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(71) Applicant(s)
Bayer Intellectual Property GmbH

(72) Inventor(s)
Schneider, Douglas;Kahnert, Antje;Heitner, Tara;Schubert, Ulrike;Parry, Renate;Satozawa, Noboru;Light, David;Steidl, Stefan

(74) Agent / Attorney
Davies Collison Cave, Level 14 255 Elizabeth Street, Sydney, NSW, 2000

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(71) Applicant *(for all designated States except US)*: **BAYER SCHERING PHARMA AKTIENGESELLSCHAFT** [DE/DE]; Müllerstrasse 178, 13353 Berlin (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KAHNERT, Antje** [DE/DE]; Barbarossaplatz 4, 40545 Düsseldorf (DE). **LIGHT, David** [US/US]; 614 South Freemont Street, San Mateo, CA 94402 (US). **SCHNEIDER, Douglas** [US/US]; 3329 Walnut Lane, Lafayette, CA 84549 (US). **PARRY, Renate** [US/US]; 21 Kingwood Road, Oakland, CA 94619 (US). **SATOZAWA, Noboru** [JP/JP]; 405-1-406 Mobara, Mobara, Chiba 297-0026 (JP). **HEITNER, Tara** [DK/DK]; Gammel Kongevej 23.3. sal, DK-1610 Kopenhagen (DK). **STEIDL, Stefan** [DE/DE]; Planeggerstrasse 37, 82141 München (DE). **SCHUBERT, Ulrike** [DE/DE]; Beinhoferstr. 3, 81247 München (DE).

(74) Common Representative: BAYER SCHERING PHARMA AKTIENGESELLSCHAFT; Law and Patents, Patents and Licensing, Building Q18, 51368 Leverkusen (DE).

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(54) Title: ANTI-MESOTHELIN ANTIBODIES AND USES THEREFOR

(57) Abstract: The present invention provides recombinant antigen-binding regions and antibodies and functional fragments containing such antigen-binding regions that are specific for the membrane-anchored, 4O.kDa mesothelin polypeptide, which is overexpressed in several tumors, such as pancreatic and ovarian tumors, mesothelioma and lung cancer cells. These antibodies, accordingly, can be used to treat these and other disorders and conditions. Antibodies of the invention also can be used in the diagnostics field, as well as for further investigating the role of mesothelin in the progression of disorders associated with cancer. The invention also provides nucleic acid sequences encoding the foregoing antibodies, vectors containing the same, pharmaceutical compositions and kits with instructions for use.

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Anti-Mesothelin Antibodies and Uses Therefor

The present invention provides recombinant antigen-binding regions and antibodies and functional fragments containing such antigen-binding regions that are specific for the membrane-anchored, 40 kDa mesothelin polypeptide, which which is overexpressed in several tumors, such as pancreatic and ovarian tumors, mesothelioma and lung cancer cells. These antibodies, accordingly, can be used to treat these and other disorders and conditions. Antibodies of the invention also can be used in the diagnostics field, as well as for further investigating the role of mesothelin in the progression of disorders associated with cancer. The invention also provides nucleic acid sequences encoding the foregoing antibodies, vectors containing the same, pharmaceutical compositions and kits with instructions for use.

BACKGROUND OF THE INVENTION

Antibody-based therapy is proving very effective in the treatment of various cancers, including solid tumors. For example, HERCEPTIN® has been used successfully to treat breast cancer. Central to the development of a successful antibody-based therapy is isolation of antibodies against cell-surface proteins found to be preferentially expressed on tumor cells. The mesothelin precursor polypeptide is a glycophosphatidylinositol (GPI)-anchored, glycosylated cell surface protein that is proteolytically cleaved to a 30 kDa N-terminal secreted polypeptide and a 40 kDa, C-terminal polypeptide, which predominantly occurs in the membrane-bound, GPI-anchored form (Chang, K. and I. Pastan, Proc. Natl. Acad. Sci. U S A, (1996) 93(1):136), and which is named mesothelin herein.

Mesothelin is preferentially expressed by certain tumor cells, particularly mesothelioma cells, pancreatic tumor cells and ovarian carcinoma cells, while its expression is limited in normal tissue, making it an ideal target for tumor therapy (Argani, P. *et al.*, Clin. Cancer Res. (2001) 7(12): 3862; Hassan, R., *et al.*, Clin. Cancer Res. (2004) 10(12 Pt 1):3937). The function of mesothelin is unknown, and no apparent reproductive, hematologic, or anatomic abnormalities were observed in mice deficient in mesothelin gene expression (Bera, T.K. and I. Pastan, Mol. Cell. Biol. (2000) 20(8):2902).

Antibody-based, targeted therapy against mesothelin-expressing cancer cells has been proposed for the treatment of lung, ovarian and pancreatic cancer. Mab K1 was the first antibody to membrane-bound mesothelin polypeptide which was described (Chang, K., *et al.*, Int. J. Cancer, (1992) 50(3):373). Mab K1 was generated by immunizing mice. Due to low affinity and poor internalization rates of the antibody, an immunotoxin consisting of Mab K1 linked to a chemically modified truncated form of Pseudomonas exotoxin A was not considered suitable for clinical development (Hassan, R., *et al.*, J. Immunother. (2000) 23(4):473; Hassan, R., *et al.*, Clin. Cancer Res. (2004) 10(12 Pt 1): 3937). Subsequently, single-chain antibodies with higher affinities were developed, including SS1-(dsFv)-PE38, which showed killing activity of tumor cells in vitro (Hassan, R., *et al.*, Clin. Cancer Res. (2002) 8(11): 3520) as well as potency in a murine model of human mesothelin-expressing tumors (Fan, D., *et al.*, Mol. Cancer Ther. (2002) 1(8): 595). These data validate mesothelin as a suitable target for immunotherapy of multiple cancers. However, in clinical trials, SS1-(dsFv)-PE38 was immunogenic, preventing a second administration for the majority of patients. Furthermore, SS1-(dsFv)-PE38 has been shown to have a fast blood clearance and attempts are being reported to increase the molecular weight by pegylating the fusion protein (Filpula, D., *et al.*, Bioconjugate Chem. (2007) 18(3): 773).

MS-1, MS-2 and MS-3 are mesothelin-binding antibodies which elicit immune effector activity at the cell surface due to their human IgG1 isotype and internalize into mesothelin expressing cells (WO 2006/099141 A2). One of these antibodies, the unconjugated IgG anti-mesothelin antibody MOR Ab 009 is currently being tested in a clinical trial for therapeutic effects in the treatment of pancreatic cancer.

The predictive value of xenograft murine cancer models for clinical outcome of immunotoxin cancer therapy is often limited by a lack of cross-reactivity of the therapeutic antibodies with their murine homologues, which leads to reduced unspecific binding to normal tissue. On the other hand, neutralizing anti-mouse Fv antibodies which are formed in patients being treated with murine or chimeric antibodies may result in either dose-limiting toxicity or diminished therapeutic potency. Thus, to fully exploit the potential of specific mesothelin expression in cancer therapy, targeting antibodies are required which combine the advantages of increased affinities and reduced dissociation rates with a fully human variable chain format, and with murine cross-reactivity.

A further necessary feature of novel antibodies is invariant affinity to different cancer cell lines expressing mesothelin on their surface. Mesothelin is a highly variable protein, undergoing post-translational proteolytic digestion as well as glycosylation at multiple sites (Hassan, R., *et al.*, Clin. Cancer Res. (2004) 10(12 Pt 1): 3937). Variability extends to the transcriptional level, since three different splice variants have been detected, although transcript variant 1 (NM_005823) seems to represent the major species present in tumor cell lines tested so far (Muminova, Z.E., *et al.*, BMC Cancer (2004) 4:19; Hellstrom, I., *et* *al.*, Cancer Epidemiol. Biomarkers Prev. (2006) 15(5):1014). Thus, effective anti-mesothelin antibodies must bind to an epitope invariantly presented by tumor cells from different patients, independently of individual variance including, but not restricted to, variances in glycosylation patterns, which leads to the expression of different forms of mesothelin.

Provided herein are antibodies, antigen-binding antibody fragments thereof, or variants thereof, that bind to mesothelin with high and invariant affinity, internalize efficiently, and that are preferably cross-reactive to mesothelin from another species. Also provided are antibody-based therapies for cancer, in particular for mesothelin expressing tumors, for example pancreatic, ovarian, or lung cancer, using antibodies, antigen-binding antibody fragments thereof, or variants thereof, that facilitate delivery of therapeutically active agents to cancer cells.

SUMMARY OF THE INVENTION

According to a first aspect of the invention there is provided an isolated human or humanized antibody or functional fragment thereof comprising an antigen-binding region that is specific for Mesothelin (SEQ ID NO:370), wherein said antibody or functional fragment thereof exhibits invariant binding of Mesothelin and has an antigen-binding region which comprises a CDR region as depicted in Table 7.

According to a second aspect of the invention there is provided an isolated nucleic acid sequence that encodes an antigen-binding region of a human antibody according to the first aspect or functional fragment thereof.

According to a third aspect of the invention there is provided an isolated nucleic acid sequence encoding a variable heavy chain of an isolated antibody or functional fragment thereof, which comprises:

(i) a sequence selected from the group consisting of sequences as depicted in Table 7 or

(ii) a nucleic acid sequence that hybridizes under high stringency conditions to the complementary strand of sequences as depicted in Table 7, wherein said antibody or functional fragment thereof is specific for an epitope of Mesothelin.

According to a fourth aspect of the invention there is provided a vector comprising a nucleic acid sequence according to the second or third aspect.

According to a fifth aspect of the invention there is provided an isolated cell comprising a vector according to the fourth aspect.

According to a sixth aspect of the invention there is provided a pharmaceutical composition comprising an antibody or functional fragment according the first aspect, and a pharmaceutically acceptable carrier or excipient.

According to a seventh aspect of the invention there is provided a method for treating a disorder or condition associated with the undesired presence of Mesothelin, the method comprising administering to a subject in need thereof an effective amount of an antibody or fragment according to the first aspect or a pharmaceutical composition according to the sixth aspect.

Disclosed herein are human and humanized antibodies, or antigen-binding antibody fragments thereof, or variants thereof, that are highly selective for the 40 kDa, C-terminal extracellular part of the mesothelin precursor polypeptide, and which may be employed in methods for detection of mesothelin expression, which is associated with disease states such as cancer of the pancreas, ovary, and lung, and in the treatment of such disease states. Toward these ends, it is an object of the invention to provide isolated human antibodies, or antigen binding antibody fragments thereof, that specifically bind to an epitope present in the mesothelin polypeptide (SEQ ID NO:370), which is invariantly presented by mesothelin-expressing cancer cell lines, and which is bound by these antibodies with comparable affinities. As used herein, the term 'invariant presentation' of the epitope refers to the presence of an epitope recognized by a particular antibody on a broad range of mesothelin expressing tumor cell lines which express different forms of mesothelin. As used herein, different 'forms' of mesothelin include, but are not restricted to, different glycoforms, different isoforms or mesothelin polypeptides which undergo different translational and posttranslational modifications. As used herein, the term 'comparable affinities' refers to half-maximal antibody potency (EC_{50}) values obtained by Scatchard Analysis of FACS data of antibody binding to cells expressing different forms of mesothelin, which do not differ by more than factor 10, or, preferably, factor 5, or, even preferably, factor 2.

Also disclosed herein are antibodies, or antigen-binding antibody fragments thereof, or variants thereof that are safe for human administration.

Also disclosed herein are antibodies, or antigen-binding antibody fragments thereof, or variants thereof, which bind to human mesothelin and are cross-reactive to mesothelin of another species. Preferably said other species is a rodent, such as for example mouse or rat. Most preferably the antibodies, or antigen-binding antibody fragments thereof, or variants thereof bind to human mesothelin and are cross-reactive to murine mesothelin.

Also disclosed herein are antibodies, or antigen-binding antibody fragments thereof, or variants thereof, which invariantly bind to different mesothelin-expressing cell lines with comparable affinity. As used herein, the term 'invariant binding' of a particular antibody to mesothelin refers to its ability to bind to mesothelin on a broad range of mesothelin-expressing cancer cell lines which express different forms of mesothelin. Invariant binding may be caused by, but is not restricted to, the fact that antibodies, or antigen-binding antibody fragments thereof, or variants thereof, recognize an epitope of mesothelin that is not masked by another extracellular antigen, such as cancer antigen 125 (CA125), which interacts with mesothelin.

Also disclosed herein are antibodies or variants thereof, which bind to different mesothelin-expressing cancer cells or tumor cells and elicit immune effector activity (e.g. ADCC or CDC) against mesothelin-expressing cancer cells, by using one or more antibodies or variants thereof, of the invention.

Also disclosed herein are antibodies, or antigen-binding antibody fragments thereof, or variants thereof, which are internalized following binding to a mesothelin expressing cell. It is also an object of the present invention to provide methods for treating disease by delivering cytotoxic drugs or drug-releasing enzymes to mesothelin-expressing cancer cells, by using one or more antibodies, or antigen-binding antibody fragments thereof, or variants thereof, of the invention.

Also disclosed herein are antibodies which constitute a tool for diagnosis of malignant or dysplastic conditions in which mesothelin expression is elevated compared to normal tissue. Provided are anti-mesothelin antibodies conjugated to a detectable marker. Preferred markers are a radiolabel, an enzyme, a chromophore or a fluorescer.

The invention is also related to polynucleotides encoding the antibodies of the invention, cells expressing the antibodies of the invention, methods for producing the antibodies of the invention, methods for inhibiting the growth of dysplastic cells using the antibodies, and methods for treating and detecting cancer using the antibodies.

The invention provides antibodies that are distinguished from Mab K1, SS1, MS-1, MS-2 and MS-3 in that they a) invariantly bind to mesothelin b) are cross-reactive to murine mesothelin c) bind to mesothelin with lower affinities d) internalize efficiently into mesothelin-expressing cells, and e) contain human variable regions.

In one aspect, the invention provides an isolated antibody or functional antibody fragment that contains an antigen-binding region that is specific for an epitope of the 40 kDa mesothelin polypeptide.

Such an antibody or functional fragment thereof may contain an antigen-binding region that contains an H-CDR3 region depicted in SEQ ID NO: 67-98; the antigen-binding region may further include an H-CDR2 region depicted in SEQ ID NO:31-66; and the antigen-binding region also may contain an H-CDR1 region depicted in SEQ ID NO:1-30. Such a mesothelin-specific antibody of the invention may contain an antigen-binding region that contains an L-CDR3 region depicted in SEQ ID NO:160-197; the antigen-binding region may further include an L-CDR1 region depicted in SEQ ID NO:99-128; and the antigen-binding region also may contain an L-CDR2 region depicted in SEQ ID NO:129-159.

Peptide variants of the sequences disclosed herein are also embraced by the present invention. Accordingly, the invention includes anti-mesothelin antibodies having a heavy chain amino acid sequence with: at least 60 percent sequence identity in the CDR regions with the CDR regions depicted in SEQ ID NO:1- 197 ; and/or at least 80 percent sequence homology in the CDR regions with the CDR regions depicted in SEQ ID NO: 1-197. Further included are anti-mesothelin antibodies having a light chain amino acid sequence with: at least 60 percent sequence identity in the CDR regions with the CDR regions depicted in SEQ ID NO: 1-197; and/or at least 80 percent sequence homology in the CDR regions with the CDR regions depicted in SEQ ID NO: 1-197.

An antibody of the invention may be an IgG (*e.g.*, IgG_1), while an antibody fragment may be a Fab or scFv, for example. An inventive antibody fragment, accordingly, may be, or may contain, an antigen-binding region that behaves in one or more ways as described herein.

The invention also is related to isolated nucleic acid sequences, each of which can encode an antigen-binding region of a human antibody or functional fragment thereof that is specific for an epitope of mesothelin. Such a nucleic acid sequence may encode a variable heavy chain of an antibody and include a sequence selected from the group consisting of SEQ ID NOS 284-326: or a nucleic acid sequence that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 284-326. The nucleic acid might encode a variable light chain of an isolated antibody or functional fragment thereof, and may contain a sequence selected from the group consisting of SEQ ID NOS: 327-369, or a nucleic acid sequence that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 327-369.

Nucleic acids of the invention are suitable for recombinant production. Thus, the invention also relates to vectors and host cells containing a nucleic acid sequence of the invention.

Compositions of the invention may be used for therapeutic or prophylactic applications. The invention, therefore, includes a pharmaceutical composition containing an inventive antibody (or functional antibody fragment) and a pharmaceutically acceptable carrier or excipient therefor. In a related aspect, the invention provides a method for treating a disorder or condition associated with the undesired presence of mesothelin expressing cells. Such method contains the steps of administering to a subject in need thereof an effective amount of the pharmaceutical composition that contains an inventive antibody as described or contemplated herein.

The invention also provides instructions for using the antibody library to isolate one or more members of such library that binds specifically and invariantly to mesothelin.

DESCRIPTION OF THE FIGURES

Figure 1 shows anti-mesothelin antibody epitope grouping by Biacore pairwise binding analysis. Competitive binding of pairs of antibodies was determined by immobilizing one antibody to the sensor chip, binding soluble mesothelin to this antibody and immediately binding a second antibody to mesothelin. Pairs of antibodies which recognize the same or overlapping epitopes on mesothelin cannot bind simultaneously. All combinations of antibody pairs were tested. Representative data for MF-T are shown (A). Panel B depicts the relative positions of epitopes of seven anti-mesothelin antibodies, in which competition is depicted by overlapping circles.

Figure 2 shows different forms of mesothelin recognized by antibodies of the invention. 1. and 2.: MF-J binding to mesothelin in OVCAR-3 cell extracts; 3. and 4.: MF-J binding to mesothelin in CHO-A9 cell extracts; 5. MF-J binding to mesothelin in NCI-H226 cell extracts; 6. MF-J binding to recombinant, deglycosylated mesothelin; 7. MOR06635 binding to OVCAR-3 cell extracts; and 8. MOR06635 binding to NCI-H226 cell extracts.

Figure 3 shows that cancer antigen 125 (CA125) binds mesothelin when it is bound to a subset of mesothelin antibodies including MOR06640 and MF-T, while other antibodies, such as MF-226, compete with CA125 for mesothelin binding. Data shown are relative light units (RLU) detected by SECTOR Light Imager (Meso Scale Discovery). Plates were coated with the mesothelin antibody depicted. Mesothelin was added at the concentrations indicated and titrated down. CA125 was bound subsequently at a constant concentration. Detection was performed with a mouse anti-CA125 antibody and an MSD Sulfo tag labelled anti mouse FAB antibody.

Figure 4 provides data on internalization of 125I-anti-mesothelin antibodies on CHO-A9 cells expressing mesothelin. Relative internalization of seven anti-mesothelin mabs, including the commercial positive control K1, in the absence (A), and in the presence (B) of the stabilizing second antibody. Representative data using MF-226 plus second antibody, showing relative amounts of dissociated, surface-bound and internalized antibody at 37o C over time (C) is compared with that at the non-permissive temperature of 0o C (D).

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DETAILED DESCRIPTION OF THE INVENTION

The present invention is based on the discovery of novel antibodies that are specific to or have a high affinity for mesothelin and can deliver a therapeutic benefit to a subject. The antibodies of the invention, which may be human or humanized, can be used in many contexts, which are more fully described herein.

Definitions

A “human” antibody or functional human antibody fragment is hereby defined as one that is not chimeric (*e.g.*, not “humanized”) and not from (either in whole or in part) a non-human species. A human antibody or functional antibody fragment can be derived from a human or can be a synthetic human antibody. A “synthetic human antibody” is defined herein as an antibody having a sequence derived, in whole or in part, *in silico* from synthetic sequences that are based on the analysis of known human antibody sequences. *In silico* design of a human antibody sequence or fragment thereof can be achieved, for example, by analyzing a database of human antibody or antibody fragment sequences and devising a polypeptide sequence utilizing the data obtained therefrom. Another example of a human antibody or functional antibody fragment is one that is encoded by a nucleic acid isolated from a library of antibody sequences of human origin (*i.e.*, such library being based on antibodies taken from a human natural source). Examples of human antibodies include HuCAL antibodies as described in Knappik et al., J. Mol. Biol. (2000) 296:57 and U.S. Patent No. 6,300,064.

A "humanized antibody" or functional humanized antibody fragment is defined herein as one that is (i) derived from a non-human source (*e.g.*, a transgenic mouse which bears a heterologous immune system), which antibody is based on a human germline sequence; or (ii) chimeric, wherein the variable domain is derived from a non-human origin and the constant domain is derived from a human origin or (iii) CDR-grafted, wherein the CDRs of the variable domain are from a non-human origin, while one or more frameworks of the variable domain are of human origin and the constant domain (if any) is of human origin.

As used herein, an antibody "binds specifically to," is "specific to/for" or "specifically recognizes" an antigen (here, mesothelin) if such antibody is able to discriminate between such antigen and one or more reference antigen(s), since binding specificity is not an absolute, but a relative property. In its most general form (and when no defined reference is mentioned), "specific binding" is referring to the ability of the antibody to discriminate between the antigen of interest and an unrelated antigen, as determined, for example, in accordance with one of the following methods. Such methods comprise, but are not limited to Western blots, ELISA-, RIA-, ECL-, IRMA-tests and peptide scans. For example, a standard

ELISA assay can be carried out. The scoring may be carried out by standard color development (*e.g.* secondary antibody with horseradish peroxide and tetramethyl benzidine with hydrogenperoxide). The reaction in certain wells is scored by the optical density, for example, at 450 nm. Typical background (=negative reaction) may be 0.1 OD; typical positive reaction may be 1 OD. This means the difference positive/negative can be more than 10-fold. Typically, determination of binding specificity is performed by using not a single reference antigen, but a set of about three to five unrelated antigens, such as milk powder, BSA, transferrin or the like.

However, "specific binding" also may refer to the ability of an antibody to discriminate between the target antigen and one or more closely related antigen(s), which are used as reference points. Additionally, "specific binding" may relate to the ability of an antibody to discriminate between different parts of its target antigen, *e.g.* different domains or regions of mesothelin, such as epitopes in the N-terminal or in the C-terminal region of mesothelin, or between one or more key amino acid residues or stretches of amino acid residues of mesothelin.

Also, as used herein, an "immunoglobulin" (Ig) hereby is defined as a protein belonging to the class IgG, IgM, IgE, IgA, or IgD (or any subclass thereof), and includes all conventionally known antibodies and functional fragments thereof. A "functional fragment" or "antigen-binding antibody fragment" of an antibody/immunoglobulin hereby is defined as a fragment of an antibody/immunoglobulin (*e.g.*, a variable region of an IgG) that retains the antigen-binding region. An "antigen-binding region" of an antibody typically is found in one or more hypervariable region(s) of an antibody, *i.e.*, the CDR-1, -2, and/or –3 regions; however, the variable "framework" regions can also play an important role in antigen binding, such as by providing a scaffold for the CDRs. Preferably, the "antigen-binding region" comprises at least amino acid residues 4 to 103 of the variable light (VL) chain and 5 to 109 of the variable heavy (VH) chain, more preferably amino acid residues 3 to 107 of VL and 4 to 111 of VH, and particularly preferred are the complete VL and VH chains (amino acid positions 1 to 109 of VL and 1 to 113 of VH; numbering according to WO 97/08320). A preferred class of immunoglobulins for use in the present invention is IgG. "Functional fragments" of the invention include Fab, Fab', F(ab')$_2$, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules (scFv); and multispecific antibodies formed from antibody fragments (C. A. K Borrebaeck, editor (1995) Antibody Engineering (Breakthroughs in Molecular Biology), Oxford University Press; R. Kontermann & S. Duebel, editors (2001) Antibody Engineering (Springer Laboratory Manual), Springer Verlag). An antibody other than a "bispecific" or "bifunctional" antibody is understood to have each of its binding sites identical. The F(ab')$_2$ or Fab may be engineered to minimize or completely remove the intermolecular disulphide interactions that occur between the C_{H1} and C_L domains.

An antibody of the invention may be derived from a recombinant antibody library that is based on amino acid sequences that have been designed *in silico* and encoded by nucleic acids that are synthetically created. *In silico* design of an antibody sequence is achieved, for example, by analyzing a database of human sequences and devising a polypeptide sequence utilizing the data obtained therefrom. Methods for designing and obtaining *in silico*-created sequences are described, for example, in Knappik *et al.*, J. Mol. Biol. (2000) 296:57; Krebs *et al.*, J. Immunol. Methods. (2001) 254:67; and U.S. Patent No. 6,300,064 issued to Knappik *et al.*, which hereby are incorporated by reference in their entirety.

As used herein, different 'forms' of antigen, e.g. mesothelin, are hereby defined as different protein molecules resulting from different translational and posttranslational modifications, such as, but not limited to, differences in splicing of the primary mesothelin transcript, differences in glycosylation, and differences in posttranslational proteolytic cleavage.

As used herein, the term ‘invariant binding’ of a particular antibody to mesothelin refers to its ability to bind to mesothelin on a broad range of mesothelin-expressing cancer cell lines which express different forms of mesothelin. For invariantly binding antibodies, EC50 values determined by FACS titration on two distinct cancer cell lines might differ no more than 10fold, or, preferably, 5fold, and most preferably between 1 and 3fold.

As used herein, the term ‘epitope’ includes any protein determinant capable of specific binding to an immunoglobulin or T-cell receptor. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. Two antibodies are said to ‘bind the same epitope’ if one antibody is shown to compete with the second antibody in a competitive binding assay, by any of the methods well known to those of skill in the art.

Antibodies of the Invention

The present invention relates to methods to inhibit growth of mesothelin-positive cancer cells and the progression of neoplastic disease by providing anti-mesothelin antibodies. Provided are human monoclonal antibodies, antigen-binding antibody fragments thereof, and variants of the antibodies and fragments, that specifically bind to the 40 kDa, C-terminal domain of the mesothelin precursor polypeptide (SEQ ID NO 370), which is named ‘mesothelin’ herein.

The antibodies, antigen-binding antibody fragments, and variants of the antibodies and fragments of the invention are comprised of a light chain variable region and a heavy chain variable region. Variants of the antibodies or antigen-binding antibody fragments contemplated in the invention are molecules in which the binding activity of the antibody or antigen-binding antibody fragment for mesothelin is maintained.

Throughout this document, reference is made to the following representative antibodies of the invention: “MF-J”, “MOR07265”, “MOR06631”, “MOR 06635”, “MOR06669”, “MOR07111”, “MOR06640”, “MOR06642”, “MOR06643”, ”MF-226”, “MOR06626”, “MOR06638”, “MF-A”, “MOR06657”, “MF-T”, “MF1”, “MF-5”, “MF-8”, “MF-24”, “MF-25”, “MF-27”, “MF-73”, “MF-78”, “MF-84”, “MF-101”, “MF-230”, “MF-236”, “MF-252”, “MF-257”, “MF-423”, “MF-427”, “MF-428”, MF-C”, “MF-I”, “MF-L”, “MF-M”, “MF-P”, “MF-Q”, MF-S”, “MF-V”, “MF-W”, and “MF-Y”. MF-J represents an antibody having a variable heavy region corresponding to SEQ ID NO: 284 (DNA)/SEQ ID NO: 198 (protein) and a variable light region corresponding to SEQ ID NO: 327 (DNA)/SEQ ID NO: 241 (protein). MOR 07265 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 285 (DNA)/SEQ ID NO: 199 (protein) and a variable light region corresponding to SEQ ID NO: 328 (DNA)/SEQ ID NO: 242 (protein). MOR 06631 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 286 (DNA)/SEQ ID NO: 200 (protein) and a variable light region corresponding to SEQ ID NO: 329 (DNA)/SEQ ID NO: 243 (protein). MOR 06669 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 287 (DNA)/SEQ ID NO: 201 (protein) and a variable light region corresponding to SEQ ID NO: 330 (DNA)/SEQ ID NO: 244 (protein). MOR 07111 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 288 (DNA)/SEQ ID NO: 202 (protein) and a variable light region corresponding to SEQ ID NO: 331 (DNA)/SEQ ID NO: 245 (protein). MOR 06640 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 289 (DNA)/SEQ ID NO: 203 (protein) and a variable light region corresponding to SEQ ID NO: 332 (DNA)/SEQ ID NO: 246 (protein). MOR 06642 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 290 (DNA)/SEQ ID NO: 204 (protein) and a variable light region corresponding to SEQ ID NO: 333 (DNA)/SEQ ID NO: 247 (protein). MOR 06643 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 291 (DNA)/SEQ ID NO: 205 (protein) and a variable light region corresponding to SEQ ID NO: 334 (DNA)/SEQ ID NO: 248 (protein). MF-226 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 292 (DNA)/SEQ ID NO: 206 (protein) and a variable light region corresponding to SEQ ID NO: 335 (DNA)/SEQ ID NO: 249 (protein). MOR 06626 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 293 (DNA)/SEQ ID NO: 207 (protein) and a variable light region corresponding to SEQ ID NO: 336 (DNA)/SEQ ID NO: 250 (protein). MOR 06635 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 294 (DNA)/SEQ ID NO: 208 (protein) and a variable light region corresponding to SEQ ID NO: 337 (DNA)/SEQ ID NO: 251 (protein). MOR 06638 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 295 (DNA)/SEQ ID NO: 209 (protein) and a variable light region corresponding to SEQ ID NO: 338 (DNA)/SEQ ID NO: 252 (protein). MF-A represents an antibody having a variable heavy region corresponding to SEQ ID NO: 296 (DNA)/SEQ ID NO: 210 (protein) and a variable light region corresponding to SEQ ID NO: 339 (DNA)/SEQ ID NO: 253 (protein). MOR 06657 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 297 (DNA)/SEQ ID NO: 211 (protein) and a variable light region corresponding to SEQ ID NO: 340 (DNA)/SEQ ID NO: 254 (protein). MF-T represents an antibody having a variable heavy region corresponding to SEQ ID NO: 298 (DNA)/SEQ ID NO: 212 (protein) and a variable light region corresponding to SEQ ID NO: 341

(DNA)/SEQ ID NO: 255 (protein). MF-L represents an antibody having a variable heavy region corresponding to SEQ ID NO: 299 (DNA)/SEQ ID NO: 213 (protein) and a variable light region corresponding to SEQ ID NO: 342 (DNA)/SEQ ID NO: 256 (protein). MF-1 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 300 (DNA)/SEQ ID NO: 214 (protein) and a variable light region corresponding to SEQ ID NO: 343 (DNA)/SEQ ID NO: 257 (protein). MF-5 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 301 (DNA)/SEQ ID NO: 215 (protein) and a variable light region corresponding to SEQ ID NO: 344 (DNA)/SEQ ID NO: 258 (protein). MF-8 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 302 (DNA)/SEQ ID NO: 216 (protein) and a variable light region corresponding to SEQ ID NO: 345 (DNA)/SEQ ID NO: 259 (protein). MF-24 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 303 (DNA)/SEQ ID NO: 217 (protein) and a variable light region corresponding to SEQ ID NO: 346 (DNA)/SEQ ID NO: 260 (protein). MF-25 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 304 (DNA)/SEQ ID NO: 218 (protein) and a variable light region corresponding to SEQ ID NO: 347 (DNA)/SEQ ID NO: 261 (protein). MF-27 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 305 (DNA)/SEQ ID NO: 219 (protein) and a variable light region corresponding to SEQ ID NO: 348 (DNA)/SEQ ID NO: 262 (protein). MF-73 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 306 (DNA)/SEQ ID NO: 220 (protein) and a variable light region corresponding to SEQ ID NO: 349 (DNA)/SEQ ID NO: 263 (protein). MF-78 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 307 (DNA)/SEQ ID NO:

221 (protein) and a variable light region corresponding to SEQ ID NO: 350 (DNA)/SEQ ID NO: 264 (protein). MF-84 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 308 (DNA)/SEQ ID NO: 222 (protein) and a variable light region corresponding to SEQ ID NO: 351 (DNA)/SEQ ID NO: 265 (protein). MF-101 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 309 (DNA)/SEQ ID NO: 223 (protein) and a variable light region corresponding to SEQ ID NO: 352 (DNA)/SEQ ID NO: 266 (protein). MF-230 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 310 (DNA)/SEQ ID NO: 224 (protein) and a variable light region corresponding to SEQ ID NO: 353 (DNA)/SEQ ID NO: 267 (protein). MF-236 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 311 (DNA)/SEQ ID NO: 225 (protein) and a variable light region corresponding to SEQ ID NO: 354 (DNA)/SEQ ID NO: 268 (protein). MF-252 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 312 (DNA)/SEQ ID NO: 226 (protein) and a variable light region corresponding to SEQ ID NO: 355 (DNA)/SEQ ID NO: 269 (protein). MF-275 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 313 (DNA)/SEQ ID NO: 227 (protein) and a variable light region corresponding to SEQ ID NO: 356 (DNA)/SEQ ID NO: 270 (protein). MF-423 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 314 (DNA)/SEQ ID NO: 228 (protein) and a variable light region corresponding to SEQ ID NO: 357 (DNA)/SEQ ID NO: 271 (protein). MF-427 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 315 (DNA)/SEQ ID NO: 229 (protein) and a variable light region corresponding to SEQ ID NO: 358 (DNA)/SEQ ID NO: 272 (protein). MF-428 represents an antibody having a

variable heavy region corresponding to SEQ ID NO: 316 (DNA)/SEQ ID NO: 230 (protein) and a variable light region corresponding to SEQ ID NO: 359 (DNA)/SEQ ID NO: 273 (protein). MF-C represents an antibody having a variable heavy region corresponding to SEQ ID NO: 317 (DNA)/SEQ ID NO: 231 (protein) and a variable light region corresponding to SEQ ID NO: 360 (DNA)/SEQ ID NO: 274 (protein). MF-I represents an antibody having a variable heavy region corresponding to SEQ ID NO: 318 (DNA)/SEQ ID NO: 232 (protein) and a variable light region corresponding to SEQ ID NO: 361 (DNA)/SEQ ID NO: 275 (protein). MF-M represents an antibody having a variable heavy region corresponding to SEQ ID NO: 319 (DNA)/SEQ ID NO: 233 (protein) and a variable light region corresponding to SEQ ID NO: 362 (DNA)/SEQ ID NO: 276 (protein). MF-P represents an antibody having a variable heavy region corresponding to SEQ ID NO: 320 (DNA)/SEQ ID NO: 234 (protein) and a variable light region corresponding to SEQ ID NO: 363 (DNA)/SEQ ID NO: 277 (protein). MF-Q represents an antibody having a variable heavy region corresponding to SEQ ID NO: 321 (DNA)/SEQ ID NO: 235 (protein) and a variable light region corresponding to SEQ ID NO: 364 (DNA)/SEQ ID NO: 278 (protein). MF-S represents an antibody having a variable heavy region corresponding to SEQ ID NO: 322 (DNA)/SEQ ID NO: 236 (protein) and a variable light region corresponding to SEQ ID NO: 365 (DNA)/SEQ ID NO: 279 (protein). MF-U represents an antibody having a variable heavy region corresponding to SEQ ID NO: 323 (DNA)/SEQ ID NO: 237 (protein) and a variable light region corresponding to SEQ ID NO: 366 (DNA)/SEQ ID NO: 280 (protein). MF-V represents an antibody having a variable heavy region corresponding to SEQ ID NO: 324 (DNA)/SEQ ID NO: 238 (protein) and a variable light region corresponding to SEQ ID NO: 367

(DNA)/SEQ ID NO: 281 (protein). MF-W represents an antibody having a variable heavy region corresponding to SEQ ID NO: 325 (DNA)/SEQ ID NO: 239 (protein) and a variable light region corresponding to SEQ ID NO: 368 (DNA)/SEQ ID NO: 282 (protein). MF-Y represents an antibody having a variable heavy region corresponding to SEQ ID NO: 326 (DNA)/SEQ ID NO: 240 (protein) and a variable light region corresponding to SEQ ID NO: 369 (DNA)/SEQ ID NO: 283 (protein).

In one aspect, the invention provides antibodies which bind to epitopes of mesothelin, whose amino acid sequence is depicted by SEQ ID NO: 370, that are distinct from the mesothelin epitope recognized by Mab K1.

In other aspects the invention provides antibodies which bind to one or more amino acids of the epitopes of antibodies MF-J or MF-T. In certain aspects said antibodies bind to at least to two, at least three, at least four, at least five or at least six amino acids of the epitopes of antibodies MF-J or MF-T. In certain aspects the antibodies of the present invention bind to one or more amino acids of the epitope recognized by the antibody MF-J. In alternative aspects the antibodies of the present invention bind to one or more amino acids of the epitope recognized by the antibody MF-T.

In another aspect, the invention provides antibodies having an antigen-binding region that can bind specifically to or has a high affinity for one or more regions of mesothelin, whose amino acid sequence is depicted by SEQ ID NO: 370. An antibody is said to have a “high affinity” for an antigen if the affinity measurement is at least 100 nM (monovalent affinity of Fab fragment). An inventive antibody or antigen-binding region preferably can bind to mesothelin with an affinity of less than about 100 nM, more preferably less than about 60 nM, and still more preferably less than about 30 nM. Further preferred are antibodies that bind to mesothelin with an affinity of less than about 10 nM, and more preferably less than about 3 nM. For instance, the affinity of an antibody of the invention against mesothelin may be about 10.0 nM or 0.19 nM (monovalent affinity of Fab fragment).

Table 1 provides a summary of dissociation constants and dissociation rates of representative antibodies of the invention, as determined by surface plasmon resonance (Biacore) on directly immobilized mesothelin.

Table 1: Monovalent dissociation constants and dissociation rates to mesothelin determined for anti-mesothelin Fabs by surface plasmon resonance

Antibody	K_D [M]	kd [1/s]
MF-A	1.9×10^{-8}	7.9×10^{-2}
MOR06657	9.5×10^{-10}	5.5×10^{-3}
MF-J	9.2×10^{-9}	2.9×10^{-3}
MOR06631	9×10^{-11}	1.4×10^{-5}
MOR06669	2.4×10^{-10}	8.1×10^{-5}
MOR06643	3.6×10^{-10}	2.8×10^{-4}
MF-226	5.8×10^{-8}	3.8×10^{-2}
MOR06626	6.7×10^{-10}	1.2×10^{-3}
MOR06638	1.6×10^{-8}	6.3×10^{-3}

The IgG1 format was used for the cell-based affinity determination, determined by fluorescence-activated cell sorting (FACS) combined with Scatchard analysis, and live cell enzyme-linked immunosorbed assay (ELISA).

Table 2 denotes the binding strength of representative IgG antibodies on mesothelin-expressing CHO-A9 cells.

Table 2: Cell-based binding potency of anti-mesothelin antibodies as determined by cell ELISA and FACS on mesothelin-expressing CHO-A9 cells

Antibody (IgG)	**EC50**	
	FACS [nM]	**Cell ELISA [nM]**
MF-A	0.05	0.8
MF-J	0.11	3.9
MF-L	0.07	0.8
MF-T	0.27	1.5
MF-226	0.15	0.4

Antibody Generation

A synthetic antibody phage display library (Knappik, A., *et al.*, J. Mol. Biol. (2000) 296(1): 57) was used to isolate high affinity, mesothelin-specific, human monoclonal antibodies, by a combination of whole cell and protein pannings and through the development of specific tools. These tools and methods include a mesothelin-expressing recombinant cell-line and the development of panning procedures and screening assays capable of identifying antibodies that preferentially bind to mesothelin displayed on the cell surface and that are crossreactive to mesothelin from other species.

Antibodies to the mesothelial cancer cell-surface marker, mesothelin, were discovered by a combination of three non-conventional approaches in phage-display technology (PDT). First, a recombinant cell line expressing the membrane-bound, 40 kDa domain of mesothelin was constructed by stable transfection of CHO-K1 cells with a plasmid encoding the GPI-anchored C-terminal part of the protein (SEQ ID 371), to give the CHO-A9 cell line. Second, dual-alternating cell-surface selections were performed with the latter recombinant cell line and the squamous cancer cell line NCI-H226. Pre-adsorption with CHO-K1 cells was included to avoid the selection of Fab fragments binding to epitopes of the parental cells. Additional selections were performed with recombinant, soluble purified human mesothelin (unique source of "MF-24", "MF-25", and "MF-27"), with recombinant, murine mesothelin, with purified deglycosylated mesothelin (unique source of "MF-5" and "MF-8"), and with biotinylated mesothelin in soluble phase. Third, screening methods were developed which allowed for successive screening of the phage outputs obtained in panning on whole NCI-H226 cells as well as CHO-A9 cells. The combination of these specific methods allowed the isolation of the unique antibodies "MF-J", "MF-226", "MF-A", "MF-T", "MF-1", "MF-5", "MF-8", "MF-24", "MF-25", "MF-27", "MF-73", "MF-78", "MF-84", "MF-101", "MF-230", "MF-236", "MF-252", "MF-275", "MF-423", "MF-427", "MF-428", MF-C", "MF-I", "MF-L", "MF-M", "MF-P", "MF-Q", MF-S", "MF-U", "MF-V", "MF-W", and "MF-Y". These unique antibodies were further characterized by their binding affinity in two cell based ELISA's, by BIAcore binding to soluble mesothelin, by their ability to recognize different epitopes on soluble mesothelin, and by their ability to cross react with murine mesothelin assessed by FACS and immunoblotting, and their ability to be internalized in three different cell based assays. Two of the internalization assays quantitatively measured the internalization of radiolabelled anti-mesothelin antibodies either in the absence of presence of a secondary antibody to human IgG. This data was used to select four antibodies for further affinity maturation.

In order to obtain antibodies with robust invariant binding to different forms of mesothelin displayed on different cancer cell lines, to increase species cross-reactivity, and to further increase affinity and decrease dissociation rates, a strategy for affinity maturation was designed. Affinity maturation was performed on antibodies 'MF-J', 'MF-226', 'MF-L' and 'MF-A'. Affinity maturation included generation of new antibody repertoires by the exchange of H-CDR2, L-CDR3, or a combination of both H-CDR2 and L-CDR3 regions of the parental antibodies. Alternating selections were performed with the two mesothelin-expressing cancer cell lines NCI-H226 and OVCAR-3, as well as recombinant purified and biotinylated human and murine meothelin in solution using magnetic beads. Increasing stringency was obtained by gradual reduction of antigen and extension of the washing procedure.

Screening was performed by first ranking the hits by decreasing affinity, as determined on antigen-coated beads in solution, by measuring an electrochemiluminescent signal in a M-384 Workstation (BioVeris). Subsequently, a resulting selection of high-affinity binders was submitted to solution-equilibrium titration (SET) screening (Haenel, C., *et al.*, Anal. Biochem. (2005) 339(1): 182). The best binders were further screened by analysis of cross-reactivity to murine mesothelin, as well as for binding to mesothelin on NCI-H226 cells by FACS. The combination of these specific methods allowed the isolation of the unique antibodies 'MOR07265', 'MOR06631', 'MOR 06635',

'MOR06669', 'MOR07111', 'MOR06640', 'MOR06642', 'MOR06643', 'MOR06626', 'MOR06638' and 'MOR06657'.

Peptide Variants

Antibodies of the invention are not limited to the specific peptide sequences provided herein. Rather, the invention also embodies variants of these polypeptides. With reference to the instant disclosure and conventionally available technologies and references, the skilled worker will be able to prepare, test and utilize functional variants of the antibodies disclosed herein, while appreciating that variants having the ability to bind to mesothelin fall within the scope of the present invention.

A variant can include, for example, an antibody that has at least one altered complementary determining region (CDR) (hyper-variable) and/or framework (FR) (variable) domain/position, vis-à-vis a peptide sequence disclosed herein. To better illustrate this concept, a brief description of antibody structure follows.

An antibody is composed of two peptide chains, each containing one (light chain) or three (heavy chain) constant domains and a variable region (VL, VH), the latter of which is in each case made up of four FR regions and three interspaced CDRs. The antigen-binding site is formed by one or more CDRs, yet the FR regions provide the structural framework for the CDRs and, hence, play an important role in antigen binding. By altering one or more amino acid residues in a CDR or FR region, the skilled worker routinely can generate mutated or diversified antibody sequences, which can be screened against the antigen, for new or improved properties, for example.

Tables 3 (VH) and 4 (VL) delineate the CDR and FR regions for certain antibodies of the invention and compare amino acids at a given position to each other and to corresponding consensus or “master gene” sequences (as described in U.S. Patent No. 6,300,064):

Table 3: VH Sequences

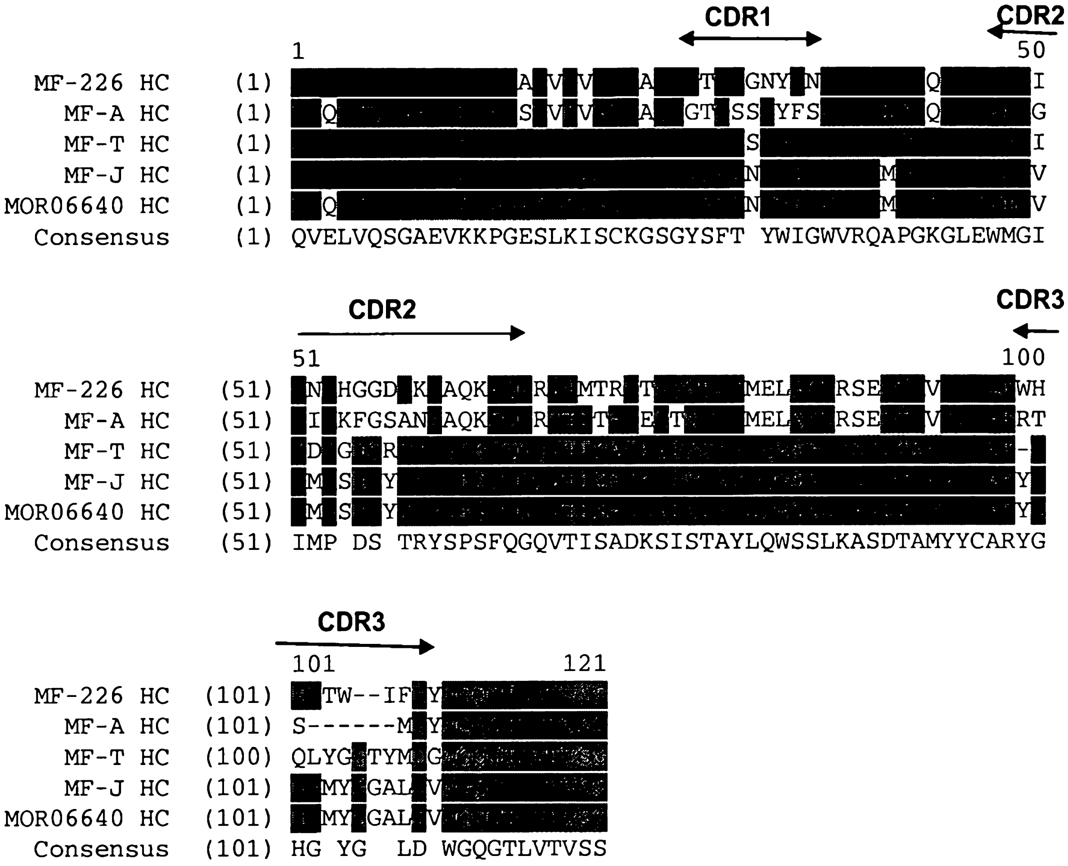
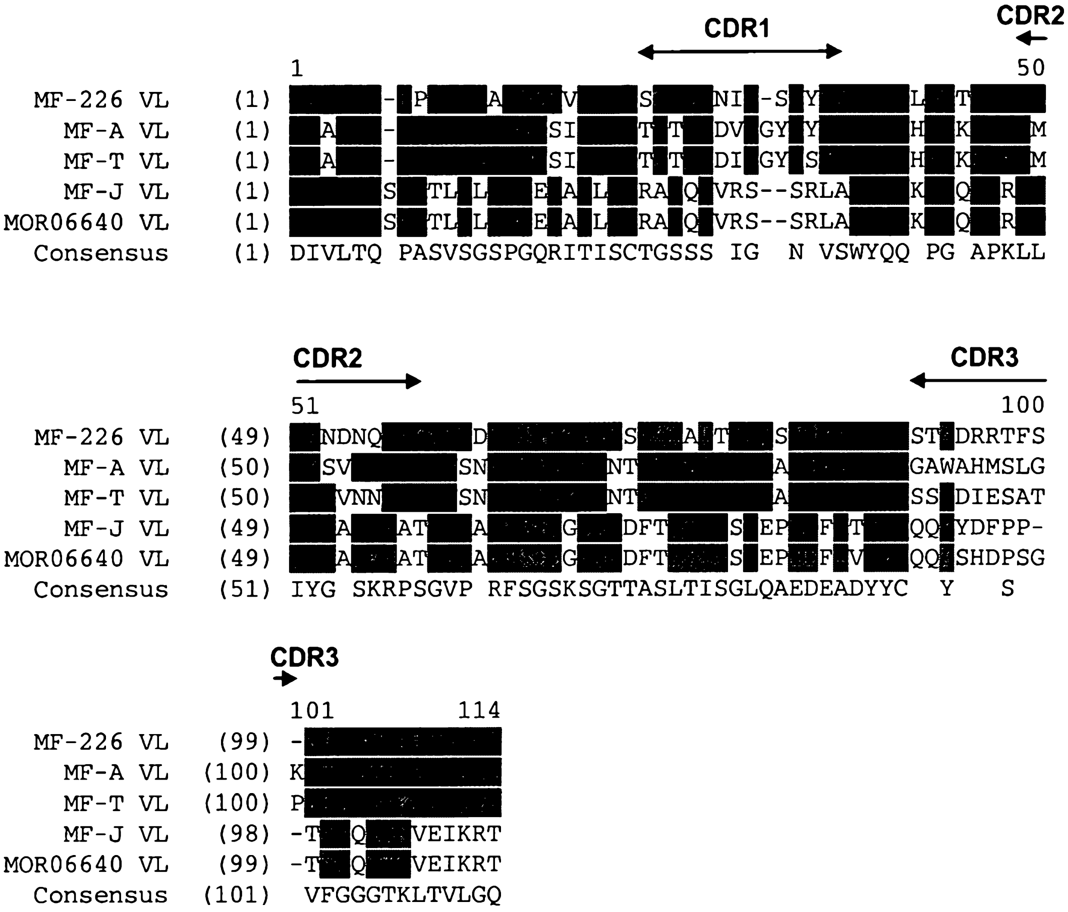


Table 4: VL Sequences



In certain aspects the present invention provides antibodies

- wherein the HCDR1 region is selected from sequemce ID's [all respective SEQ IDs of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30.

- wherein the HCDR2 region is selected from sequemce ID's 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65 or 66.

- wherein the HCDR3 region is selected from sequemce ID's 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97or 98.

- wherein the LCDR1 region is selected from sequemce ID's 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 102 or 128.

- wherein the LCDR2 region is selected from sequemce ID's 129, 130, 131 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159 or 155.

- wherein the LCDR3 region is selected from sequemce ID's 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196 or 197. or combinations of these CDR regions.

Preferred aspects are antibodies: in which the CDR sequences are selected from the MF-J series as shown in table 7 or other combinations of the CDR regions shown in table 7.

In certain aspects the present invention provides antibodies

- wherein the VH is selected from sequence ID 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239 or 240,
- wherein the VL is selected from sequence ID 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282 or 283.

As above, preferred aspects for MF-J series as shown in table 7 or other combinations of the VH and VL regions shown in table 7.

The skilled worker can use the data in Tables 3, 4 and 7 to design peptide variants that are within the scope of the present invention. It is preferred that variants are constructed by changing amino acids within one or more CDR regions; a variant might also have one or more altered framework regions. With reference to a comparison of the novel antibodies to each other, candidate residues that can be changed include *e.g.* residues 3 or 45 of the variable light and *e.g.* residues 16 or 43 of the variable heavy chains of MF-226 and MF-T, since these are positions of variance vis-à-vis each other. Alterations also may be made in the framework regions. For example, a peptide FR domain might be altered where there is a deviation in a residue compared to a germline sequence.

With reference to a comparison of the novel antibodies to the corresponding consensus or “master gene” sequence, which are listed in Knappik *et al.*, 2000, candidate residues that can be changed include *e.g.* residues 29 or 52 of the variable light chain of MF-T compared to VLλ2 and *e.g.* residues 43 or 57 of the variable heavy chain of MF-A compared to VH1A (Knappik, A., *et al.*, J. Mol.

Biol. (2000) 296(1): 57). Alternatively, the skilled worker could make the same analysis by comparing the amino acid sequences disclosed herein to known sequences of the same class of such antibodies, using, for example, the procedure described by Knappik, A., *et al.* (2000) and U.S. Patent No. 6,300,064 issued to Knappik *et al.*

Furthermore, variants may be obtained by using one antibody as starting point for optimization by diversifying one or more amino acid residues in the antibody, preferably amino acid residues in one or more CDRs, and by screening the resulting collection of antibody variants for variants with improved properties. Particularly preferred is diversification of one or more amino acid residues in CDR-3 of VL, CDR-3 of VH, CDR-1 of VL and/or CDR-2 of VH. Diversification can be done by synthesizing a collection of DNA molecules using trinucleotide mutagenesis (TRIM) technology (Virnekäs, B., Ge, L., Plückthun, A., Schneider, K.C., Wellnhofer, G., and Moroney S.E. (1994) Trinucleotide phosphoramidites: ideal reagents for the synthesis of mixed oligonucleotides for random mutagenesis. Nucl. Acids Res. 22, 5600.).

Conservative Amino Acid Variants

Polypeptide variants may be made that conserve the overall molecular structure of an antibody peptide sequence described herein. Given the properties of the individual amino acids, some rational substitutions will be recognized by the skilled worker. Amino acid substitutions, *i.e.*, "conservative substitutions," may be made, for instance, on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues involved.

For example, (a) nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine; (b) polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine; (c) positively charged (basic) amino acids include arginine, lysine, and histidine; and (d) negatively charged (acidic) amino acids include aspartic acid and glutamic acid. Substitutions typically may be made within groups (a)-(d). In addition, glycine and proline may be substituted for one another based on their ability to disrupt α-helices. Similarly, certain amino acids, such as alanine, cysteine, leucine, methionine, glutamic acid, glutamine, histidine and lysine are more commonly found in α-helices, while valine, isoleucine, phenylalanine, tyrosine, tryptophan and threonine are more commonly found in β-pleated sheets. Glycine, serine, aspartic acid, asparagine, and proline are commonly found in turns. Some preferred substitutions may be made among the following groups: (i) S and T; (ii) P and G; and (iii) A, V, L and I. Given the known genetic code, and recombinant and synthetic DNA techniques, the skilled scientist readily can construct DNAs encoding the conservative amino acid variants. In one particular example, amino acid position 3 in SEQ ID NOS: 199-205, 207-211 or 213-240 can be changed from a Q to an E.

As used herein, "sequence identity" between two polypeptide sequences, indicates the percentage of amino acids that are identical between the sequences. "Sequence homology" indicates the percentage of amino acids that either are identical or that represent conservative amino acid substitutions. Preferred polypeptide sequences of the invention have a sequence identity in the CDR regions of at least 60%, more preferably, at least 70% or 80%, still more preferably at least 90% and most preferably at least 95%. Preferred antibodies also have a sequence homology in the CDR regions of at least 80%, more preferably 90% and most preferably 95%.

DNA molecules of the invention

The present invention also relates to the DNA molecules that encode an antibody of the invention. These sequences include, but are not limited to, those DNA molecules set forth in SEQ IDs 284-369.

DNA molecules of the invention are not limited to the sequences disclosed herein, but also include variants thereof. DNA variants within the invention may be described by reference to their physical properties in hybridization. The skilled worker will recognize that DNA can be used to identify its complement and, since DNA is double stranded, its equivalent or homolog, using nucleic acid hybridization techniques. It also will be recognized that hybridization can occur with less than 100% complementarity. However, given appropriate choice of conditions, hybridization techniques can be used to differentiate among DNA sequences based on their structural relatedness to a particular probe. For guidance regarding such conditions see, Sambrook et al., 1989 (Sambrook, J., Fritsch, E. F. and Maniatis, T. (1989) Molecular Cloning: A laboratory manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, USA) and Ausubel et al., 1995 (Ausubel, F. M., Brent, R., Kingston, R. E., Moore, D. D., Sedman, J. G., Smith, J. A., & Struhl, K. eds. (1995). Current Protocols in Molecular Biology. New York: John Wiley and Sons).

Structural similarity between two polynucleotide sequences can be expressed as a function of "stringency" of the conditions under which the two sequences will hybridize with one another. As used herein, the term "stringency" refers to the extent that the conditions disfavor hybridization. Stringent conditions strongly disfavor hybridization, and only the most structurally related molecules will hybridize to one another under such conditions. Conversely, non-stringent conditions favor hybridization of molecules displaying a lesser degree of structural relatedness. Hybridization stringency, therefore, directly correlates with the structural relationships of two nucleic acid sequences. The following relationships are useful in correlating hybridization and relatedness (where T_m is the melting temperature of a nucleic acid duplex):

a. $T_m = 69.3 + 0.41(G+C)\%$

b. The T_m of a duplex DNA decreases by 1°C with every increase of 1% in the number of mismatched base pairs.

c. $(T_m)_{\mu 2} - (T_m)_{\mu 1} = 18.5 \log_{10}\mu 2/\mu 1$
where $\mu 1$ and $\mu 2$ are the ionic strengths of two solutions.

Hybridization stringency is a function of many factors, including overall DNA concentration, ionic strength, temperature, probe size and the presence of agents which disrupt hydrogen bonding. Factors promoting hybridization include high DNA concentrations, high ionic strengths, low temperatures, longer probe size and the absence of agents that disrupt hydrogen bonding. Hybridization typically is performed in two phases: the “binding” phase and the “washing” phase.

First, in the binding phase, the probe is bound to the target under conditions favoring hybridization. Stringency is usually controlled at this stage by altering the temperature. For high stringency, the temperature is usually between 65°C and 70°C, unless short (< 20 nt) oligonucleotide probes are used. A representative hybridization solution comprises 6X SSC, 0.5% SDS, 5X Denhardt's solution and 100 µg of nonspecific carrier DNA. See Ausubel *et al.,* section 2.9, supplement 27 (1994). Of course, many different, yet functionally equivalent, buffer conditions are known. Where the degree of relatedness is lower, a lower temperature may be chosen. Low stringency binding temperatures are between about 25°C and 40°C. Medium stringency is between at least about 40°C to less than about 65°C. High stringency is at least about 65°C.

Second, the excess probe is removed by washing. It is at this phase that more stringent conditions usually are applied. Hence, it is this "washing" stage that is most important in determining relatedness via hybridization. Washing solutions typically contain lower salt concentrations. One exemplary medium stringency solution contains 2X SSC and 0.1% SDS. A high stringency wash solution contains the equivalent (in ionic strength) of less than about 0.2X SSC, with a preferred stringent solution containing about O.1X SSC. The temperatures associated with various stringencies are the same as discussed above for "binding." The washing solution also typically is replaced a number of times during washing. For example, typical high stringency washing conditions comprise washing twice for 30 minutes at 55° C. and three times for 15 minutes at 60° C.

Accordingly, the present invention includes nucleic acid molecules that hybridize to the molecules of set forth in SEQ ID 284-369 under high stringency binding and washing conditions, where such nucleic molecules encode an antibody or functional fragment thereof having properties as described herein. Preferred molecules (from an mRNA perspective) are those that have at least 75% or 80% (preferably at least 85%, more preferably at least 90% and most preferably at least 95%) homology or sequence identity with one of the DNA molecules described herein. In one particular example of a variant of the invention, nucleic acid position 7 in SEQ ID NOS: 285-291, 293-297, or 299-326 can be substituted from a C to a G, thereby changing the codon from CAA to GAA.

Functionally Equivalent Variants

Yet another class of DNA variants within the scope of the invention may be described with reference to the product they encode. These functionally equivalent genes are characterized by the fact that they encode the same peptide sequences found in SEQ ID 284-369 due to the degeneracy of the genetic code.

It is recognized that variants of DNA molecules provided herein can be constructed in several different ways. For example, they may be constructed as completely synthetic DNAs. Methods of efficiently synthesizing oligonucleotides in the range of 20 to about 150 nucleotides are widely available. *See* Ausubel *et al.*, section 2.11, Supplement 21 (1993). Overlapping oligonucleotides may be synthesized and assembled in a fashion first reported by Khorana *et al.,* J. Mol. Biol. 72:209-217 (1971); *see also* Ausubel *et al.*, *supra*, Section 8.2. Synthetic DNAs preferably are designed with convenient restriction sites engineered at the 5' and 3' ends of the gene to facilitate cloning into an appropriate vector.

As indicated, a method of generating variants is to start with one of the DNAs disclosed herein and then to conduct site-directed mutagenesis. *See* Ausubel et al., *supra,* chapter 8, Supplement 37 (1997). In a typical method, a target DNA is cloned into a single-stranded DNA bacteriophage vehicle. Single-stranded DNA is isolated and hybridized with an oligonucleotide containing the desired nucleotide alteration(s). The complementary strand is synthesized and the double stranded phage is introduced into a host. Some of the resulting progeny will contain the desired mutant, which can be confirmed using DNA sequencing. In addition, various methods are available that increase the probability that the progeny phage will be the desired mutant. These methods are well known to those in the field and kits are commercially available for generating such mutants.

Recombinant DNA constructs and expression

The present invention further provides recombinant DNA constructs comprising one or more of the nucleotide sequences of the present invention. The recombinant constructs of the present invention are used in connection with a vector, such as a plasmid, phagemid, phage or viral vector, into which a DNA molecule encoding an antibody of the invention is inserted.

The encoded gene may be produced by techniques described in Sambrook *et al.*, 1989, and Ausubel *et al.*, 1989. Alternatively, the DNA sequences may be chemically synthesized using, for example, synthesizers. See, for example, the techniques described in OLIGONUCLEOTIDE SYNTHESIS (1984, Gait, ed., IRL Press, Oxford), which is incorporated by reference herein in its entirety. Recombinant constructs of the invention are comprised with expression vectors that are capable of expressing the RNA and/or protein products of the encoded DNA(s). The vector may further comprise regulatory sequences, including a promoter operably linked to the open reading frame (ORF). The vector may further comprise a selectable marker sequence. Specific initiation and bacterial secretory signals also may be required for efficient translation of inserted target gene coding sequences.

The present invention further provides host cells containing at least one of the DNAs of the present invention. The host cell can be virtually any cell for which expression vectors are available. It may be, for example, a higher eukaryotic host cell, such as a mammalian cell, a lower eukaryotic host cell, such as a yeast cell, and may be a prokaryotic cell, such as a bacterial cell. Introduction of the recombinant construct into the host cell can be effected by calcium phosphate transfection, DEAE, dextran mediated transfection, electroporation or phage infection.

Bacterial Expression

Useful expression vectors for bacterial use are constructed by inserting a structural DNA sequence encoding a desired protein together with suitable translation initiation and termination signals in operable reading phase with a functional promoter. The vector will comprise one or more phenotypic selectable markers and an origin of replication to ensure maintenance of the vector and, if desirable, to provide amplification within the host. Suitable prokaryotic hosts for transformation include *E. coli*, *Bacillus subtilis, Salmonella typhimurium* and various species within the genera Pseudomonas, Streptomyces, and Staphylococcus.

Bacterial vectors may be, for example, bacteriophage-, plasmid- or phagemid-based. These vectors can contain a selectable marker and bacterial origin of replication derived from commercially available plasmids typically containing elements of the well known cloning vector pBR322 (ATCC 37017). Following transformation of a suitable host strain and growth of the host strain to an appropriate cell density, the selected promoter is de-repressed/induced by appropriate means (*e.g.*, temperature shift or chemical induction) and cells are cultured for an additional period. Cells are typically harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract retained for further purification.

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the protein being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of antibodies or to screen peptide libraries, for example, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable.

Therapeutic Methods

Therapeutic methods involve administering to a subject in need of treatment a therapeutically effective amount of an antibody contemplated by the invention. A "therapeutically effective" amount hereby is defined as the amount of an antibody that is of sufficient quantity to deplete mesothelin -positive cells in a treated area of a subject—either as a single dose or according to a multiple dose regimen, alone or in combination with other agents, which leads to the alleviation of an adverse condition, yet which amount is toxicologically tolerable. The subject may be a human or non-human animal (*e.g.*, rabbit, rat, mouse, monkey or other lower-order primate).

An antibody of the invention might be co-administered with known medicaments, and in some instances the antibody might itself be modified. For example, an antibody could be conjugated to an immunotoxin or radioisotope to potentially further increase efficacy.

The inventive antibodies can be used as a therapeutic or a diagnostic tool in a variety of situations where mesothelin undesirably expressed or found. Disorders and conditions particularly suitable for treatment with an antibody of the inventions are pancreatic cancer, ovarian cancer, mesothelioma and lung cancer.

To treat any of the foregoing disorders, pharmaceutical compositions for use in accordance with the present invention may be formulated in a conventional manner using one or more physiologically acceptable carriers or excipients. An antibody of the invention can be administered by any suitable means, which can vary, depending on the type of disorder being treated. Possible administration routes include parenteral (*e.g.*, intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous), intrapulmonary and intranasal, and, if desired for local immunosuppressive treatment, intralesional administration. In addition, an antibody of the invention might be administered by pulse infusion, with, *e.g.*, declining doses of the antibody. Preferably, the dosing is given by injections, most preferably intravenous or subcutaneous injections, depending in part on whether the administration is brief or chronic. The amount to be administered will depend on a variety of factors such as the clinical symptoms, weight of the individual, whether other drugs are administered. The skilled artisan will recognize that the route of administration will vary depending on the disorder or condition to be treated.

Determining a therapeutically effective amount of the novel polypeptide, according to this invention, largely will depend on particular patient characteristics, route of administration, and the nature of the disorder being treated. General guidance can be found, for example, in the publications of the International Conference on Harmonisation and in REMINGTON'S PHARMACEUTICAL SCIENCES, chapters 27 and 28, pp. 484-528 (18th ed., Alfonso R. Gennaro, Ed., Easton, Pa.: Mack Pub. Co., 1990). More specifically, determining a therapeutically effective amount will depend on such factors as toxicity and efficacy of the medicament. Toxicity may be determined using methods well known in the art and found in the foregoing references. Efficacy may be determined utilizing the same guidance in conjunction with the methods described below in the Examples.

Diagnostic Methods

Mesothelin antibodies can be used for detecting the presence of mesothelin-expressing tumors. The presence of mesothelin-containing cells within various biological samples, including serum, prostate and other tissue biopsy specimens, may be detected with mesothelin antibodies. In addition, mesothelin antibodies may be used in various imaging methodologies such as immunoscintigraphy with a .sup.99mTc (or other isotope) conjugated antibody. For example, an imaging protocol similar to the one recently described using a .sup.111In conjugated anti-PSMA antibody may be used to detect pancreaetic or ovarian carcinomas (Sodee et al., Clin. Nuc. Med. 21: 759-766, 1997). Another method of detection that can be used is positron emitting tomography (see Herzog et al., J. Nucl. Med. 34:2222-2226, 1993).

Pharmaceutical Compositions and Administration

The present invention also relates to pharmaceutical compositions which may comprise mesothelin antibodies, alone or in combination with at least one other agent, such as stabilizing compound, which may be administered in any sterile, biocompatible pharmaceutical carrier, including, but not limited to, saline, buffered saline, dextrose, and water. Any of these molecules can be administered to a patient alone, or in combination with other agents, drugs or hormones, in pharmaceutical compositions where it is mixed with excipient(s) or pharmaceutically acceptable carriers. In one embodiment of the present invention, the pharmaceutically acceptable carrier is pharmaceutically inert.

The present invention also relates to the administration of pharmaceutical compositions. Such administration is accomplished orally or parenterally. Methods of parenteral delivery include topical, intra-arterial (directly to the tumor), intramuscular, subcutaneous, intramedullary, intrathecal, intraventricular, intravenous, intraperitoneal, or intranasal administration. In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers comprising excipients and auxilliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Ed. Maack Publishing Co, Easton, Pa.).

Pharmaceutical compositions for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for ingestion by the patient.

Pharmaceutical preparations for oral use can be obtained through combination of active compounds with solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxilliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are carbohydrate or protein fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose such as methyl, cellulose, hydroxypropylmethylcellulose, or sodium carboxymethylcellulose; and gums including arabic and tragacanth; and proteins such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate.

Dragee cores are provided with suitable coatings such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, ie. dosage.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating such as glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with a filler or binders such as lactose or starches, lubricants such as talc or magnesium stearate, and optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycol with or without stabilizers.

Pharmaceutical formulations for parenteral administration include aqueous solutions of active compounds. For injection, the pharmaceutical compositions of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiologically buffered saline. Aqueous injection suspensions may contain substances that increase viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

For topical or nasal administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

Kits

The invention further relates to pharmaceutical packs and kits comprising one or more containers filled with one or more of the ingredients of the aforementioned compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, reflecting approval by the agency of the manufacture, use or sale of the product for human administration.

In another embodiment, the kits may contain DNA sequences encoding the antibodies of the invention. Preferably the DNA sequences encoding these antibodies are provided in a plasmid suitable for transfection into and expression by a host cell. The plasmid may contain a promoter (often an inducible promoter) to regulate expression of the DNA in the host cell. The plasmid may also contain appropriate restriction sites to facilitate the insertion of other DNA sequences into the plasmid to produce various antibodies. The plasmids may also contain numerous other elements to facilitate cloning and expression of the encoded proteins. Such elements are well known to those of skill in the art and include, for example, selectable markers, initiation codons, termination codons, and the like.

Manufacture and Storage.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

The pharmaceutical composition may be provided as a salt and can be formed with may acids, including by not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents that are the corresponding free base forms. In other cases, the preferred preparation may be a lyophilized powder in 1 mM-50 mM histidine, 0.1%-2% sucrose, 2%-7% mannitol at a pH range of 4.5 to 5.5 that is combined with buffer prior to use.

After pharmaceutical compositions comprising a compound of the invention formulated in an acceptable carrier have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. For administration of mesothelin antibodies, such labeling would include amount, frequency and method of administration.

Therapeutically Effective Dose.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose, i.e. treatment of a particular disease state characterized by mesothelin expression. The determination of an effective dose is well within the capability of those skilled in the art.

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., neoplastic cells, or in animal models, usually mice, rabbits, dogs, or pigs. The animal model is also used to achieve a desirable concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

A therapeutically effective dose refers to that amount of protein or its antibodies, antagonists, or inhibitors that ameliorate the symptoms or condition. Therapeutic efficacy and toxicity of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., ED_{50} (the dose therapeutically effective in 50% of the population) and LD_{50} (the dose lethal to 50% of the population). The dose ratio between therapeutic and toxic effects is the therapeutic index, and it can be expressed as the ratio, ED_{50}/LD_{50}. Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used in formulating a range of dosage for human use. The dosage of such compounds lies preferably within a range of circulating concentrations what include the ED_{50}

with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

The exact dosage is chosen by the individual physician in view of the patient to be treated. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Additional factors that may be taken into account include the severity of the disease state, eg, tumor size and location; age, weight and gender of the patient; diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long acting pharmaceutical compositions might be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from 0.1 to 100,000 micrograms, up to a total dose of about 1 g, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature. See U.S. Pat. No. 4,657,760; 5,206,344; or 5,225,212. Those skilled in the art will employ different formulations for polynucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc. Preferred specific activities for for a radiolabeled antibody may range from 0.1 to 10 mCi/mg of protein (Riva et al., Clin. Cancer Res. 5:3275s-3280s, 1999; Wong et al., Clin. Cancer Res. 6:3855-3863, 2000; Wagner et al., J. Nuclear Med. 43:267-272, 2002).

The present invention is further described by the following examples. The examples are provided solely to illustrate the invention by reference to specific embodiments. These exemplifications, while illustrating certain specific aspects of the invention, do not portray the limitations or circumscribe the scope of the disclosed invention.

All examples were carried out using standard techniques, which are well known and routine to those of skill in the art, except where otherwise described in detail. Routine molecular biology techniques of the following examples can be carried out as described in standard laboratory manuals, such as Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Ed.; Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989.

EXAMPLES

EXAMPLE 1: Antibody Generation from HuCAL Libraries

For the generation of therapeutic antibodies against mesothelin, selections with the MorphoSys HuCAL GOLD phage display library were carried out. HuCAL GOLD® is a Fab library based on the HuCAL® concept (Knappik, A., *et al.*, J. Mol. Biol. (2000) 296(1): 57; Krebs, B., *et al.*, J. Immunol. Methods. (2001) 254(1-2): 67), in which all six CDRs are diversified, and which employs the CysDisplay™ technology for linking Fab fragments to the phage surface (Löhning, 2001; WO 01/05950).

A. Phagemid rescue, phage amplification and purification

HuCAL GOLD® phagemid library was amplified in 2 x TY medium containing 34 µg/ml chloramphenicol and 1 % glucose (2 x TY-CG). After helper phage infection (VCSM13) at an OD600 of 0.5 (30 min at 37°C without shaking; 30 min at 37°C shaking at 250 rpm), cells were spun down (4120 g; 5 min; 4°C), resuspended in 2 x TY / 34 µg/ml chloramphenicol / 50 µg/ml kanamycin and grown overnight at 22°C. Phages were PEG-precipitated from the supernatant, resuspended in PBS / 20 % glycerol and stored at -80°C. Phage amplification between two panning rounds was conducted as follows: mid-log phase TG1 cells were infected with eluted phages and plated onto LB-agar supplemented with 1 % of glucose and 34 µg/ml of chloramphenicol (LB-CG). After overnight incubation at 30°C, colonies were scraped off, adjusted to an OD600 of 0.5 and helper phage added as described above.

B. Pannings with HuCAL GOLD®

For the selections HuCAL GOLD® antibody-phages were divided into three pools corresponding to different VH master genes (pool 1: VH1/5λκ, pool 2: VH3 λκ, pool 3: VH2/4/6 λκ). These pools were individually pre-absorbed on mesothelin-negative CHO-K1 cells for depletion of irrelevant antibody phages and subsequently subjected to 3 rounds of alternating whole cell panning on mesothelin-expressing CHO-A9 and NCI-H226 cells followed by pH-elution. Finally, the remaining antibody phages were used to infect *E. coli* TG1 cells. After centrifugation the bacterial pellet was resuspended in 2 x TY medium, plated on agar plates and incubated overnight at 30°C. The selected clones were then scraped from the plates, phages were rescued and amplified. The second and the third round of selections were performed as the initial one.

The Fab encoding inserts of the selected HuCAL GOLD® phages were subcloned into the expression vector pMORPH®x9_Fab_FS (Rauchenberger, R., *et al.*, J. Biol. Chem. (2003) 278(40): 38194) to facilitate rapid expression of soluble Fab. The DNA of the selected clones was digested with XbaI and EcoRI thereby cutting out the Fab encoding insert (ompA-VLCL and phoA-Fd), and cloned into the XbaI / EcoRI cut vector pMORPH®x9_Fab_FS. Fab expressed in this vector carry two C-terminal tags (FLAG™ and Strep-tag® II) for detection and purification.

C. Affinity maturation Affinity maturation of selected Fab by stepwise exchange of CDR cassettes

To increase affinity and biological activity of selected antibody fragments (MF-L, MF-A, MF-J, MF-T and MF-226) , L-CDR3 and H-CDR2 regions were optimized in parallel by cassette mutagenesis using trinucleotide directed mutagenesis (Virnekäs et al, Nucleic Acids Res. 22(25): 5600-7), while the framework regions were kept constant (WO2006122797). Pannings for selection of high affinity phage displayed Fab fragments were performed either on purified biotinylated recombinant mesothelin (human or murine mesothelin) or directly on mesothelin expressing cell lines (NCI-H226 or OVCAR-3). Combinations of these different panning strategies were also applied throughout the three panning rounds which were performed.

EXAMPLE 2: Epitope Grouping

Epitope grouping experiments were performed using Biacore by monitering simultaneous binding of pairs of anti-mesothelin antibodies to immobilized mesothelin. Briefly, the first antibody was covalently immobilized to the sensor chip through primary amine coupling using n-hydroxysuccinamide (NHC) and N-ethyl-N'- dimethylaminopropyl carbodiimide (EDC). Unoccupied binding sites on the surface were then blocked with ethanolamide. Soluble mesothelin was captured on the surface via the immobilized antibody, therefore, the epitope of the capture antibody is blocked for all bound mesothelin molecules. A second antibody was immediately passed over the surface to bind to the immobilized mesothelin. Two antibodies recognizing the same or overlapping epitopes cannot bind to the mesothelin, whereas antibodies with distinct epitopes are able to bind. The antibody surface was regenerated with glycine, pH 2.8, to remove bound proteins and then the process was repeated with other antibodies. All combinations of seven antibodies were tested. Representative results using MF-T and several other antibodies are shown in Figure 1A. Use of MF-T as the second antibody served as a positive control and anti-FLAG served as a negative control. Figure 1B depicts a summary of the pairwise binding results for seven anti-mesothelin antibodies in a Venn diagram with circles representing individual epitopes. Overlapping circles represent overlapping epitopes. MF428 competed for binding with all other antibodies tested. MF-J and MF-T bind to distinct epitopes compared to each other and to MF-A, MF-226 and MF-L, which seem to compete for the same epitope region. The commercially available mouse antibody K1 binds to an epitope region distinct from the one recognized by MF-J and MF-T, but seems to share a similar epitope region to MF-A, MF-L and MF-226.

EXAMPLE 3: Cross-reactivity to murine mesothelin

Shown in Table 5 are results of Biacore and ELISA studies showing cross-reactivity of antibodies of the invention to murine mesothelin. The kinetic constants k_{on} and k_{off} were determined with serial dilutions of the respective purified Fab fragment binding to covalently immobilized human or murine mesothelin using the Biacore 3000 instrument (Biacore, Uppsala, Sweden). Covalent antigen immobilization was achieved by a standard EDC-NHS coupling procedure. Kinetic measurements were done in PBS, pH 7.2 at a flow rate of 20 µl/min using Fab concentration ranging from 1.5-500 nM. Injection time for each concentration was 1 min, followed by 3 min dissociation phase. For regeneration 5 µl 10 mM glycine buffer, pH 1.8 was used. All sensograms were fitted using the BIA evaluation software 3.1 (Biacore).

Table 5: Monovalent anti-mesothelin antibody affinities to human and murine mesothelin (Fab formats)

Antibody (Fab)	Human mesothelin		Murine mesothelin	
	K_D [M]	kd [1/s]	K_D [M]	kd [1/s]
MF-226	5.8×10^{-8}	3.8×10^{-2}	1.28×10^{-6}	1.4×10^{-1}
MOR 06626	6.7×10^{-10}	1.2×10^{-3}	6.7×10^{-9}	9.8×10^{-3}
MOR 06638	1.6×10^{-8}	6.3×10^{-3}	3.2×10^{-7}	4.0×10^{-2}
MF-A	1.9×10^{-8}	7.9×10^{-2}	6.7×10^{-7}	2.7×10^{-1}
MOR 06657	9.5×10^{-10}	5.5×10^{-3}	3.6×10^{-7}	1.6×10^{-1}

EXAMPLE 4: Invariant binding to mesothelin on different cancer cell lines

Figure 2 depicts immunoblots of mesothelin-expressing cell lines generated with anti-mesothelin antibody MF-J (A) and MOR 06635 (B). Briefly, cell extracts were generated by a standard lysis protocol by sonicating the cells for 3 min in the presence of DNAse and RNAse. Cell proteins were separated by SDS-PAGE under denaturing and reducing conditions, blotted onto nitrocellulose membranes and incubated with the appropriate primary antibody (MF-J-IgG or MOR 06635-Fab). Anti-human IgG peroxidase-coupled secondary antibody was used for detection, which was performed with ECL substrate. While only one band appeared when extracts of OVCAR-3 cells were blotted with mesothelin antibodies, multiple bands were observed in CHO-A9 and NCI-H226 cells. This indicates the presence of different isoforms of mesothelin in OVCAR-3, CHO-A9 and NCI-H226 cell lines. Since OVCAR-3 and CHO-A9 express the same, fully spliced transcript variant (Muminova, Z.E., *et al.*, BMC Cancer (2004) 4:19), and SEQ ID 371, the multiple bands must be caused by translational or posttranslational modifications, which might consist in, but are not limited to, for example, differences in glycosylation patterns.

Table 6 shows that EC_{50} values obtained by FACS titration of representative affinity matured antibodies of the invention on NCI-H226 and OVCAR-3 cells do not vary significantly for a subset of IgGs (i.e. MOR07265, -6631, -6669, -7111,-6640, -6642) while other IgGs show a more than eight fold higher EC_{50} value on OVCAR-3 than NCI-H226 (i.e. MOR06626, -6638, -6657. -6643). Most notably IgGs MOR07265, -6631, -6635, -6669, -7111,- 6640, -6642 are affinity matured derivatives of parental IgG MF-J, indicating that these IgGs bind to a related epitope which is invariably present on OVCAR-3 as well as NCI-H226 cells. Thus these data demonstrate the quality of invariant binding provided in the present invention.

FACS titration was performed in a 96 well microtiter plate, in which serial dilutions of the primary antibody in a volume of 80 μl of FACS buffer (3% FCS, 0.02% NaN_3 in PBS) were mixed with 20 µl of a cell suspension consisting of 10^6 cells/ml which had been detached with accutase or trypsin/EDTA, and resuspended in FACS buffer. Incubation was performed at 4 °C for 1 hour with agitation. Cells were washed twice with FACS buffer and resuspended in 100 µl/well of anti-human PE conjugate solution in FACS buffer. Incubation and washing was performed as before. Analysis of cell-bound antibodies was done using the FACS Array device. EC_{50} values were determined from fluorescence medians of duplicates using Prism 4.0 software (GraphPad) applying non-linear regression fit.

Table 6: FACS titration of IgG antibodies on NCI-H226 and OVCAR-3 cells

Antibody (IgG)	**EC$_{50}$ [nM]**		**x-fold different EC$_{50}$ on OVCAR-3 vs. NCI-H226**
	NCI-H226	**OVCAR-3**	
MOR06626	0.44	9.68	22.0
MOR06638	0.19	4.19	22.1
MOR07265	1.11	1.06	1.0
MOR06631	2.02	0.96	0.5
MOR 06669	0.41	1.40	3.4
MOR07111	0.80	1.35	1.7
MOR06640	0.63	0.53	0.8
MOR06642	0.58	0.54	0.9
MOR06657	0.14	0.53	14
MOR06643	0.23	1.86	8.1

EXAMPLE 5: Binding to mesothelin in the presence of cancer antigen 125 (CA125)

Figure 3 shows that cancer antigen 125 (CA125) binds to mesothelin which is in turn bound to a subset of mesothelin antibodies including MOR06640 and MF-T, while other antibodies, such as MF-226, compete with CA125 for mesothelin binding. Data shown are relative light units (RLU) detected by SECTOR Light Imager (Meso Scale Discovery). Plates were coated with the mesothelin antibody depicted at 15 µg/ml, and washed and blocked after each subsequent incubation. Mesothelin was added at the concentrations indicated and titrated down from 10 µg/ml to 0.08 µg/ml. Plates were subsequently incubated with CA125 (Lee Biosolutions, Cat # 150-11, 50 000 U/ml diluted 1:300). Detection was performed with a mouse anti-CA125 antibody and an MSD Sulfo tag (Meso Scale Discovery) labelled anti mouse Fab antibody. An unspecific human control antibody was coated as a control. Further controls included the full assay setup with mesothelin at the highest concentrations tested (10 µg/ml) and omission of either CA125 or the mouse anti-CA125 antibody, or full assay setup without mesothelin. This example shows that antibodies, antigen-binding antibody fragments, or variants thereof, which invariantly bind mesothelin can be identified by in vitro testing.

EXAMPLE 6: Internalization

Relative internalization of anti-mesothelin antibodies on CHO-A9 cells is shown in Figure 4. Briefly, CHO-A9 cells expressing mesothelin protein were labeled with ^{125}I-anti-mesothelin antibodies for 2 hours at 0 °C, to bind the labeled antibody to cell surface mesothelin. The low temperature inhibited internalization. Unbound antibody was washed away using cold buffer and individual aliquots of labeled cells were placed in a 37° C water bath to initiate internalization. A time course was run in which triplicate samples were collected at: 0, 15, 30, 45, 60, 75 and 90 minutes. At each time point, samples were centrifuged to pellet cells and the supernatant was collected, which contained antibody that had dissociated from the cells. The cell pellet was then briefly washed with acid (PBS + 1% glucose pH1.0) in order to remove cell surface-bound labeled antibody, and then pelleted by centrifugation. The supernatant, containing antibody eluted from the cell surface was collected. The pellet fraction, containing internalized antibody, was collected separately. After completion of the time course, the radioactivity in each of the fractions from all time points was determined using a gamma counter. The percentage of total counts present in the fractions represents the percentage of the antibody that was dissociated, bound to the cell surface or internalized at each time point. In experiments in which a second antibody (goat anti-human IgG Fc, or goat anti-mouse IgG Fc, respectively) was added along with the primary labeled antibody to crosslink and thus stabilize the cell surface-bound antibody, much lower antibody dissociation rates were observed compared to cells only treated with the primary antibody. Correspondingly higher internalization levels were also achieved for all antibodies tested with the second antibody. In the absence of a second antibody, the relatively rapid off-rates of the antibodies, as seen in the Biacore studies, reduced the antibodies' residency time on the cell surface such that internalization was significantly reduced. Therefore, four candidate antibodies were chosen for affinity maturation to obtain progenitor antibodies with reduced dissociation rates.

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Table 7: Sequences of the antibodies

Antibody	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3	VH Protein	VL Protein	VH Nucleotide	VL Nucleotide
	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID
MF-J	1	31	67	99	129	160	198	241	284	327
MOR 07265	1	32	67	99	129	161	199	242	285	328
MOR 06631	1	32	67	99	129	160	200	243	286	329
MOR 06669	1	33	67	99	129	160	201	244	287	330
MOR 07111	1	31	67	99	129	162	202	245	288	331
MOR 06640	1	31	67	99	129	161	203	246	289	332
MOR 06642	1	31	67	99	129	163	204	247	290	333
MOR 06643	2	34	68	100	130	164	205	248	291	334
MF-226	3	35	69	101	131	165	206	249	292	335
MOR 06626	3	36	69	101	131	165	207	250	293	336
MOR 06635	1	37	67	99	129	160	208	251	294	337
MOR 06638	3	35	69	101	131	166	209	252	295	338

Antibody	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3	VH Protein	VL Protein	VH Nucleotide	VL Nucleotide
	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID
MF-A	4	38	70	102	132	167	210	253	296	339
MOR 06657	4	38	70	102	132	168	211	254	297	340
MF-T	5	39	71	103	133	169	212	255	298	341
MF-L	2	34	68	100	130	170	213	256	299	342
MF-1	6	40	72	104	134	171	214	257	300	343
MF-5	7	41	73	105	135	172	215	258	301	344
MF-8	8	42	74	106	136	173	216	259	302	345
MF-24	9	43	75	107	137	174	217	260	303	346
MF-25	10	44	76	108	138	175	218	261	304	347
MF-27	1	45	77	109	139	176	219	262	305	348
MF-73	11	46	78	110	140	177	220	263	306	349
MF-78	12	47	79	111	141	178	221	264	307	350
MF-84	13	48	80	112	142	179	222	265	308	351
MF-101	14	49	81	113	143	180	223	266	309	352
MF-230	15	50	82	114	144	181	224	267	310	353

Antibody	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3	VH Protein	VL Protein	VH Nucleotide	VL Nucleotide
	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID	SEQ ID
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MF-423	18	54	86	118	148	185	228	271	314	357
MF-427	19	55	87	119	149	186	229	272	315	358
MF-428	20	56	88	120	150	187	230	273	316	359
MF-C	21	57	89	121	151	188	231	274	317	360
MF-I	22	58	90	102	152	189	232	275	318	361
MF-M	23	59	91	122	153	190	233	276	319	362
MF-P	24	60	92	123	154	191	234	277	320	363
MF-Q	25	61	93	124	155	192	235	278	321	364
MF-S	26	62	94	125	156	193	236	279	322	365
MF-U	27	63	95	126	157	194	237	280	323	366
MF-V	28	64	96	127	158	195	238	281	324	367
MF-W	29	65	97	102	159	196	239	282	325	368
MF-Y	30	66	98	128	155	197	240	283	326	369

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or "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 integers or steps.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as, an acknowledgement or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

The claims defining the invention are as follows:

1. An isolated human or humanized antibody or functional fragment thereof comprising an antigen-binding region that is specific for Mesothelin (SEQ ID NO:370), wherein said antibody or functional fragment thereof exhibits invariant binding of Mesothelin and has an antigen-binding region which comprises a CDR region as depicted in Table 7.

2. An antibody or fragment according to claim 1, which comprises a CDR region selected from the group consisting of the sequences set forth in SEQ ID NO: 5, 39, 71, 103, 133 and/or 169.

3. An antibody or fragment according to claim 1 or 2, which comprises a variable heavy chain or a variable light chain amino acid sequence selected from the group consisting of the sequences depicted in Table 7.

4. An antibody or fragment according to claim 1 or 2, which comprises a variable heavy chain amino acid sequence as set forth in SEQ ID NO: 212.

5. An antibody or fragment according to claim 1 or 2, which comprises a variable light chain amino acid sequence as set forth in SEQ ID NO: 372.

6. An antibody to according to any one of claims 1 to 5, which is an IgG antibody.

7. An isolated functional fragment of an antibody according to any one of claims 1 to 6, which is a Fab or scFv antibody fragment.

8. A human antibody or fragment according to any one of claims 1 to 7, wherein the human antibody or fragment is a synthetic human antibody or fragment.

9. An isolated nucleic acid sequence that encodes an antigen-binding region of a human antibody according to any one of claims 1 to 8 or functional fragment thereof.

10. An isolated nucleic acid sequence encoding a variable heavy chain of an isolated antibody or functional fragment thereof, which comprises:

(i) a sequence selected from the group consisting of sequences as depicted in Table 7 or

(ii) a nucleic acid sequence that hybridizes under high stringency conditions to the complementary strand of sequences as depicted in Table 7, wherein said antibody or functional fragment thereof is specific for an epitope of Mesothelin.

11. A vector comprising a nucleic acid sequence according to claim 9 or 10.

12. An isolated cell comprising a vector according to claim 11.

13. An isolated cell according to claim 12, wherein said cell is a bacterial or mammalian cell.

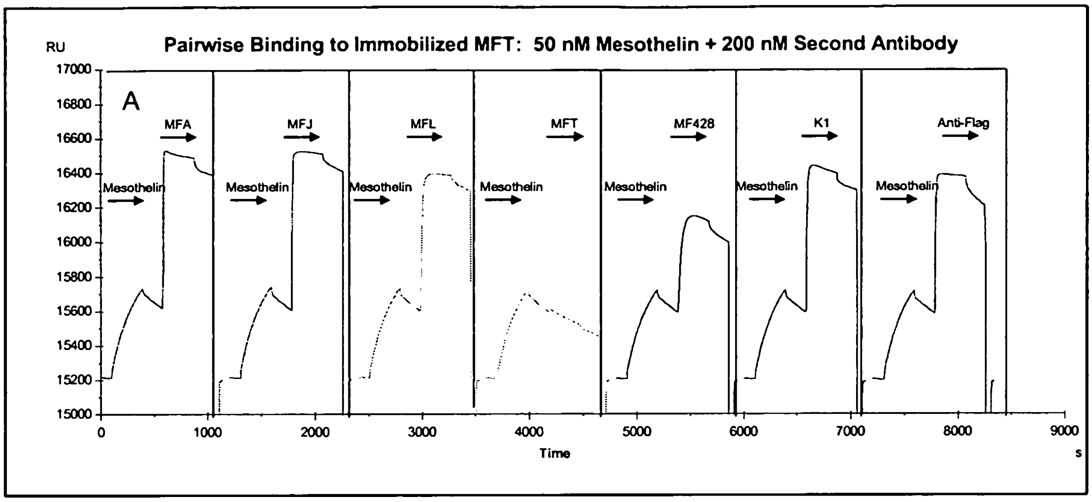
14. A pharmaceutical composition comprising an antibody or functional fragment according to any one of claims 1 to 8, and a pharmaceutically acceptable carrier or excipient.

15. An antibody or fragment according to any one of claims 1 to 8 for use as a pharmaceutical in the treatment of a disorder or condition associated with the undesired presence of Mesothelin.

16. A method for treating a disorder or condition associated with the undesired presence of Mesothelin, the method comprising administering to a subject in need thereof an effective amount of an antibody or fragment according to any one of claims 1 to 8 or a pharmaceutical composition according to claim 14.

17. An isolated human or humanized antibody or functional fragment thereof as claimed in claim 1 and uses thereof substantially as herein described with reference to the examples.

Figure 1 / 4



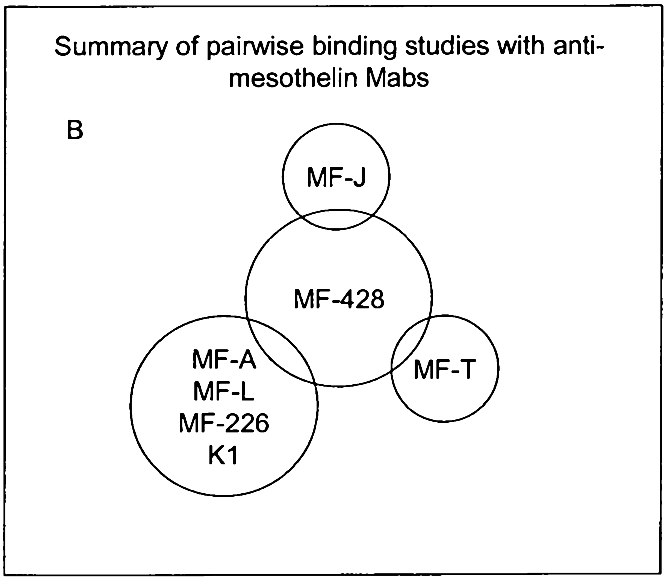


Figure 1

Figure 2 / 4

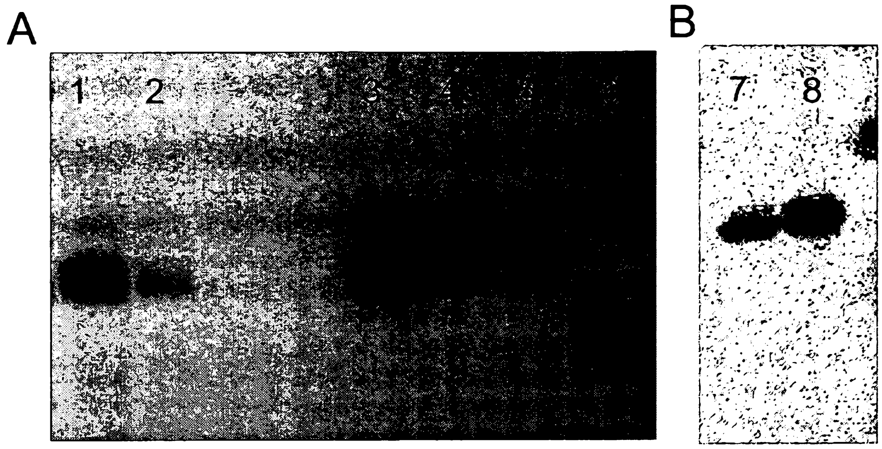


Figure 2

Figure 3 / 4

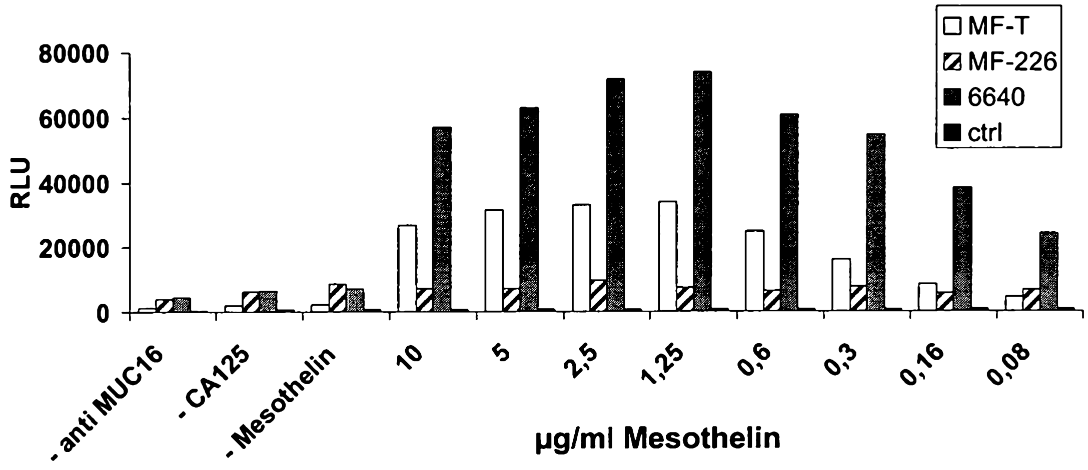


Figure 3

Figure 4 / 4

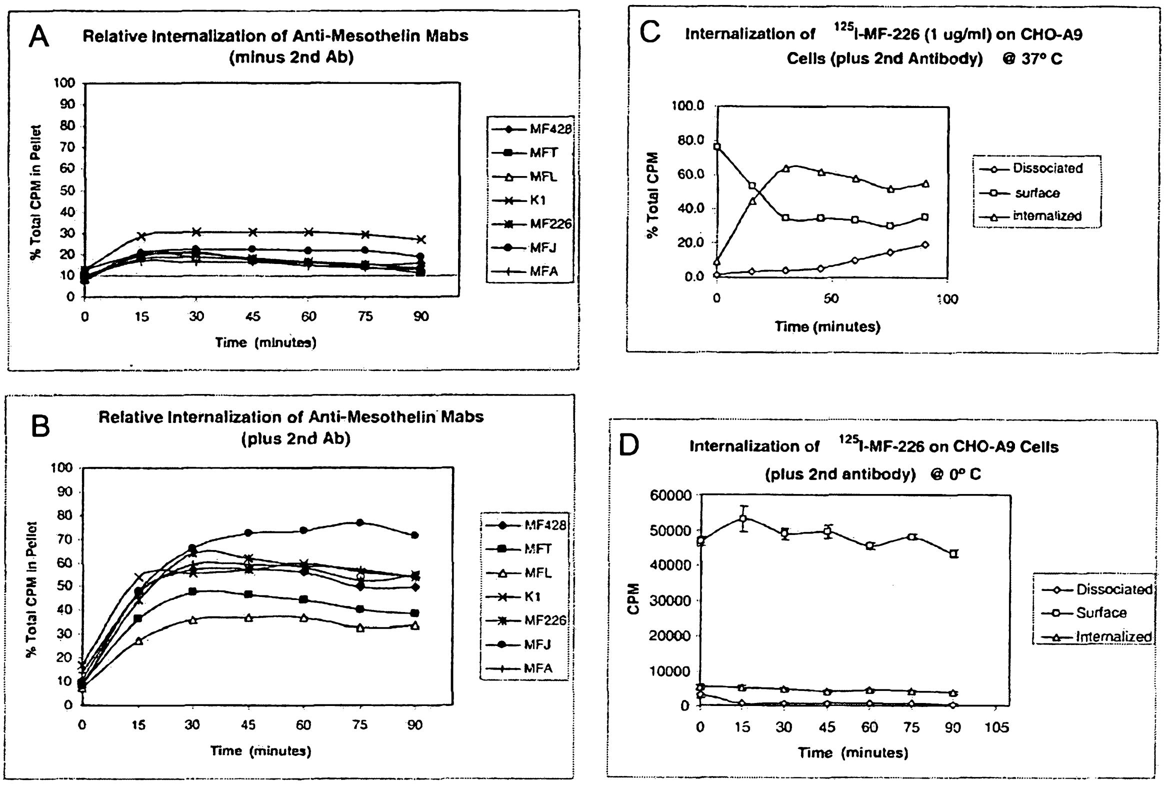


Figure 4

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Trp Val Ser Thr Ile Ser Ser Asn Gly Ser Tyr Thr Tyr Tyr Ala Asp
1 5 10 15

Ser Val Lys Gly
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<210> 64
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<400> 64

Trp Met Gly Asn Ile Ile Pro Ala Phe Gly Tyr Ala Asn Tyr Ala Gln
1 5 10 15

Lys Phe Gln Gly
20

<210> 65
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<400> 65

Trp Val Ser Asn Ile Ser Gly Asn Gly Ser Ser Thr Tyr Tyr Ala Asp
1 5 10 15

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Ser Val Lys Gly
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<400>  66

Trp Val Ser Tyr Ile Arg Ser Gly Ser Ser Asp Thr Tyr Tyr Ala Asp
1               5                   10                  15


Ser Val Lys Gly
            20


<210>  67
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<400>  67

Tyr Gly His Gly Met Tyr Gly Gly Ala Leu Asp Val
1               5                   10



<210>  68
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<400>  68

Ile Asn Tyr Ile Tyr Lys Gly Val His Phe Asp Tyr
1               5                   10


<210>  69
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<400>  69

Trp His His Gly Thr Trp Ile Phe Asp Tyr
1               5                   10


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<400>  70
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Arg Thr Ser Met Asp Tyr
1               5


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<400>  71

Gly Gln Leu Tyr Gly Gly Thr Tyr Met Asp Gly
1               5                   10


<210>  72
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<400>  72

Pro Met Asp Asn Leu Pro Asp Ile
1               5


<210>  73
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<400>  73

Tyr Leu Tyr Tyr Phe Asp Val
1               5


<210>  74
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<400>  74

Thr Lys Phe Phe Ala Asn
1               5



<210>  75
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<400>  75

Gly Ile Tyr Phe Ala Phe
1               5


<210>  76
<211>  11
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<212> PRT
<213> Homo sapiens

<400> 76

Lys His Lys Tyr Arg Ile Gly Ser Met Asp Val
1 5 10

<210> 77
<211> 8
<212> PRT
<213> Homo sapiens

<400> 77

Tyr Met Lys Gly Gly Tyr Asp Tyr
1 5

<210> 78
<211> 8
<212> PRT
<213> Homo sapiens

<400> 78

Met Gln Gly Phe Gln Leu Asp Tyr
1 5

<210> 79
<211> 6
<212> PRT
<213> Homo sapiens

<400> 79

Thr Tyr Thr Phe Ala Val
1 5

<210> 80
<211> 7
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<213> Homo sapiens

<400> 80

Lys Trp Leu Phe Tyr Asp Tyr
1 5

<210> 81
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<212> PRT
<213> Homo sapiens

<400> 81

Gly Trp Gln Asp Phe
1 5

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<210>  82
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<213>  Homo sapiens

<400>  82

Tyr Tyr Ser Asp His Phe Gly Leu Tyr Pro Tyr Phe Asp Tyr
1               5                   10


<210>  83
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<213>  Homo sapiens

<400>  83

Gly Asp Gly Gly Pro Ser Ser Gln Gly Asn Tyr Phe Gly Trp Val Tyr
1               5                   10                  15


Asp Val



<210>  84
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<400>  84

Asn Tyr Ser Gly Pro Met Tyr Tyr Tyr Gly Asp Val
1               5                   10


<210>  85
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<213>  Homo sapiens

<400>  85

Gly Phe His Gly Ser Thr Met Tyr Phe Asp Val
1               5                   10


<210>  86
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<213>  Homo sapiens

<400>  86

Gly Leu Gly Gly Ser Phe Asp Val
1               5


<210>  87
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<400>  87

Gly Trp Ile Thr Gly Trp Arg Ile Phe Asp Tyr
1               5                   10


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<213>  Homo sapiens

<400>  88

Lys Met Tyr Trp Trp Ser Asp Gly Phe Asp Tyr
1               5                   10


<210>  89
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<212>  PRT
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<400>  89

Tyr Pro Gly Pro Thr Gly His Val Phe Phe Asp Ile
1               5                   10


<210>  90
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<400>  90

Tyr Pro Gly Pro Thr Gly His Val Phe Phe Asp Ile
1               5                   10


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<400>  91

Glu Met Arg Leu Ala Tyr
1               5


<210>  92
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<212>  PRT
<213>  Homo sapiens

<400>  92

Gly Tyr His Gln Gly Leu Tyr Gly Asn His Met Phe Asp Val
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1               5                   10


<210>  93
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<400>  93

Ile Gln Gly Trp Asn Tyr Asp Val
1               5


<210>  94
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<213>  Homo sapiens

<400>  94

Ser Arg Phe Gly Tyr Phe Asp Val
1               5


<210>  95
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<212>  PRT
<213>  Homo sapiens

<400>  95

Phe Val Ala Arg Leu Asn Val Phe Asp Tyr
1               5                   10


<210>  96
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<400>  96

Lys Phe Thr Phe Asp Val
1               5


<210>  97
<211>  10
<212>  PRT
<213>  Homo sapiens

<400>  97

Leu Ile Ala Thr Leu Gly Thr Phe Asp Tyr
1               5                   10


<210>  98
<211>  11
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<400>  98

Thr Ala Pro Ala Gly His Gly Val Phe Ala Asn
1               5                   10


<210>  99
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<213>  Homo sapiens

<400>  99

Arg Ala Ser Gln Ser Val Arg Ser Ser Arg Leu Ala
1               5                   10


<210>  100
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<213>  Homo sapiens

<400>  100

Arg Ala Ser Gln Ile Val Ser Gly Tyr Leu Ala
1               5                   10


<210>  101
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<213>  Homo sapiens

<400>  101

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Tyr Val Ser
1               5                   10


<210>  102
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<213>  Homo sapiens

<400>  102

Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
1               5                   10


<210>  103
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<212>  PRT
<213>  Homo sapiens

<400>  103

Thr Gly Thr Ser Ser Asp Ile Gly Gly Tyr Asn Ser Val Ser
1               5                   10
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<213>  Homo sapiens

<400>  104

Arg Ala Ser Gln Asn Ile Gly Ser Tyr Leu Asn
1               5                   10


<210>  105
<211>  14
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<213>  Homo sapiens

<400>  105

Thr Gly Thr Ser Ser Asp Val Gly Ala Ser Asp Thr Val Thr
1               5                   10


<210>  106
<211>  16
<212>  PRT
<213>  Homo sapiens

<400>  106

Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr Thr Tyr Leu Ser
1               5                   10                  15


<210>  107
<211>  13
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<213>  Homo sapiens

<400>  107

Ser Gly Ser Ser Ser Asn Ile Gly Pro Asn Tyr Val Ser
1               5                   10


<210>  108
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<213>  Homo sapiens

<400>  108

Arg Ala Ser Gln Ser Leu Thr Ser Asn Gln Leu Ala
1               5                   10


<210>  109
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<213>  Homo sapiens

<400>  109
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Thr Gly Thr Ser Ser Asp Val Gly Gly Asn Asn Phe Val Ser
1               5                   10


<210>  110
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<400>  110

Arg Ala Ser Gln Thr Ile Ser Ser Ala Leu Ala
1               5                   10


<210>  111
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<400>  111

Thr Gly Thr Ser Ser Asp Val Gly Asn Phe Asn Tyr Val Asn
1               5                   10


<210>  112
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<400>  112

Arg Ala Ser Gln Ser Val Thr Ser Asn Tyr Leu Ala
1               5                   10


<210>  113
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<213>  Homo sapiens

<400>  113

Arg Ala Ser Gln Ser Ile Asn Arg Ser Leu Thr
1               5                   10


<210>  114
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<213>  Homo sapiens

<400>  114

Thr Gly Thr Ser Ser Asp Ile Gly Gly Phe Asn Tyr Val Ser
1               5                   10


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<213>  Homo sapiens

<400>  115

Ser Gly Asp Asn Ile Pro Asn Phe Tyr Val His
1               5                   10


<210>  116
<211>  14
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<213>  Homo sapiens

<400>  116

Thr Gly Thr Ser Ser Asp Ile Gly Arg Tyr His Tyr Val Ser
1               5                   10


<210>  117
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<213>  Homo sapiens

<400>  117

Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn Ser Val Asn
1               5                   10


<210>  118
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<213>  Homo sapiens

<400>  118

Thr Gly Thr Ser Ser Asp Val Gly Asp Tyr Asn Tyr Val Ser
1               5                   10


<210>  119
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<213>  Homo sapiens

<400>  119

Thr Gly Thr Ser Ser Asp Val Gly Asp Tyr Asn Tyr Val Ser
1               5                   10


<210>  120
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<400>  120

Ser Gly Asp Asn Leu Arg Ser Lys Tyr Ala His
1               5                   10
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<400>  121

Ser Gly Asp Asn Ile Gly Ser Lys Val Ala Thr
1               5                   10


<210>  122
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<400>  122

Thr Gly Thr Ser Ser Asp Ile Gly His Phe Asn Tyr Val Ser
1               5                   10


<210>  123
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<213>  Homo sapiens

<400>  123

Ser Gly Ser Ser Ser Asn Ile Gly Ser His Thr Val Asn
1               5                   10


<210>  124
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<213>  Homo sapiens

<400>  124

Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn Arg Val Ser
1               5                   10


<210>  125
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<400>  125

Thr Gly Thr Ser Ser Asp Ile Gly Thr Tyr Asn His Val Ser
1               5                   10


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<400>  126
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Thr Gly Ser Ser Ser Asn Ile Gly Ile Gly Tyr Asp Val Asn
1               5                   10


<210>  127
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<400>  127

Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Ser Tyr Val Ser
1               5                   10


<210>  128
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<213>  Homo sapiens

<400>  128

Ser Gly Ser Ser Ser Asn Ile Gly Asn Tyr Arg Val Ser
1               5                   10


<210>  129
<211>  11
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<213>  Homo sapiens

<400>  129

Leu Leu Ile Tyr Gly Ala Ser Lys Arg Ala Thr
1               5                   10


<210>  130
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<213>  Homo sapiens

<400>  130

Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr
1               5                   10


<210>  131
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<213>  Homo sapiens

<400>  131

Leu Leu Ile Tyr Asn Asp Asn Gln Arg Pro Ser
1               5                   10


<210>  132
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<400> 132

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Leu Met Ile Tyr Ser Val Ser Lys Arg Pro Ser
1               5                   10
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<210> 133
<211> 11
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<400> 133

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Leu Met Ile Tyr Gly Val Asn Asn Arg Pro Ser
1               5                   10
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<210> 134
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<400> 134

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Leu Leu Ile Tyr Asn Ser Ser Thr Leu Gln Ser
1               5                   10
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<210> 135
<211> 11
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<400> 135

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Leu Met Ile Tyr Ala Val Asn Lys Arg Pro Ser
1               5                   10
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<210> 136
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<400> 136

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Leu Leu Ile Tyr Leu Gly Ser Lys Arg Ala Ser
1               5                   10
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<210> 137
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<400> 137

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Leu Leu Ile His Gly Asn Ala Asn Arg Pro Ser
1               5                   10
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<400>  138

Leu Leu Ile Tyr Asp Ser Ser Asn Arg Ala Thr
1               5                   10


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<213>  Homo sapiens

<400>  139

Leu Met Ile Tyr Tyr Gly Asp Ser Arg Pro Ser
1               5                   10


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<400>  140

Leu Leu Ile Tyr Gly Ala Ser Thr Leu Gln Ser
1               5                   10


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<400>  141

Leu Met Ile Tyr Ser Val Ser Ser Arg Pro Ser
1               5                   10


<210>  142
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<400>  142

Leu Leu Ile Tyr Gly Ser Ser Ser Arg Ala Thr
1               5                   10


<210>  143
<211>  11
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<213>  Homo sapiens
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<400> 143

Leu Leu Ile Tyr Ala Ala Ser Asn Leu Gln Ser
1 5 10

<210> 144
<211> 11
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<400> 144

Leu Met Ile Tyr Asp Val Ser Asn Arg Pro Ser
1 5 10

<210> 145
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<400> 145

Leu Val Ile Tyr Glu Asp Ser Asp Arg Pro Ser
1 5 10

<210> 146
<211> 11
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<400> 146

Val Met Ile Tyr Ser Val Ser Lys Arg Pro Ser
1 5 10

<210> 147
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<400> 147

Leu Leu Ile Tyr Asn Asn Gln Arg Pro Ser
1 5 10

<210> 148
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Leu Met Ile Tyr Arg Val Asp Asn Arg Pro Ser
1 5 10

<210> 149

<211> 11
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<400> 149

Leu Leu Ile Tyr Ser Asn Ser Gln Arg Pro Ser
1 5 10

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Leu Val Ile Tyr Ser Lys Asp Asn Arg Pro Ser
1 5 10

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<400> 151

Leu Val Ile Tyr Tyr Asp Asn Asp Arg Pro Ser
1 5 10

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<400> 152

Leu Met Ile Tyr Ser Val Asn Asn Arg Pro Ser
1 5 10

<210> 153
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<400> 153

Leu Met Ile Tyr Ser Val Ile Ser Arg Pro Ser
1 5 10

<210> 154
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<400> 154

Leu Leu Ile Tyr Asp Val Asn Lys Arg Pro Ser

1   5   10

<210> 155
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Leu Leu Ile Tyr Gly Asn Asn Lys Arg Pro Ser
1   5   10

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Leu Met Ile Tyr Asn Val Asn Lys Arg Pro Ser
1   5   10

<210> 157
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<400> 157

Leu Leu Ile Tyr Lys Asn Thr Asn Arg Pro Ser
1   5   10

<210> 158
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<400> 158

Leu Met Ile Tyr Asn Val Asn Asn Arg Pro Ser
1   5   10

<210> 159
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<400> 159

Val Met Ile Tyr Gly Val Thr Lys Arg Pro Ser
1   5   10

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Gln Gln Tyr Tyr Asp Phe Pro Pro
1               5


<210>  161
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<400>  161

Gln Gln Tyr Ser His Asp Pro Ser Gly
1               5


<210>  162
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<400>  162

Gln Gln Phe Tyr Ser Lys Pro Ile
1               5


<210>  163
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<400>  163

Gln Gln Tyr Ser Gln Asp Pro Ser Ser
1               5


<210>  164
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<400>  164

Gln Gln Trp Ser Leu Arg Ser Pro Phe
1               5


<210>  165
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<400>  165

Ser Thr Tyr Asp Arg Arg Thr Phe Ser
1               5
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<400>  166

Ser Ser Trp Asp Arg Ala Asp Gly Ser Tyr
1               5                   10


<210>  167
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<400>  167

Gly Ala Trp Ala His Met Ser Leu Gly Lys
1               5                   10


<210>  168
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<400>  168

Ala Thr Trp Asp His Ser Gln Met Gly Lys
1               5                   10


<210>  169
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<400>  169

Ser Ser Tyr Asp Ile Glu Ser Ala Thr Pro
1               5                   10


<210>  170
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<400>  170

Gln Gln Tyr Tyr Asn Phe Ser Phe
1               5


<210>  171

<211>  8
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<400>  171
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Gln Gln Arg Ser Asn Met Pro Ile
1               5


<210>  172
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<400>  172

Ala Ser Arg Asp Ser Ser Ser Met
1               5


<210>  173
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<400>  173

Gln Gln Tyr Tyr Asp Ser Ser Ser
1               5


<210>  174
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<400>  174

Gln Ser Tyr Asp Phe Phe Thr Asn Ser Ser
1               5                   10


<210>  175
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<400>  175

Gln Gln Tyr Gly Ser Phe Pro Ala
1               5


<210>  176
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<400>  176

Gln Ser Trp Asp Ala Pro Met Gly Met Trp
1               5                   10


<210>  177
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<212> PRT
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<400> 177

Gln Gln Tyr Tyr Ser Tyr Ser Val
1   5

<210> 178
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<400> 178

Gly Ala Tyr Thr Thr Asp Thr Leu Ser
1   5

<210> 179
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<400> 179

Gln Gln Tyr Ser Asp Ile Pro Ala
1   5

<210> 180
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<400> 180

Leu Gln Val Tyr Asn Leu Pro Leu
1   5

<210> 181
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<213> Homo sapiens

<400> 181

Ser Thr Tyr Asp Asp Asp Gln Gln Asp Ala
1   5   10

<210> 182
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<213> Homo sapiens

<400> 182

Gln Ser Tyr Asp Lys Pro Thr Phe Ser Gly
1   5   10

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<211>  10
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<213>  Homo sapiens

<400>  183

Ser Ala Tyr Asp Thr Asn Asn Tyr Leu Ser
1               5                   10


<210>  184
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<400>  184

Gln Ala Tyr Ala Ser Asn Ile
1               5


<210>  185
<211>  8
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<400>  185

Gln Ser Trp Val Gly Pro Ser Thr
1               5


<210>  186
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<212>  PRT
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<400>  186

Gln Ser Tyr Asp His Asn Ser Tyr Thr
1               5


<210>  187
<211>  8
<212>  PRT
<213>  Homo sapiens

<400>  187

Ser Ser Trp Ala His Asp His Lys
1               5


<210>  188
<211>  10
<212>  PRT
<213>  Homo sapiens
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<400> 188

Gln Ser Tyr Asp Gly Gln Met Ser Thr Ser
1   5   10

<210> 189
<211> 10
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<400> 189

Ser Thr Tyr Asp His Thr Ser Ser Gly Phe
1   5   10

<210> 190
<211> 8
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<400> 190

Ala Ser Phe Thr Phe Pro Ser Leu
1   5

<210> 191
<211> 10
<212> PRT
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<400> 191

Ala Ser Trp Asp Ser Val Gln Val Ser Pro
1   5   10

<210> 192
<211> 9
<212> PRT
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<400> 192

Ser Ala Trp Asp Leu Leu Glu Val Tyr
1   5

<210> 193
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<212> PRT
<213> Homo sapiens

<400> 193

Ser Ala Tyr Ala Pro Ser Ala Val
1   5

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<210>  194
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<212>  PRT
<213>  Homo sapiens

<400>  194

Ser Ser Tyr Asp Ser Phe His His Gly Ile
1               5                   10


<210>  195
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<213>  Homo sapiens

<400>  195

Ser Ser Tyr Asp Tyr Val Ser Ser Asp Thr
1               5                   10


<210>  196
<211>  10
<212>  PRT
<213>  Homo sapiens

<400>  196

Gln Thr Tyr Asp Glu His Gly Phe His Ile
1               5                   10


<210>  197
<211>  10
<212>  PRT
<213>  Homo sapiens

<400>  197

Ser Thr Tyr Thr Gly Leu Pro Phe Thr Thr
1               5                   10


<210>  198
<211>  121
<212>  PRT
<213>  Homo sapiens

<400>  198

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


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


Trp Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
        35                  40                  45
```

```
Gly Val Ile Met Pro Ser Asp Ser Tyr Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60


Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95


Ala Arg Tyr Gly His Gly Met Tyr Gly Gly Ala Leu Asp Val Trp Gly
            100                 105                 110


Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  199
<211>  121
<212>  PRT
<213>  Homo sapiens

<400>  199

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


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


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


Gly Phe Ile Trp Pro Val Asp Ser Trp Thr Gln Tyr Ser Pro Ser Phe
    50                  55                  60


Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95


Ala Arg Tyr Gly His Gly Met Tyr Gly Gly Ala Leu Asp Val Trp Gly
            100                 105                 110


Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  200
<211>  121
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<212>  PRT
<213>  Homo sapiens

<400>  200

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


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


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


Gly Phe Ile Trp Pro Val Asp Ser Trp Thr Gln Tyr Ser Pro Ser Phe
    50                  55                  60


Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95



Ala Arg Tyr Gly His Gly Met Tyr Gly Gly Ala Leu Asp Val Trp Gly
            100                 105                 110


Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  201
<211>  121
<212>  PRT
<213>  Homo sapiens

<400>  201

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


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


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


Gly Ile Ile Trp Pro Ile Asp Ser Phe Thr Gln Tyr Ser Pro Ser Phe
    50                  55                  60


Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
```

```
65                  70                  75                  80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Tyr Gly His Gly Met Tyr Gly Gly Ala Leu Asp Val Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  202
<211>  121
<212>  PRT
<213>  Homo sapiens

<400>  202

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

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

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

Gly Val Ile Met Pro Ser Asp Ser Tyr Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Tyr Gly His Gly Met Tyr Gly Gly Ala Leu Asp Val Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  203
<211>  121
<212>  PRT
<213>  Homo sapiens

<400>  203

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

1 5 10 15

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

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

Gly Val Ile Met Pro Ser Asp Ser Tyr Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Tyr Gly His Gly Met Tyr Gly Gly Ala Leu Asp Val Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 204
<211> 121
<212> PRT
<213> Homo sapiens

<400> 204

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

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

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

Gly Val Ile Met Pro Ser Asp Ser Tyr Thr Arg Tyr Ser Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

```
Ala Arg Tyr Gly His Gly Met Tyr Gly Gly Ala Leu Asp Val Trp Gly
            100                 105                 110


Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  205
<211>  121
<212>  PRT
<213>  Homo sapiens

<400>  205

Gln 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 Ser Asp Tyr
            20                  25                  30


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


Ser Ala Ile Met Tyr Asp Ser Ser Ser Thr Phe Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr 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 Ile Asn Tyr Ile Tyr Lys Gly Val His Phe Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  206
<211>  119
<212>  PRT
<213>  Homo sapiens

<400>  206

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


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

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


Gly Ile Ile Asn Pro His Gly Gly Asp Thr Lys Tyr Ala Gln Lys Phe
    50                  55                  60


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


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


Ala Arg Trp His His Gly Thr Trp Ile Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Leu Val Thr Val Ser Ser
        115


<210>  207
<211>  119
<212>  PRT
<213>  Homo sapiens

<400>  207

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


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


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


Gly Ile Ile Asn Pro Thr Lys Gly Trp Thr Leu Tyr Ala Gln Lys Phe
    50                  55                  60


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


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


Ala Arg Trp His His Gly Thr Trp Ile Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Leu Val Thr Val Ser Ser
        115
```

```
<210>  208
<211>  121
<212>  PRT
<213>  Homo sapiens

<400>  208

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


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


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


Gly Phe Ile Trp Pro Ser Asp Ser Trp Thr Ser Tyr Ser Pro Ser Phe
    50                  55                  60


Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95


Ala Arg Tyr Gly His Gly Met Tyr Gly Gly Ala Leu Asp Val Trp Gly
            100                 105                 110


Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  209
<211>  119
<212>  PRT
<213>  Homo sapiens

<400>  209

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


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


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


Gly Ile Ile Asn Pro His Gly Gly Asp Thr Lys Tyr Ala Gln Lys Phe
    50                  55                  60
```

```
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Trp His His Gly Thr Trp Ile Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115


<210>  210
<211>  115
<212>  PRT
<213>  Homo sapiens

<400>  210

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

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

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

Gly Gly Ile Ile Pro Lys Phe Gly Ser Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Arg Thr Ser Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser
        115


<210>  211
<211>  115
<212>  PRT
<213>  Homo sapiens

<400>  211
```

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

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

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

Gly Gly Ile Ile Pro Lys Phe Gly Ser Ala Asn Tyr Ala Gln Lys Phe
    50   55   60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65   70   75   80

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

Ala Arg Arg Thr Ser Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100   105   110

Val Ser Ser
        115

<210> 212
<211> 120
<212> PRT
<213> Homo sapiens

<400> 212

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

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

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

Gly Ile Ile Asp Pro Gly Asp Ser Arg Thr Arg Tyr Ser Pro Ser Phe
    50   55   60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65   70   75   80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85   90   95

```
Ala Arg Gly Gln Leu Tyr Gly Gly Thr Tyr Met Asp Gly Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  213
<211>  121
<212>  PRT
<213>  Homo sapiens

<400>  213

Gln 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 Ser Asp Tyr
            20                  25                  30


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


Ser Ala Ile Met Tyr Asp Ser Ser Ser Thr Phe Tyr Ala Asp Ser Val
    50                  55                  60


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr 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 Ile Asn Tyr Ile Tyr Lys Gly Val His Phe Asp Tyr Trp Gly
            100                 105                 110


Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  214
<211>  116
<212>  PRT
<213>  Homo sapiens

<400>  214

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


Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Asn Tyr
            20                  25                  30
```

```
Tyr Trp Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45


Gly Glu Ile Tyr His Ser Gly Gly Thr Tyr Tyr Asn Pro Ser Leu Lys
    50                  55                  60


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


Lys Leu Ser Ser Val Thr Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95


Arg Pro Met Asp Asn Leu Pro Asp Ile Trp Gly Gln Gly Thr Leu Val
            100                 105                 110


Thr Val Ser Ser
        115


<210>  215
<211>  116
<212>  PRT
<213>  Homo sapiens

<400>  215

Gln 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 Ser Ser Tyr
            20                  25                  30


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


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


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr 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 Tyr Leu Tyr Tyr Phe Asp Val Trp Gly Gln Gly Thr Leu Val
            100                 105                 110


Thr Val Ser Ser
```

```
        115


<210>  216
<211>  115
<212>  PRT
<213>  Homo sapiens

<400>  216

Gln 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 Ser Asn Ser
            20                  25                  30


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


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


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr 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 Thr Lys Phe Phe Ala Asn Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110


Val Ser Ser
        115


<210>  217
<211>  115
<212>  PRT
<213>  Homo sapiens

<400>  217

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


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


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


Gly Arg Ile Ile Pro Asn Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
```

```
    50                  55                  60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Gly Ile Tyr Phe Ala Phe Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ser
        115


<210>  218
<211>  120
<212>  PRT
<213>  Homo sapiens

<400>  218

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

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

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

Gly Ile Ile Asn Pro Gln Asn Gly Gly Thr Asn Tyr Ala Gln Lys Phe
    50                  55                  60

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

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

Ala Arg Lys His Lys Tyr Arg Ile Gly Ser Met Asp Val Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  219
<211>  117
<212>  PRT
<213>  Homo sapiens
```

<400> 219

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


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


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


Gly Ile Ile Asp Pro Arg Glu Ser Phe Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60


Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80


Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95


Ala Arg Tyr Met Lys Gly Gly Tyr Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ser
        115
```

<210> 220
<211> 120
<212> PRT
<213> Homo sapiens

<400> 220

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


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


Ser Ala Ala Trp Gly Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
        35                  40                  45


Trp Leu Gly Arg Ile Gly Tyr Arg Ser Lys Trp Met Asn Asp Tyr Ala
    50                  55                  60


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

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Met Gln Gly Phe Gln Leu Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 221
<211> 115
<212> PRT
<213> Homo sapiens

<400> 221

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

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

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

Gly Gly Ile Val Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Thr Tyr Thr Phe Ala Val Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 222
<211> 116
<212> PRT
<213> Homo sapiens

<400> 222

Gln 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 Ser Ser Tyr
20 25 30

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

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

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr 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 Lys Trp Leu Phe Tyr Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 223
<211> 114
<212> PRT
<213> Homo sapiens

<400> 223

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

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

Asp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Tyr Ile Ser Pro Tyr Ser Gly Asp Thr Asn Tyr Ala Gln Lys Phe
50 55 60

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

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

Ala Arg Gly Trp Gln Asp Phe Trp Gly Gln Gly Thr Leu Val Thr Val
100 105 110

```
Ser Ser


<210>  224
<211>  126
<212>  PRT
<213>  Homo sapiens

<400>  224

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


Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
            20                  25                  30


Ser Ala Ala Trp Gly Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
        35                  40                  45


Trp Leu Gly Arg Ile Ser Tyr Arg Ser Arg Trp Tyr Asn Asn Tyr Ala
    50                  55                  60


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


Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
                85                  90                  95


Tyr Tyr Cys Ala Arg Tyr Tyr Ser Asp His Phe Gly Leu Tyr Pro Tyr
            100                 105                 110


Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125


<210>  225
<211>  126
<212>  PRT
<213>  Homo sapiens

<400>  225

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


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


Trp Ile Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly
        35                  40                  45
```

```
Ile Ile His Pro Gly His Ser Tyr Thr Arg Tyr Ser Pro Ser Phe Gln
    50                  55                  60


Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65                  70                  75                  80


Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
                85                  90                  95


Arg Gly Asp Gly Gly Pro Ser Ser Gln Gly Asn Tyr Phe Gly Trp Val
            100                 105                 110


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


<210>  226
<211>  125
<212>  PRT
<213>  Homo sapiens

<400>  226

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


Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
            20                  25                  30


Ser Ala Ala Trp Ser Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
        35                  40                  45


Trp Leu Gly Arg Ile Tyr Tyr Arg Ser Lys Lys Trp Tyr Asn Asp Tyr
    50                  55                  60


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


Asn Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala
                85                  90                  95


Val Tyr Tyr Cys Ala Arg Asn Tyr Ser Gly Pro Met Tyr Tyr Tyr Gly
            100                 105                 110


Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125


<210>  227
<211>  123
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```
<212>  PRT
<213>  Homo sapiens

<400>  227

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


Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
            20                  25                  30


Ser Ala Ala Trp Ser Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
        35                  40                  45


Trp Leu Gly Arg Ile Gln Tyr Arg Ser Lys Trp Tyr Asn Ala Tyr Ala
    50                  55                  60


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


Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
                85                  90                  95


Tyr Tyr Cys Ala Arg Gly Phe His Gly Ser Thr Met Tyr Phe Asp Val
            100                 105                 110


Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  228
<211>  117
<212>  PRT
<213>  Homo sapiens

<400>  228

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


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


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


Gly Phe Ile Tyr Pro Asp Lys Ser Tyr Thr Asn Tyr Ser Pro Ser Phe
    50                  55                  60


Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80
```

```
Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95


Ala Arg Gly Leu Gly Gly Ser Phe Asp Val Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ser
        115


<210>  229
<211>  123
<212>  PRT
<213>  Homo sapiens

<400>  229

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


Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
            20                  25                  30


Ser Ala Ser Trp Ser Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
        35                  40                  45


Trp Leu Gly Arg Ile Tyr Tyr Arg Ser Gln Trp Tyr Asn Asp Tyr Ala
    50                  55                  60


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


Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
                85                  90                  95


Tyr Tyr Cys Ala Arg Gly Trp Ile Thr Gly Trp Arg Ile Phe Asp Tyr
            100                 105                 110


Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  230
<211>  120
<212>  PRT
<213>  Homo sapiens

<400>  230

Gln 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 Ser Thr Tyr
            20                  25                  30


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


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


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr 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 Lys Met Tyr Trp Trp Ser Asp Gly Phe Asp Tyr Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  231
<211>  121
<212>  PRT
<213>  Homo sapiens

<400>  231

Gln 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 Ser Arg Tyr
            20                  25                  30


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


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


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr 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 Tyr Pro Gly Pro Thr Gly His Val Phe Phe Asp Ile Trp Gly
```

```
            100                 105                 110


Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  232
<211>  116
<212>  PRT
<213>  Homo sapiens

<400>  232

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


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


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


Gly Gly Ile Ile Pro Lys Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60


Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80


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


Ala Arg Thr Ile Gly Ile Tyr Asp Ser Trp Gly Gln Gly Thr Leu Val
            100                 105                 110


Thr Val Ser Ser
        115


<210>  233
<211>  115
<212>  PRT
<213>  Homo sapiens

<400>  233

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


Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser His
            20                  25                  30


Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
```

35 40 45

Gly Asn Ile Met Pro Ile Phe Gly Val Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Glu Met Arg Leu Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 234
<211> 126
<212> PRT
<213> Homo sapiens

<400> 234

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

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
20 25 30

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

Trp Leu Gly Arg Ile Arg Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60

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

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Gly Tyr His Gln Gly Leu Tyr Gly Asn His Met
100 105 110

Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 235
<211> 118
<212> PRT
<213> Homo sapiens

<400> 235

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

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

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

Trp Leu Ala Leu Ile Asp Trp Asp Asp Asp Lys Ser Tyr Ser Thr Ser
50 55 60

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Ile Gln Gly Trp Asn Tyr Asp Val Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 236
<211> 120
<212> PRT
<213> Homo sapiens

<400> 236

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

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

Ser Ala Ala Trp Ser Trp Ile Arg Gln Ser Pro Gly Arg Gly Leu Glu
35 40 45

Trp Leu Gly Arg Ile Gly Gln Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60

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

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Ser Arg Phe Gly Tyr Phe Asp Val Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 237
<211> 118
<212> PRT
<213> Homo sapiens

<400> 237

Gln 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 Ser Ser His
20 25 30

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

Thr Ile Ser Ser Asn Gly Ser Tyr 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 Phe Val Ala Arg Leu Asn Val Phe Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> 238
<211> 115
<212> PRT
<213> Homo sapiens

<400> 238

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

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

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

Gly Asn Ile Ile Pro Ala Phe Gly Tyr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Lys Phe Thr Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ser
115

<210> 239
<211> 118
<212> PRT
<213> Homo sapiens

<400> 239

Gln 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 Ser Ser Tyr
20 25 30

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

Asn Ile Ser Gly Asn Gly Ser Ser 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 Leu Ile Ala Thr Leu Gly Thr Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110


Leu Val Thr Val Ser Ser
        115


<210>  240
<211>  120
<212>  PRT
<213>  Homo sapiens

<400>  240

Gln 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 Ser Asn Tyr
            20                  25                  30


Gly Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45


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


Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr 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 Thr Ala Pro Ala Gly His Gly Val Phe Ala Asn Trp Gly Gln
            100                 105                 110


Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  241
<211>  110
<212>  PRT
<213>  Homo sapiens

<400>  241

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Arg Ser Ser
            20                  25                  30
```

```
Arg Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45

Ile Tyr Gly Ala Ser Lys Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65                  70                  75                  80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Asp Phe Pro
                85                  90                  95

Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110


<210>  242
<211>  111
<212>  PRT
<213>  Homo sapiens

<400>  242

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Arg Ser Ser
            20                  25                  30

Arg Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45

Ile Tyr Gly Ala Ser Lys Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65                  70                  75                  80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser His Asp Pro
                85                  90                  95

Ser Gly Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110


<210>  243
<211>  110
<212>  PRT
<213>  Homo sapiens
```

<400> 243

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Arg Ser Ser
20 25 30

Arg Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Lys Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Asp Phe Pro
85 90 95

Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 244
<211> 110
<212> PRT
<213> Homo sapiens

<400> 244

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Arg Ser Ser
20 25 30

Arg Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Lys Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Asp Phe Pro
85 90 95

Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr

```
            100                 105                 110


<210>  245

<211>  110
<212>  PRT
<213>  Homo sapiens

<400>  245

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Arg Ser Ser
            20                  25                  30


Arg Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45


Ile Tyr Gly Ala Ser Lys Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
    50                  55                  60


Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65                  70                  75                  80


Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Phe Tyr Ser Lys Pro
                85                  90                  95


Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110


<210>  246
<211>  111
<212>  PRT
<213>  Homo sapiens

<400>  246

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Arg Ser Ser
            20                  25                  30


Arg Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45


Ile Tyr Gly Ala Ser Lys Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
    50                  55                  60
```

```
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65                  70                  75                  80


Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser His Asp Pro
                85                  90                  95


Ser Gly Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110


<210>  247
<211>  111
<212>  PRT
<213>  Homo sapiens

<400>  247

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Arg Ser Ser
            20                  25                  30


Arg Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45


Ile Tyr Gly Ala Ser Lys Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
    50                  55                  60


Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65                  70                  75                  80


Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Gln Asp Pro
                85                  90                  95


Ser Ser Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110


<210>  248
<211>  110
<212>  PRT
<213>  Homo sapiens

<400>  248

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ile Val Ser Gly Tyr
            20                  25                  30
```

```
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Trp Ser Leu Arg Ser Pro
                85                  90                  95

Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110


<210>  249
<211>  111
<212>  PRT
<213>  Homo sapiens

<400>  249

Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30

Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Asn Asp Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Thr Tyr Asp Arg Arg Thr
                85                  90                  95

Phe Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210>  250
<211>  111
<212>  PRT
<213>  Homo sapiens

<400>  250
```

```
Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30

Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Asn Asp Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Thr Tyr Asp Arg Arg Thr
                85                  90                  95

Phe Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110
```

<210> 251
<211> 110
<212> PRT
<213> Homo sapiens

<400> 251

```
Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Arg Ser Ser
            20                  25                  30

Arg Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45

Ile Tyr Gly Ala Ser Lys Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65                  70                  75                  80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Asp Phe Pro
                85                  90                  95

Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110
```

```
<210>  252
<211>  112
<212>  PRT
<213>  Homo sapiens

<400>  252

Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1               5                   10                  15


Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30


Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45


Ile Tyr Asn Asp Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60


Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65                  70                  75                  80


Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Trp Asp Arg Ala Asp
                85                  90                  95


Gly Ser Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210>  253
<211>  113
<212>  PRT
<213>  Homo sapiens

<400>  253

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15


Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30


Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45


Met Ile Tyr Ser Val Ser Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60


Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
```

```
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ala Trp Ala His Met
                85                  90                  95


Ser Leu Gly Lys Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110


Gln




<210>  254
<211>  113
<212>  PRT
<213>  Homo sapiens

<400>  254

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15


Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30


Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45


Met Ile Tyr Ser Val Ser Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60


Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80


Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Trp Asp His Ser
                85                  90                  95


Gln Met Gly Lys Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110


Gln




<210>  255
<211>  224
<212>  PRT
<213>  Homo sapiens

<400>  255

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15
```

```
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Ile Gly Gly Tyr
            20                  25                  30

Asn Ser Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45

Met Ile Tyr Gly Val Asn Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Asp Ile Glu
                85                  90                  95

Ser Ala Thr Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly
        115                 120                 125

Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser
    130                 135                 140

Asn Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
145                 150                 155                 160

Leu Ile Tyr Asn Asp Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe
                165                 170                 175

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
            180                 185                 190

Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Thr Tyr Asp Arg Arg
        195                 200                 205

Thr Phe Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
    210                 215                 220


<210>  256
<211>  109
<212>  PRT
<213>  Homo sapiens

<400>  256

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
```

1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ile Val Ser Gly Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Asn Phe Ser Phe
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105

<210> 257
<211> 109
<212> PRT
<213> Homo sapiens

<400> 257

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asn Ile Gly Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asn Ser Ser Thr 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 Arg Ser Asn Met Pro Ile
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105

```
<210>  258
<211>  111
<212>  PRT
<213>  Homo sapiens

<400>  258

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ala Pro Gly Gln
1               5                   10                  15


Arg Val Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Ala Ser
            20                  25                  30


Asp Thr Val Thr Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45


Met Ile Tyr Ala Val Asn Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60


Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80


Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Arg Asp Ser Ser
                85                  90                  95


Ser Met Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210>  259
<211>  114
<212>  PRT
<213>  Homo sapiens

<400>  259

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1               5                   10                  15


Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
            20                  25                  30


Asn Gly Tyr Thr Tyr Leu Ser Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45


Pro Gln Leu Leu Ile Tyr Leu Gly Ser Lys Arg Ala Ser Gly Val Pro
    50                  55                  60


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

```
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Tyr
                85                  90                  95


Tyr Asp Ser Ser Ser Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105                 110


Arg Thr



<210>  260
<211>  112
<212>  PRT
<213>  Homo sapiens

<400>  260

Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1               5                   10                  15


Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Pro Asn
            20                  25                  30


Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45


Ile His Gly Asn Ala Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60


Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65                  70                  75                  80


Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Phe Phe Thr
                85                  90                  95


Asn Ser Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210>  261
<211>  110
<212>  PRT
<213>  Homo sapiens

<400>  261

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15


Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Leu Thr Ser Asn
            20                  25                  30
```

```
Gln Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45


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


Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65                  70                  75                  80


Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Phe Pro
                85                  90                  95


Ala Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110


<210>  262
<211>  113
<212>  PRT
<213>  Homo sapiens

<400>  262

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15


Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Asn
            20                  25                  30


Asn Phe Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45


Met Ile Tyr Tyr Gly Asp Ser Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60


Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80


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


Met Gly Met Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110


Gln



<210>  263
<211>  109
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```
<212>  PRT
<213>  Homo sapiens

<400>  263

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Ser Ser Ala
            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 Thr 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 Tyr Tyr Ser Tyr Ser Val
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105


<210>  264
<211>  112
<212>  PRT
<213>  Homo sapiens

<400>  264

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15


Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Asn Phe
            20                  25                  30


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


Met Ile Tyr Ser Val Ser Ser Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60


Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80


Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ala Tyr Thr Thr Asp
                85                  90                  95
```

Thr Leu Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

<210> 265
<211> 110
<212> PRT
<213> Homo sapiens

<400> 265

Asp Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

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

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ser Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Ser Asp Ile Pro
85 90 95

Ala Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105 110

<210> 266
<211> 109
<212> PRT
<213> Homo sapiens

<400> 266

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Arg Ser
20 25 30

Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Asn 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 Val Tyr Tyr Cys Leu Gln Val Tyr Asn Leu Pro Leu
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105


<210>  267
<211>  109
<212>  PRT
<213>  Homo sapiens

<400>  267

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15


Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Arg Ser
            20                  25                  30


Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45


Tyr Ala Ala Ser Asn 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 Val Tyr Tyr Cys Leu Gln Val Tyr Asn Leu Pro Leu
                85                  90                  95


Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105


<210>  268
<211>  110
<212>  PRT
<213>  Homo sapiens

<400>  268

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


Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Pro Asn Phe Tyr Val
            20                  25                  30
```

```
His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45

Glu Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65                  70                  75                  80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Lys Pro Thr Phe Ser
                85                  90                  95

Gly Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210>  269
<211>  113
<212>  PRT
<213>  Homo sapiens

<400>  269

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Ile Gly Arg Tyr
            20                  25                  30

His Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Val
        35                  40                  45

Met Ile Tyr Ser Val Ser Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ala Tyr Asp Thr Asn
                85                  90                  95

Asn Tyr Leu Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln


<210>  270
```

<211> 108
<212> PRT
<213> Homo sapiens

<400> 270

Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn
20 25 30

Ser Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln Ser
65 70 75 80

Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Tyr Ala Ser Asn Ile Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105

<210> 271
<211> 111
<212> PRT
<213> Homo sapiens

<400> 271

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Asp Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Arg Val Asp Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Val Gly Pro

85 90 95

Ser Thr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

<210> 272
<211> 111
<212> PRT
<213> Homo sapiens

<400> 272

Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn
20 25 30

Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Ser Asn Ser Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp His Asn Ser
85 90 95

Tyr Thr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

<210> 273
<211> 108
<212> PRT
<213> Homo sapiens

<400> 273

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

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

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Ser Lys Asp Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser

```
    50                  55                  60


Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65                  70                  75                  80


Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Trp Ala His Asp His Lys Val
                85                  90                  95


Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105


<210>  274
<211>  110
<212>  PRT
<213>  Homo sapiens

<400>  274

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


Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Ser Lys Val Ala
            20                  25                  30


Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45


Tyr Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60


Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65                  70                  75                  80


Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Gly Gln Met Ser Thr
                85                  90                  95


Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210>  275
<211>  113
<212>  PRT
<213>  Homo sapiens

<400>  275

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15


Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
```

20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Ser Val Asn Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Thr Tyr Asp His Thr
85 90 95

Ser Ser Gly Phe Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

Gln

<210> 276
<211> 111
<212> PRT
<213> Homo sapiens

<400> 276

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Ile Gly His Phe
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Ser Val Ile Ser Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Phe Thr Phe Pro
85 90 95

Ser Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

```
<210>  277
<211>  112
<212>  PRT
<213>  Homo sapiens

<400>  277

Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1               5                   10                  15


Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser His
            20                  25                  30


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


Ile Tyr Asp Val Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60


Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65                  70                  75                  80


Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Trp Asp Ser Val Gln
                85                  90                  95


Val Ser Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210>  278
<211>  111
<212>  PRT
<213>  Homo sapiens

<400>  278

Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1               5                   10                  15


Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn
            20                  25                  30


Arg Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45


Ile Tyr Gly Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60


Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65                  70                  75                  80
```

```
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ala Trp Asp Leu Leu Glu

                85                  90                  95


Val Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210>  279
<211>  111
<212>  PRT
<213>  Homo sapiens

<400>  279

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15


Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Ile Gly Thr Tyr
            20                  25                  30


Asn His Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45


Met Ile Tyr Asn Val Asn Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60


Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80


Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ala Tyr Ala Pro Ser
                85                  90                  95


Ala Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210>  280
<211>  113
<212>  PRT
<213>  Homo sapiens

<400>  280

Asp Ile 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 Ile Gly
            20                  25                  30


Tyr Asp Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45
```

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

His His Gly Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

Gln

<210> 281
<211> 113
<212> PRT
<213> Homo sapiens

<400> 281

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr
20 25 30

Ser Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asn Val Asn Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Asp Tyr Val
85 90 95

Ser Ser Asp Thr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

Gln

<210> 282
<211> 113

<212> PRT
<213> Homo sapiens

<400> 282

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

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

Met Ile Tyr Gly Val Thr Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Asp Glu His
85 90 95

Gly Phe His Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

Gln

<210> 283
<211> 112
<212> PRT
<213> Homo sapiens

<400> 283

Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Tyr
20 25 30

Arg Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Gly Asn Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65 70 75 80

```
Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Thr Tyr Thr Gly Leu Pro
                85                  90                  95


Phe Thr Thr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110
```

<210> 284
<211> 363
<212> DNA
<213> Homo sapiens

<400> 284

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caggtggaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt
60

agctgcaaag gttccggata ttcctttact aattattgga ttggttgggt gcgccagatg
120

cctgggaagg gtctcgagtg gatgggcgtt atcatgccgt ctgatagcta tacccgttat
180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat
240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatggt
300

catggtatgt atggtggtgc tcttgatgtt tggggccaag gcaccctggt gacggttagc
360


tca
363
```

<210> 285
<211> 363
<212> DNA
<213> Homo sapiens

<400> 285

```
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt
60

agctgcaaag gttccggata ttcctttact aattattgga ttggttgggt gcgccagatg
120

cctgggaagg gtctcgagtg gatgggcttt atttggcctg ttgattcttg gactcagtat
180

tctccttctt ttcagggtca ggtcaccatt agcgcggata aaagcattag caccgcgtat
240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatggt
300

catggtatgt atggtggtgc tcttgatgtt tggggccaag gcaccctggt gacggttagc
360
```

tca
363

<210> 286
<211> 363
<212> DNA
<213> Homo sapiens

<400> 286
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt
60

agctgcaaag gttccggata ttcctttact aattattgga ttggttgggt gcgccagatg
120

cctgggaagg gtctcgagtg gatgggcttt atttggcctg ttgattcttg gactcagtat
180

tctccttctt ttcagggtca ggtcaccatt agcgcggata aaagcattag caccgcgtat
240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatggt
300

catggtatgt atggtggtgc tcttgatgtt tggggccaag gcaccctggt gacggttagc
360

tca
363

<210> 287
<211> 363
<212> DNA
<213> Homo sapiens

<400> 287
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt
60

agctgcaaag gttccggata ttcctttact aattattgga ttggttgggt gcgccagatg
120

cctgggaagg gtctcgagtg gatgggcatt atttggccta ttgattcttt tactcagtat
180

tctccttctt ttcagggtca ggtgaccatt agcgcggata aaagcattag caccgcgtat
240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatggt
300

catggtatgt atggtggtgc tcttgatgtt tggggccaag gcaccctggt gacggttagc
360

tca
363

<210> 288

<211> 363
<212> DNA
<213> Homo sapiens

<400> 288
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt
60

agctgcaaag gttccggata ttcctttact aattattgga ttggttgggt gcgccagatg
120

cctgggaagg gtctcgagtg gatgggcgtt atcatgccgt ctgatagcta tacccgttat
180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat
240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatggt
300

catggtatgt atggtggtgc tcttgatgtt tggggccaag gcaccctggt gacggttagc
360

tca
363

<210> 289
<211> 363
<212> DNA
<213> Homo sapiens

<400> 289
caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt
60

agctgcaaag gttccggata ttcctttact aattattgga ttggttgggt gcgccagatg
120

cctgggaagg gtctcgagtg gatgggcgtt atcatgccgt ctgatagcta tacccgttat
180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat
240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatggt
300

catggtatgt atggtggtgc tcttgatgtt tggggccaag gcaccctggt gacggttagc
360

tca
363

<210> 290
<211> 363
<212> DNA
<213> Homo sapiens

<400> 290

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt
60

agctgcaaag gttccggata ttcctttact aattattgga ttggttgggt gcgccagatg
120

cctgggaagg gtctcgagtg gatgggcgtt atcatgccgt ctgatagcta tacccgttat
180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat
240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatggt
300

catggtatgt atggtggtgc tcttgatgtt tggggccaag gcaccctggt gacggttagc
360

tca
363

<210> 291
<211> 363
<212> DNA
<213> Homo sapiens

<400> 291
caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg
60

agctgcgcgg cctccggatt taccttttct gattatgcta tgtcttgggt gcgccaagcc
120

cctgggaagg gtctcgagtg ggtgagcgct atcatgtatg attctagctc taccttttat
180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat
240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtattaat
300

tatatttata agggtgttca ttttgattat tggggccaag gcaccctggt gacggttagc
360

tca
363

<210> 292
<211> 357
<212> DNA
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120

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240

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cctgggaagg gtctcgagtg gatgggcatt atcgatccgc gtgagagctt tacccgttat
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240

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360**

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378**

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**cagtctcctg ggcgtggcct cgagtggctg ggccgtatct attatcgtag caagaagtgg
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**tataacgatt atgcggtgag cgtgaaaagc cggattacca tcaacccgga tacttcgaaa
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**aaccagttta gcctgcaact gaacagcgtg accccggaag atacggccgt gtattattgc
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**gcgcgtaatt attctggtcc tatgtattat tatggtgatg tttggggcca aggcaccctg
360**

**gtgacggtta gctca
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**cagtctcctg ggcgtggcct cgagtggctg ggccgtatcc agtatcgtag caagtggtat
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**aacgcttatg cggtgagcgt gaaaagccgg attaccatca acccggatac ttcgaaaaac
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**cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg
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<211> 369
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<211> 348
<212> DNA
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<211> 378
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<211> 354
<212> DNA
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120

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300

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cagtttagcc tgcaactgaa cagcgtgacc ccggaagata cggccgtgta ttattgcgcg
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120

cccgggacgg cgccgaaact tctgatttat aataatcagc gtccctcagg cgtgccggat
180

cgttttagcg gatccaaaag cggcaccagc gcgagccttg cgattacggg cctgcaaagc
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180

agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg
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gatcgtttta gcggatccaa aagcggcacc agcgcgagcc ttgcgattac gggcctgcaa
240

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180**

**agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg
240**

**caagcggaag acgaagcgga ttattattgc tctgcttatg ctccttctgc tgttgtgttt
300**

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333**

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120**

**ttgcccggga cggcgccgaa acttctgatt tataagaata ctaatcgtcc ctcaggcgtg
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**caaagcgaag acgaagcgga ttattattgc tcttcttatg attcttttca tcatggtatt
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**agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg
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**caagcggaag acgaagcgga ttattattgc tcttcttatg attatgtttc ttctgatact
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300

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cccgggacgg cgccgaaact tctgatttat ggtaataata agcgtccctc aggcgtgccg
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<210> 370
<211> 327
<212> PRT
<213> Homo sapiens

<400> 370

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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
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```
            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 Gly
    290                 295                 300

Thr Pro Cys Leu Leu Gly Pro Gly Pro Val Leu Thr Val Leu Ala Leu
305                 310                 315                 320

Leu Leu Ala Ser Thr Leu Ala
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<210>  371
<211>  340
<212>  PRT
<213>  Homo sapiens

<400>  371

Gly Gly Ser Ser Thr Ile Leu Arg Pro Arg Phe Arg Arg Glu Val Glu
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Lys Thr Ala Cys Pro Ser Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser
            20                  25                  30

Leu Ile Phe Tyr Lys Lys Trp Glu Leu Glu Ala Cys Val Asp Ala Ala
        35                  40                  45

Leu Leu Ala Thr Gln Met Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr
    50                  55                  60

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

Gly Tyr Pro Glu Ser Val Ile Gln His Leu Gly Tyr Leu Phe Leu Lys
                85                  90                  95

Met Ser Pro Glu Asp Ile Arg Lys Trp Asn Val Thr Ser Leu Glu Thr
            100                 105                 110

Leu Lys Ala Leu Leu Glu Val Asn Lys Gly His Glu Met Ser Pro Gln
        115                 120                 125

Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln Leu Asp
    130                 135                 140
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```
Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr Leu Cys
145                 150                 155                 160

Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser Ile Trp
                165                 170                 175

Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln Leu Asp
            180                 185                 190

Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn Gly Ser
        195                 200                 205

Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro Thr Glu
    210                 215                 220

Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu Ala Thr
225                 230                 235                 240

Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val Ala Glu
                245                 250                 255

Val Gln Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys Ala Glu Glu
            260                 265                 270

Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp
        275                 280                 285

Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr
    290                 295                 300

Leu Val Leu Asp Leu Ser Val Gln Glu Ala Leu Ser Gly Thr Pro Cys
305                 310                 315                 320

Leu Leu Gly Pro Gly Pro Val Leu Thr Val Leu Ala Leu Leu Leu Ala
                325                 330                 335

Ser Thr Leu Ala
            340
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<210>  372
<211>  113
<212>  PRT
<213>  Homo sapiens

<400>  372

Asp Ile Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15


Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Ile Gly Gly Tyr
            20                  25                  30


Asn Ser Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45


Met Ile Tyr Gly Val Asn Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60


Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80


Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Asp Ile Glu
                85                  90                  95


Ser Ala Thr Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110


Gln
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