 445

Leu Cys Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser
    450                 455                 460

Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln
465                 470                 475                 480

Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn
                485                 490                 495

Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro
            500                 505                 510
```

```
Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu
        515                 520                 525

Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val
    530                 535                 540

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

Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln
                565                 570                 575

Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn
            580                 585                 590

Gly Tyr Leu Val Leu Asp Leu Ser Met Gln Glu Ala Leu Ser Gly Thr
        595                 600                 605

Pro Cys Leu Leu Gly Pro Gly Pro Val Leu Thr Val Leu Ala Leu Leu
    610                 615                 620

Leu Ala Ser Thr Leu Ala
625                 630
```

<210> 233
<211> 622
<212> PRT
<213> Homo sapiens

<400> 233

```
Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro
1               5                   10                  15

Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
            20                  25                  30

Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
        35                  40                  45

Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
```

```
    50                  55                  60

Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65                  70                  75                  80

Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
                85                  90                  95

Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
            100                 105                 110

Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
        115                 120                 125

Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr His Phe Phe Ser Arg Ile
    130                 135                 140

Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145                 150                 155                 160

Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
                165                 170                 175

Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
            180                 185                 190

Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
        195                 200                 205

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

Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225                 230                 235                 240

Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
                245                 250                 255

Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
            260                 265                 270
```

```
Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile
        275                 280                 285

Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
    290                 295                 300

Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
305                 310                 315                 320

Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
                325                 330                 335

Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
            340                 345                 350

Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
        355                 360                 365

Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
    370                 375                 380

Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
385                 390                 395                 400

Val Asn Lys Gly His Glu Met Ser Pro Gln Val Ala Thr Leu Ile Asp
                405                 410                 415

Arg Phe Val Lys Gly Arg Gly Gln Leu Asp Lys Asp Thr Leu Asp Thr
            420                 425                 430

Leu Thr Ala Phe Tyr Pro Gly Tyr Leu Cys Ser Leu Ser Pro Glu Glu
        435                 440                 445

Leu Ser Ser Val Pro Pro Ser Ser Ile Trp Ala Val Arg Pro Gln Asp
    450                 455                 460

Leu Asp Thr Cys Asp Pro Arg Gln Leu Asp Val Leu Tyr Pro Lys Ala
465                 470                 475                 480

Arg Leu Ala Phe Gln Asn Met Asn Gly Ser Glu Tyr Phe Val Lys Ile
```

485 490 495

Gln Ser Phe Leu Gly Gly Ala Pro Thr Glu Asp Leu Lys Ala Leu Ser
500 505 510

Gln Gln Asn Val Ser Met Asp Leu Ala Thr Phe Met Lys Leu Arg Thr
515 520 525

Asp Ala Val Leu Pro Leu Thr Val Ala Glu Val Gln Lys Leu Leu Gly
530 535 540

Pro His Val Glu Gly Leu Lys Ala Glu Glu Arg His Arg Pro Val Arg
545 550 555 560

Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu
565 570 575

Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Val Leu Asp Leu Ser
580 585 590

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

Val Leu Thr Val Leu Ala Leu Leu Leu Ala Ser Thr Leu Ala
610 615 620

<210> 234
<211> 622
<212> PRT
<213> Macaca fascicularis

<400> 234

Met Ala Leu Pro Met Ala Arg Pro Leu Ser Gly Ser Cys Gly Thr Pro
1 5 10 15

Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
20 25 30

Pro Ser Arg Val Leu Ala Gly Glu Thr Arg Gln Glu Ala Ala Pro Leu
35 40 45

```
Asp Gly Ile Leu Thr Asn Ala Pro Asp Ile Ala Ser Leu Ser Pro Arg
    50                  55                  60

Gln Leu Leu Gly Phe Thr Cys Val Glu Val Ser Gly Leu Ser Thr Glu
65                  70                  75                  80

Leu Val Gln Glu Leu Ala Val Ala Leu Gly Gln Lys Asn Val Lys Leu
                85                  90                  95

Ser Ala Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
            100                 105                 110

Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
        115                 120                 125

Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr His Phe Phe Ser Arg Val
    130                 135                 140

Ala Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145                 150                 155                 160

Arg Leu Leu Pro Ala Ala Leu Thr Cys Trp Gly Val Arg Gly Ser Leu
                165                 170                 175

Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
            180                 185                 190

Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Val Leu Pro Arg Leu
        195                 200                 205

Val Arg Cys Leu Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg
    210                 215                 220

Ala Ala Leu Gln Arg Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225                 230                 235                 240

Ser Ile Ser Thr Leu Asp Asp Leu Gln Ser Leu Leu Pro Val Leu Gly
                245                 250                 255

Gln Pro Val Ile His Ser Ile Pro Gln Gly Ile Leu Ala Ala Trp Arg
            260                 265                 270
```

```
Gln Arg Ser Ser Arg Asp Pro Ser Trp Gln Gln Pro Glu Gln Thr Val
        275                 280                 285

Leu Arg Pro Arg Phe Arg Arg Asp Val Glu Arg Thr Thr Cys Pro Pro
    290                 295                 300

Glu Lys Glu Val His Glu Ile Asp Glu Asn Leu Ile Phe Tyr Lys Lys
305                 310                 315                 320

Arg Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Ala Gln Met
                325                 330                 335

Asp Arg Val Asp Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
            340                 345                 350

Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
        355                 360                 365

Ile Arg His Leu Gly His Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
    370                 375                 380

Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Lys
385                 390                 395                 400

Val Ser Lys Gly His Glu Met Ser Ala Gln Val Ala Thr Leu Ile Asp
                405                 410                 415

Arg Val Val Val Gly Arg Gly Gln Leu Asp Lys Asp Thr Ala Asp Thr
            420                 425                 430

Leu Thr Ala Phe Cys Pro Gly Cys Leu Cys Ser Leu Ser Pro Glu Arg
        435                 440                 445

Leu Ser Ser Val Pro Pro Ser Val Ile Gly Ala Val Arg Pro Gln Asp
    450                 455                 460

Leu Asp Thr Cys Gly Pro Arg Gln Leu Asp Val Leu Tyr Pro Lys Ala
465                 470                 475                 480
```

```
Arg Leu Ala Phe Gln Asn Met Ser Gly Ser Glu Tyr Phe Val Lys Ile
                485                 490                 495

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

Gln Gln Asn Val Ser Met Asp Leu Ala Thr Phe Met Lys Leu Arg Arg
        515                 520                 525

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

Pro His Val Glu Gly Leu Lys Val Glu Glu Gln His Ser Pro Val Arg
545                 550                 555                 560

Asp Trp Ile Leu Lys Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu
                565                 570                 575

Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Ile Leu Asp Leu Ser
            580                 585                 590

Val Arg Glu Ala Leu Ser Gly Thr Pro Cys Leu Leu Gly Pro Gly Pro
        595                 600                 605

Val Leu Thr Ile Leu Ala Leu Leu Leu Ala Ser Thr Leu Ala
    610                 615                 620
```

<210> 235
<211> 286
<212> PRT
<213> Homo sapiens

<400> 235

```
Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro
1               5                   10                  15

Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
            20                  25                  30

Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
        35                  40                  45
```

```
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
    50                  55                  60

Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65                  70                  75                  80

Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
                85                  90                  95

Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
            100                 105                 110

Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
        115                 120                 125

Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
    130                 135                 140

Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145                 150                 155                 160

Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
                165                 170                 175

Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
            180                 185                 190

Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
        195                 200                 205

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

Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225                 230                 235                 240

Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
                245                 250                 255

Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
```

```
            260                 265                 270

Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg
        275                 280                 285


<210>  236
<211>  303
<212>  PRT
<213>  Homo sapiens

<400>  236

Glu Val Glu Lys Thr Ala Cys Pro Ser Gly Lys Lys Ala Arg Glu Ile
1               5                   10                  15


Asp Glu Ser Leu Ile Phe Tyr Lys Lys Trp Glu Leu Glu Ala Cys Val
            20                  25                  30


Asp Ala Ala Leu Leu Ala Thr Gln Met Asp Arg Val Asn Ala Ile Pro
        35                  40                  45


Phe Thr Tyr Glu Gln Leu Asp Val Leu Lys His Lys Leu Asp Glu Leu
    50                  55                  60


Tyr Pro Gln Gly Tyr Pro Glu Ser Val Ile Gln His Leu Gly Tyr Leu
65                  70                  75                  80


Phe Leu Lys Met Ser Pro Glu Asp Ile Arg Lys Trp Asn Val Thr Ser
                85                  90                  95


Leu Glu Thr Leu Lys Ala Leu Leu Glu Val Asn Lys Gly His Glu Met
            100                 105                 110


Ser Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly
        115                 120                 125


Gln Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly
    130                 135                 140


Tyr Leu Cys Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser
145                 150                 155                 160
```

```
Ser Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg
                165                 170                 175


Gln Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met
            180                 185                 190


Asn Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala
        195                 200                 205


Pro Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp
    210                 215                 220


Leu Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr
225                 230                 235                 240


Val Ala Glu Val Gln Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys
                245                 250                 255


Ala Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg
            260                 265                 270


Gln Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro
        275                 280                 285


Asn Gly Tyr Leu Val Leu Asp Leu Ser Met Gln Glu Ala Leu Ser
    290                 295                 300


<210>  237
<211>  24
<212>  PRT
<213>  Homo sapiens

<400>  237

Gly Thr Pro Cys Leu Leu Gly Pro Gly Pro Val Leu Thr Val Leu Ala
1               5                   10                  15


Leu Leu Leu Ala Ser Thr Leu Ala
            20


<210>  238
<211>  51
<212>  PRT
```

<213> Homo sapiens

<400> 238

Glu Val Glu Lys Thr Ala Cys Pro Ser Gly Lys Lys Ala Arg Glu Ile
1 5 10 15

Asp Glu Ser Leu Ile Phe Tyr Lys Lys Trp Glu Leu Glu Ala Cys Val
20 25 30

Asp Ala Ala Leu Leu Ala Thr Gln Met Asp Arg Val Asn Ala Ile Pro
35 40 45

Phe Thr Tyr
50

<210> 239
<211> 38
<212> PRT
<213> Homo sapiens

<400> 239

Glu Gln Leu Asp Val Leu Lys His Lys Leu Asp Glu Leu Tyr Pro Gln
1 5 10 15

Gly Tyr Pro Glu Ser Val Ile Gln His Leu Gly Tyr Leu Phe Leu Lys
20 25 30

Met Ser Pro Glu Asp Ile
35

<210> 240
<211> 69
<212> PRT
<213> Homo sapiens

<400> 240

Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
1 5 10 15

Val Asn Lys Gly His Glu Met Ser Pro Gln Val Ala Thr Leu Ile Asp
20 25 30

Arg Phe Val Lys Gly Arg Gly Gln Leu Asp Lys Asp Thr Leu Asp Thr
        35   40   45

Leu Thr Ala Phe Tyr Pro Gly Tyr Leu Cys Ser Leu Ser Pro Glu Glu
    50   55   60

Leu Ser Ser Val Pro
65

<210> 241
<211> 48
<212> PRT
<213> Homo sapiens

<400> 241

Pro Ser Ser Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp
1   5   10   15

Pro Arg Gln Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln
            20   25   30

Asn Met Asn Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly
        35   40   45

<210> 242
<211> 44
<212> PRT
<213> Homo sapiens

<400> 242

Gly Ala Pro Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser
1   5   10   15

Met Asp Leu Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro
            20   25   30

Leu Thr Val Ala Glu Val Gln Lys Leu Leu Gly Pro
        35   40

<210> 243
<211> 52
<212> PRT
<213> Homo sapiens

<400> 243

His Val Glu Gly Leu Lys Ala Glu Glu Arg His Arg Pro Val Arg Asp
1 5 10 15

Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu Gly
20 25 30

Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Val Leu Asp Leu Ser Met
35 40 45

Gln Glu Ala Leu
50

<210> 244
<211> 89
<212> PRT
<213> Homo sapiens

<400> 244

Glu Val Glu Lys Thr Ala Cys Pro Ser Gly Lys Lys Ala Arg Glu Ile
1 5 10 15

Asp Glu Ser Leu Ile Phe Tyr Lys Lys Trp Glu Leu Glu Ala Cys Val
20 25 30

Asp Ala Ala Leu Leu Ala Thr Gln Met Asp Arg Val Asn Ala Ile Pro
35 40 45

Phe Thr Tyr Glu Gln Leu Asp Val Leu Lys His Lys Leu Asp Glu Leu
50 55 60

Tyr Pro Gln Gly Tyr Pro Glu Ser Val Ile Gln His Leu Gly Tyr Leu
65 70 75 80

Phe Leu Lys Met Ser Pro Glu Asp Ile
85

<210> 245
<211> 107
<212> PRT
<213> Homo sapiens

<400> 245

Glu Gln Leu Asp Val Leu Lys His Lys Leu Asp Glu Leu Tyr Pro Gln
1 5 10 15

Gly Tyr Pro Glu Ser Val Ile Gln His Leu Gly Tyr Leu Phe Leu Lys
20 25 30

Met Ser Pro Glu Asp Ile Arg Lys Trp Asn Val Thr Ser Leu Glu Thr
35 40 45

Leu Lys Ala Leu Leu Glu Val Asn Lys Gly His Glu Met Ser Pro Gln
50 55 60

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

Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr Leu Cys
85 90 95

Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro
100 105

<210> 246
<211> 622
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 246

Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro
1 5 10 15

Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
20 25 30

Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
35 40 45

Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg

```
    50                  55                  60

Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65                  70                  75                  80

Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
                85                  90                  95

Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
            100                 105                 110

Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
        115                 120                 125

Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
    130                 135                 140

Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145                 150                 155                 160

Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
                165                 170                 175

Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
            180                 185                 190

Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
        195                 200                 205

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

Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225                 230                 235                 240

Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
                245                 250                 255

Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
            260                 265                 270
```

```
Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile
        275                 280                 285

Leu Arg Pro Arg Phe Arg Arg Asp Ala Glu Gln Lys Ala Cys Pro Pro
    290                 295                 300

Gly Lys Glu Pro Tyr Lys Val Asp Glu Asp Leu Ile Phe Tyr Gln Asn
305                 310                 315                 320

Trp Glu Leu Glu Ala Cys Val Asp Gly Thr Met Leu Ala Arg Gln Met
                325                 330                 335

Asp Leu Val Asn Glu Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
            340                 345                 350

Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
        355                 360                 365

Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
    370                 375                 380

Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
385                 390                 395                 400

Val Asn Lys Gly His Glu Met Ser Pro Gln Val Ala Thr Leu Ile Asp
                405                 410                 415

Arg Phe Val Lys Gly Arg Gly Gln Leu Asp Lys Asp Thr Leu Asp Thr
            420                 425                 430

Leu Thr Ala Phe Tyr Pro Gly Tyr Leu Cys Ser Leu Ser Pro Glu Glu
        435                 440                 445

Leu Ser Ser Val Pro Pro Ser Ser Ile Trp Ala Val Arg Pro Gln Asp
    450                 455                 460

Leu Asp Thr Cys Asp Pro Arg Gln Leu Asp Val Leu Tyr Pro Lys Ala
465                 470                 475                 480

Arg Leu Ala Phe Gln Asn Met Asn Gly Ser Glu Tyr Phe Val Lys Ile
```

```
               485                 490                 495

Gln Ser Phe Leu Gly Gly Ala Pro Thr Glu Asp Leu Lys Ala Leu Ser
            500                 505                 510

Gln Gln Asn Val Ser Met Asp Leu Ala Thr Phe Met Lys Leu Arg Thr
        515                 520                 525

Asp Ala Val Leu Pro Leu Thr Val Ala Glu Val Gln Lys Leu Leu Gly
    530                 535                 540

Pro His Val Glu Gly Leu Lys Ala Glu Glu Arg His Arg Pro Val Arg
545                 550                 555                 560

Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu
                565                 570                 575

Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Val Leu Asp Leu Ser
            580                 585                 590

Met Gln Glu Ala Leu Ser Gly Thr Pro Cys Leu Leu Gly Pro Gly Pro
        595                 600                 605

Val Leu Thr Val Leu Ala Leu Leu Leu Ala Ser Thr Leu Ala
    610                 615                 620


<210>  247
<211>  622
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  247

Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro
1               5                   10                  15

Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
            20                  25                  30

Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
```

```
        35                  40                  45

Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
    50                  55                  60

Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65                  70                  75                  80

Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
                85                  90                  95

Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
            100                 105                 110

Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
        115                 120                 125

Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
    130                 135                 140

Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145                 150                 155                 160

Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
                165                 170                 175

Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
            180                 185                 190

Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
        195                 200                 205

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

Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225                 230                 235                 240

Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
                245                 250                 255
```

```
Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
            260                 265                 270

Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile
        275                 280                 285

Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
    290                 295                 300

Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
305                 310                 315                 320

Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
                325                 330                 335

Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Ser Ile Phe
            340                 345                 350

Lys His Lys Leu Asp Lys Thr Tyr Pro Gln Gly Tyr Pro Glu Ser Leu
        355                 360                 365

Ile Gln Gln Leu Gly His Phe Phe Arg Tyr Val Ser Pro Glu Asp Ile
    370                 375                 380

Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
385                 390                 395                 400

Val Asn Lys Gly His Glu Met Ser Pro Gln Val Ala Thr Leu Ile Asp
                405                 410                 415

Arg Phe Val Lys Gly Arg Gly Gln Leu Asp Lys Asp Thr Leu Asp Thr
            420                 425                 430

Leu Thr Ala Phe Tyr Pro Gly Tyr Leu Cys Ser Leu Ser Pro Glu Glu
        435                 440                 445

Leu Ser Ser Val Pro Pro Ser Ser Ile Trp Ala Val Arg Pro Gln Asp
    450                 455                 460

Leu Asp Thr Cys Asp Pro Arg Gln Leu Asp Val Leu Tyr Pro Lys Ala
```

```
465                 470                 475                 480

Arg Leu Ala Phe Gln Asn Met Asn Gly Ser Glu Tyr Phe Val Lys Ile
                485                 490                 495

Gln Ser Phe Leu Gly Gly Ala Pro Thr Glu Asp Leu Lys Ala Leu Ser
            500                 505                 510

Gln Gln Asn Val Ser Met Asp Leu Ala Thr Phe Met Lys Leu Arg Thr
        515                 520                 525

Asp Ala Val Leu Pro Leu Thr Val Ala Glu Val Gln Lys Leu Leu Gly
    530                 535                 540

Pro His Val Glu Gly Leu Lys Ala Glu Glu Arg His Arg Pro Val Arg
545                 550                 555                 560

Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu
                565                 570                 575

Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Val Leu Asp Leu Ser
            580                 585                 590

Met Gln Glu Ala Leu Ser Gly Thr Pro Cys Leu Leu Gly Pro Gly Pro
        595                 600                 605

Val Leu Thr Val Leu Ala Leu Leu Leu Ala Ser Thr Leu Ala
    610                 615                 620


<210>  248
<211>  622
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  248

Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro
1               5                   10                  15

Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
```

```
            20                  25                  30

Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
        35                  40                  45

Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
    50                  55                  60

Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65                  70                  75                  80

Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
                85                  90                  95

Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
            100                 105                 110

Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
        115                 120                 125

Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
    130                 135                 140

Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145                 150                 155                 160

Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
                165                 170                 175

Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
            180                 185                 190

Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
        195                 200                 205

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

Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225                 230                 235                 240
```

```
Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
                245                 250                 255

Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
            260                 265                 270

Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile
        275                 280                 285

Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
    290                 295                 300

Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
305                 310                 315                 320

Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
                325                 330                 335

Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
            340                 345                 350

Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
        355                 360                 365

Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
    370                 375                 380

His Gln Trp Asn Val Thr Ser Pro Asp Thr Val Lys Thr Leu Leu Lys
385                 390                 395                 400

Val Ser Lys Gly Gln Lys Met Asn Ala Gln Ala Ile Ala Leu Val Ala
                405                 410                 415

Cys Tyr Leu Arg Gly Gly Gly Gln Leu Asp Glu Asp Met Val Lys Ala
            420                 425                 430

Leu Gly Asp Ile Pro Leu Ser Tyr Leu Cys Asp Phe Ser Pro Gln Asp
        435                 440                 445

Leu His Ser Val Pro Pro Ser Ser Ile Trp Ala Val Arg Pro Gln Asp
```

```
    450                 455                 460

Leu Asp Thr Cys Asp Pro Arg Gln Leu Asp Val Leu Tyr Pro Lys Ala
465                 470                 475                 480

Arg Leu Ala Phe Gln Asn Met Asn Gly Ser Glu Tyr Phe Val Lys Ile
                485                 490                 495

Gln Ser Phe Leu Gly Gly Ala Pro Thr Glu Asp Leu Lys Ala Leu Ser
            500                 505                 510

Gln Gln Asn Val Ser Met Asp Leu Ala Thr Phe Met Lys Leu Arg Thr
        515                 520                 525

Asp Ala Val Leu Pro Leu Thr Val Ala Glu Val Gln Lys Leu Leu Gly
    530                 535                 540

Pro His Val Glu Gly Leu Lys Ala Glu Glu Arg His Arg Pro Val Arg
545                 550                 555                 560

Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu
                565                 570                 575

Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Val Leu Asp Leu Ser
            580                 585                 590

Met Gln Glu Ala Leu Ser Gly Thr Pro Cys Leu Leu Gly Pro Gly Pro
        595                 600                 605

Val Leu Thr Val Leu Ala Leu Leu Leu Ala Ser Thr Leu Ala
    610                 615                 620


<210>  249
<211>  622
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  249

Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro
```

```
1               5                   10                  15

Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
            20                  25                  30

Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
        35                  40                  45

Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
    50                  55                  60

Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65                  70                  75                  80

Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
                85                  90                  95

Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
            100                 105                 110

Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
        115                 120                 125

Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
    130                 135                 140

Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145                 150                 155                 160

Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
                165                 170                 175

Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
            180                 185                 190

Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
        195                 200                 205

Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg
    210                 215                 220
```

```
Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225                 230                 235                 240

Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
                245                 250                 255

Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
            260                 265                 270

Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile
        275                 280                 285

Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
    290                 295                 300

Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
305                 310                 315                 320

Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
                325                 330                 335

Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
            340                 345                 350

Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
        355                 360                 365

Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
    370                 375                 380

Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
385                 390                 395                 400

Val Asn Lys Gly His Glu Met Ser Pro Gln Val Ala Thr Leu Ile Asp
                405                 410                 415

Arg Phe Val Lys Gly Arg Gly Gln Leu Asp Lys Asp Thr Leu Asp Thr
            420                 425                 430

Leu Thr Ala Phe Tyr Pro Gly Tyr Leu Cys Ser Leu Ser Pro Glu Glu
```

```
        435                 440                 445

Leu Ser Ser Val Pro Ser Ser Val Met Trp Leu Val Gly Pro Gln Asp
    450                 455                 460

Leu Asp Lys Cys Ser Gln Arg His Leu Gly Leu Leu Tyr Gln Lys Ala
465                 470                 475                 480

Cys Ser Ala Phe Gln Asn Val Ser Gly Leu Glu Tyr Phe Glu Lys Ile
                485                 490                 495

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

Gln Gln Asn Val Ser Met Asp Leu Ala Thr Phe Met Lys Leu Arg Thr
        515                 520                 525

Asp Ala Val Leu Pro Leu Thr Val Ala Glu Val Gln Lys Leu Leu Gly
    530                 535                 540

Pro His Val Glu Gly Leu Lys Ala Glu Glu Arg His Arg Pro Val Arg
545                 550                 555                 560

Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu
                565                 570                 575

Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Val Leu Asp Leu Ser
            580                 585                 590

Met Gln Glu Ala Leu Ser Gly Thr Pro Cys Leu Leu Gly Pro Gly Pro
        595                 600                 605

Val Leu Thr Val Leu Ala Leu Leu Leu Ala Ser Thr Leu Ala
    610                 615                 620
```

<210> 250
<211> 622
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 250

```
Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro
1               5                  10                  15

Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
            20                  25                  30

Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
        35                  40                  45

Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
    50                  55                  60

Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65                  70                  75                  80

Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
                85                  90                  95

Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
            100                 105                 110

Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
        115                 120                 125

Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
    130                 135                 140

Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145                 150                 155                 160

Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
                165                 170                 175

Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
            180                 185                 190

Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
        195                 200                 205
```

```
Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg
    210                 215                 220

Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225                 230                 235                 240

Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
                245                 250                 255

Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
            260                 265                 270

Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile
        275                 280                 285

Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
    290                 295                 300

Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
305                 310                 315                 320

Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
                325                 330                 335

Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
            340                 345                 350

Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
        355                 360                 365

Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
    370                 375                 380

Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
385                 390                 395                 400

Val Asn Lys Gly His Glu Met Ser Pro Gln Val Ala Thr Leu Ile Asp
                405                 410                 415

Arg Phe Val Lys Gly Arg Gly Gln Leu Asp Lys Asp Thr Leu Asp Thr
```

```
            420                 425                 430

Leu Thr Ala Phe Tyr Pro Gly Tyr Leu Cys Ser Leu Ser Pro Glu Glu
        435                 440                 445

Leu Ser Ser Val Pro Pro Ser Ser Ile Trp Ala Val Arg Pro Gln Asp
    450                 455                 460

Leu Asp Thr Cys Asp Pro Arg Gln Leu Asp Val Leu Tyr Pro Lys Ala
465                 470                 475                 480

Arg Leu Ala Phe Gln Asn Met Asn Gly Ser Glu Tyr Phe Val Lys Ile
                485                 490                 495

Gln Ser Phe Leu Gly Gly Ala Ser Val Lys Asp Leu Arg Ala Leu Ser
            500                 505                 510

Gln His Asn Val Ser Met Asp Ile Ala Thr Phe Lys Arg Leu Gln Val
        515                 520                 525

Asp Ser Leu Val Gly Leu Ser Val Ala Glu Val Gln Lys Leu Leu Gly
    530                 535                 540

Pro His Val Glu Gly Leu Lys Ala Glu Glu Arg His Arg Pro Val Arg
545                 550                 555                 560

Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu
                565                 570                 575

Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Val Leu Asp Leu Ser
            580                 585                 590

Met Gln Glu Ala Leu Ser Gly Thr Pro Cys Leu Leu Gly Pro Gly Pro
        595                 600                 605

Val Leu Thr Val Leu Ala Leu Leu Leu Ala Ser Thr Leu Ala
    610                 615                 620

<210>  251
<211>  622
<212>  PRT
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<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 251

Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro
1 5 10 15

Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
20 25 30

Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
35 40 45

Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
50 55 60

Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65 70 75 80

Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
85 90 95

Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
100 105 110

Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
115 120 125

Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
130 135 140

Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145 150 155 160

Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
165 170 175

Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
180 185 190

```
Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
        195                 200                 205

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

Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225                 230                 235                 240

Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
                245                 250                 255

Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
            260                 265                 270

Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile
        275                 280                 285

Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
    290                 295                 300

Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
305                 310                 315                 320

Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
                325                 330                 335

Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
            340                 345                 350

Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
        355                 360                 365

Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
    370                 375                 380

Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
385                 390                 395                 400

Val Asn Lys Gly His Glu Met Ser Pro Gln Val Ala Thr Leu Ile Asp
```

```
                405                 410                 415

Arg Phe Val Lys Gly Arg Gly Gln Leu Asp Lys Asp Thr Leu Asp Thr
            420                 425                 430

Leu Thr Ala Phe Tyr Pro Gly Tyr Leu Cys Ser Leu Ser Pro Glu Glu
        435                 440                 445

Leu Ser Ser Val Pro Pro Ser Ser Ile Trp Ala Val Arg Pro Gln Asp
    450                 455                 460

Leu Asp Thr Cys Asp Pro Arg Gln Leu Asp Val Leu Tyr Pro Lys Ala
465                 470                 475                 480

Arg Leu Ala Phe Gln Asn Met Asn Gly Ser Glu Tyr Phe Val Lys Ile
                485                 490                 495

Gln Ser Phe Leu Gly Gly Ala Pro Thr Glu Asp Leu Lys Ala Leu Ser
            500                 505                 510

Gln Gln Asn Val Ser Met Asp Leu Ala Thr Phe Met Lys Leu Arg Thr
        515                 520                 525

Asp Ala Val Leu Pro Leu Thr Val Ala Glu Val Gln Lys Leu Leu Gly
    530                 535                 540

Pro Asn Ile Val Asp Leu Lys Thr Glu Glu Asp Lys Ser Pro Val Arg
545                 550                 555                 560

Asp Trp Leu Phe Arg Gln His Gln Lys Asp Leu Asp Arg Leu Gly Leu
                565                 570                 575

Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Val Leu Asp Phe Asn
            580                 585                 590

Val Arg Glu Ala Phe Ser Gly Thr Pro Cys Leu Leu Gly Pro Gly Pro
        595                 600                 605

Val Leu Thr Val Leu Ala Leu Leu Leu Ala Ser Thr Leu Ala
    610                 615                 620
```

<210> 252
<211> 227
<212> PRT
<213> artificial

<220>
<223> Fc monomer-1

<400> 252

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                  10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr
65                  70                  75                  80


Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110


Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    130                 135                 140


Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160


Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175
```

```
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220


Pro Gly Lys
225


<210>  253
<211>  225
<212>  PRT
<213>  artificial

<220>
<223>  Fc monomer-2

<400>  253

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                   10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr
65                  70                  75                  80


Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110
```

```
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    130                 135                 140


Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160


Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175


Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220


Pro
225


<210>  254
<211>  227
<212>  PRT
<213>  artificial

<220>
<223>  Fc monomer-3

<400>  254

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                   10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45
```

```
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys
225
```

<210> 255
<211> 225
<212> PRT
<213> artificial

<220>
<223> Fc monomer-4

<400> 255

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                  10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110


Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    130                 135                 140


Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160


Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175


Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
```

195 200 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
210 215 220

Pro
225

<210> 256
<211> 227
<212> PRT
<213> artificial

<220>
<223> Fc monomer-5

<400> 256

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr
65 70 75 80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
100 105 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115 120 125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser

```
    130                 135                 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys
225


<210>  257
<211>  225
<212>  PRT
<213>  artificial

<220>
<223>  Fc monomer-6

<400>  257

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                   10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr
```

65 70 75 80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
100 105 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115 120 125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
130 135 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145 150 155 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
165 170 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
180 185 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
195 200 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
210 215 220

Pro
225

<210> 258
<211> 227
<212> PRT
<213> artificial

<220>
<223> Fc monomer-7

<400> 258

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly

```
1               5                   10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220
```

Pro Gly Lys
225

<210> 259
<211> 225
<212> PRT
<213> artificial

<220>
<223> Fc monomer-8

<400> 259

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1   5   10   15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20   25   30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35   40   45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50   55   60

His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Asn Ser Thr Tyr
65   70   75   80

Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85   90   95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100   105   110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115   120   125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    130   135   140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145   150   155   160

```
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175


Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190


Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205


His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220


Pro
225


<210>  260
<211>  484
<212>  PRT
<213>  artificial

<220>
<223>  scFc-1

<400>  260

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                   10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr
65                  70                  75                  80


Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95
```

```
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
225                 230                 235                 240

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
                245                 250                 255

Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
            260                 265                 270

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
        275                 280                 285

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
    290                 295                 300

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
```

305 310 315 320

Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr
325 330 335

Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
340 345 350

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
355 360 365

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
370 375 380

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
385 390 395 400

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
405 410 415

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
420 425 430

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
435 440 445

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
450 455 460

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
465 470 475 480

Ser Pro Gly Lys

<210> 261
<211> 480
<212> PRT
<213> artificial

<220>
<223> scFc-2

<400> 261

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                  10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr
65                  70                  75                  80

Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205
```

```
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp
                245                 250                 255

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

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        275                 280                 285

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    290                 295                 300

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
305                 310                 315                 320

Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
                325                 330                 335

Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            340                 345                 350

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
        355                 360                 365

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
    370                 375                 380

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
385                 390                 395                 400

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                405                 410                 415

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
```

```
            420                 425                 430

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
        435                 440                 445

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
    450                 455                 460

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
465                 470                 475                 480

<210>  262
<211>  484
<212>  PRT
<213>  artificial

<220>
<223>  scFc-3

<400>  262

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                   10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
```

```
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
225                 230                 235                 240

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
                245                 250                 255

Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
            260                 265                 270

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
        275                 280                 285

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
    290                 295                 300

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
305                 310                 315                 320

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
                325                 330                 335
```

```
Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
            340                 345                 350

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
        355                 360                 365

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
    370                 375                 380

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
385                 390                 395                 400

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
                405                 410                 415

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
            420                 425                 430

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
        435                 440                 445

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
    450                 455                 460

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
465                 470                 475                 480

Ser Pro Gly Lys
```

<210> 263
<211> 480
<212> PRT
<213> artificial

<220>
<223> scFc-4

<400> 263

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                   10                  15
```

```
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
```

```
225                 230                 235                 240

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp
                245                 250                 255

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

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        275                 280                 285

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    290                 295                 300

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
305                 310                 315                 320

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                325                 330                 335

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            340                 345                 350

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
        355                 360                 365

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
    370                 375                 380

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
385                 390                 395                 400

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                405                 410                 415

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

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
        435                 440                 445
```

```
Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
    450                 455                 460


Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
465                 470                 475                 480


<210>  264
<211>  484
<212>  PRT
<213>  artificial

<220>
<223>  scFc-5

<400>  264

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                   10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60


His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr
65                  70                  75                  80


Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95


Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110


Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125


Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    130                 135                 140
```

```
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
225                 230                 235                 240

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
                245                 250                 255

Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
            260                 265                 270

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
        275                 280                 285

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
    290                 295                 300

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
305                 310                 315                 320

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr
                325                 330                 335

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
            340                 345                 350

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
```

```
        355                 360                 365

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
    370                 375                 380

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
385                 390                 395                 400

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
                405                 410                 415

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
            420                 425                 430

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
        435                 440                 445

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
    450                 455                 460

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
465                 470                 475                 480

Ser Pro Gly Lys
```

<210> 265
<211> 480
<212> PRT
<213> artificial

<220>
<223> scFc-6

<400> 265

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                   10                  15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
```

```
        35                  40                  45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr
65                  70                  75                  80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp
                245                 250                 255
```

```
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
            260                 265                 270

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
        275                 280                 285

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    290                 295                 300

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
305                 310                 315                 320

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Gly Ser Thr Tyr Arg
                325                 330                 335

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            340                 345                 350

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
        355                 360                 365

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
    370                 375                 380

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
385                 390                 395                 400

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                405                 410                 415

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

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
        435                 440                 445

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
    450                 455                 460

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
```

465 470 475 480

<210> 266
<211> 484
<212> PRT
<213> artificial

<220>
<223> scFc-7

<400> 266

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80

Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
100 105 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115 120 125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
130 135 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145 150 155 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro

```
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
225                 230                 235                 240

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
                245                 250                 255

Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
            260                 265                 270

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
        275                 280                 285

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
    290                 295                 300

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
305                 310                 315                 320

Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Asn Ser Thr
                325                 330                 335

Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
            340                 345                 350

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
        355                 360                 365

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
    370                 375                 380
```

```
Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
385                 390                 395                 400


Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
                405                 410                 415


Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
            420                 425                 430


Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
        435                 440                 445


Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
    450                 455                 460


Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
465                 470                 475                 480


Ser Pro Gly Lys
```

<210> 267
<211> 480
<212> PRT
<213> artificial

<220>
<223> scFc-8

<400> 267

```
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1               5                   10                  15


Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            20                  25                  30


Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        35                  40                  45


Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    50                  55                  60
```

```
His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Asn Ser Thr Tyr
65                  70                  75                  80

Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                85                  90                  95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            100                 105                 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        115                 120                 125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    130                 135                 140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145                 150                 155                 160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                165                 170                 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            180                 185                 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        195                 200                 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    210                 215                 220

Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp
                245                 250                 255

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

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
```

```
        275                 280                 285

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
    290                 295                 300

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
305                 310                 315                 320

Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
                325                 330                 335

Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
            340                 345                 350

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
        355                 360                 365

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
    370                 375                 380

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
385                 390                 395                 400

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
                405                 410                 415

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

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
        435                 440                 445

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
    450                 455                 460

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
465                 470                 475                 480

<210>  268
<211>  988
<212>  PRT
```

<213> artificial

<220>
<223> MS_1xCD3-scFc

<400> 268

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                  10                  15


Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30


Ser Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
        35                  40                  45


Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ile Thr Asn Tyr Asn Pro Ser
    50                  55                  60


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


Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95


Cys Ala Arg Pro Ser Asn Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110


Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125


Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro Ser Val
    130                 135                 140


Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr Gly Ser Ser
145                 150                 155                 160


Ser Asn Ile Gly Ala Gly Tyr Asp Val His Trp Tyr Gln Gln Val Pro
                165                 170                 175


Gly Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asn Ser Lys Arg Pro Ser
            180                 185                 190
```

```
Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser
        195                 200                 205

Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys
    210                 215                 220

Gln Ser Tyr Asp Ser Ser Leu Gly Gly Trp Val Phe Gly Gly Gly Thr
225                 230                 235                 240

Lys Leu Thr Val Leu Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val
                245                 250                 255

Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser
            260                 265                 270

Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val
        275                 280                 285

Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser
    290                 295                 300

Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg
305                 310                 315                 320

Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met
                325                 330                 335

Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His
            340                 345                 350

Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln
        355                 360                 365

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    370                 375                 380

Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser
385                 390                 395                 400

Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser
```

```
                405                 410                 415

Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys
            420                 425                 430

Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala
        435                 440                 445

Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala
    450                 455                 460

Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr
465                 470                 475                 480

Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys
                485                 490                 495

Leu Thr Val Leu Gly Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro
            500                 505                 510

Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
        515                 520                 525

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
    530                 535                 540

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
545                 550                 555                 560

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys
                565                 570                 575

Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val
            580                 585                 590

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
        595                 600                 605

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
    610                 615                 620
```

```
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
625                 630                 635                 640

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
                645                 650                 655

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
            660                 665                 670

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
        675                 680                 685

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
    690                 695                 700

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
705                 710                 715                 720

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser
                725                 730                 735

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
            740                 745                 750

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro
        755                 760                 765

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
    770                 775                 780

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
785                 790                 795                 800

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
                805                 810                 815

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
            820                 825                 830

Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr
```

```
        835                 840                 845

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
    850                 855                 860

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
865                 870                 875                 880

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
                885                 890                 895

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
            900                 905                 910

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
        915                 920                 925

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
    930                 935                 940

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
945                 950                 955                 960

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
                965                 970                 975

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            980                 985


<210>  269
<211>  986
<212>  PRT
<213>  artificial

<220>
<223>  MS_1xCD3-scFc_delGK

<400>  269

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
```

```
            20                  25                  30

Ser Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
        35                  40                  45

Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ile Thr Asn Tyr Asn Pro Ser
    50                  55                  60

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

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Arg Pro Ser Asn Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110

Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro Ser Val
    130                 135                 140

Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr Gly Ser Ser
145                 150                 155                 160

Ser Asn Ile Gly Ala Gly Tyr Asp Val His Trp Tyr Gln Gln Val Pro
                165                 170                 175

Gly Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asn Ser Lys Arg Pro Ser
            180                 185                 190

Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser
        195                 200                 205

Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys
    210                 215                 220

Gln Ser Tyr Asp Ser Ser Leu Gly Gly Trp Val Phe Gly Gly Gly Thr
225                 230                 235                 240
```

```
Lys Leu Thr Val Leu Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val
                245                 250                 255

Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser
            260                 265                 270

Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val
        275                 280                 285

Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser
    290                 295                 300

Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg
305                 310                 315                 320

Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met
                325                 330                 335

Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His
            340                 345                 350

Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln
        355                 360                 365

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    370                 375                 380

Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser
385                 390                 395                 400

Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser
                405                 410                 415

Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys
            420                 425                 430

Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala
        435                 440                 445

Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala
```

```
    450                 455                 460

Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr
465                 470                 475                 480

Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys
                485                 490                 495

Leu Thr Val Leu Gly Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro
            500                 505                 510

Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
        515                 520                 525

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
    530                 535                 540

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
545                 550                 555                 560

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys
                565                 570                 575

Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val
            580                 585                 590

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
        595                 600                 605

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
    610                 615                 620

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
625                 630                 635                 640

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
                645                 650                 655

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
            660                 665                 670
```

```
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
        675                 680                 685

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
    690                 695                 700

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
705                 710                 715                 720

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Gly Gly
                725                 730                 735

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
            740                 745                 750

Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys
        755                 760                 765

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
    770                 775                 780

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
785                 790                 795                 800

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
                805                 810                 815

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
            820                 825                 830

Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu
        835                 840                 845

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
    850                 855                 860

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
865                 870                 875                 880

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
```

```
                885                 890                 895

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
            900                 905                 910

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
        915                 920                 925

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
    930                 935                 940

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
945                 950                 955                 960

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
                965                 970                 975

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            980                 985


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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30

Ser Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Cys Leu Glu
        35                  40                  45

Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ile Thr Asn Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
```

```
65                  70                  75                  80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Arg Pro Ser Asn Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110

Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro Ser Val
    130                 135                 140

Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr Gly Ser Ser
145                 150                 155                 160

Ser Asn Ile Gly Ala Gly Tyr Asp Val His Trp Tyr Gln Gln Val Pro
                165                 170                 175

Gly Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asn Ser Lys Arg Pro Ser
            180                 185                 190

Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser
        195                 200                 205

Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys
    210                 215                 220

Gln Ser Tyr Asp Ser Ser Leu Gly Gly Trp Val Phe Gly Cys Gly Thr
225                 230                 235                 240

Lys Leu Thr Val Leu Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val
                245                 250                 255

Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser
            260                 265                 270

Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val
        275                 280                 285
```

```
Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser
    290                 295                 300

Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg
305                 310                 315                 320

Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met
                325                 330                 335

Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His
            340                 345                 350

Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln
        355                 360                 365

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    370                 375                 380

Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser
385                 390                 395                 400

Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser
                405                 410                 415

Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys
            420                 425                 430

Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala
        435                 440                 445

Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala
    450                 455                 460

Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr
465                 470                 475                 480

Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys
                485                 490                 495

Leu Thr Val Leu Gly Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro
```

```
            500                 505                 510

Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
        515                 520                 525

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
    530                 535                 540

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
545                 550                 555                 560

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys
                565                 570                 575

Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val
            580                 585                 590

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
        595                 600                 605

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
    610                 615                 620

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
625                 630                 635                 640

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
                645                 650                 655

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
            660                 665                 670

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
        675                 680                 685

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
    690                 695                 700

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
705                 710                 715                 720
```

```
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser
                725                 730                 735

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
            740                 745                 750

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro
        755                 760                 765

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
    770                 775                 780

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
785                 790                 795                 800

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
                805                 810                 815

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
            820                 825                 830

Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr
        835                 840                 845

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
    850                 855                 860

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
865                 870                 875                 880

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
                885                 890                 895

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
            900                 905                 910

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
        915                 920                 925

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
```

```
    930                 935                 940

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
945                 950                 955                 960

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
                965                 970                 975

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            980                 985

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Ser
            20                  25                  30

Ser Tyr Tyr Trp Gly Trp Ile Arg Gln Pro Pro Gly Lys Cys Leu Glu
        35                  40                  45

Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Ile Thr Asn Tyr Asn Pro Ser
    50                  55                  60

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

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Arg Pro Ser Asn Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110

Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
```

```
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro Ser Val
    130                 135                 140

Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr Gly Ser Ser
145                 150                 155                 160

Ser Asn Ile Gly Ala Gly Tyr Asp Val His Trp Tyr Gln Gln Val Pro
                165                 170                 175

Gly Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asn Ser Lys Arg Pro Ser
            180                 185                 190

Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser
        195                 200                 205

Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys
    210                 215                 220

Gln Ser Tyr Asp Ser Ser Leu Gly Gly Trp Val Phe Gly Cys Gly Thr
225                 230                 235                 240

Lys Leu Thr Val Leu Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val
                245                 250                 255

Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser
            260                 265                 270

Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val
        275                 280                 285

Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser
    290                 295                 300

Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg
305                 310                 315                 320

Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met
                325                 330                 335
```

```
Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His
            340                 345                 350

Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln
        355                 360                 365

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
    370                 375                 380

Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser
385                 390                 395                 400

Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser
                405                 410                 415

Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys
            420                 425                 430

Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala
        435                 440                 445

Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala
    450                 455                 460

Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr
465                 470                 475                 480

Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys
                485                 490                 495

Leu Thr Val Leu Gly Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro
            500                 505                 510

Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
        515                 520                 525

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
    530                 535                 540

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
```

```
545                 550                 555                 560

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys
                565                 570                 575

Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val
            580                 585                 590

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
        595                 600                 605

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
    610                 615                 620

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
625                 630                 635                 640

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
                645                 650                 655

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
            660                 665                 670

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
        675                 680                 685

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
    690                 695                 700

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
705                 710                 715                 720

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Gly Gly
                725                 730                 735

Gly Gly Ser Gly Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
            740                 745                 750

Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys
        755                 760                 765
```

```
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
    770                 775                 780

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
785                 790                 795                 800

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
                805                 810                 815

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
            820                 825                 830

Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu
        835                 840                 845

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
    850                 855                 860

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
865                 870                 875                 880

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
                885                 890                 895

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
            900                 905                 910

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
        915                 920                 925

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
    930                 935                 940

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
945                 950                 955                 960

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
                965                 970                 975

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
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980 985

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

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

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

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

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

Ala Arg Asp Leu Gly Pro Ser Phe Asp Tyr Trp Gly Gln Gly Ser Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
145 150 155 160

Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro

```
                165                 170                 175

Lys Leu Leu Ile Asp Ala Ala Ser Arg Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380
```

```
Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
                405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430

Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
    450                 455                 460

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

Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly
                485                 490                 495

Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
            500                 505                 510

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        515                 520                 525

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    530                 535                 540

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
545                 550                 555                 560

Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser
                565                 570                 575

Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            580                 585                 590

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
```

```
        595                 600                 605

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    610                 615                 620

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
625                 630                 635                 640

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
                645                 650                 655

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
            660                 665                 670

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
        675                 680                 685

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
    690                 695                 700

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
705                 710                 715                 720

Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
                725                 730                 735

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            740                 745                 750

Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
        755                 760                 765

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    770                 775                 780

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
785                 790                 795                 800

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
                805                 810                 815
```

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Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly
            820                 825                 830

Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        835                 840                 845

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
    850                 855                 860

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
865                 870                 875                 880

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
                885                 890                 895

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            900                 905                 910

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        915                 920                 925

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
    930                 935                 940

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
945                 950                 955                 960

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                965                 970                 975

Ser Leu Ser Pro Gly Lys
            980


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

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

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

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

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

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

Ala Arg Asp Leu Gly Pro Ser Phe Asp Tyr Trp Gly Gln Gly Ser Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
145                 150                 155                 160

Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Lys Leu Leu Ile Asp Ala Ala Ser Arg Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn
```

```
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
                405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430
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Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
    450                 455                 460

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

Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly
                485                 490                 495

Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
            500                 505                 510

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        515                 520                 525

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    530                 535                 540

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
545                 550                 555                 560

Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser
                565                 570                 575

Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            580                 585                 590

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
        595                 600                 605

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    610                 615                 620

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
625                 630                 635                 640

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
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                645                 650                 655

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
            660                 665                 670

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
        675                 680                 685

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
    690                 695                 700

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
705                 710                 715                 720

Leu Ser Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
                725                 730                 735

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
            740                 745                 750

Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        755                 760                 765

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    770                 775                 780

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
785                 790                 795                 800

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                805                 810                 815

Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr
            820                 825                 830

Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        835                 840                 845

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    850                 855                 860
```

```
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
865                 870                 875                 880


Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
                885                 890                 895


Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            900                 905                 910


Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        915                 920                 925


Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    930                 935                 940


Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
945                 950                 955                 960


Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                965                 970                 975


Ser Pro Gly Lys
            980


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<213>  artificial

<220>
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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15


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


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

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

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

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

Ala Arg Asp Leu Gly Pro Ser Phe Asp Tyr Trp Gly Gln Gly Ser Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
145                 150                 155                 160

Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Lys Leu Leu Ile Asp Ala Ala Ser Arg Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Cys Gly Thr Lys Val Glu Ile Lys Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
```

```
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
                405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430

Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
    450                 455                 460

Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser
465                 470                 475                 480
```

```
Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly
                485                 490                 495

Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
            500                 505                 510

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        515                 520                 525

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    530                 535                 540

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
545                 550                 555                 560

Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser
                565                 570                 575

Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            580                 585                 590

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
        595                 600                 605

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    610                 615                 620

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
625                 630                 635                 640

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
                645                 650                 655

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
            660                 665                 670

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
        675                 680                 685

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
```

```
    690                 695                 700

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
705                 710                 715                 720

Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
                725                 730                 735

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            740                 745                 750

Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
        755                 760                 765

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    770                 775                 780

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
785                 790                 795                 800

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
                805                 810                 815

Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly
            820                 825                 830

Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        835                 840                 845

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
    850                 855                 860

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
865                 870                 875                 880

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
                885                 890                 895

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            900                 905                 910
```

```
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        915                 920                 925

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
    930                 935                 940

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
945                 950                 955                 960

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                965                 970                 975

Ser Leu Ser Pro Gly Lys
            980
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<213> artificial

<220>
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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15

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

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

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

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

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

```
Ala Arg Asp Leu Gly Pro Ser Phe Asp Tyr Trp Gly Gln Gly Ser Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
145                 150                 155                 160

Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Lys Leu Leu Ile Asp Ala Ala Ser Arg Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Cys Gly Thr Lys Val Glu Ile Lys Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
```

```
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
                405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430

Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
    450                 455                 460

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

Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly
                485                 490                 495

Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
            500                 505                 510

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        515                 520                 525
```

```
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    530                 535                 540

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
545                 550                 555                 560

Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser
                565                 570                 575

Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            580                 585                 590

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
        595                 600                 605

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    610                 615                 620

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
625                 630                 635                 640

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
                645                 650                 655

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
            660                 665                 670

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
        675                 680                 685

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
    690                 695                 700

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
705                 710                 715                 720

Leu Ser Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
                725                 730                 735

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
```

```
            740                 745                 750

Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        755                 760                 765

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    770                 775                 780

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
785                 790                 795                 800

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                805                 810                 815

Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr
            820                 825                 830

Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        835                 840                 845

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    850                 855                 860

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
865                 870                 875                 880

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
                885                 890                 895

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            900                 905                 910

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        915                 920                 925

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    930                 935                 940

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
945                 950                 955                 960
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```
Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                965                 970                 975


Ser Pro Gly Lys
            980


<210>  276
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<400>  276

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


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


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


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


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


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


Ala Arg Asp Arg Asn Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125


Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140
```

```
Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
145                 150                 155                 160

Ile Thr Arg Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Lys Leu Leu Ile Tyr Ala Ala Ser Val Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
```

```
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
                405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430

Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
    450                 455                 460

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

Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly
                485                 490                 495

Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
            500                 505                 510

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        515                 520                 525

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    530                 535                 540

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
545                 550                 555                 560

Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser
                565                 570                 575
```

```
Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            580                 585                 590

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
        595                 600                 605

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    610                 615                 620

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
625                 630                 635                 640

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
                645                 650                 655

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
            660                 665                 670

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
        675                 680                 685

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
    690                 695                 700

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
705                 710                 715                 720

Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
                725                 730                 735

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            740                 745                 750

Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
        755                 760                 765

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    770                 775                 780

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
```

785 790 795 800

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
805 810 815

Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly
820 825 830

Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp
835 840 845

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
850 855 860

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
865 870 875 880

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
885 890 895

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
900 905 910

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
915 920 925

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
930 935 940

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
945 950 955 960

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
965 970 975

Ser Leu Ser Pro Gly Lys
980

<210> 277
<211> 980
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<223> MS_3xCD3-scFc_delGK

<400> 277

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


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


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


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


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


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


Ala Arg Asp Arg Asn Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125


Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140


Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
145                 150                 155                 160


Ile Thr Arg Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175


Lys Leu Leu Ile Tyr Ala Ala Ser Val Leu Gln Ser Gly Val Pro Ser
            180                 185                 190
```

```
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
```

```
                405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430

Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
    450                 455                 460

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

Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly
                485                 490                 495

Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
            500                 505                 510

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        515                 520                 525

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    530                 535                 540

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
545                 550                 555                 560

Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser
                565                 570                 575

Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            580                 585                 590

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
        595                 600                 605

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    610                 615                 620
```

```
Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
625                 630                 635                 640

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
                645                 650                 655

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
            660                 665                 670

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
        675                 680                 685

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
    690                 695                 700

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
705                 710                 715                 720

Leu Ser Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
                725                 730                 735

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
            740                 745                 750

Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        755                 760                 765

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    770                 775                 780

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
785                 790                 795                 800

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                805                 810                 815

Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr
            820                 825                 830

Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
```

```
        835                 840                 845

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    850                 855                 860

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
865                 870                 875                 880

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
                885                 890                 895

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            900                 905                 910

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        915                 920                 925

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    930                 935                 940

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
945                 950                 955                 960

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                965                 970                 975

Ser Pro Gly Lys
            980


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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
```

```
            20                  25                  30

Tyr Met Thr Trp Ile Arg Gln Ala Pro Gly Lys Cys Leu Glu Trp Ile
        35                  40                  45

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

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

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

Ala Arg Asp Arg Asn Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
145                 150                 155                 160

Ile Thr Arg Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Lys Leu Leu Ile Tyr Ala Ala Ser Val Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Cys Gly Thr Lys Val Glu Ile Lys Ser
225                 230                 235                 240
```

```
Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
                405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430

Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
```

```
    450                 455                 460

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

Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly
                485                 490                 495

Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
            500                 505                 510

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        515                 520                 525

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    530                 535                 540

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
545                 550                 555                 560

Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser
                565                 570                 575

Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            580                 585                 590

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
        595                 600                 605

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    610                 615                 620

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
625                 630                 635                 640

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
                645                 650                 655

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
            660                 665                 670
```

```
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
        675                 680                 685

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
    690                 695                 700

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
705                 710                 715                 720

Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
                725                 730                 735

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            740                 745                 750

Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
        755                 760                 765

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    770                 775                 780

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
785                 790                 795                 800

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
                805                 810                 815

Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly
            820                 825                 830

Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        835                 840                 845

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
    850                 855                 860

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
865                 870                 875                 880

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
```

```
                885                 890                 895

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            900                 905                 910

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        915                 920                 925

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
    930                 935                 940

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
945                 950                 955                 960

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                965                 970                 975

Ser Leu Ser Pro Gly Lys
            980


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<400>  279

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

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

Tyr Met Thr Trp Ile Arg Gln Ala Pro Gly Lys Cys Leu Glu Trp Ile
        35                  40                  45

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
```

```
65                  70                  75                  80

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

Ala Arg Asp Arg Asn Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
145                 150                 155                 160

Ile Thr Arg Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Lys Leu Leu Ile Tyr Ala Ala Ser Val Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Asn
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Cys Gly Thr Lys Val Glu Ile Lys Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285
```

```
Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
                405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430

Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
    450                 455                 460

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

Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly
                485                 490                 495

Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
```

```
            500                 505                 510

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        515                 520                 525

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    530                 535                 540

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
545                 550                 555                 560

Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser
                565                 570                 575

Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            580                 585                 590

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
        595                 600                 605

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    610                 615                 620

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
625                 630                 635                 640

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
                645                 650                 655

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
            660                 665                 670

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
        675                 680                 685

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
    690                 695                 700

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
705                 710                 715                 720
```

```
Leu Ser Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
                725                 730                 735

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
            740                 745                 750

Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        755                 760                 765

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    770                 775                 780

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
785                 790                 795                 800

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                805                 810                 815

Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr
            820                 825                 830

Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        835                 840                 845

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    850                 855                 860

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
865                 870                 875                 880

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
                885                 890                 895

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            900                 905                 910

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        915                 920                 925

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
```

```
    930                 935                 940

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
945                 950                 955                 960

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                965                 970                 975

Ser Pro Gly Lys
            980
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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

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

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

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

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

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

Ala Arg Asp Arg Asn Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
```

```
        115                 120                 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
145                 150                 155                 160

Ile Asn Thr Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Lys Leu Leu Ile Tyr Gly Ala Ser Gly Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Lys
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335
```

```
Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
                405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430

Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
    450                 455                 460

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

Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly
                485                 490                 495

Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
            500                 505                 510

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        515                 520                 525

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    530                 535                 540

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
```

```
545                 550                 555                 560

Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser
                565                 570                 575

Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            580                 585                 590

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
        595                 600                 605

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    610                 615                 620

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
625                 630                 635                 640

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
                645                 650                 655

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
            660                 665                 670

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
        675                 680                 685

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
    690                 695                 700

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
705                 710                 715                 720

Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
                725                 730                 735

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            740                 745                 750

Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
        755                 760                 765
```

```
Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    770                 775                 780

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
785                 790                 795                 800

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
                805                 810                 815

Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly
            820                 825                 830

Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        835                 840                 845

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
    850                 855                 860

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
865                 870                 875                 880

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
                885                 890                 895

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            900                 905                 910

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        915                 920                 925

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
    930                 935                 940

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
945                 950                 955                 960

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                965                 970                 975

Ser Leu Ser Pro Gly Lys
```

980

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

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

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

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

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

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

Ala Arg Asp Arg Asn Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
145 150 155 160

Ile Asn Thr Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro

```
                165                 170                 175

Lys Leu Leu Ile Tyr Gly Ala Ser Gly Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Lys
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380
```

```
Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
                405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430

Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
    450                 455                 460

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

Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly
                485                 490                 495

Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
            500                 505                 510

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        515                 520                 525

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    530                 535                 540

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
545                 550                 555                 560

Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser
                565                 570                 575

Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            580                 585                 590

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
```

```
        595                 600                 605

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    610                 615                 620

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
625                 630                 635                 640

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
                645                 650                 655

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
            660                 665                 670

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
        675                 680                 685

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
    690                 695                 700

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
705                 710                 715                 720

Leu Ser Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
                725                 730                 735

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
            740                 745                 750

Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        755                 760                 765

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    770                 775                 780

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
785                 790                 795                 800

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                805                 810                 815
```

```
Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr
            820                 825                 830

Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        835                 840                 845

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    850                 855                 860

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
865                 870                 875                 880

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
                885                 890                 895

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            900                 905                 910

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        915                 920                 925

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    930                 935                 940

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
945                 950                 955                 960

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                965                 970                 975

Ser Pro Gly Lys
            980
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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

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

Tyr Met Thr Trp Ile Arg Gln Ala Pro Gly Lys Cys Leu Glu Trp Leu
        35                  40                  45

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

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

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

Ala Arg Asp Arg Asn Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
145                 150                 155                 160

Ile Asn Thr Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Lys Leu Leu Ile Tyr Gly Ala Ser Gly Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Lys
```

```
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Cys Gly Thr Lys Val Glu Ile Lys Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
                405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430
```

```
Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
    450                 455                 460

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

Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly
                485                 490                 495

Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
            500                 505                 510

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        515                 520                 525

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    530                 535                 540

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
545                 550                 555                 560

Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser
                565                 570                 575

Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            580                 585                 590

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
        595                 600                 605

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    610                 615                 620

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
625                 630                 635                 640

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
```

```
                645                 650                 655

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
            660                 665                 670

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
        675                 680                 685

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
    690                 695                 700

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
705                 710                 715                 720

Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
                725                 730                 735

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            740                 745                 750

Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
        755                 760                 765

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    770                 775                 780

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
785                 790                 795                 800

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
                805                 810                 815

Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly
            820                 825                 830

Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        835                 840                 845

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
    850                 855                 860
```

```
Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
865                 870                 875                 880


Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
                885                 890                 895


Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            900                 905                 910


Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        915                 920                 925


Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
    930                 935                 940


Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
945                 950                 955                 960


Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                965                 970                 975


Ser Leu Ser Pro Gly Lys
            980


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


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


Tyr Met Thr Trp Ile Arg Gln Ala Pro Gly Lys Cys Leu Glu Trp Leu
        35                  40                  45
```

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

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

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

Ala Arg Asp Arg Asn Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
145                 150                 155                 160

Ile Asn Thr Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Lys Leu Leu Ile Tyr Gly Ala Ser Gly Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Lys
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Cys Gly Thr Lys Val Glu Ile Lys Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
```

```
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
                405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430

Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
    450                 455                 460

Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser
465                 470                 475                 480
```

```
Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly
                485                 490                 495

Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
            500                 505                 510

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        515                 520                 525

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    530                 535                 540

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
545                 550                 555                 560

Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser
                565                 570                 575

Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            580                 585                 590

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
        595                 600                 605

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    610                 615                 620

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
625                 630                 635                 640

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
                645                 650                 655

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
            660                 665                 670

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
        675                 680                 685

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
```

```
    690                 695                 700

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
705                 710                 715                 720

Leu Ser Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
                725                 730                 735

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
            740                 745                 750

Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        755                 760                 765

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    770                 775                 780

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
785                 790                 795                 800

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                805                 810                 815

Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr
            820                 825                 830

Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        835                 840                 845

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    850                 855                 860

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
865                 870                 875                 880

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
                885                 890                 895

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            900                 905                 910
```

```
Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        915                 920                 925

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    930                 935                 940

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
945                 950                 955                 960

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                965                 970                 975

Ser Pro Gly Lys
            980
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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp His
            20                  25                  30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Phe
        35                  40                  45

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

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

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

```
Ala Arg Asp Val Gly Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp
145                 150                 155                 160

Ile Ser Arg Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Lys Leu Leu Ile Ser Ala Ala Ser Arg Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Ile Tyr Tyr Cys Gln Gln Ala Lys
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
```

```
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
                405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430

Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
    450                 455                 460

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

Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly
                485                 490                 495

Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
            500                 505                 510

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        515                 520                 525
```

```
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    530                 535                 540

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
545                 550                 555                 560

Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser
                565                 570                 575

Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            580                 585                 590

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
        595                 600                 605

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    610                 615                 620

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
625                 630                 635                 640

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
                645                 650                 655

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
            660                 665                 670

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
        675                 680                 685

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
    690                 695                 700

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
705                 710                 715                 720

Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
                725                 730                 735

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
```

```
            740                 745                 750

Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
        755                 760                 765

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    770                 775                 780

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
785                 790                 795                 800

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
                805                 810                 815

Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly
            820                 825                 830

Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        835                 840                 845

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
    850                 855                 860

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
865                 870                 875                 880

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
                885                 890                 895

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            900                 905                 910

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        915                 920                 925

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
    930                 935                 940

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
945                 950                 955                 960
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Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                965                 970                 975


Ser Leu Ser Pro Gly Lys
            980


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


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


Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Phe
        35                  40                  45


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


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


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


Ala Arg Asp Val Gly Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125


Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140
```

```
Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp
145                 150                 155                 160

Ile Ser Arg Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Lys Leu Leu Ile Ser Ala Ala Ser Arg Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Ile Tyr Tyr Cys Gln Gln Ala Lys
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
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```
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
                405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430

Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
    450                 455                 460

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

Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly
                485                 490                 495

Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
            500                 505                 510

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        515                 520                 525

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    530                 535                 540

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
545                 550                 555                 560

Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser
                565                 570                 575
```

```
Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            580                 585                 590

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
        595                 600                 605

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    610                 615                 620

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
625                 630                 635                 640

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
                645                 650                 655

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
            660                 665                 670

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
        675                 680                 685

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
    690                 695                 700

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
705                 710                 715                 720

Leu Ser Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
                725                 730                 735

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
            740                 745                 750

Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        755                 760                 765

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    770                 775                 780

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
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785 790 795 800

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
805 810 815

Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr
820 825 830

Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
835 840 845

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
850 855 860

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
865 870 875 880

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
885 890 895

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
900 905 910

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
915 920 925

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
930 935 940

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
945 950 955 960

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
965 970 975

Ser Pro Gly Lys
980

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1               5                   10                  15


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


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


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


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


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


Ala Arg Asp Val Gly Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125


Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140


Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp
145                 150                 155                 160


Ile Ser Arg Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175


Lys Leu Leu Ile Ser Ala Ala Ser Arg Leu Gln Ser Gly Val Pro Ser
            180                 185                 190
```

```
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Ile Tyr Tyr Cys Gln Gln Ala Lys
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Cys Gly Thr Lys Val Glu Ile Lys Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
```

```
               405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430

Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
    450                 455                 460

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

Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly
                485                 490                 495

Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
            500                 505                 510

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        515                 520                 525

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    530                 535                 540

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
545                 550                 555                 560

Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser
                565                 570                 575

Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            580                 585                 590

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
        595                 600                 605

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    610                 615                 620
```

```
Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
625                 630                 635                 640

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
                645                 650                 655

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
            660                 665                 670

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
        675                 680                 685

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
    690                 695                 700

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
705                 710                 715                 720

Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
                725                 730                 735

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            740                 745                 750

Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
        755                 760                 765

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    770                 775                 780

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
785                 790                 795                 800

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
                805                 810                 815

Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly
            820                 825                 830

Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp
```

```
        835                 840                 845

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
    850                 855                 860

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
865                 870                 875                 880

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
                885                 890                 895

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            900                 905                 910

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        915                 920                 925

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
    930                 935                 940

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
945                 950                 955                 960

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                965                 970                 975

Ser Leu Ser Pro Gly Lys
            980


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

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

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

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

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

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

Ala Arg Asp Val Gly Ser His Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp
145                 150                 155                 160

Ile Ser Arg Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Lys Leu Leu Ile Ser Ala Ala Ser Arg Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Ile Tyr Tyr Cys Gln Gln Ala Lys
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Cys Gly Thr Lys Val Glu Ile Lys Ser
225                 230                 235                 240
```

```
Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
                405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430

Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
```

```
    450                 455                 460

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

Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly
                485                 490                 495

Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
            500                 505                 510

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        515                 520                 525

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    530                 535                 540

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
545                 550                 555                 560

Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser
                565                 570                 575

Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            580                 585                 590

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
        595                 600                 605

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    610                 615                 620

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
625                 630                 635                 640

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
                645                 650                 655

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
            660                 665                 670
```

```
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
        675                 680                 685

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
    690                 695                 700

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
705                 710                 715                 720

Leu Ser Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
                725                 730                 735

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
            740                 745                 750

Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        755                 760                 765

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    770                 775                 780

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
785                 790                 795                 800

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                805                 810                 815

Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr
            820                 825                 830

Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        835                 840                 845

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    850                 855                 860

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
865                 870                 875                 880

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
```

```
                885                 890                 895

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            900                 905                 910

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        915                 920                 925

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    930                 935                 940

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
945                 950                 955                 960

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                965                 970                 975

Ser Pro Gly Lys
            980


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

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

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

Ser Tyr Ile Ser Asn Ser Gly Ser Ile Ile Tyr Tyr Val Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
```

```
65                  70                  75                  80

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

Ala Arg Asp Val Arg Thr Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser
145                 150                 155                 160

Ile Gly Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Asn Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285
```

```
Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
                405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430

Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
    450                 455                 460

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

Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly
                485                 490                 495

Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
```

```
            500                 505                 510

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        515                 520                 525

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    530                 535                 540

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
545                 550                 555                 560

Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser
                565                 570                 575

Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            580                 585                 590

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
        595                 600                 605

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    610                 615                 620

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
625                 630                 635                 640

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
                645                 650                 655

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
            660                 665                 670

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
        675                 680                 685

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
    690                 695                 700

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
705                 710                 715                 720
```

```
Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
                725                 730                 735

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            740                 745                 750

Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
        755                 760                 765

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    770                 775                 780

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
785                 790                 795                 800

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
                805                 810                 815

Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly
            820                 825                 830

Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        835                 840                 845

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
    850                 855                 860

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
865                 870                 875                 880

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
                885                 890                 895

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            900                 905                 910

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        915                 920                 925

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
```

```
    930                 935                 940

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
945                 950                 955                 960

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                965                 970                 975

Ser Leu Ser Pro Gly Lys
            980
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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

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

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

Ser Tyr Ile Ser Asn Ser Gly Ser Ile Ile Tyr Tyr Val Asp Ser Val
    50                  55                  60

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

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

Ala Arg Asp Val Arg Thr Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
```

```
        115                 120                 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser
145                 150                 155                 160

Ile Gly Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Asn Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335
```

```
Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
                405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430

Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
    450                 455                 460

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

Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly
                485                 490                 495

Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
            500                 505                 510

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        515                 520                 525

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    530                 535                 540

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
```

```
545                 550                 555                 560

Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser
                565                 570                 575

Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            580                 585                 590

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
        595                 600                 605

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    610                 615                 620

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
625                 630                 635                 640

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
                645                 650                 655

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
            660                 665                 670

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
        675                 680                 685

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
    690                 695                 700

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
705                 710                 715                 720

Leu Ser Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
                725                 730                 735

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
            740                 745                 750

Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        755                 760                 765
```

```
Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    770                 775                 780

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
785                 790                 795                 800

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                805                 810                 815

Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr
            820                 825                 830

Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        835                 840                 845

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    850                 855                 860

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
865                 870                 875                 880

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
                885                 890                 895

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            900                 905                 910

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        915                 920                 925

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    930                 935                 940

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
945                 950                 955                 960

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                965                 970                 975

Ser Pro Gly Lys
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980

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp His
20 25 30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Cys Leu Glu Trp Ile
35 40 45

Ser Tyr Ile Ser Asn Ser Gly Ser Ile Ile Tyr Tyr Val Asp Ser Val
50 55 60

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

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

Ala Arg Asp Val Arg Thr Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
130 135 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser
145 150 155 160

Ile Gly Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro

```
                165                 170                 175

Asn Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Cys Gly Thr Lys Val Asp Ile Lys Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380
```

```
Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
                405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430

Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
    450                 455                 460

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

Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly
                485                 490                 495

Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
            500                 505                 510

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        515                 520                 525

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    530                 535                 540

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
545                 550                 555                 560

Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser
                565                 570                 575

Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            580                 585                 590

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
```

```
        595                 600                 605

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    610                 615                 620

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
625                 630                 635                 640

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
                645                 650                 655

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
            660                 665                 670

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
        675                 680                 685

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
    690                 695                 700

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
705                 710                 715                 720

Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
                725                 730                 735

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            740                 745                 750

Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
        755                 760                 765

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
    770                 775                 780

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
785                 790                 795                 800

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
                805                 810                 815
```

```
Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly
            820                 825                 830

Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp
        835                 840                 845

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
    850                 855                 860

Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
865                 870                 875                 880

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
                885                 890                 895

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
            900                 905                 910

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
        915                 920                 925

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
    930                 935                 940

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
945                 950                 955                 960

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
                965                 970                 975

Ser Leu Ser Pro Gly Lys
            980


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

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

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Cys Leu Glu Trp Ile
        35                  40                  45

Ser Tyr Ile Ser Asn Ser Gly Ser Ile Ile Tyr Tyr Val Asp Ser Val
    50                  55                  60

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

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

Ala Arg Asp Val Arg Thr Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
        115                 120                 125

Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser
    130                 135                 140

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser
145                 150                 155                 160

Ile Gly Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
                165                 170                 175

Asn Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser
            180                 185                 190

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
        195                 200                 205

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn
```

```
    210                 215                 220

Ser Phe Pro Arg Thr Phe Gly Cys Gly Thr Lys Val Asp Ile Lys Ser
225                 230                 235                 240

Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                245                 250                 255

Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe
            260                 265                 270

Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys
        275                 280                 285

Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala
    290                 295                 300

Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe Thr Ile Ser Arg Asp
305                 310                 315                 320

Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Asn Leu Lys Thr Glu
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly Asn Phe Gly Asn Ser
            340                 345                 350

Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly
385                 390                 395                 400

Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser
                405                 410                 415

Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg
            420                 425                 430
```

```
Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg
        435                 440                 445

Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly
    450                 455                 460

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

Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gly
                485                 490                 495

Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
            500                 505                 510

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
        515                 520                 525

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
    530                 535                 540

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
545                 550                 555                 560

Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser
                565                 570                 575

Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
            580                 585                 590

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
        595                 600                 605

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
    610                 615                 620

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
625                 630                 635                 640

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
```

```
                645                 650                 655

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
            660                 665                 670

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
        675                 680                 685

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
    690                 695                 700

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
705                 710                 715                 720

Leu Ser Pro Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
                725                 730                 735

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
            740                 745                 750

Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
        755                 760                 765

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
    770                 775                 780

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
785                 790                 795                 800

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
                805                 810                 815

Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu Gln Tyr Gly Ser Thr
            820                 825                 830

Tyr Arg Cys Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
        835                 840                 845

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
    850                 855                 860
```

```
Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
865                 870                 875                 880


Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
                885                 890                 895


Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
            900                 905                 910


Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
        915                 920                 925


Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
    930                 935                 940


Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
945                 950                 955                 960


Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                965                 970                 975


Ser Pro Gly Lys
            980


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


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


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

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

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

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

Arg Asp Ser Gly Gly Trp Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125

Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu
    130                 135                 140

Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln
145                 150                 155                 160

Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln
                165                 170                 175

Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr
            180                 185                 190

Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
        195                 200                 205

Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val
    210                 215                 220

Tyr Tyr Cys Gln Gln Tyr Tyr Ser Thr Pro Pro Thr Phe Gly Gln Gly
225                 230                 235                 240

Thr Lys Val Glu Ile Lys Ser Gly Gly Gly Gly Ser Glu Val Gln Leu
                245                 250                 255

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

```
            260                 265                 270

Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp
        275                 280                 285

Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg
    290                 295                 300

Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp
305                 310                 315                 320

Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln
                325                 330                 335

Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg
            340                 345                 350

His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly
        355                 360                 365

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
    370                 375                 380

Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro
385                 390                 395                 400

Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser
                405                 410                 415

Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln
            420                 425                 430

Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu
        435                 440                 445

Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys
    450                 455                 460

Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr
465                 470                 475                 480
```

```
Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr
                485                 490                 495

Lys Leu Thr Val Leu Gly Gly Gly Gly Asp Lys Thr His Thr Cys Pro
            500                 505                 510

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
        515                 520                 525

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
    530                 535                 540

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
545                 550                 555                 560

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
                565                 570                 575

Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr
            580                 585                 590

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
        595                 600                 605

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
    610                 615                 620

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
625                 630                 635                 640

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
                645                 650                 655

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
            660                 665                 670

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
        675                 680                 685

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
```

```
    690                 695                 700

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
705                 710                 715                 720

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly
                725                 730                 735

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
            740                 745                 750

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys
        755                 760                 765

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
    770                 775                 780

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
785                 790                 795                 800

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
                805                 810                 815

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
            820                 825                 830

Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu
        835                 840                 845

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
    850                 855                 860

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
865                 870                 875                 880

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
                885                 890                 895

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
            900                 905                 910
```

```
Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
        915                 920                 925

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
    930                 935                 940

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
945                 950                 955                 960

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
                965                 970                 975

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            980                 985
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1               5                   10                  15

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

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

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

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

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

```
Arg Asp Ser Gly Gly Trp Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125

Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu
    130                 135                 140

Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln
145                 150                 155                 160

Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln
                165                 170                 175

Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr
            180                 185                 190

Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
        195                 200                 205

Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val
    210                 215                 220

Tyr Tyr Cys Gln Gln Tyr Tyr Ser Thr Pro Pro Thr Phe Gly Gln Gly
225                 230                 235                 240

Thr Lys Val Glu Ile Lys Ser Gly Gly Gly Gly Ser Glu Val Gln Leu
                245                 250                 255

Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu
            260                 265                 270

Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp
        275                 280                 285

Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg
    290                 295                 300

Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp
```

```
305                 310                 315                 320

Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln
                325                 330                 335

Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg
            340                 345                 350

His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly
        355                 360                 365

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
    370                 375                 380

Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro
385                 390                 395                 400

Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser
                405                 410                 415

Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln
            420                 425                 430

Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu
        435                 440                 445

Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys
    450                 455                 460

Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr
465                 470                 475                 480

Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr
                485                 490                 495

Lys Leu Thr Val Leu Gly Gly Gly Gly Asp Lys Thr His Thr Cys Pro
            500                 505                 510

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
        515                 520                 525
```

```
Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
    530                 535                 540

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
545                 550                 555                 560

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
                565                 570                 575

Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr
            580                 585                 590

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
        595                 600                 605

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
    610                 615                 620

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
625                 630                 635                 640

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
                645                 650                 655

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
            660                 665                 670

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
        675                 680                 685

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
    690                 695                 700

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
705                 710                 715                 720

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Gly
                725                 730                 735

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
```

```
            740                 745                 750

Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro
        755                 760                 765

Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
    770                 775                 780

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
785                 790                 795                 800

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
                805                 810                 815

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys
            820                 825                 830

Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val
        835                 840                 845

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
    850                 855                 860

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
865                 870                 875                 880

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
                885                 890                 895

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
            900                 905                 910

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
        915                 920                 925

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
    930                 935                 940

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
945                 950                 955                 960
```

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Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
                965                 970                 975


Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            980                 985


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


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


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


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


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


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


Arg Asp Ser Gly Gly Trp Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125


Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu
    130                 135                 140
```

```
Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln
145                 150                 155                 160


Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln
                165                 170                 175


Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr
            180                 185                 190


Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
        195                 200                 205


Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val
    210                 215                 220


Tyr Tyr Cys Gln Gln Tyr Tyr Ser Thr Pro Pro Thr Phe Gly Cys Gly
225                 230                 235                 240


Thr Lys Val Glu Ile Lys Ser Gly Gly Gly Gly Ser Glu Val Gln Leu
                245                 250                 255


Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu
            260                 265                 270


Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp
        275                 280                 285


Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg
    290                 295                 300


Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp
305                 310                 315                 320


Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln
                325                 330                 335


Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg
            340                 345                 350


His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly
```

```
        355                 360                 365

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
    370                 375                 380

Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro
385                 390                 395                 400

Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser
                405                 410                 415

Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln
            420                 425                 430

Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu
        435                 440                 445

Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys
    450                 455                 460

Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr
465                 470                 475                 480

Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr
                485                 490                 495

Lys Leu Thr Val Leu Gly Gly Gly Gly Asp Lys Thr His Thr Cys Pro
            500                 505                 510

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
        515                 520                 525

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
    530                 535                 540

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
545                 550                 555                 560

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
                565                 570                 575
```

```
Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr
            580                 585                 590

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
        595                 600                 605

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
    610                 615                 620

Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
625                 630                 635                 640

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
                645                 650                 655

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
            660                 665                 670

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
        675                 680                 685

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
    690                 695                 700

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
705                 710                 715                 720

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly
                725                 730                 735

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
            740                 745                 750

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys
        755                 760                 765

Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
    770                 775                 780

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
```

785 790 795 800

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
805 810 815

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
820 825 830

Pro Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu
835 840 845

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
850 855 860

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
865 870 875 880

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
885 890 895

Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
900 905 910

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
915 920 925

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
930 935 940

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
945 950 955 960

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


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


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


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


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


Arg Asp Ser Gly Gly Trp Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125


Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu
    130                 135                 140


Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln
145                 150                 155                 160


Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln
                165                 170                 175


Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr
            180                 185                 190
```

```
Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
        195                 200                 205

Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val
    210                 215                 220

Tyr Tyr Cys Gln Gln Tyr Tyr Ser Thr Pro Pro Thr Phe Gly Cys Gly
225                 230                 235                 240

Thr Lys Val Glu Ile Lys Ser Gly Gly Gly Gly Ser Glu Val Gln Leu
                245                 250                 255

Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu
            260                 265                 270

Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp
        275                 280                 285

Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg
    290                 295                 300

Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp
305                 310                 315                 320

Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln
                325                 330                 335

Met Asn Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg
            340                 345                 350

His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly
        355                 360                 365

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
    370                 375                 380

Gly Gly Ser Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro
385                 390                 395                 400

Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser
```

```
                405                 410                 415

Ser Thr Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln
            420                 425                 430

Lys Pro Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu
        435                 440                 445

Ala Pro Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys
    450                 455                 460

Ala Ala Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr
465                 470                 475                 480

Tyr Cys Val Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr
                485                 490                 495

Lys Leu Thr Val Leu Gly Gly Gly Gly Asp Lys Thr His Thr Cys Pro
            500                 505                 510

Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe
        515                 520                 525

Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val
    530                 535                 540

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe
545                 550                 555                 560

Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro
                565                 570                 575

Cys Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr
            580                 585                 590

Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
        595                 600                 605

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala
    610                 615                 620
```

```
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg
625                 630                 635                 640

Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly
                645                 650                 655

Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro
            660                 665                 670

Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser
        675                 680                 685

Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln
    690                 695                 700

Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His
705                 710                 715                 720

Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Gly
                725                 730                 735

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            740                 745                 750

Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro
        755                 760                 765

Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
    770                 775                 780

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
785                 790                 795                 800

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
                805                 810                 815

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys
            820                 825                 830

Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val
```

```
        835                 840                 845

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
    850                 855                 860

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
865                 870                 875                 880

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
                885                 890                 895

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
            900                 905                 910

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
        915                 920                 925

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
    930                 935                 940

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
945                 950                 955                 960

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
                965                 970                 975

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            980                 985


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Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
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Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
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            20                  25                  30

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

Gly Arg Ile Tyr Tyr Asn Gly Asn Thr Tyr Tyr Asn Pro Ser Leu Lys
    50                  55                  60

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Arg Pro Lys Leu Gly Ile Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
            100                 105                 110

Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125

Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser
    130                 135                 140

Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser
145                 150                 155                 160

Asn Ile Gly Ala Gly Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly
                165                 170                 175

Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly
            180                 185                 190

Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu
        195                 200                 205

Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln
    210                 215                 220

Ser Tyr Asp Ser Ser Leu Ser Gly Trp Val Phe Gly Gly Gly Thr Lys
225                 230                 235                 240
```

```
Leu Thr Val Leu Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu
                245                 250                 255

Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys
            260                 265                 270

Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg
        275                 280                 285

Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys
    290                 295                 300

Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe
305                 310                 315                 320

Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn
                325                 330                 335

Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly
            340                 345                 350

Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly
        355                 360                 365

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu
385                 390                 395                 400

Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr
                405                 410                 415

Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro
            420                 425                 430

Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro
        435                 440                 445

Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala
```

```
    450                 455                 460

Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys
465                 470                 475                 480

Val Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu
                485                 490                 495

Thr Val Leu Gly Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys
            500                 505                 510

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        515                 520                 525

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    530                 535                 540

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
545                 550                 555                 560

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                565                 570                 575

Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu
            580                 585                 590

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        595                 600                 605

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    610                 615                 620

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
625                 630                 635                 640

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                645                 650                 655

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            660                 665                 670
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```
Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        675                 680                 685

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    690                 695                 700

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
705                 710                 715                 720

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly
                725                 730                 735

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            740                 745                 750

Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro
        755                 760                 765

Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
    770                 775                 780

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
785                 790                 795                 800

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
                805                 810                 815

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys
            820                 825                 830

Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val
        835                 840                 845

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
    850                 855                 860

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
865                 870                 875                 880

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
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                885                 890                 895

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
            900                 905                 910

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
        915                 920                 925

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
    930                 935                 940

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
945                 950                 955                 960

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
                965                 970                 975

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
            980                 985


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Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
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Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
            20                  25                  30

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

Gly Arg Ile Tyr Tyr Asn Gly Asn Thr Tyr Tyr Asn Pro Ser Leu Lys
    50                  55                  60

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Arg Pro Lys Leu Gly Ile Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
            100                 105                 110

Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125

Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser
    130                 135                 140

Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser
145                 150                 155                 160

Asn Ile Gly Ala Gly Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly
                165                 170                 175

Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly
            180                 185                 190

Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu
        195                 200                 205

Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln
    210                 215                 220

Ser Tyr Asp Ser Ser Leu Ser Gly Trp Val Phe Gly Gly Gly Thr Lys
225                 230                 235                 240

Leu Thr Val Leu Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu
                245                 250                 255

Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys
            260                 265                 270

Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg
        275                 280                 285
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```
Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys
    290                 295                 300

Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe
305                 310                 315                 320

Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn
                325                 330                 335

Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly
            340                 345                 350

Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly
        355                 360                 365

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu
385                 390                 395                 400

Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr
                405                 410                 415

Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro
            420                 425                 430

Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro
        435                 440                 445

Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala
    450                 455                 460

Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys
465                 470                 475                 480

Val Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu
                485                 490                 495

Thr Val Leu Gly Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys
```

```
            500                 505                 510

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        515                 520                 525

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    530                 535                 540

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
545                 550                 555                 560

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                565                 570                 575

Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu
            580                 585                 590

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        595                 600                 605

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    610                 615                 620

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
625                 630                 635                 640

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                645                 650                 655

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            660                 665                 670

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        675                 680                 685

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    690                 695                 700

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
705                 710                 715                 720
```

```
Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Gly Gly Gly
                725                 730                 735

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
            740                 745                 750

Ser Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro
        755                 760                 765

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
    770                 775                 780

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
785                 790                 795                 800

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
                805                 810                 815

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu
            820                 825                 830

Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His
        835                 840                 845

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
    850                 855                 860

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
865                 870                 875                 880

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
                885                 890                 895

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
            900                 905                 910

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
        915                 920                 925

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
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```
    930                 935                 940

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
945                 950                 955                 960

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
                965                 970                 975

Lys Ser Leu Ser Leu Ser Pro Gly Lys
            980                 985

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Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
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Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
            20                  25                  30

Tyr Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Cys Leu Glu Trp Ile
        35                  40                  45

Gly Arg Ile Tyr Tyr Asn Gly Asn Thr Tyr Tyr Asn Pro Ser Leu Lys
    50                  55                  60

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Arg Pro Lys Leu Gly Ile Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
            100                 105                 110

Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
```

```
        115                 120                 125

Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser
    130                 135                 140

Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser
145                 150                 155                 160

Asn Ile Gly Ala Gly Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly
                165                 170                 175

Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly
            180                 185                 190

Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu
        195                 200                 205

Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln
    210                 215                 220

Ser Tyr Asp Ser Ser Leu Ser Gly Trp Val Phe Gly Cys Gly Thr Lys
225                 230                 235                 240

Leu Thr Val Leu Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu
                245                 250                 255

Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys
            260                 265                 270

Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg
        275                 280                 285

Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys
    290                 295                 300

Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe
305                 310                 315                 320

Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn
                325                 330                 335
```

```
Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly
            340                 345                 350

Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly
        355                 360                 365

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu
385                 390                 395                 400

Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr
                405                 410                 415

Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro
            420                 425                 430

Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro
        435                 440                 445

Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala
    450                 455                 460

Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys
465                 470                 475                 480

Val Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu
                485                 490                 495

Thr Val Leu Gly Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys
            500                 505                 510

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        515                 520                 525

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    530                 535                 540

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
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545                 550                 555                 560

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                565                 570                 575

Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu
            580                 585                 590

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        595                 600                 605

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    610                 615                 620

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
625                 630                 635                 640

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                645                 650                 655

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            660                 665                 670

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        675                 680                 685

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    690                 695                 700

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
705                 710                 715                 720

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly
                725                 730                 735

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            740                 745                 750

Gly Gly Ser Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro
        755                 760                 765
```

```
Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
    770                 775                 780

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
785                 790                 795                 800

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
                805                 810                 815

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys
            820                 825                 830

Glu Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val
        835                 840                 845

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
    850                 855                 860

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
865                 870                 875                 880

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
                885                 890                 895

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
            900                 905                 910

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
        915                 920                 925

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
    930                 935                 940

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
945                 950                 955                 960

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
                965                 970                 975

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
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35 40 45

Gly Arg Ile Tyr Tyr Asn Gly Asn Thr Tyr Tyr Asn Pro Ser Leu Lys
50 55 60

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Pro Lys Leu Gly Ile Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr
100 105 110

Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
115 120 125

Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser
130 135 140

Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser
145 150 155 160

Asn Ile Gly Ala Gly Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly

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                165                 170                 175

Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly
            180                 185                 190

Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu
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Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln
    210                 215                 220

Ser Tyr Asp Ser Ser Leu Ser Gly Trp Val Phe Gly Cys Gly Thr Lys
225                 230                 235                 240

Leu Thr Val Leu Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu
                245                 250                 255

Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Lys Leu Ser Cys
            260                 265                 270

Ala Ala Ser Gly Phe Thr Phe Asn Lys Tyr Ala Met Asn Trp Val Arg
        275                 280                 285

Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Arg Ser Lys
    290                 295                 300

Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser Val Lys Asp Arg Phe
305                 310                 315                 320

Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn
                325                 330                 335

Asn Leu Lys Thr Glu Asp Thr Ala Val Tyr Tyr Cys Val Arg His Gly
            340                 345                 350

Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr Trp Gly Gln Gly
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Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
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Ser Gly Gly Gly Gly Ser Gln Thr Val Val Thr Gln Glu Pro Ser Leu
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                405                 410                 415

Gly Ala Val Thr Ser Gly Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro
            420                 425                 430

Gly Gln Ala Pro Arg Gly Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro
        435                 440                 445

Gly Thr Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala
    450                 455                 460

Leu Thr Leu Ser Gly Val Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys
465                 470                 475                 480

Val Leu Trp Tyr Ser Asn Arg Trp Val Phe Gly Gly Gly Thr Lys Leu
                485                 490                 495

Thr Val Leu Gly Gly Gly Gly Asp Lys Thr His Thr Cys Pro Pro Cys
            500                 505                 510

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        515                 520                 525

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    530                 535                 540

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
545                 550                 555                 560

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu
                565                 570                 575

Glu Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu
            580                 585                 590

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
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        595                 600                 605

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
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Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
625                 630                 635                 640

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                645                 650                 655

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            660                 665                 670

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        675                 680                 685

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    690                 695                 700

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
705                 710                 715                 720

Gln Lys Ser Leu Ser Leu Ser Pro Gly Gly Gly Gly Ser Gly Gly Gly
                725                 730                 735

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
            740                 745                 750

Ser Gly Gly Gly Gly Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro
        755                 760                 765

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
    770                 775                 780

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
785                 790                 795                 800

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
                805                 810                 815
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Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Cys Glu Glu
            820                 825                 830

Gln Tyr Gly Ser Thr Tyr Arg Cys Val Ser Val Leu Thr Val Leu His
        835                 840                 845

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
    850                 855                 860

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
865                 870                 875                 880

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
                885                 890                 895

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
            900                 905                 910

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
        915                 920                 925

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
    930                 935                 940

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
945                 950                 955                 960

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
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Lys Ser Leu Ser Leu Ser Pro Gly Lys
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<213>  artificial

<220>
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<400>  300
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<212> PRT
<213> artificial

<220>
<223> (G4S)5 linker

<400> 301

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<210> 302
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<212> PRT
<213> artificial

<220>
<223> (G4S)6 linker

<400> 302

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            20   25   30

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<211> 35
<212> PRT
<213> artificial

<220>
<223> (G4S)7 linker

<400> 303

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Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            20   25   30

Gly Gly Ser
        35

<210> 304
<211> 40
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<220>
<223> (G4S)8 linker

<400> 304

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Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            20   25   30

Gly Gly Ser Gly Gly Gly Gly Ser
        35   40

Claims

1. A bispecific antibody construct comprising a first binding domain which binds to human and macaque MSLN on the surface of a target cell and a second binding domain which binds to human CD3 on the surface of a T cell, wherein the first binding domain binds to an epitope of MSLN which is comprised within the MSLN variants as depicted in SEQ ID NOs: 231, 232, and 233 and further binds to *Macaca fascicularis* MSLN as depicted in SEQ ID NO: 234.

2. The antibody construct according to claim 1, wherein the second binding domain binds to human CD3 epsilon and to *Callithrix jacchus, Saguinus Oedipus* or *Saimiri sciureus* CD3 epsilon.

3. The antibody construct according to any one of the preceding claims, wherein the antibody construct is in a format selected from the group consisting of $(scFv)_2$, scFv-single domain mAb, diabodies and oligomers of those formats.

4. The antibody construct according to any one of the preceding claims, wherein the first binding domain binds to an epitope of MSLN which is comprised within the region of the human MSLN having a sequence as depicted in SEQ ID NO selected form the group consisting of SEQ ID NO: 244, SEQ ID NO: 245 and SEQ ID NO: 241 .

5. The antibody construct according to claim 4, wherein the first binding domain comprises a VH region comprising CDR-H1, CDR-H2 and CDR-H3 and a VL region comprising CDR-L1, CDR-L2 and CDR-L3 selected from the group consisting of:
   a) CDR-H1 as depicted in SEQ ID NO: 151, CDR-H2 as depicted in SEQ ID NO: 152, CDR-H3 as depicted in SEQ ID NO: 153, CDR-L1 as depicted in SEQ ID NO: 154, CDR-L2 as depicted in SEQ ID NO: 155 and CDR-L3 as depicted in SEQ ID NO: 156;
   b) CDR-H1 as depicted in SEQ ID NO: 161, CDR-H2 as depicted in SEQ ID NO: 162, CDR-H3 as depicted in SEQ ID NO: 163, CDR-L1 as depicted in SEQ ID NO: 164, CDR-L2 as depicted in SEQ ID NO: 165 and CDR-L3 as depicted in SEQ ID NO: 166;
   c) CDR-H1 as depicted in SEQ ID NO: 171, CDR-H2 as depicted in SEQ ID NO: 172, CDR-H3 as depicted in SEQ ID NO: 173, CDR-L1 as depicted in SEQ ID NO: 174, CDR-L2 as depicted in SEQ ID NO: 175 and CDR-L3 as depicted in SEQ ID NO: 176;

d) CDR-H1 as depicted in SEQ ID NO: 181, CDR-H2 as depicted in SEQ ID NO: 182, CDR-H3 as depicted in SEQ ID NO: 183, CDR-L1 as depicted in SEQ ID NO: 184, CDR-L2 as depicted in SEQ ID NO: 185 and CDR-L3 as depicted in SEQ ID NO: 186;
e) CDR-H1 as depicted in SEQ ID NO: 191, CDR-H2 as depicted in SEQ ID NO: 192, CDR-H3 as depicted in SEQ ID NO: 193, CDR-L1 as depicted in SEQ ID NO: 194, CDR-L2 as depicted in SEQ ID NO: 195 and CDR-L3 as depicted in SEQ ID NO: 196;
f) CDR-H1 as depicted in SEQ ID NO: 201, CDR-H2 as depicted in SEQ ID NO: 202, CDR-H3 as depicted in SEQ ID NO: 203, CDR-L1 as depicted in SEQ ID NO: 204, CDR-L2 as depicted in SEQ ID NO: 205 and CDR-L3 as depicted in SEQ ID NO: 206;
g) CDR-H1 as depicted in SEQ ID NO: 211, CDR-H2 as depicted in SEQ ID NO: 212, CDR-H3 as depicted in SEQ ID NO: 213, CDR-L1 as depicted in SEQ ID NO: 214, CDR-L2 as depicted in SEQ ID NO: 215 and CDR-L3 as depicted in SEQ ID NO: 216; and
h) CDR-H1 as depicted in SEQ ID NO: 221, CDR-H2 as depicted in SEQ ID NO: 222, CDR-H3 as depicted in SEQ ID NO: 223, CDR-L1 as depicted in SEQ ID NO: 224, CDR-L2 as depicted in SEQ ID NO: 225 and CDR-L3 as depicted in SEQ ID NO: 226.

6. The antibody construct according to claim 4 or 5, wherein the first binding domain comprises a VH region selected from the group consisting of those depicted in SEQ ID NO: 157, SEQ ID NO: 167, SEQ ID NO: 177, SEQ ID NO: 187, SEQ ID NO: 197, SEQ ID NO: 207, SEQ ID NO: 217, and SEQ ID NO: 227.

7. The antibody construct according to any one of claims 4 to 6, wherein the first binding domain comprises a VL region selected from the group consisting of those depicted in SEQ ID NO: 158, SEQ ID NO: 168, SEQ ID NO: 178, SEQ ID NO: 188, SEQ ID NO: 198, SEQ ID NO: 208, SEQ ID NO: 218, and SEQ ID NO: 228.

8. The antibody construct according to any one of claims 4 to 7, wherein the first binding domain comprises a VH region and a VL region selected from the group consisting of pairs of a VH region and a VL region as depicted in SEQ ID NO: 157+158, SEQ ID NO: 167+168, SEQ ID NO: 177+178, SEQ ID NO: 187+188, SEQ ID NO: 197+198, SEQ ID NO: 207+208, SEQ ID NO: 217+218, and SEQ ID NO: 227+228.

9. The antibody construct according to any one of claims 4 to 8, wherein the first binding domain comprises a polypeptide selected from the group consisting of those depicted in

SEQ ID NO: 159, SEQ ID NO: 169, SEQ ID NO: 179, SEQ ID NO: 189, SEQ ID NO: 199, SEQ ID NO: 209, SEQ ID NO: 219, and SEQ ID NO: 229.

10. The antibody construct according to any one of claims 1 to 7, comprising:

(a) a polypeptide comprising in the following order starting from the N-terminus:
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 159, SEQ ID NO: 169, SEQ ID NO: 179, SEQ ID NO: 189, SEQ ID NO: 199, SEQ ID NO: 209, SEQ ID NO: 219, and SEQ ID NO: 229;
- a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-9; and
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 28, SEQ ID NO: 37, SEQ ID NO: 46, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 73, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 100, and SEQ ID NO: 103; and
- optionally a His-tag, such as the one depicted in SEQ ID NO 10;

(b) a polypeptide comprising in following order starting from the N-terminus:
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 159, SEQ ID NO: 169, SEQ ID NO: 179, SEQ ID NO: 189, SEQ ID NO: 199, SEQ ID NO: 209, SEQ ID NO: 219, and SEQ ID NO: 229;
- a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-9;
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 28, SEQ ID NO: 37, SEQ ID NO: 46, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 73, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 100, and SEQ ID NO: 103;
- optionally a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-9;
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NOs: 104-134; and
- optionally a His-tag, such as the one depicted in SEQ ID NO 10;

(c) a polypeptide comprising in the following order starting from the N-terminus:
- a polypeptide having the amino acid sequence QRFVTGHFGGLX$_1$PANG (SEQ ID NO: 135) whereas X$_1$ is Y or H; and

- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 159, SEQ ID NO: 169, SEQ ID NO: 179, SEQ ID NO: 189, SEQ ID NO: 199, SEQ ID NO: 209, SEQ ID NO: 219, and SEQ ID NO: 229;
- a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-9;
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 28, SEQ ID NO: 37, SEQ ID NO: 46, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 73, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 100, and SEQ ID NO: 103;
- a polypeptide having the amino acid sequence QRFVTGHFGGLHPANG (SEQ ID NO: 137) or QRFCTGHFGGLHPCNG (SEQ ID NO: 139); and
- optionally a His-tag, such as the one depicted in SEQ ID NO 10;

(d) a polypeptide comprising in the following order starting from the N-terminus

- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 17, SEQ ID NO: 26, SEQ ID NO: 35, SEQ ID NO: 44, SEQ ID NO: 53, SEQ ID NO: 62, SEQ ID NO: 71, SEQ ID NO: 80, SEQ ID NO: 89, SEQ ID NO: 98, and SEQ ID NO: 101;
- a peptide linker having the amino acid sequence depicted in SEQ ID NO: 8;
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 158, SEQ ID NO: 168, SEQ ID NO: 178, SEQ ID NO: 188, SEQ ID NO: 198, SEQ ID NO: 208, SEQ ID NO: 218, and SEQ ID NO: 228 and a serine residue at the C-terminus;
- a polypeptide having the amino acid sequence depicted in SEQ ID NO: 140;and

a polypeptide comprising in the following order starting from the N-terminus:

- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 157, SEQ ID NO: 167, SEQ ID NO: 177, SEQ ID NO: 187, SEQ ID NO: 197, SEQ ID NO: 207, SEQ ID NO: 217, and SEQ ID NO: 227;
- a peptide linker having the amino acid sequence depicted in SEQ ID NO: 8;
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 18, SEQ ID NO: 27, SEQ ID NO: 36, SEQ ID NO: 45, SEQ ID NO: 54, SEQ ID NO: 63, SEQ ID NO: 72, SEQ ID NO: 81, SEQ ID NO: 90, SEQ ID NO: 99, and SEQ ID NO: 102 and a serine residue at the C-terminus;
- a polypeptide having the amino acid sequence depicted in SEQ ID NO: 141;

(e) a polypeptide comprising in the following order starting from the N-terminus:

- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 17, SEQ ID NO: 26, SEQ ID NO: 35, SEQ ID NO: 44, SEQ ID NO: 53, SEQ ID NO: 62, SEQ ID NO: 71, SEQ ID NO: 80, SEQ ID NO: 89, SEQ ID NO: 98, and SEQ ID NO: 101;
- a peptide linker having the amino acid sequence depicted in SEQ ID NO: 8;
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 158, SEQ ID NO: 168, SEQ ID NO: 178, SEQ ID NO: 188, SEQ ID NO: 198, SEQ ID NO: 208, SEQ ID NO: 218, and SEQ ID NO: 228;
- a polypeptide having the amino acid sequence depicted in SEQ ID NO: 142;and

a polypeptide comprising in the following order starting from the N-terminus:

- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 157, SEQ ID NO: 167, SEQ ID NO: 177, SEQ ID NO: 187, SEQ ID NO: 197, SEQ ID NO: 207, SEQ ID NO: 217, and SEQ ID NO: 227;
- a peptide linker having an amino acid sequence depicted in SEQ ID NO: 8;
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 18, SEQ ID NO: 27, SEQ ID NO: 36, SEQ ID NO: 45, SEQ ID NO: 54, SEQ ID NO: 63, SEQ ID NO: 72, SEQ ID NO: 81, SEQ ID NO: 90, SEQ ID NO: 99, and SEQ ID NO: 102 and a serine residue at the C-terminus;
- a polypeptide having the amino acid sequence depicted in SEQ ID NO: 143;

(f) a polypeptide comprising in the following order starting from the N-terminus:

- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 159, SEQ ID NO: 169, SEQ ID NO: 179, SEQ ID NO: 189, SEQ ID NO: 199, SEQ ID NO: 209, SEQ ID NO: 219, and SEQ ID NO: 229;
- a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-9; and
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 28, SEQ ID NO: 37, SEQ ID NO: 46, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 73, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 100, and SEQ ID NO: 103; and
- a polypeptide having the amino acid sequence depicted in SEQ ID NO: 144; and

a polypeptide having the amino acid sequence depicted in SEQ ID NO: 145;

(g) a polypeptide comprising in the following order starting from the N-terminus:

- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 159, SEQ ID NO: 169, SEQ ID NO: 179, SEQ ID NO: 189, SEQ ID NO: 199, SEQ ID NO: 209, SEQ ID NO: 219, and SEQ ID NO: 229; and

- a polypeptide having the amino acid sequence depicted in SEQ ID NO: 146;and

a polypeptide comprising in the following order starting from the N-terminus:

- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 28, SEQ ID NO: 37, SEQ ID NO: 46, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 73, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 100, and SEQ ID NO: 103; and
- a polypeptide having the amino acid sequence depicted in SEQ ID NO: 147;

(h) a polypeptide comprising in the following order starting from the N-terminus:

- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 159, SEQ ID NO: 169, SEQ ID NO: 179, SEQ ID NO: 189, SEQ ID NO: 199, SEQ ID NO: 209, SEQ ID NO: 219, and SEQ ID NO: 229; and
- a polypeptide having the amino acid sequence depicted in SEQ ID NO: 148;and

a polypeptide comprising in the following order starting from the N-terminus:

- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 28, SEQ ID NO: 37, SEQ ID NO: 46, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 73, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 100, and SEQ ID NO: 103; and
- a polypeptide having the amino acid sequence depicted in SEQ ID NO: 149; or

(i) a polypeptide comprising in the following order starting from the N-terminus:

- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 159, SEQ ID NO: 169, SEQ ID NO: 179, SEQ ID NO: 189, SEQ ID NO: 199, SEQ ID NO: 209, SEQ ID NO: 219, and SEQ ID NO: 229;
- a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-9; and
- a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 28, SEQ ID NO: 37, SEQ ID NO: 46, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 73, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 100, and SEQ ID NO: 103; and
- a polypeptide having the amino acid sequence depicted in SEQ ID NO: 150.

11. The antibody construct according to any one of claims 1 to 9 comprising in an N- to C-terminal order:

- the first binding domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 159, SEQ ID NO: 169, SEQ ID NO: 179, SEQ ID

NO: 189, SEQ ID NO: 199, SEQ ID NO: 209, SEQ ID NO: 219, and SEQ ID NO: 229;

- a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 8 and 9;
- the second binding domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 19, SEQ ID NO: 28, SEQ ID NO: 37, SEQ ID NO: 46, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 73, SEQ ID NO: 82, SEQ ID NO: 91, SEQ ID NO: 100, and SEQ ID NO: 103 (see also SEQ ID NOs: 23, 25, 41, 43, 59, 61, 77, 79, 95, 97, 113, 115, 131, 133, 149, 151, 167, 169, 185 or 187 of WO 2008/119567);
- a peptide linker having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 2, 4, 5, 6, 8 and 9; and
- the third domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 260-267.

12. The antibody construct according to claim 11, comprising a sequence seceted from the group consisting of SEQ ID NOs: 276 to 287

13. The antibody construct according to any one of claims 1 to 12, wherein the ratio of the binding affinity of the first binding domain for macaque MSLN/human MSLN (measured in a Scatchard analysis) is <100, preferably <20, more preferably <15, further preferably <10, even more preferably<8, more preferably <6 and most preferably <2.

14. A polynucleotide encoding an antibody construct as defined in any one of the preceding claims.

15. A vector comprising a polynucleotide as defined in claim 14.

16. A host cell transformed or transfected with the polynucleotide as defined in claim 14 or with the vector as defined in claim 15.

17. A process for the production of an antibody construct according to any one of claims 1 to 13, said process comprising culturing a host cell as defined in claim 16 under conditions allowing the expression of the antibody construct as defined in any one of claims 1 to 13 and recovering the produced antibody construct from the culture.

17. A pharmaceutical composition comprising an antibody construct according to any one of claims 1 to 14, or produced according to the process of claim 17.

19. The antibody construct according to any one of claims 1 to 13, or produced according to the process of claim 17, for use in the prevention, treatment or amelioration of a *solid tumor* disease or a metastatic cancer disease.

20. A method for the treatment or amelioration of a *solid tumor* disease or a metastatic cancer disease, comprising the step of administering to a subject in need thereof the antibody construct according to any one of claims 1 to 13, or produced according to the process of claim 17.

21. The method according to claim 20 or the antibody construct according to claim 19, wherein the *solid tumor* disease is selected from the group consisting of ovarian cancer, pancreatic cancer, mesothelioma, lung cancer, gastric cancer and triple negative breast cancer disease or a metastatic cancer disease derived from any of the forgoing.

22. A kit comprising an antibody construct according to any one of claims 1 to 13, an antibody construct produced according to the process of claim 17, a polynucleotide as defined in claim 14, a vector as defined in claim 15, and/or a host cell as defined in claim 16.