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(54) **BIOMARKERS FOR LIVER DISEASES AND METHOD FOR USING THE SAME**

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(57) **ABSTRACT**

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Biomarkers for liver diseases and method for using the same are provided. For detecting liver cirrhosis and liver cancer, the biomarkers are selected from any one of the amino acid sequences with SEQ ID NO:1 to SEQ ID NO:24 or derivatives or fragments or variants or the combination thereof or the antibodies against the amino acid sequences. Then the biomarkers are further developed into detection kits, such that by detecting the existence of autoantibodies or autoantigens in screened specimens, liver diseases are detected with higher accuracy and sensitivity.

(21) Appl. No.: **11/013,684**

(22) Filed: **Dec. 17, 2004**

Provide a specimen



**Use biomarker to detect
autoantibody in the specimen**

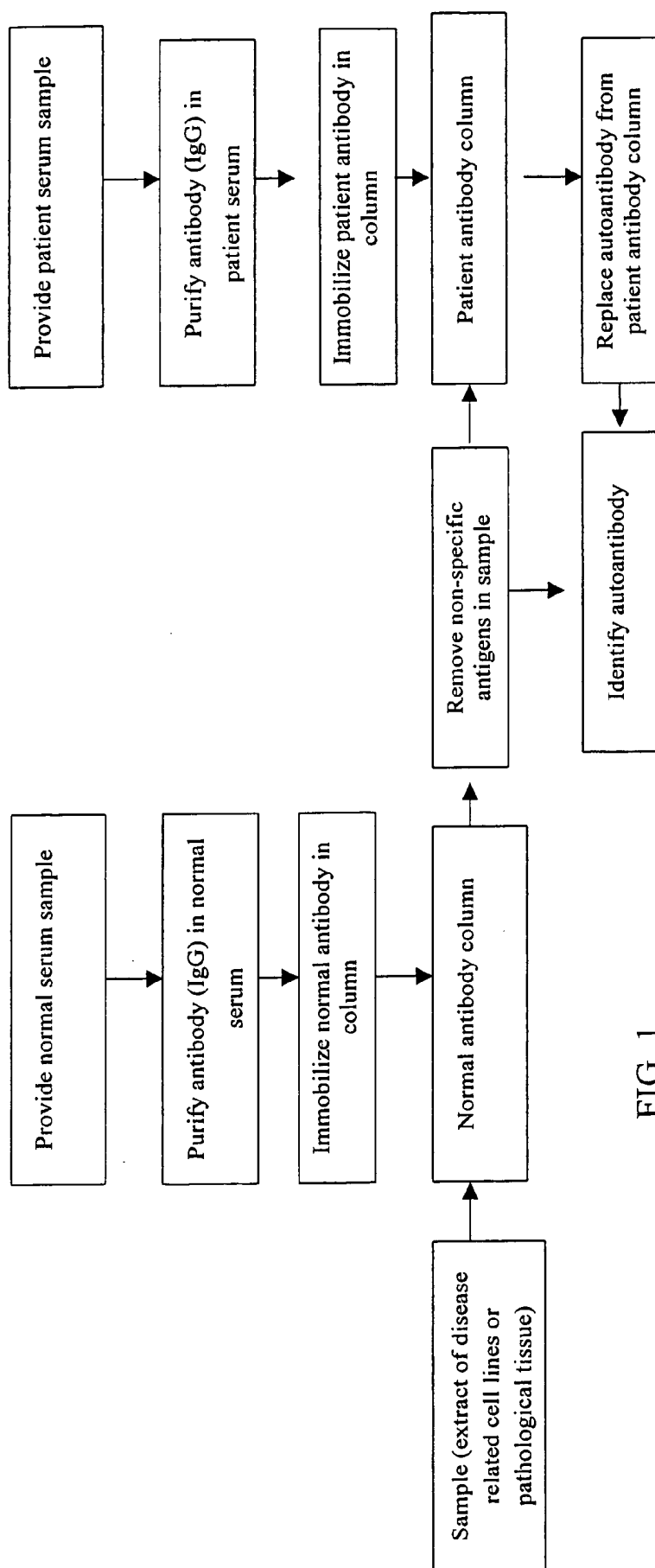


FIG. 1

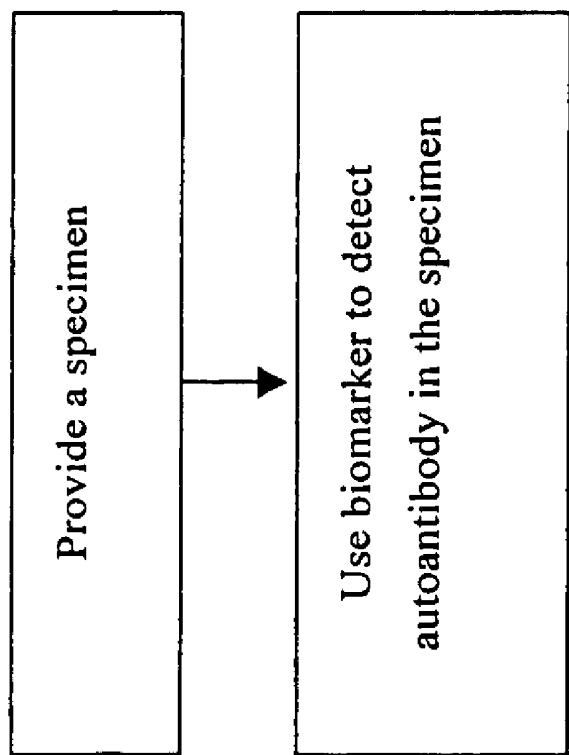


FIG. 2

BIOMARKERS FOR LIVER DISEASES AND METHOD FOR USING THE SAME

BACKGROUND OF THE INVENTION

[0001] 1. Field of the Invention

[0002] The present invention is related to biomarkers for liver diseases and method for using the same, in which a method for screening autoantigens is employed to identify biomarkers that can be used in detecting liver diseases. The identified biomarkers are further developed into detection kits to detect the presence of autoantibodies or autoantigens in specimens for screening of liver diseases.

[0003] 2. Description of Related Art

[0004] People with impaired immune functions are prone to develop immune diseases. The etiology of many human diseases may be traced to our immune system in any of the three conditions described below. The first is reduced immunity, lower activity of immune cells, or reduced quantity of immune cells, such that the human body cannot fight off the invading bacteria, virus or mold, and becomes susceptible to contagious diseases, such as common cold, flu, pneumonia, enteritis, or even hepatitis and AIDS. The second condition is immunodeficiency or over-reaction of the immune system where the invading substances are not germs, but tiny pollens or macromolecular proteins in the food ingested, against which the immune system releases a large amount of antibodies. Such attack and defense occur in our cells, causing a chain of reactions which is also called allergy. When real pathogens such as bacteria, virus or mold attack the human body at this time, the immune system is no longer able to put up resistance. The third condition of impaired immune system is the immune cells attack normal cells in the human body, called autoimmune disorder as in the case of rheumatoid arthritis, lupus erythematosus, and herpes. Such immune diseases arise from our own immune system having an identification problem that autoantibodies are produced against human body's own cells, resulting in tissue damage and illnesses.

[0005] It is now known that autoantibodies are present not just in autoimmune diseases. More and more studies indicate that in the immune response to cancer, autoantigen (from the tumor) and autoantibody (from the body) exist in some cases. Thus the detection of tumor autoantigen that elicits body response may be directed towards and applied in the testing, diagnosis, or prognosis of cancer, and furthermore, in the treatment of disease.

[0006] U.S. Pat. Nos. 6,631,330, 5,137,807, 5,830,667, 6,264,949, and 5,985,542 disclose the use of biomarkers in the diagnosis of cirrhosis, fibrosis or autoimmune hepatitis (AIH); U.S. Pat. Nos. 4,994,374 and 5,175,084 disclose the use of biomarkers in the diagnosis of hepatocellular carcinoma; U.S. Pat. No. 6,410,724 uses DNA primer associated with hepatocellular carcinoma as a diagnostic tool. But the biomarkers disclosed in those patents lack accuracy or are susceptible to interference to a certain extent.

[0007] U.S. Pat. No. 5,891,436 and Publication No. 20030138860 disclose the use of biomarkers to detect the presence of autoantibodies in human serum as a diagnostic tool for primary biliary cirrhosis or hepatocellular carcinoma. Those patents confirm the existence of autoantibodies

in cancer patients and thereby establish the rational for using biomarkers in cancer screening.

[0008] Cancer has been the leading cause of death in Taiwan since 1982, whereas liver cancer is ranked among the top as the cause of death in both men or women. Thus it is important to find biomarkers with high accuracy and not susceptible to interference and use those biomarkers to develop detection kits for liver cirrhosis and cancer to effectively screen patients with liver diseases in the hope that early diagnosis and early treatment can help lower the mortality rate.

SUMMARY OF THE INVENTION

[0009] In addressing the drawbacks of prior arts, the present invention provides biomarkers for liver diseases, which can be developed into detection kits for diagnosis of liver cirrhosis and liver cancer based on the knowledge of the existence of autoantibodies.

[0010] An objective of the present invention is to provide biomarkers for detecting liver cirrhosis and liver cancer, which are selected from any one of the amino acid sequences with SEQ ID NO:1 to SEQ ID NO:24 or derivatives or fragments or variants or the combination thereof or the antibodies against the amino acid sequences.

[0011] According to the present invention, the aforesaid variants are obtained by substituting, deleting, inserting and/or adding to the amino acid in the amino acid sequences of the biomarker with one or more amino acids; the amino acid sequence of the variant and that of the biomarker have sequence homology greater than 80%.

[0012] Another objective of the present invention is to provide a detection kit for liver diseases, comprising a set of biomarkers selected from any one of the amino acid sequences with SEQ ID NO:1 to SEQ ID NO:24 or derivatives or fragments or variants or the combination thereof.

[0013] In one embodiment of the present invention, the aforesaid detection kit may further include secondary antibodies that can recognize the antibodies against any one of the amino acid sequences with SEQ ID NO:1 to SEQ ID NO:24 or derivatives or fragments or variants thereof.

[0014] A further objective of the present invention is to provide a method for screening liver diseases, comprising the steps of: providing a specimen; using biomarkers selected from any one of the amino acid sequences with SEQ ID NO:1 to SEQ ID NO:24 or derivatives or fragments or variants or the combination thereof to capture the autoantibody in the specimen; and detecting the autoantibody.

[0015] Yet another objective of the present invention is to provide a detection kit for liver diseases, comprising a set of antibodies against any one of the amino acid sequences with SEQ ID NO:1 to SEQ ID NO:24.

[0016] A further objective of the present invention is to provide a method using the aforesaid detection kit to screen liver diseases, comprising the steps of: providing a specimen; using the antibody against any one of the amino acid sequences with SEQ ID NO:1 to SEQ ID NO:24 to capture the antigen in the specimen; and detecting the antibody-antigen complex.

[0017] This invention is based on the use of autoantigen screening method, comprising the steps of: firstly purifying

antibodies from normal persons, liver cirrhosis patients, and liver cancer patients respectively and immobilizing them in different columns; passing the cell extracts from liver disease related cell lines (HepG2 C3A & SNU-387) in sequence through the normal antibody column and patient antibody column to obtain autoantigens associated with liver cirrhosis and liver cancer; using those autoantigens as biomarker kits coupled with enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), or immunofluorescence to detect the presence of autoantibodies against said autoantigens in the screened specimen, and based on which, to determine whether the patient has liver cirrhosis or liver cancer. Since those biomarkers are identified based on existing autoantibodies, they can be developed into diagnostic kits to determine if the patient has such diseases based on the presence of autoantibodies against the biomarkers. Such method is much easier than direct screening of the antigen and offers greater accuracy and sensitivity.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] **FIG. 1** shows a flow chart of an autoantigen screening method according to the present invention.

[0019] **FIG. 2** shows a flow chart of using biomarkers for screening autoantibody according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0020] The present invention relates to the use of an autoantigen screening method to identify biomarkers that may be used in the detection of liver diseases, such as liver cirrhosis and liver cancer. Said autoantigen screening method as shown in **FIG. 1** comprises the following steps: firstly obtaining serum samples from normal persons and patients and passing the respective samples over affinity columns that can capture antibodies to purify the antibodies contained in the serum samples; next packing respectively the resulting purified normal antibodies and patient antibodies into columns to obtain a column containing antibodies from normal persons (normal antibody column) and a column containing antibodies from patients (patient antibody column) in which antibodies are immobilized through the chemical bonding formed between the antibodies and chemical functional groups in the column; obtaining a sample which may be the extract of disease related cell lines or pathological tissues; the aforesaid serum sample may be that of a single patient or a mixture sample containing the sera of a plurality of patients.

[0021] To continue the procedure, passing the sample from the extract of disease related cell lines or pathological tissues over the normal antibody column where non-specific antigens are captured and retained in the column through the specific affinity of normal antibodies; this step may be viewed as pre-treatment of the sample before the patient antibody column is used to screen autoantigens in the sample. After non-specific antigens are removed, the sample constitutes only specific antigens. Next, passing the sample over the column packed with patient antibodies to screen disease related autoantigen. Since non-specific antigens have been removed by normal serum antibodies, the autoantigens as identified by patient's autoantibodies are more specific.

[0022] Finally, the autoantigens displaced from the patient antibody column are subjected to determination by the mass

spectrum technology; the aforesaid determination procedure involves comparing the signals from mass spectrograph with the database to obtain the information on the autoantigens.

[0023] Autoantigens in liver disease related cell lines are purified and identified according to the method described above. Given that those autoantigens are identified by the antibodies in patient sera, the autoantigens or derivatives or fragments or variants or combinations thereof can be utilized as biomarkers and developed into detection kits. By detecting the presence of autoantibodies in screened specimen, it can be determined whether the patient has liver cirrhosis or other liver diseases. In addition to biomarkers, the detection kits can further include secondary antibodies that can recognize the autoantibodies against the biomarkers to facilitate the application of the detection method.

[0024] As shown in **FIG. 2**, the method utilizing the detection kits described above comprises the steps of: providing a specimen; using biomarkers to detect the autoantibody in the specimen. Said biomarkers are selected from autoantigens screened by the autoantigen screening method or its derivatives or fragments or variants or the combination thereof. The aforesaid specimen is whole blood or serum, preferably serum.

[0025] To facilitate the detection, the aforesaid biomarker may come in any form, including but not limited to, a detection kit or pre-immobilized on a substrate, said substrate may be an immunoassay plate or a biochip, said substrate may be an immunoassay plate or a biochip. The autoantibodies in the specimen captured by the biomarkers can be recognized and adsorbed by the secondary antibodies, which are modified antibodies having special functional groups for color reaction, radio detection or fluorescence detection.

[0026] After autoantibody is adsorbed by the secondary antibody, a special reagent is added to undergo color reaction and enzyme-linked immunosorbent assay (ELISA) is employed to determine the presence of the secondary antibody, and from which to learn the presence of the autoantibody as a basis for determining if the patient has liver cancer or liver cirrhosis. The presence of the secondary antibody and thereby the presence of the autoantibody can also be determined by radioimmunoassay (RIA) or immunofluorescence.

[0027] If the screening method does not include the secondary antibody, the specimen may be labeled with a fluorescence marker (e.g. cy3 or Cy5) prior to reacting with the biomarkers. The fluorescence-labeled autoantibodies screened by the biomarkers can then be detected by a fluorescence scanner without the use of the secondary antibody.

[0028] Besides detecting the presence of the autoantibody, detection of the antigen may also be used as a basis for determining whether a patient has liver cirrhosis or liver cancer. To achieve this purpose, the present invention also provides a detection kit containing antibodies that can recognize autoantigens identified by the autoantigen screening method for the screening of liver diseases.

[0029] The method of using the aforesaid detection kit for screening liver cancer and liver cirrhosis comprises the steps of: providing a serum specimen; using the aforesaid anti-

body to recognize and capture the antigen in the serum; and detecting the antibody-antigen complex.

[0030] The advantages of the present invention are further depicted with the illustration of an example, but the descriptions made in the example should not be construed as a limitation on the actual application of the present invention.

EXAMPLE 1

[0031] Screening of Autoantigens Using Autoantibodies in Sera of Patients with Liver Diseases Purification of Autoantibodies in the Serum Sample

[0032] Firstly obtaining a serum of a patient with liver cirrhosis or liver cancer, diluting the serum with a binding buffer (20 mM PBS, pH 7.0) at the ratio of 1:10, and then filtering the diluted serum using a 0.45 μ m filter membrane to prevent the blockage of column in subsequent steps; next rinsing a Protein G affinity column with the binding buffer ten times the column volume at the rate of 1 ml/min, and then passing the filtered serum sample over the Protein G affinity column at the rate of 0.2 ml/min to retain the antibodies in the column through affinity; rinsing the Protein G affinity column again using the binding buffer 5-10 times the column volume at the rate of 1 ml/min to remove substances in the serum sample that do not form affinity bonding with the column. Eluting antibodies from the column using an elution buffer (0.1 M Glycine-HCl, pH 2.7) 2-5 times the column volume at the rate of 1 ml/min and collecting the eluted antibodies in a test tube which is added beforehand with 60-200 μ l Tris-HCl solution (1M, pH 9.0). Finally displacing the sample in a coupling buffer (0.2M NaHCO₃, 0.5M NaCl, pH 8.3) to complete the purification of autoantibodies (IgG) in the serum sample.

[0033] The method according to the present invention requires one normal IgG and patient IgG column each. Thus sera from normal persons and patients should be obtained and subject to the purification steps described above.

[0034] Preparation of Columns Containing Autoantibodies

[0035] Pipette one drop of an acidification solution (1 mM HCl, ice bathed) into a NHS-activated column to prevent the formation of bubbles. After connecting the upper end of the column with a syringe or pump, removing the adapter at the bottom of the column. Rinsing out isopropanol in the column using the acidification solution two times the column volume. After repeating the wash step three times, injecting the sample containing autoantibodies into the column. Preparing the aforesaid coupling buffer containing purified autoantibodies into a solution with a volume equivalent to one time the column volume and a concentration of 0.5-10 mg/ml. After passing the aforesaid sample containing autoantibodies over the column, sealing the column and let the reaction go on for 15-30 minutes under 25° C. or 4 hours under 4° C. to immobilize the antibodies in the column through chemical bonding.

[0036] After the bonding between the autoantibodies and the column, eluting the column with a blocking buffer (0.5M ethanolamine, 0.5M NaCl, pH 8.3) two times the column volume, and repeating the steps three times. Then rinsing the column with a washing buffer (0.1M acetate, 0.5M NaCl, pH 4) two times the column volume and also repeating the steps three times. Again eluting the column three times using the

aforesaid blocking buffer two times the column volume each time, and then let the column react 15-30 minutes to block and inactivate the functional groups in the column that are not bound with autoantibodies. After completing the blocking reaction, rinsing the column three times using the aforesaid washing buffer two times the column volume each time, followed by eluting the column three times using the aforesaid blocking buffer two times the column volume to make sure all functional groups not bound with autoantibodies are blocked. Again rinsing three times the column using the washing buffer two times the column volume each time. Finally eluting the column with a pH neutral buffer 2-5 times the column volume to complete the preparation of the column packed with the autoantibodies.

[0037] Identification of Autoantigens from Extract of Liver Disease Related Cell Lines

[0038] Firstly rinsing 2.68 mg of HepG2 C3A cells with culture medium removed with an ice-bathed Tris saline solution (50 mM Tris pH 7.5, 150 mM NaCl, 1.5 mM PMSF, phosphatase inhibitors) twice, then adding in 1 ml of Triton Extraction solution (15 mM Tris pH 7.5, 120 mM NaCl, 25 mM KCl, 2 mM EGTA, 0.5 mM DTT, 0.5% Triton X-100, 10 μ g/ml leupeptin, 0.5 mM PMSF, and phosphatase inhibitors) and let it stand for 30 minutes under 4° C. At this time, cells start to decompose and release proteins. Centrifuging (with a tabletop centrifuge) the solution at 14,000 rpm under 4° C. for 15 minutes to remove solid, insoluble cell structures. Collecting the supernatants to carry on immunoaffinity chromatography.

[0039] After diluting the cell extract collected with the binding buffer at the ratio of 1:10, passing it through a 0.45 μ m filter membrane to prevent the blockage of the column in subsequent steps. Prior to injecting the sample into the IgG column, rinsing the normal and patient antibody columns with the binding buffer ten times the column volume at the rate of 1 ml/min. Then passing the filtered cell extract over the normal antibody column at the rate of 0.2 ml/min. Eluting the normal antibody column with the binding buffer 5-10 times the column volume at the rate of 1 ml/min. At this time, antigens in the cell extract that are identified and captured by the normal antibodies will be retained in the column. The purpose of this step is to remove non-specific antigens in the HepG2 C3A cells. As a result, the cell extract that has passed through the column is free of non-specific antigens. Injecting the resulting cell extract into the patient antibody column. Eluting the column with the binding buffer 5-10 times the column volume at the rate of 1 ml/min. At this time, the autoantigens present in the cell extract will be captured by the autoantibodies from the patients and retained in the column. When the cell extract passes over the normal antibody column, the antigens captured by the normal antibodies are retained in the column, whereas the cell extract free of antigens can be identified and captured by the normal antibodies, only antigens that can be identified and captured by the patient antibodies will be retained by the column. The antigens retained in the patient antibody column are eluted and collected using the elution buffer 2-5 times the column volume at the rate of 1 ml/min. Subjecting the flow-through to protein hydrolysis using trypsin and the resulting peptides are assayed using the mass spectrum technology. The resulting spectrographs are compared with the database to obtain the information on the proteins.

[0040] By screening liver disease related cell lines with autoantibodies in the serum of the patients with liver cirrhosis or liver cancer, the following autoantigens are obtained:

[0041] 1. Nucleoside diphosphate kinase (gi|1421609, SEQ ID NO.1).

[0042] 2. NM23 protein (gi|35068, SEQ ID NO.2).

[0043] 3. ATP synthase beta chain, mitochondrial [precursor] (gi|28940, SEQ ID NO.3).

[0044] 4. 14-3-3 zeta protein (tyrosine 3/tryptophan 5-monooxygenase activation protein) (gi|4507953, SEQ ID NO.4).

[0045] 5. 14-3-3 epsilon protein (tyrosine 3/tryptophan 5-monooxygenase activation protein) (gi|4507953, SEQ ID NO.5).

[0046] 6. Protein disulfide isomerase-related protein 5 (gi|1710248, SEQ ID NO.6).

[0047] 7. Unnamed protein product (gi|21750187, SEQ ID NO.7).

[0048] 8. Tropomyosin alpha 3 (gi|37403, SEQ ID NO.8).

[0049] 9. Tropomyosin alpha 4 (gi|10435300, SEQ ID NO.9).

[0050] 10. Calreticulin precursor (gi|4757900, SEQ ID NO.10).

[0051] 11. Human pre-mRNA splicing factor SF2p32 (gi|338043, SEQ ID NO.11).

[0052] 12. Tumor necrosis factor type I receptor associated protein TRAP-1 (gi|1082886, SEQ ID NO.12).

[0053] 13. Tumor rejection antigen (gp96) 1; glucose regulated protein (gi|4507677, SEQ ID NO.13).

[0054] 14. Heat shock protein 90-beta (gi|72222, SEQ ID NO.14).

[0055] 15. Heat shock protein 90-alpha (gi|123678, SEQ ID NO.15).

[0056] 16. Heat shock 60 kDa protein 1 (gi|31542947, SEQ ID NO.16).

[0057] 17. HMG-1 (gi|968888, SEQ ID NO.17).

[0058] 18. KIAA0144 gene product (NICE-4 protein) (gi|13111995, SEQ ID NO.18).

[0059] 19. Valosin-containing protein (p97); transitional endoplasmic reticulum ATPase (gi|6005942, SEQ ID NO.19).

[0060] 20. Glyceraldehyde 3-phosphate dehydrogenase, liver (gi|30157565, SEQ ID NO.20).

[0061] 21. Cytokeratin (gi|1419564, SEQ ID NO.21).

[0062] 22. IGF-II mRNA-binding protein 1 (gi|4191608, SEQ ID NO.22).

[0063] 23. NADPH: quinone reductase (gi|13236495, SEQ ID NO.23).

[0064] 24. Crystal Structure of The Human Co-Chaperone P23 (hsp-90 co-chaperone) (gi|9257073, SEQ ID NO.24).

[0065] The autoantigens identified with the antibodies from liver disease related cell lines are shown in Table 1; the left side of the Table 1 lists the GI number and name of the proteins and the right side indicates the autoantigens that may be identified from cell lines using sera of patients with liver cirrhosis or liver cancer. As shown, those autoantigens are not just present in one liver disease, they are repeatedly identified in different cell lines using autoantibodies in sera of different sources, indicating their close correlation with liver diseases. Some proteins listed in Table 1 have two GI numbers. That is because the protein and its variant had similar results in the mass spectrometry.

TABLE 2

Autoantigens screened from liver disease related cell lines					
GI number	Name of protein	Liver cirrhosis		Liver cancer	
		serum vs. HepG2 C3A	serum vs. HepG2 C3A	serum vs. SNU-387	serum vs. SNU-387
1421609	Nucleoside Diphosphate Kinase (=NM23 protein)	●	●	●	●
28940	ATP synthase beta chain, mitochondrial [Precursor]	●		●	
4507953, 5803225	14-3-3 protein	●		●	
1710248	Protein disulfide isomerase-related protein 5		●		●
21750187	Gi 21750187 Unnamed protein product (RAN_rec_mot.)		●		
37403, 10435300	Tropomyosin			●	●
4757900	Calreticulin precursor	●	●		
338043	Human pre-mRNA splicing factor SF2p32, complete sequence	●	●		
1082886	Tumor necrosis factor type 1 receptor associated protein TRAP-1	●	●		
4507677	Tumor protein antigen (gp96)1; glucose regulated protein	●	●		
72222, 123678	Heat shock protein 90	●	●		
31542947	Heat shock 60 kDa protein 1 (chaperonin); mitochondrial matrix protein P1	●			
968888	HMG-1 (high-mobility group-1)	●			
13111995	KIAA0144 gene product (NICE-4 protein)	●			
6005942	Valosin-containing protein (p97); transitional endoplasmic reticulum ATPase	●			
30157565	Glyceraldehyde 3-phosphate dehydrogenase, liver	●			
1419564	Cytokeratin	●			
4191608	IGF-II mRNA-binding protein 1	●			

TABLE 2-continued

Autoantigens screened from liver disease related cell lines					
GI number	Name of protein	Liver cirrhosis serum vs. HepG2 C3A	Liver cancer serum vs. HepG2 C3A	Liver cirrhosis serum vs. SNU-387	Liver cancer serum vs. SNU-387
13236495	NADPH-quinone reductase		●		
9257073	Crystal Structure of The Human Co-Chaperone P23 (hsp-90 co-chaperone)		●		

EXAMPLE 2

[0066] Determining the Availability of Autoantigens Identified by the Autoantigen Screening Method

[0067] To demonstrate the availability of 24 autoantigens identified in Example 1, further assay of serum samples from normal persons, liver cirrhosis patients and liver cancer patients using immunoassay (ELISA, RIA or immunofluorescence) and the aforesaid 24 biomarkers is carried out. The assay method includes the following steps as shown in FIG. 2: providing a specimen; using the biomarker selected from any one of the amino acid sequences with SEQ ID NO:1 to SEQ ID NO:24 or derivatives or fragments or variants or the combination thereof to capture the autoantibody in the specimen; and detecting the auto antibody.

[0068] In the example of enzyme-linked immunosorbent assay (ELISA), the following steps are taken: firstly diluting the biomarker with a coating buffer (choice of a. 50 mM Na₂HCO₃, pH=9.6, or b. 20 mM Tris-HCl, pH=8.5, or c. 10 mM PBS, pH=7.4) to a concentration of 0.5~10 µg/ml, where the coating buffer is selected according to the PI value of the biomarker, preferably a buffer having pH 1~2 higher than pI. Adding 100 µl/well biomarker solution to ELISA plate and let it stand overnight under 4° C. for immobilization.

assayed (a serum solution is obtained by diluting the serum sample 1000 times with the blocking buffer). At this time, the autoantibodies in the serum will react with immobilized biomarkers. After reaction for at least 2 hours under ambient temperature, washing the plate four times with the PBST buffer and then adding in a 100 µl/well secondary antibody (diluted 5000 times with the blocking buffer). At this time, the secondary antibody would recognize and adsorb the autoantibody. After reaction for at least 1 hour under ambient temperature, washing the plate five times with the PBST buffer. Then adding in a 100 µl/well TMB to elicit color reaction for 30 minutes. Afterwards, adding a 100 µl/well 0.5M H₂SO₄ and detecting absorbance at 450 nm.

[0070] To make sure the expression of the autoantibody can be used for diagnosis of liver cirrhosis and/or liver cancer, ELISA is employed to obtain the absorbance values of autoantibodies in the sera of normal persons, liver cirrhosis patients and liver cancer patients as identified by respective autoantigens. The data derived from five proteins-GADPH, NADPH, HMG-1, NM23 and Cytokeratin are subject to biostatistical analysis and Wilcoxon-Mann-Whitney Test. The following results at a 95% confidence level as shown in the table below are obtained:

	GADPH	NADPH	HMG-1	NM23	Cytokeratin
Normal person vs. Liver cirrhosis patient	p = 0.001	p = 0.001	p = 0.00006	p = 0.0001	p = 0.001
Normal person vs. Liver cancer patient	p = 0.017	p = 0.016	p = 0.015	p = 0.002	p = 0.016
Liver cirrhosis patient vs. Liver cancer patient	p > 0.05	p > 0.05	p > 0.05	p > 0.05	p > 0.05

Normal person: N = 10;
liver cirrhosis patient: N = 15;
liver cancer patient: N = 21 (the assumption of p < 0.05 is valid)

[0069] To continue the procedure, removing an unattached biomarker by washing the plate with a PBST buffer twice (PBST buffer: PSB buffer+0.05% Tween-20), then adding a 200 µl/well blocking buffer (choice of a. Gelatin-NET: 0.5% Gelatin, 0.15M NaCl, 5 mM EDTA.2Na, 0.05% Tween-20, 50 mM Tris base, or b. 1% BSA-PBS, pH=7.4, or c. 5% non-fat milk-PBS, pH=7.4) and let blocking reaction go on for at least 2 hours under ambient temperature; after the reaction is completed, washing with a PBST buffer three times and then depositing a 100 µl/well serum solution to be

[0071] Assuming there are differences between the expressions of biomarker-detected autoantibodies in normal persons, liver cirrhosis patients and liver cancer patients, the table above shows that such assumption was valid in normal persons versus liver cirrhosis patients and normal persons versus liver cancer patients, meaning the differences in the expression levels of biomarker-detected autoantibodies between normal persons and liver cirrhosis patients and between normal persons and liver cancer patients are statistically significant.

[0072] Statistics shows that the expression levels of GADPH-detected autoantibodies in normal persons and liver cirrhosis patients differed by 8.375 folds, while that in normal persons and liver cancer patients differed by 4.86 folds; the expression levels of HMG-1-detected autoantibodies in normal persons and liver cirrhosis patients differed by 74 folds; the expression levels of NM23-detected autoantibodies in normal persons and liver cirrhosis patients differed by 24 folds, while that in normal persons and liver cancer patients differed by 8.545 folds. These results demonstrate that the expression levels of the antibodies in liver cirrhosis and liver cancer patients as detected by the 24 autoantigens provided herein were higher than those in

normal persons. Thus a detection kit using those 24 autoantigens coupled with immunoassay may be applied in the screening of liver cirrhosis and liver cancer based on the expression levels of autoantibodies in the screened specimens.

[0073] The preferred embodiment of the present invention as disclosed above is not meant to limit this invention. All modifications and alterations made by those familiar with the skill without departing from the spirits of the invention and appended claims shall remain within the protected scope and claims of the invention.

SEQUENCE LISTING

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<211> LENGTH: 151

<212> TYPE: PRT

<213> ORGANISM: Human

<400> SEQUENCE: 1

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Gln His Tyr Ile Asp Leu Lys Asp Arg Pro Phe Phe Pro Gly Leu Val
50 55 60

Lys Tyr Met Asn Ser Gly Pro Val Val Ala Met Val Trp Glu Gly Leu
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Asn Val Val Lys Thr Gly Arg Val Met Leu Gly Glu Thr Asn Pro Ala
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Asp Ser Lys Pro Gly Thr Ile Arg Gly Asp Phe Cys Ile Gln Val Gly
100 105 110

Arg Asn Ile Ile His Gly Ser Asp Ser Val Lys Ser Ala Glu Lys Glu
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Ile Ser Leu Trp Phe Lys Pro Glu Glu Leu Val Asp Tyr Lys Ser Cys
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<210> SEQ ID NO 2

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Glu Arg Thr Phe Ile Ala Ile Lys Pro Asp Gly Val Gln Arg Gly Leu
35 40 45

-continued

Val	Gly	Glu	Ile	Ile	Lys	Arg	Phe	Glu	Gln	Lys	Gly	Phe	Arg	Leu	Val		
						50							55				
Gly	Leu	Lys	Phe	Met	Gln	Ala	Ser	Glu	Asp	Leu	Leu	Lys	Glu	His	Tyr		
						65							70				
Val	Asp	Leu	Lys	Asp	Arg	Pro	Phe	Phe	Ala	Gly	Leu	Val	Lys	Tyr	Met		
						85							90				
His	Ser	Gly	Pro	Val	Val	Ala	Met	Val	Trp	Glu	Gly	Leu	Asn	Val	Val		
						100							105				
Lys	Thr	Gly	Arg	Val	Met	Leu	Gly	Glu	Thr	Asn	Pro	Ala	Asp	Ser	Lys		
						115							120				
Pro	Gly	Thr	Ile	Arg	Gly	Asp	Phe	Cys	Ile	Gln	Val	Gly	Arg	Asn	Ile		
						130							135				
Ile	His	Gly	Ser	Asp	Ser	Val	Glu	Ser	Ala	Glu	Lys	Glu	Ile	Gly	Leu		
						145							150				
Trp	Phe	His	Pro	Glu	Glu	Leu	Val	Asp	Tyr	Thr	Ser	Cys	Ala	Gln	Asn		
						165							170				
Trp	Ile	Tyr	Glu														
						180											

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<210> SEQ ID NO 3
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: Human
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<400> SEQUENCE: 3

Met	Thr	Ser	Leu	Trp	Gly	Lys	Gly	Thr	Gly	Cys	Lys	Leu	Phe	Lys	Phe
1				5					10					15	
Arg	Val	Ala	Ala	Ala	Pro	Ala	Ser	Gly	Ala	Leu	Arg	Arg	Leu	Thr	Pro
			20					25					30		
Ser	Ala	Ser	Leu	Pro	Pro	Ala	Gln	Leu	Leu	Leu	Arg	Ala	Val	Arg	Arg
		35					40					45			
Arg	Ser	His	Pro	Val	Arg	Asp	Tyr	Ala	Ala	Gln	Thr	Ser	Pro	Ser	Pro
	50					55					60				
Lys	Ala	Gly	Ala	Ala	Thr	Gly	Arg	Ile	Val	Ala	Val	Ile	Gly	Ala	Val
65					70					75					80
Val	Asp	Val	Gln	Phe	Asp	Glu	Gly	Leu	Pro	Pro	Ile	Leu	Asn	Ala	Leu
				85					90					95	
Glu	Val	Gln	Gly	Arg	Glu	Thr	Arg	Leu	Val	Leu	Glu	Val	Ala	Gln	His
			100					105					110		
Leu	Gly	Glu	Ser	Thr	Val	Arg	Thr	Ile	Ala	Met	Asp	Gly	Thr	Glu	Gly
		115					120					125			
Leu	Val	Arg	Gly	Gln	Lys	Val	Leu	Asp	Ser	Gly	Ala	Pro	Ile	Lys	Ile
		130				135					140				
Pro	Val	Gly	Pro	Glu	Thr	Leu	Gly	Arg	Ile	Met	Asn	Val	Ile	Gly	Glu
145					150					155					160
Pro	Ile	Asp	Glu	Arg	Gly	Pro	Ile	Lys	Thr	Lys	Gln	Phe	Ala	Pro	Ile
				165					170					175	
His	Ala	Glu	Ala	Pro	Glu	Phe	Met	Glu	Met	Ser	Val	Glu	Gln	Glu	Ile
			180					185					190		
Leu	Val	Thr	Gly	Ile	Lys	Val	Val	Asp	Leu	Leu	Ala	Pro	Tyr	Ala	Lys
		195					200					205			
Gly	Gly	Lys	Ile	Gly	Leu	Phe	Gly	Gly	Ala	Gly	Val	Gly	Lys	Thr	Val
	210					215					220				

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Leu Ile Met Glu Leu Ile Asn Asn Val Ala Lys Ala His Gly Gly Tyr
225                230                235                240

Ser Val Phe Ala Gly Val Gly Glu Arg Thr Arg Glu Gly Asn Asp Leu
                245                250                255

Tyr His Glu Met Ile Glu Ser Gly Val Ile Asn Leu Lys Asp Ala Thr
                260                265                270

Ser Lys Val Ala Leu Val Tyr Gly Gln Met Asn Gln Pro Pro Gly Ala
                275                280                285

Arg Ala Arg Val Ala Leu Thr Gly Leu Thr Val Ala Glu Tyr Phe Arg
                290                295                300

Asp Gln Glu Gly Gln Asp Val Leu Leu Phe Ile Asp Asn Ile Phe Arg
305                310                315                320

Phe Thr Gln Ala Gly Ser Glu Val Ser Ala Leu Leu Gly Arg Ile Pro
                325                330                335

Ser Ala Val Gly Tyr Gln Pro Thr Leu Ala Thr Asp Met Gly Thr Met
                340                345                350

Gln Glu Arg Ile Thr Thr Thr Lys Lys Gly Ser Ile Thr Ser Val Gln
                355                360                365

Ala Ile Tyr Val Pro Ala Asp Asp Leu Thr Asp Pro Ala Pro Ala Thr
                370                375                380

Thr Phe Ala His Leu Asp Ala Thr Thr Val Leu Ser Arg Ala Ile Ala
385                390                395                400

Glu Leu Gly Ile Tyr Pro Ala Val Asp Pro Leu Asp Ser Thr Ser Arg
                405                410                415

Ile Met Asp Pro Asn Ile Val Gly Ser Glu His Tyr Asp Val Ala Arg
                420                425                430

Gly Val Gln Lys Ile Leu Gln Asp Tyr Lys Ser Leu Gln Asp Ile Ile
                435                440                445

Ala Ile Leu Gly Met Asp Glu Leu Ser Glu Glu Asp Lys Leu Thr Val
                450                455                460

Ser Arg Ala Arg Lys Ile Gln Arg Phe Leu Ser Gln Pro Phe Gln Val
465                470                475                480

Ala Glu Val Phe Thr Gly His Met Gly Lys Leu Val Pro Leu Lys Glu
                485                490                495

Thr Ile Lys Gly Phe Gln Gln Ile Leu Ala Gly Glu Tyr Asp His Leu
                500                505                510

Pro Glu Gln Ala Phe Tyr Met Val Gly Pro Ile Glu Glu Ala Val Ala
                515                520                525

Lys Ala Asp Lys Leu Ala Glu Glu His Ser Ser
530                535

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<210> SEQ ID NO 4

<211> LENGTH: 245

<212> TYPE: PRT

<213> ORGANISM: Human

<400> SEQUENCE: 4

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Met Asp Lys Asn Glu Leu Val Gln Lys Ala Lys Leu Ala Glu Gln Ala
1                5                10                15

Glu Arg Tyr Asp Asp Met Ala Ala Cys Met Lys Ser Val Thr Glu Gln
                20                25                30

Gly Ala Glu Leu Ser Asn Glu Glu Arg Asn Leu Leu Ser Val Ala Tyr

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35					40					45					
Lys	Asn	Val	Val	Gly	Ala	Arg	Arg	Ser	Ser	Trp	Arg	Val	Val	Ser	Ser
50					55					60					
Ile	Glu	Gln	Lys	Thr	Glu	Gly	Ala	Glu	Lys	Lys	Gln	Gln	Met	Ala	Arg
65					70					75					80
Glu	Tyr	Arg	Glu	Lys	Ile	Glu	Thr	Glu	Leu	Arg	Asp	Ile	Cys	Asn	Asp
			85						90					95	
Val	Leu	Ser	Leu	Leu	Glu	Lys	Phe	Leu	Ile	Pro	Asn	Ala	Ser	Gln	Ala
			100					105						110	
Glu	Ser	Lys	Val	Phe	Tyr	Leu	Lys	Met	Lys	Gly	Asp	Tyr	Tyr	Arg	Tyr
		115					120					125			
Leu	Ala	Glu	Val	Ala	Ala	Gly	Asp	Asp	Lys	Lys	Gly	Ile	Val	Asp	Gln
	130					135					140				
Ser	Gln	Gln	Ala	Tyr	Gln	Glu	Ala	Phe	Glu	Ile	Ser	Lys	Lys	Glu	Met
145					150					155					160
Gln	Pro	Thr	His	Pro	Ile	Arg	Leu	Gly	Leu	Ala	Leu	Asn	Phe	Ser	Val
			165						170					175	
Phe	Tyr	Tyr	Glu	Ile	Leu	Asn	Ser	Pro	Glu	Lys	Ala	Cys	Ser	Leu	Ala
			180						185					190	
Lys	Thr	Ala	Phe	Asp	Glu	Ala	Ile	Ala	Glu	Leu	Asp	Thr	Leu	Ser	Glu
		195						200				205			
Glu	Ser	Tyr	Lys	Asp	Ser	Thr	Leu	Ile	Met	Gln	Leu	Leu	Arg	Asp	Asn
	210					215					220				
Leu	Thr	Leu	Trp	Thr	Ser	Asp	Thr	Gln	Gly	Asp	Glu	Ala	Glu	Ala	Gly
225					230					235					240
Glu	Gly	Gly	Glu	Asn											
			245												

<210> SEQ ID NO 5

<211> LENGTH: 255

<212> TYPE: PRT

<213> ORGANISM: Human

<400> SEQUENCE: 5

Met	Asp	Asp	Arg	Glu	Asp	Leu	Val	Tyr	Gln	Ala	Lys	Leu	Ala	Glu	Gln
1				5					10					15	
Ala	Glu	Arg	Tyr	Asp	Glu	Met	Val	Glu	Ser	Met	Lys	Lys	Val	Ala	Gly
			20					25					30		
Met	Asp	Val	Glu	Leu	Thr	Val	Glu	Glu	Arg	Asn	Leu	Leu	Ser	Val	Ala
		35					40					45			
Tyr	Lys	Asn	Val	Ile	Gly	Ala	Arg	Arg	Ala	Ser	Trp	Arg	Ile	Ile	Ser
	50					55					60				
Ser	Ile	Glu	Gln	Lys	Glu	Glu	Asn	Lys	Gly	Gly	Glu	Asp	Lys	Leu	Lys
65					70					75					80
Met	Ile	Arg	Glu	Tyr	Arg	Gln	Met	Val	Glu	Thr	Glu	Leu	Lys	Leu	Ile
			85						90					95	
Cys	Cys	Asp	Ile	Leu	Asp	Val	Leu	Asp	Lys	His	Leu	Ile	Pro	Ala	Ala
			100						105				110		
Asn	Thr	Gly	Glu	Ser	Lys	Val	Phe	Tyr	Tyr	Lys	Met	Lys	Gly	Asp	Tyr
		115						120					125		
His	Arg	Tyr	Leu	Ala	Glu	Phe	Ala	Thr	Gly	Asn	Asp	Arg	Lys	Glu	Ala
	130						135						140		

-continued

Ala	Glu	Asn	Ser	Leu	Val	Ala	Tyr	Lys	Ala	Ala	Ser	Asp	Ile	Ala	Met
145					150					155					160
Thr	Glu	Leu	Pro	Pro	Thr	His	Pro	Ile	Arg	Leu	Gly	Leu	Ala	Leu	Asn
					165				170					175	
Phe	Ser	Val	Phe	Tyr	Tyr	Glu	Ile	Leu	Asn	Ser	Pro	Asp	Arg	Ala	Cys
			180					185					190		
Arg	Leu	Ala	Lys	Ala	Ala	Phe	Asp	Asp	Ala	Ile	Ala	Glu	Leu	Asp	Thr
		195					200					205			
Leu	Ser	Glu	Glu	Ser	Tyr	Lys	Asp	Ser	Thr	Leu	Ile	Met	Gln	Leu	Leu
	210					215					220				
Arg	Asp	Asn	Leu	Thr	Leu	Trp	Thr	Ser	Asp	Met	Gln	Gly	Asp	Gly	Glu
225					230					235					240
Glu	Gln	Asn	Lys	Glu	Ala	Leu	Gln	Asp	Val	Glu	Asp	Glu	Asn	Gln	
			245						250					255	

<210> SEQ ID NO 6

<211> LENGTH: 421

<212> TYPE: PRT

<213> ORGANISM: Human

<400> SEQUENCE: 6

Leu	Tyr	Ser	Ser	Ser	Asp	Asp	Val	Ile	Glu	Leu	Thr	Pro	Ser	Asn	Phe
1				5					10					15	
Asn	Arg	Glu	Val	Ile	Gln	Ser	Asp	Ser	Leu	Trp	Leu	Val	Glu	Phe	Tyr
		20						25					30		
Ala	Pro	Trp	Cys	Gly	His	Cys	Gln	Arg	Leu	Thr	Pro	Glu	Trp	Lys	Lys
		35					40					45			
Ala	Ala	Thr	Ala	Leu	Lys	Asp	Val	Val	Lys	Val	Gly	Ala	Val	Asp	Ala
	50					55					60				
Asp	Lys	His	His	Ser	Leu	Gly	Gly	Gln	Tyr	Gly	Val	Gln	Gly	Phe	Pro
65					70				75					80	
Thr	Ile	Lys	Ile	Phe	Gly	Ser	Asn	Lys	Asn	Arg	Pro	Glu	Asp	Tyr	Gln
				85					90					95	
Gly	Gly	Arg	Thr	Gly	Glu	Ala	Ile	Val	Asp	Ala	Ala	Leu	Ser	Ala	Leu
			100					105					110		
Arg	Gln	Leu	Val	Lys	Asp	Arg	Leu	Gly	Gly	Arg	Ser	Gly	Gly	Tyr	Ser
		115					120					125			
Ser	Gly	Lys	Gln	Gly	Arg	Ser	Asp	Ser	Ser	Ser	Lys	Lys	Asp	Val	Ile
	130					135						140			
Glu	Leu	Thr	Asp	Asp	Ser	Phe	Asp	Lys	Asn	Val	Leu	Asp	Ser	Glu	Asp
145					150					155				160	
Val	Trp	Met	Val	Glu	Phe	Tyr	Ala	Pro	Trp	Cys	Gly	His	Cys	Lys	Asn
			165						170					175	
Leu	Glu	Pro	Glu	Trp	Ala	Ala	Ala	Ala	Ser	Glu	Val	Lys	Glu	Gln	Thr
		180						185					190		
Lys	Gly	Arg	Val	Lys	Leu	Ala	Ala	Val	Asp	Ala	Thr	Val	Asn	Gln	Val
	195					200						205			
Leu	Ala	Ser	Arg	Tyr	Gly	Ile	Arg	Gly	Phe	Pro	Thr	Ile	Lys	Ile	Phe
	210					215					220				
Gln	Lys	Gly	Glu	Ser	Pro	Val	Asp	Tyr	Asp	Gly	Gly	Arg	Thr	Arg	Ser
225					230					235				240	
Asp	Ile	Val	Ser	Arg	Ala	Leu	Asp	Leu	Phe	Ser	Asp	Asn	Ala	Pro	Pro
			245						250					255	

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Pro Glu Leu Leu Glu Ile Ile Asn Glu Asp Ile Ala Lys Arg Thr Cys
 260 265 270
 Glu Glu His Gln Leu Cys Val Val Ala Val Leu Pro His Ile Leu Asp
 275 280 285
 Thr Gly Ala Ala Gly Arg Asn Ser Tyr Leu Glu Val Leu Leu Lys Leu
 290 295 300
 Ala Asp Lys Tyr Lys Lys Lys Met Trp Gly Trp Leu Trp Thr Glu Ala
 305 310 315 320
 Gly Ala Gln Ser Glu Leu Glu Thr Ala Leu Gly Ile Gly Gly Phe Gly
 325 330 335
 Tyr Pro Ala Met Ala Ala Ile Asn Ala Arg Lys Met Lys Phe Ala Leu
 340 345 350
 Leu Lys Gly Ser Phe Ser Glu Gln Gly Ile Asn Glu Phe Leu Arg Glu
 355 360 365
 Leu Ser Phe Gly Arg Gly Ser Thr Ala Pro Val Gly Gly Gly Ala Phe
 370 375 380
 Pro Thr Ile Val Glu Arg Glu Pro Trp Asp Gly Arg Asp Gly Glu Leu
 385 390 395 400
 Pro Val Glu Asp Asp Ile Asp Leu Ser Asp Val Glu Leu Asp Asp Leu
 405 410 415
 Gly Lys Asp Glu Leu
 420

<210> SEQ ID NO 7

<211> LENGTH: 687

<212> TYPE: PRT

<213> ORGANISM: Human

<400> SEQUENCE: 7

Met Val Lys Leu Ala Lys Ala Gly Lys Asn Gln Gly Asp Pro Lys Lys
 1 5 10 15
 Met Ala Pro Pro Pro Lys Glu Val Glu Glu Asp Ser Glu Asp Glu Glu
 20 25 30
 Met Ser Glu Asp Glu Glu Asp Asp Ser Ser Gly Glu Glu Val Val Ile
 35 40 45
 Pro Gln Lys Lys Gly Lys Lys Ala Ala Ala Thr Ser Ala Lys Lys Val
 50 55 60
 Val Val Ser Pro Thr Lys Lys Val Ala Val Ala Thr Pro Ala Lys Ala
 65 70 75 80
 Val Thr Thr Pro Gly Lys Lys Gly Ala Thr Pro Gly Lys Ala Leu Val
 85 90 95
 Ala Thr Pro Gly Lys Lys Gly Ala Ala Ile Pro Ala Lys Gly Ala Lys
 100 105 110
 Asn Gly Lys Asn Ala Lys Lys Glu Asp Ser Asp Glu Glu Glu Asp Asp
 115 120 125
 Asp Ser Glu Glu Asp Glu Glu Asp Asp Glu Asp Glu Asp Glu Asp Glu
 130 135 140
 Asp Glu Ile Glu Pro Ala Ala Met Lys Ala Ala Ala Ala Pro Ala
 145 150 155 160
 Ser Glu Asp Glu Asp Asp Glu Asp Asp Glu Asp Asp Glu Asp Asp Asp
 165 170 175
 Asp Asp Glu Glu Asp Asp Ser Glu Glu Glu Ala Met Glu Thr Thr Pro

-continued

180						185						190					
Ala	Lys	Gly	Lys	Lys	Ala	Ala	Lys	Val	Val	Pro	Val	Lys	Ala	Lys	Asn		
195						200						205					
Val	Ala	Glu	Asp	Glu	Asp	Glu	Glu	Glu	Asp	Asp	Glu	Asp	Glu	Asp	Asp		
210						215						220					
Asp	Asp	Asp	Glu	Asp	Asp	Glu	Asp	Asp	Asp	Asp	Glu	Asp	Asp	Glu	Glu		
225						230						235					
Glu	Glu	Glu	Glu	Glu	Glu	Glu	Glu	Pro	Val	Lys	Glu	Ala	Pro	Gly	Lys		
245						250						255					
Arg	Lys	Lys	Glu	Met	Ala	Lys	Gln	Lys	Ala	Ala	Pro	Glu	Ala	Lys	Lys		
260						265						270					
Gln	Lys	Val	Glu	Gly	Thr	Glu	Pro	Thr	Thr	Ala	Phe	Asn	Leu	Phe	Val		
275						280						285					
Gly	Asn	Leu	Asn	Phe	Asn	Lys	Ser	Ala	Pro	Glu	Leu	Lys	Thr	Gly	Ile		
290						295						300					
Ser	Asp	Val	Phe	Ala	Lys	Asn	Asp	Leu	Ala	Val	Val	Asp	Val	Arg	Ile		
305						310						315					
Gly	Met	Thr	Arg	Lys	Phe	Gly	Tyr	Val	Asp	Phe	Glu	Ser	Ala	Glu	Asp		
325						330						335					
Leu	Glu	Lys	Ala	Leu	Glu	Leu	Thr	Gly	Leu	Lys	Val	Phe	Gly	Asn	Glu		
340						345						350					
Ile	Lys	Leu	Glu	Lys	Pro	Lys	Gly	Lys	Asp	Ser	Lys	Lys	Glu	Arg	Asp		
355						360						365					
Ala	Arg	Thr	Leu	Leu	Ala	Lys	Asn	Leu	Pro	Tyr	Lys	Val	Thr	Gln	Asp		
370						375						380					
Glu	Leu	Lys	Glu	Val	Phe	Glu	Asp	Ala	Ala	Glu	Ile	Arg	Leu	Val	Ser		
385						390						395					
Lys	Asp	Gly	Lys	Ser	Lys	Gly	Ile	Ala	Tyr	Ile	Glu	Phe	Lys	Thr	Glu		
405						410						415					
Ala	Asp	Ala	Glu	Lys	Thr	Phe	Glu	Glu	Lys	Gln	Gly	Thr	Glu	Ile	Asp		
420						425						430					
Gly	Arg	Ser	Ile	Ser	Leu	Tyr	Tyr	Thr	Gly	Glu	Lys	Gly	Gln	Asn	Gln		
435						440						445					
Asp	Tyr	Arg	Gly	Gly	Lys	Asn	Ser	Thr	Trp	Ser	Gly	Glu	Ser	Lys	Thr		
450						455						460					
Leu	Val	Leu	Ser	Asn	Leu	Ser	Tyr	Ser	Ala	Thr	Glu	Glu	Thr	Leu	Gln		
465						470						475					
Glu	Val	Phe	Glu	Lys	Ala	Thr	Phe	Ile	Lys	Val	Pro	Gln	Asn	Gln	Asn		
485						490						495					
Gly	Lys	Ser	Lys	Gly	Tyr	Ala	Phe	Ile	Glu	Phe	Ala	Ser	Phe	Glu	Asp		
500						505						510					
Ala	Lys	Glu	Ala	Leu	Asn	Ser	Cys	Asn	Lys	Arg	Glu	Ile	Gly	Gly	Arg		
515						520						525					
Ala	Ile	Arg	Leu	Glu	Leu	Gln	Gly	Pro	Arg	Gly	Ser	Pro	Asn	Ala	Arg		
530						535						540					
Ser	Gln	Pro	Ser	Lys	Thr	Leu	Phe	Val	Lys	Gly	Leu	Ser	Glu	Asp	Thr		
545						550						555					
Thr	Glu	Glu	Thr	Leu	Lys	Glu	Ser	Phe	Asp	Gly	Ser	Val	Arg	Ala	Arg		
565						570						575					
Ile	Val	Thr	Asp	Arg	Glu	Thr	Gly	Ser	Ser	Lys	Gly	Phe	Gly	Phe	Val		
580						585						590					

-continued

Asp Phe Asn Ser Glu Glu Asp Ala Lys Ala Ala Lys Glu Ala Met Glu
595 600 605

Asp Gly Glu Ile Asp Gly Asn Lys Val Thr Leu Asp Trp Ala Lys Pro
610 615 620

Lys Gly Glu Gly Gly Phe Gly Gly Arg Gly Gly Gly Arg Gly Gly Phe
625 630 635 640

Gly Gly Arg Gly Gly Gly Arg Gly Gly Arg Gly Gly Phe Gly Gly Arg
645 650 655

Gly Arg Gly Gly Phe Gly Gly Arg Gly Gly Phe Arg Gly Gly Arg Gly
660 665 670

Gly Gly Gly Asp His Lys Pro Gln Gly Lys Lys Thr Lys Phe Glu
675 680 685

<210> SEQ ID NO 8
 <211> LENGTH: 641
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 8

Met Ala Gly Ile Thr Thr Ile Glu Ala Val Lys Arg Lys Ile Gln Val
1 5 10 15

Leu Gln Gln Gln Ala Asp Asp Ala Glu Glu Arg Ala Glu Arg Leu Gln
20 25 30

Arg Glu Val Glu Gly Glu Arg Arg Ala Arg Glu Gln Ala Glu Ala Glu
35 40 45

Val Ala Ser Leu Asn Arg Arg Ile Gln Leu Val Glu Glu Glu Leu Asp
50 55 60

Arg Ala Gln Glu Arg Leu Ala Thr Ala Leu Gln Lys Leu Glu Glu Ala
65 70 75 80

Glu Lys Ala Ala Asp Glu Ser Glu Arg Gly Met Lys Val Ile Glu Asn
85 90 95

Arg Ala Leu Lys Asp Glu Glu Lys Met Glu Leu Gln Glu Ile Gln Leu
100 105 110

Glu Glu Ala Lys His Ile Ala Glu Glu Ala Asp Arg Lys Tyr Glu Glu
115 120 125

Val Ala Arg Lys Leu Val Ile Ile Glu Gly Asp Leu Glu Arg Thr Glu
130 135 140

Glu Arg Ala Glu Leu Ala Glu Ser Arg Cys Arg Glu Met Asp Glu Gln
145 150 155 160

Ile Arg Leu Met Asp Gln Asn Leu Lys Cys Leu Ser Ala Ala Glu Glu
165 170 175

Lys Tyr Ser Gln Lys Glu Asp Lys Tyr Glu Glu Glu Ile Lys Ile Leu
180 185 190

Thr Asp Lys Leu Lys Glu Ala Glu Thr Arg Ala Glu Phe Ala Glu Arg
195 200 205

Ser Val Ala Lys Leu Glu Lys Thr Ile Asp Asp Leu Glu Asp Thr Asn
210 215 220

Ser Thr Ser Gly Asp Pro Val Glu Lys Lys Asp Glu Thr Pro Phe Gly
225 230 235 240

Val Ser Val Ala Val Gly Leu Ala Val Phe Ala Cys Leu Phe Leu Ser
245 250 255

Thr Leu Leu Leu Val Leu Asn Lys Cys Gly Arg Arg Asn Lys Phe Gly

-continued

260				265				270							
Ile	Asn	Arg	Pro	Ala	Val	Leu	Ala	Pro	Glu	Asp	Gly	Leu	Ala	Met	Ser
	275						280					285			
Leu	His	Phe	Met	Thr	Leu	Gly	Gly	Ser	Ser	Leu	Ser	Pro	Thr	Glu	Gly
	290					295					300				
Lys	Gly	Ser	Gly	Leu	Gln	Gly	His	Ile	Ile	Glu	Asn	Pro	Gln	Tyr	Phe
305					310					315					320
Ser	Asp	Ala	Cys	Val	His	His	Ile	Lys	Arg	Arg	Asp	Ile	Val	Leu	Lys
			325						330					335	
Trp	Glu	Leu	Gly	Glu	Gly	Ala	Phe	Gly	Lys	Val	Phe	Leu	Ala	Glu	Cys
		340							345				350		
His	Asn	Leu	Leu	Pro	Glu	Gln	Asp	Lys	Met	Leu	Val	Ala	Val	Lys	Ala
	355						360					365			
Leu	Lys	Glu	Ala	Ser	Glu	Ser	Ala	Arg	Gln	Asp	Phe	Gln	Arg	Glu	Ala
	370					375					380				
Glu	Leu	Leu	Thr	Met	Leu	Gln	His	Gln	His	Ile	Val	Arg	Phe	Phe	Gly
385					390					395					400
Val	Cys	Thr	Glu	Gly	Arg	Pro	Leu	Leu	Met	Val	Phe	Glu	Tyr	Met	Arg
			405						410					415	
His	Gly	Asp	Leu	Asn	Arg	Phe	Leu	Arg	Ser	His	Gly	Pro	Asp	Ala	Lys
		420							425				430		
Leu	Leu	Ala	Gly	Gly	Glu	Asp	Val	Ala	Pro	Gly	Pro	Leu	Gly	Leu	Gly
	435						440					445			
Gln	Leu	Leu	Ala	Val	Ala	Ser	Gln	Val	Ala	Ala	Gly	Met	Val	Tyr	Leu
	450					455					460				
Ala	Gly	Leu	His	Phe	Val	His	Arg	Asp	Leu	Ala	Thr	Arg	Asn	Cys	Leu
465					470					475					480
Val	Gly	Gln	Gly	Leu	Val	Val	Lys	Ile	Gly	Asp	Phe	Gly	Met	Ser	Arg
		485							490				495		
Asp	Ile	Tyr	Ser	Thr	Asp	Tyr	Tyr	Arg	Val	Gly	Gly	Arg	Thr	Met	Leu
	500							505				510			
Pro	Ile	Arg	Trp	Met	Pro	Pro	Glu	Ser	Ile	Leu	Tyr	Arg	Lys	Phe	Thr
	515						520					525			
Thr	Glu	Ser	Asp	Val	Trp	Ser	Phe	Gly	Val	Val	Leu	Trp	Glu	Ile	Phe
	530					535					540				
Thr	Tyr	Gly	Lys	Gln	Pro	Trp	Tyr	Gln	Leu	Ser	Asn	Thr	Glu	Ala	Ile
545					550					555					560
Asp	Cys	Ile	Thr	Gln	Gly	Arg	Glu	Leu	Glu	Arg	Pro	Arg	Ala	Cys	Pro
			565						570					575	
Pro	Glu	Val	Tyr	Ala	Ile	Met	Arg	Gly	Cys	Trp	Gln	Arg	Glu	Pro	Ser
	580							585				590			
Asn	Ala	Thr	Ala	Ser	Arg	Met	Cys	Thr	Pro	Gly	Cys	Lys	Pro	Trp	Pro
	595						600					605			
Arg	His	Leu	Leu	Ser	Thr	Trp	Met	Ser	Trp	Ala	Arg	Gly	Pro	Ala	Gln
	610					615					620				
Gly	Leu	Gly	Val	Val	Ser	Arg	Asn	Thr	Gly	Ala	Cys	Pro	Gln	His	Pro
625					630					635					640
Pro															

<210> SEQ ID NO 9

<211> LENGTH: 284

-continued

<212> TYPE: PRT

<213> ORGANISM: Human

<400> SEQUENCE: 9

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Met Glu Ala Ile Lys Lys Lys Met Gln Met Leu Lys Leu Asp Lys Glu
1           5           10           15

Asn Ala Ile Asp Arg Ala Glu Gln Ala Glu Ala Asp Lys Lys Ala Ala
20           25           30

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

Lys Leu Lys Gly Thr Glu Asp Glu Leu Asp Lys Tyr Ser Glu Asp Leu
50           55           60

Lys Asp Ala Gln Glu Lys Leu Glu Leu Thr Glu Lys Lys Ala Ser Asp
65           70           75           80

Ala Glu Gly Asp Val Ala Ala Leu Asn Arg Arg Ile Gln Leu Val Glu
85           90           95

Glu Glu Leu Asp Arg Ala Gln Glu Arg Leu Ala Thr Ala Leu Gln Lys
100          105          110

Leu Glu Glu Ala Glu Lys Ala Ala Asp Glu Ser Glu Arg Gly Met Lys
115          120          125

Val Ile Glu Asn Arg Ala Met Lys Asp Glu Glu Lys Met Glu Ile Gln
130          135          140

Glu Met Gln Leu Lys Glu Ala Lys His Ile Ala Glu Glu Ala Asp Arg
145          150          155          160

Lys Tyr Glu Glu Val Ala Arg Lys Leu Val Ile Leu Glu Gly Glu Leu
165          170          175

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

Leu Glu Glu Glu Leu Lys Asn Val Thr Asn Asn Leu Lys Ser Leu Glu
195          200          205

Ala Ala Ser Glu Lys Tyr Ser Glu Lys Glu Asp Lys Tyr Glu Glu Glu
210          215          220

Ile Lys Leu Leu Ser Asp Lys Leu Lys Glu Ala Glu Thr Arg Ala Glu
225          230          235          240

Phe Ala Glu Arg Thr Val Ala Lys Leu Glu Lys Thr Ile Asp Asp Leu
245          250          255

Glu Glu Lys Leu Ala Gln Ala Lys Glu Glu Asn Val Gly Leu His Gln
260          265          270

Thr Leu Asp Gln Thr Leu Asn Glu Leu Asn Cys Ile
275          280

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<210> SEQ ID NO 10

<211> LENGTH: 417

<212> TYPE: PRT

<213> ORGANISM: Human

<400> SEQUENCE: 10

```

Met Leu Leu Ser Val Pro Leu Leu Leu Gly Leu Leu Gly Leu Ala Val
1           5           10           15

Ala Glu Pro Ala Val Tyr Phe Lys Glu Gln Phe Leu Asp Gly Asp Gly
20           25           30

Trp Thr Ser Arg Trp Ile Glu Ser Lys His Lys Ser Asp Phe Gly Lys
35           40           45

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Phe Val Leu Ser Ser Gly Lys Phe Tyr Gly Asp Glu Glu Lys Asp Lys
 50                               55                               60

Gly Leu Gln Thr Ser Gln Asp Ala Arg Phe Tyr Ala Leu Ser Ala Ser
 65                               70                               75                               80

Phe Glu Pro Phe Ser Asn Lys Gly Gln Thr Leu Val Val Gln Phe Thr
                               85                               90                               95

Val Lys His Glu Gln Asn Ile Asp Cys Gly Gly Gly Tyr Val Lys Leu
                               100                               105                               110

Phe Pro Asn Ser Leu Asp Gln Thr Asp Met His Gly Asp Ser Glu Tyr
                               115                               120                               125

Asn Ile Met Phe Gly Pro Asp Ile Cys Gly Pro Gly Thr Lys Lys Val
 130                               135                               140

His Val Ile Phe Asn Tyr Lys Gly Lys Asn Val Leu Ile Asn Lys Asp
 145                               150                               155                               160

Ile Arg Cys Lys Asp Asp Glu Phe Thr His Leu Tyr Thr Leu Ile Val
                               165                               170                               175

Arg Pro Asp Asn Thr Tyr Glu Val Lys Ile Asp Asn Ser Gln Val Glu
                               180                               185                               190

Ser Gly Ser Leu Glu Asp Asp Trp Asp Phe Leu Pro Pro Lys Lys Ile
                               195                               200                               205

Lys Asp Pro Asp Ala Ser Lys Pro Glu Asp Trp Asp Glu Arg Ala Lys
 210                               215                               220

Ile Asp Asp Pro Thr Asp Ser Lys Pro Glu Asp Trp Asp Lys Pro Glu
 225                               230                               235                               240

His Ile Pro Asp Pro Asp Ala Lys Lys Pro Glu Asp Trp Asp Glu Glu
                               245                               250                               255

Met Asp Gly Glu Trp Glu Pro Pro Val Ile Gln Asn Pro Glu Tyr Lys
                               260                               265                               270

Gly Glu Trp Lys Pro Arg Gln Ile Asp Asn Pro Asp Tyr Lys Gly Thr
 275                               280                               285

Trp Ile His Pro Glu Ile Asp Asn Pro Glu Tyr Ser Pro Asp Pro Ser
 290                               295                               300

Ile Tyr Ala Tyr Asp Asn Phe Gly Val Leu Gly Leu Asp Leu Trp Gln
 305                               310                               315                               320

Val Lys Ser Gly Thr Ile Phe Asp Asn Phe Leu Ile Thr Asn Asp Glu
                               325                               330                               335

Ala Tyr Ala Glu Glu Phe Gly Asn Glu Thr Trp Gly Val Thr Lys Ala
                               340                               345                               350

Ala Glu Lys Gln Met Lys Asp Lys Gln Asp Glu Glu Gln Arg Leu Lys
                               355                               360                               365

Glu Glu Glu Glu Asp Lys Lys Arg Lys Glu Glu Glu Glu Ala Glu Asp
 370                               375                               380

Lys Glu Asp Asp Glu Asp Lys Asp Glu Asp Glu Glu Asp Glu Glu Asp
 385                               390                               395                               400

Lys Glu Glu Asp Glu Glu Glu Asp Val Pro Gly Gln Ala Lys Asp Glu
                               405                               410                               415

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Leu

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<210> SEQ ID NO 11
<211> LENGTH: 278
<212> TYPE: PRT
<213> ORGANISM: Human

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<400> SEQUENCE: 11

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Leu Arg Cys Val Pro Arg Val Leu Gly Ser Ser Val Ala Gly Leu Arg
1          5          10          15
Ala Ala Ala Pro Ala Ser Pro Phe Arg Gln Leu Leu Gln Pro Ala Pro
20          25          30
Arg Leu Cys Thr Arg Pro Phe Gly Leu Leu Ser Val Arg Ala Gly Ser
35          40          45
Glu Arg Arg Pro Gly Leu Leu Arg Pro Arg Gly Pro Cys Ala Cys Gly
50          55          60
Cys Gly Cys Gly Ser Leu His Thr Asp Gly Asp Lys Ala Phe Val Asp
65          70          75          80
Phe Leu Ser Asp Glu Ile Lys Glu Glu Arg Lys Ile Gln Lys His Lys
85          90          95
Thr Leu Pro Lys Met Ser Gly Gly Trp Glu Leu Glu Leu Asn Gly Thr
100         105         110
Glu Ala Lys Leu Val Arg Lys Val Ala Gly Glu Lys Ile Thr Val Thr
115         120         125
Phe Asn Ile Asn Asn Ser Ile Pro Pro Thr Phe Asp Gly Glu Glu Glu
130         135         140
Pro Ser Gln Gly Gln Lys Val Glu Glu Gln Glu Pro Glu Leu Thr Ser
145         150         155         160
Thr Pro Asn Phe Val Val Glu Val Ile Lys Asn Asp Asp Gly Lys Lys
165         170         175
Ala Leu Val Leu Asp Cys His Tyr Pro Glu Asp Glu Val Gly Gln Glu
180         185         190
Asp Glu Ala Glu Ser Asp Ile Phe Ser Ile Arg Glu Val Ser Phe Gln
195         200         205
Ser Thr Gly Glu Ser Glu Trp Lys Asp Thr Asn Tyr Thr Leu Asn Thr
210         215         220
Asp Ser Leu Asp Trp Ala Leu Tyr Asp His Leu Met Asp Phe Leu Ala
225         230         235         240
Asp Arg Gly Val Asp Asn Thr Phe Ala Asp Glu Leu Val Glu Leu Ser
245         250         255
Thr Ala Leu Glu His Gln Glu Tyr Ile Thr Phe Leu Glu Asp Leu Lys
260         265         270
Ser Phe Val Lys Ser Gln
275

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<210> SEQ ID NO 12

<211> LENGTH: 661

<212> TYPE: PRT

<213> ORGANISM: Human

<400> SEQUENCE: 12

```

Arg Ala Leu Arg Arg Ala Pro Ala Leu Ala Ala Val Pro Gly Gly Lys
1          5          10          15
Pro Ile Leu Cys Pro Arg Arg Thr Thr Ala Gln Leu Gly Pro Arg Arg
20          25          30
Asn Pro Ala Trp Ser Leu Gln Ala Gly Arg Leu Phe Ser Thr Gln Thr
35          40          45
Ala Glu Asp Lys Glu Glu Pro Leu His Ser Ile Ile Ser Ser Thr Glu
50          55          60

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Ser	Val	Gln	Gly	Ser	Thr	Ser	Lys	His	Glu	Phe	Gln	Ala	Glu	Thr	Lys	65	70	75	80
Lys	Leu	Leu	Asp	Ile	Val	Ala	Arg	Ser	Leu	Tyr	Ser	Glu	Lys	Glu	Val	85	90	95	
Phe	Ile	Arg	Glu	Leu	Ile	Ser	Asn	Ala	Ser	Asp	Ala	Leu	Glu	Lys	Leu	100	105	110	
Arg	His	Lys	Leu	Val	Ser	Asp	Gly	Gln	Ala	Leu	Pro	Glu	Met	Glu	Ile	115	120	125	
His	Leu	Gln	Thr	Asn	Ala	Glu	Lys	Gly	Thr	Ile	Thr	Ile	Gln	Asp	Thr	130	135	140	
Gly	Ile	Gly	Met	Thr	Gln	Glu	Glu	Leu	Val	Ser	Asn	Leu	Gly	Thr	Ile	145	150	155	160
Ala	Arg	Ser	Gly	Ser	Lys	Ala	Phe	Leu	Asp	Ala	Leu	Gln	Asn	Gln	Ala	165	170	175	
Glu	Ala	Ser	Ser	Lys	Ile	Ile	Gly	Gln	Phe	Gly	Val	Gly	Phe	Tyr	Ser	180	185	190	
Ala	Phe	Met	Val	Ala	Asp	Arg	Val	Glu	Val	Tyr	Ser	Arg	Ser	Ala	Ala	195	200	205	
Pro	Gly	Ser	Leu	Gly	Tyr	Gln	Trp	Leu	Ser	Asp	Gly	Ser	Gly	Val	Phe	210	215	220	
Glu	Ile	Ala	Glu	Ala	Ser	Gly	Val	Arg	Thr	Gly	Thr	Lys	Ile	Ile	Ile	225	230	235	240
His	Leu	Lys	Ser	Asp	Cys	Lys	Glu	Phe	Ser	Ser	Glu	Ala	Arg	Val	Arg	245	250	255	
Asp	Val	Val	Thr	Lys	Tyr	Ser	Asn	Phe	Val	Ser	Phe	Pro	Leu	Tyr	Leu	260	265	270	
Asn	Gly	Arg	Arg	Met	Asn	Thr	Leu	Gln	Ala	Ile	Trp	Met	Met	Asp	Pro	275	280	285	
Lys	Asp	Val	Gly	Glu	Trp	Gln	His	Glu	Glu	Phe	Tyr	Arg	Tyr	Val	Ala	290	295	300	
Gln	Ala	His	Asp	Lys	Pro	Arg	Tyr	Thr	Leu	His	Tyr	Lys	Thr	Asp	Ala	305	310	315	320
Pro	Leu	Asn	Ile	Arg	Ser	Ile	Phe	Tyr	Val	Pro	Asp	Met	Lys	Pro	Ser	325	330	335	
Met	Phe	Asp	Val	Ser	Arg	Glu	Leu	Gly	Ser	Ser	Val	Ala	Leu	Tyr	Ser	340	345	350	
Arg	Lys	Val	Leu	Ile	Gln	Thr	Lys	Ala	Thr	Asp	Ile	Leu	Pro	Lys	Trp	355	360	365	
Leu	Arg	Phe	Ile	Arg	Gly	Val	Val	Asp	Ser	Glu	Asp	Ile	Pro	Leu	Asn	370	375	380	
Leu	Ser	Arg	Glu	Leu	Leu	Gln	Glu	Ser	Ala	Leu	Ile	Arg	Lys	Leu	Arg	385	390	395	400
Asp	Val	Leu	Gln	Gln	Arg	Leu	Ile	Lys	Phe	Phe	Ile	Asp	Gln	Ser	Lys	405	410	415	
Lys	Asp	Ala	Glu	Lys	Tyr	Ala	Lys	Phe	Phe	Glu	Asp	Tyr	Gly	Leu	Phe	420	425	430	
Met	Arg	Glu	Gly	Ile	Val	Thr	Ala	Thr	Glu	Gln	Glu	Val	Lys	Glu	Asp	435	440	445	
Ile	Ala	Lys	Leu	Leu	Arg	Tyr	Glu	Ser	Ser	Ala	Leu	Pro	Ser	Gly	Gln	450	455	460	

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Leu Thr Ser Leu Ser Glu Tyr Ala Ser Arg Met Arg Ala Gly Thr Arg
 465 470 475 480
 Asn Ile Tyr Tyr Leu Cys Ala Pro Asn Arg His Leu Ala Glu His Ser
 485 490 495
 Pro Tyr Tyr Glu Ala Met Lys Lys Lys Asp Thr Glu Val Leu Phe Cys
 500 505 510
 Phe Glu Gln Phe Asp Glu Leu Thr Leu Leu His Leu Arg Glu Phe Asp
 515 520 525
 Lys Lys Lys Leu Ile Ser Val Glu Thr Asp Ile Val Val Asp His Tyr
 530 535 540
 Lys Glu Glu Lys Phe Glu Asp Arg Ser Pro Ala Ala Glu Cys Leu Ser
 545 550 555 560
 Glu Lys Glu Thr Glu Glu Leu Met Ala Trp Met Arg Asn Val Leu Gly
 565 570 575
 Ser Arg Val Thr Asn Val Lys Val Thr Leu Arg Leu Asp Thr His Pro
 580 585 590
 Ala Met Val Thr Val Leu Glu Met Gly Ala Ala Arg His Phe Leu Arg
 595 600 605
 Met Gln Gln Leu Ala Lys Thr Gln Glu Glu Arg Ala Gln Leu Leu Gln
 610 615 620
 Pro Thr Leu Glu Ile Asn Pro Arg His Ala Leu Ile Lys Lys Leu Asn
 625 630 635 640
 His Cys Ala Gln Ala Ser Leu Ala Trp Leu Ser Cys Trp Trp Ile Arg
 645 650 655
 Tyr Thr Arg Thr Pro
 660

<210> SEQ ID NO 13
 <211> LENGTH: 803
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 13

Met Arg Ala Leu Trp Val Leu Gly Leu Cys Cys Val Leu Leu Thr Phe
 1 5 10 15
 Gly Ser Val Arg Ala Asp Asp Glu Val Asp Val Asp Gly Thr Val Glu
 20 25 30
 Glu Asp Leu Gly Lys Ser Arg Glu Gly Ser Arg Thr Asp Asp Glu Val
 35 40 45
 Val Gln Arg Glu Glu Glu Ala Ile Gln Leu Asp Gly Leu Asn Ala Ser
 50 55 60
 Gln Ile Arg Glu Leu Arg Glu Lys Ser Glu Lys Phe Ala Phe Gln Ala
 65 70 75 80
 Glu Val Asn Arg Met Met Lys Leu Ile Ile Asn Ser Leu Tyr Lys Asn
 85 90 95
 Lys Glu Ile Phe Leu Arg Glu Leu Ile Ser Asn Ala Ser Asp Ala Leu
 100 105 110
 Asp Lys Ile Arg Leu Ile Ser Leu Thr Asp Glu Asn Ala Leu Ser Gly
 115 120 125
 Asn Glu Glu Leu Thr Val Lys Ile Lys Cys Asp Lys Glu Lys Asn Leu
 130 135 140
 Leu His Val Thr Asp Thr Gly Val Gly Met Thr Arg Glu Glu Leu Val
 145 150 155 160

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Lys	Asn	Leu	Gly	Thr	Ile	Ala	Lys	Ser	Gly	Thr	Ser	Glu	Phe	Leu	Asn	165	170	175
Lys	Met	Thr	Glu	Ala	Gln	Glu	Asp	Gly	Gln	Ser	Thr	Ser	Glu	Leu	Ile	180	185	190
Gly	Gln	Phe	Gly	Val	Gly	Phe	Tyr	Ser	Ala	Phe	Leu	Val	Ala	Asp	Lys	195	200	205
Val	Ile	Val	Thr	Ser	Lys	His	Asn	Asn	Asp	Thr	Gln	His	Ile	Trp	Glu	210	215	220
Ser	Asp	Ser	Asn	Glu	Phe	Ser	Val	Ile	Ala	Asp	Pro	Arg	Gly	Asn	Thr	225	230	235
Leu	Gly	Arg	Gly	Thr	Thr	Ile	Thr	Leu	Val	Leu	Lys	Glu	Glu	Ala	Ser	245	250	255
Asp	Tyr	Leu	Glu	Leu	Asp	Thr	Ile	Lys	Asn	Leu	Val	Lys	Lys	Tyr	Ser	260	265	270
Gln	Phe	Ile	Asn	Phe	Pro	Ile	Tyr	Val	Trp	Ser	Ser	Lys	Thr	Glu	Thr	275	280	285
Val	Glu	Glu	Pro	Met	Glu	Glu	Glu	Ala	Ala	Lys	Glu	Glu	Lys	Glu		290	295	300
Glu	Ser	Asp	Asp	Glu	Ala	Ala	Val	Glu	Glu	Glu	Glu	Glu	Lys	Lys		305	310	315
Pro	Lys	Thr	Lys	Lys	Val	Glu	Lys	Thr	Val	Trp	Asp	Trp	Glu	Leu	Met	325	330	335
Asn	Asp	Ile	Lys	Pro	Ile	Trp	Gln	Arg	Pro	Ser	Lys	Glu	Val	Glu	Glu	340	345	350
Asp	Glu	Tyr	Lys	Ala	Phe	Tyr	Lys	Ser	Phe	Ser	Lys	Glu	Ser	Asp	Asp	355	360	365
Pro	Met	Ala	Tyr	Ile	His	Phe	Thr	Ala	Glu	Gly	Glu	Val	Thr	Phe	Lys	370	375	380
Ser	Ile	Leu	Phe	Val	Pro	Thr	Ser	Ala	Pro	Arg	Gly	Leu	Phe	Asp	Glu	385	390	395
Tyr	Gly	Ser	Lys	Lys	Ser	Asp	Tyr	Ile	Lys	Leu	Tyr	Val	Arg	Arg	Val	405	410	415
Phe	Ile	Thr	Asp	Asp	Phe	His	Asp	Met	Met	Pro	Lys	Tyr	Leu	Asn	Phe	420	425	430
Val	Lys	Gly	Val	Val	Asp	Ser	Asp	Asp	Leu	Pro	Leu	Asn	Val	Ser	Arg	435	440	445
Glu	Thr	Leu	Gln	Gln	His	Lys	Leu	Leu	Lys	Val	Ile	Arg	Lys	Lys	Leu	450	455	460
Val	Arg	Lys	Thr	Leu	Asp	Met	Ile	Lys	Lys	Ile	Ala	Asp	Asp	Lys	Tyr	465	470	475
Asn	Asp	Thr	Phe	Trp	Lys	Glu	Phe	Gly	Thr	Asn	Ile	Lys	Leu	Gly	Val	485	490	495
Ile	Glu	Asp	His	Ser	Asn	Arg	Thr	Arg	Leu	Ala	Lys	Leu	Leu	Arg	Phe	500	505	510
Gln	Ser	Ser	His	His	Pro	Thr	Asp	Ile	Thr	Ser	Leu	Asp	Gln	Tyr	Val	515	520	525
Glu	Arg	Met	Lys	Glu	Lys	Gln	Asp	Lys	Ile	Tyr	Phe	Met	Ala	Gly	Ser	530	535	540
Ser	Arg	Lys	Glu	Ala	Glu	Ser	Ser	Pro	Phe	Val	Glu	Arg	Leu	Leu	Lys	545	550	555

-continued

Lys Gly Tyr Glu Val Ile Tyr Leu Thr Glu Pro Val Asp Glu Tyr Cys
 565 570 575
 Ile Gln Ala Leu Pro Glu Phe Asp Gly Lys Arg Phe Gln Asn Val Ala
 580 585 590
 Lys Glu Gly Val Lys Phe Asp Glu Ser Glu Lys Thr Lys Glu Ser Arg
 595 600 605
 Glu Ala Val Glu Lys Glu Phe Glu Pro Leu Leu Asn Trp Met Lys Asp
 610 615 620
 Lys Ala Leu Lys Asp Lys Ile Glu Lys Ala Val Val Ser Gln Arg Leu
 625 630 635 640
 Thr Glu Ser Pro Cys Ala Leu Val Ala Ser Gln Tyr Gly Trp Ser Gly
 645 650 655
 Asn Met Glu Arg Ile Met Lys Ala Gln Ala Tyr Gln Thr Gly Lys Asp
 660 665 670
 Ile Ser Thr Asn Tyr Tyr Ala Ser Gln Lys Lys Thr Phe Glu Ile Asn
 675 680 685
 Pro Arg His Pro Leu Ile Arg Asp Met Leu Arg Arg Ile Lys Glu Asp
 690 695 700
 Glu Asp Asp Lys Thr Val Leu Asp Leu Ala Val Val Leu Phe Glu Thr
 705 710 715 720
 Ala Thr Leu Arg Ser Gly Tyr Leu Leu Pro Asp Thr Lys Ala Tyr Gly
 725 730 735
 Asp Arg Ile Glu Arg Met Leu Arg Leu Ser Leu Asn Ile Asp Pro Asp
 740 745 750
 Ala Lys Val Glu Glu Glu Pro Glu Glu Glu Pro Glu Glu Thr Ala Glu
 755 760 765
 Asp Thr Thr Glu Asp Thr Glu Gln Asp Glu Asp Glu Glu Met Asp Val
 770 775 780
 Gly Thr Asp Glu Glu Glu Glu Thr Ala Lys Glu Ser Thr Ala Glu Lys
 785 790 795 800
 Asp Glu Leu

<210> SEQ ID NO 14
 <211> LENGTH: 724
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 14

Met Pro Glu Glu Val His His Gly Glu Glu Glu Val Glu Thr Phe Ala
 1 5 10 15
 Phe Gln Ala Glu Ile Ala Gln Leu Met Ser Leu Ile Ile Asn Thr Phe
 20 25 30
 Tyr Ser Asn Lys Glu Ile Phe Leu Arg Glu Leu Ile Ser Asn Ala Ser
 35 40 45
 Asp Ala Leu Asp Lys Ile Arg Tyr Glu Ser Leu Thr Asp Pro Ser Lys
 50 55 60
 Leu Asp Ser Gly Lys Glu Leu Lys Ile Asp Ile Ile Pro Asn Pro Gln
 65 70 75 80
 Glu Arg Thr Leu Thr Leu Val Asp Thr Gly Ile Gly Met Thr Lys Ala
 85 90 95
 Asp Leu Ile Asn Asn Leu Gly Thr Ile Ala Lys Ser Gly Thr Lys Ala
 100 105 110

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Phe	Met	Glu	Ala	Leu	Gln	Ala	Gly	Ala	Asp	Ile	Ser	Met	Ile	Gly	Gln	115	120	125	
Phe	Gly	Val	Gly	Phe	Tyr	Ser	Ala	Tyr	Leu	Val	Ala	Glu	Lys	Val	Val	130	135	140	
Val	Ile	Arg	Lys	His	Asn	Asp	Asp	Glu	Gln	Tyr	Ala	Trp	Glu	Ser	Ser	145	150	155	160
Ala	Gly	Gly	Ser	Phe	Thr	Val	Arg	Ala	Asp	His	Gly	Glu	Pro	Ile	Gly	165	170	175	
Met	Gly	Thr	Lys	Val	Ile	Leu	His	Leu	Lys	Glu	Asp	Gln	Thr	Glu	Tyr	180	185	190	
Leu	Glu	Glu	Arg	Arg	Val	Lys	Glu	Val	Val	Lys	Lys	His	Ser	Gln	Phe	195	200	205	
Ile	Gly	Tyr	Pro	Ile	Thr	Leu	Tyr	Leu	Glu	Lys	Glu	Arg	Glu	Lys	Glu	210	215	220	
Ile	Ser	Asp	Asp	Glu	Ala	Glu	Glu	Glu	Lys	Gly	Glu	Lys	Glu	Glu	Glu	225	230	235	240
Asp	Lys	Asp	Asp	Glu	Glu	Lys	Pro	Lys	Ile	Glu	Asp	Val	Gly	Ser	Asp	245	250	255	
Glu	Glu	Asp	Asp	Ser	Gly	Lys	Asp	Lys	Lys	Lys	Lys	Thr	Lys	Lys	Ile	260	265	270	
Lys	Glu	Lys	Tyr	Ile	Asp	Gln	Glu	Glu	Leu	Asn	Lys	Thr	Lys	Pro	Ile	275	280	285	
Trp	Thr	Arg	Asn	Pro	Asp	Asp	Ile	Thr	Gln	Glu	Glu	Tyr	Gly	Glu	Phe	290	295	300	
Tyr	Lys	Ser	Leu	Thr	Asn	Asp	Trp	Glu	Asp	His	Leu	Ala	Val	Lys	His	305	310	315	320
Phe	Ser	Val	Glu	Gly	Gln	Leu	Glu	Phe	Arg	Ala	Leu	Leu	Phe	Ile	Pro	325	330	335	
Arg	Arg	Ala	Pro	Phe	Asp	Leu	Phe	Glu	Asn	Lys	Lys	Lys	Lys	Asn	Asn	340	345	350	
Ile	Lys	Leu	Tyr	Val	Arg	Arg	Val	Phe	Ile	Met	Asp	Ser	Cys	Asp	Glu	355	360	365	
Leu	Ile	Pro	Glu	Tyr	Leu	Asn	Phe	Ile	Arg	Gly	Val	Val	Asp	Ser	Glu	370	375	380	
Asp	Leu	Pro	Leu	Asn	Ile	Ser	Arg	Glu	Met	Leu	Gln	Gln	Ser	Lys	Ile	385	390	395	400
Leu	Lys	Val	Ile	Arg	Lys	Asn	Ile	Val	Lys	Lys	Cys	Leu	Glu	Leu	Phe	405	410	415	
Ser	Glu	Leu	Ala	Glu	Asp	Lys	Glu	Asn	Tyr	Lys	Lys	Phe	Tyr	Glu	Ala	420	425	430	
Phe	Ser	Lys	Asn	Leu	Lys	Leu	Gly	Ile	His	Glu	Asp	Ser	Thr	Asn	Arg	435	440	445	
Arg	Arg	Leu	Ser	Glu	Leu	Leu	Arg	Tyr	His	Thr	Ser	Gln	Ser	Gly	Asp	450	455	460	
Glu	Met	Thr	Ser	Leu	Ser	Glu	Tyr	Val	Ser	Arg	Met	Lys	Glu	Thr	Gln	465	470	475	480
Lys	Ser	Ile	Tyr	Tyr	Ile	Thr	Gly	Glu	Ser	Lys	Glu	Gln	Val	Ala	Asn	485	490	495	
Ser	Ala	Phe	Val	Glu	Arg	Val	Arg	Lys	Arg	Gly	Phe	Glu	Val	Val	Tyr	500	505	510	
Met	Thr	Glu	Pro	Ile	Asp	Glu	Tyr	Cys	Val	Gln	Gln	Leu	Lys	Glu	Phe				

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515				520				525							
Asp	Gly	Lys	Ser	Leu	Val	Ser	Val	Thr	Lys	Glu	Gly	Leu	Glu	Leu	Pro
530						535					540				
Glu	Asp	Glu	Glu	Glu	Lys	Lys	Met	Glu	Glu	Ser	Lys	Ala	Lys	Phe	
545				550					555					560	
Glu	Asn	Leu	Cys	Lys	Leu	Met	Lys	Glu	Ile	Leu	Asp	Lys	Lys	Val	Glu
			565						570					575	
Lys	Val	Thr	Ile	Ser	Asn	Arg	Leu	Val	Ser	Ser	Pro	Cys	Cys	Ile	Val
			580						585					590	
Thr	Ser	Thr	Tyr	Gly	Trp	Thr	Ala	Asn	Met	Glu	Arg	Ile	Met	Lys	Ala
			595				600							605	
Gln	Ala	Leu	Arg	Asp	Asn	Ser	Thr	Met	Gly	Tyr	Met	Met	Ala	Lys	Lys
	610					615					620				
His	Leu	Glu	Ile	Asn	Pro	Asp	His	Pro	Ile	Val	Glu	Thr	Leu	Arg	Gln
	625				630					635					640
Lys	Ala	Glu	Ala	Asp	Lys	Asn	Asp	Lys	Ala	Val	Lys	Asp	Leu	Val	Val
			645						650					655	
Leu	Leu	Phe	Glu	Thr	Ala	Leu	Leu	Ser	Ser	Gly	Phe	Ser	Leu	Glu	Asp
			660						665					670	
Pro	Gln	Thr	His	Ser	Asn	Arg	Ile	Tyr	Arg	Met	Ile	Lys	Leu	Gly	Leu
			675				680							685	
Gly	Ile	Asp	Glu	Asp	Glu	Val	Ala	Ala	Glu	Glu	Pro	Asn	Ala	Ala	Val
	690					695					700				
Pro	Asp	Glu	Ile	Pro	Pro	Leu	Glu	Gly	Asp	Glu	Asp	Ala	Ser	Arg	Met
	705				710				715					720	
Glu	Glu	Val	Asp												

<210> SEQ ID NO 15
 <211> LENGTH: 732
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 15

Met	Pro	Glu	Glu	Thr	Gln	Thr	Gln	Asp	Gln	Pro	Met	Glu	Glu	Glu	Glu
1				5					10					15	
Val	Glu	Thr	Phe	Ala	Phe	Gln	Ala	Glu	Ile	Ala	Gln	Leu	Met	Ser	Leu
			20					25				30			
Ile	Ile	Asn	Thr	Phe	Tyr	Ser	Asn	Lys	Glu	Ile	Phe	Leu	Arg	Glu	Leu
		35					40					45			
Ile	Ser	Asn	Ser	Ser	Asp	Ala	Leu	Asp	Lys	Ile	Arg	Tyr	Glu	Thr	Leu
		50				55					60				
Thr	Asp	Pro	Ser	Lys	Leu	Asp	Ser	Gly	Lys	Glu	Leu	His	Ile	Asn	Leu
		65			70					75				80	
Ile	Pro	Asn	Lys	Gln	Asp	Arg	Thr	Leu	Thr	Ile	Val	Asp	Thr	Gly	Ile
			85						90					95	
Gly	Met	Thr	Lys	Ala	Asp	Leu	Ile	Asn	Asn	Leu	Gly	Thr	Ile	Ala	Lys
			100					105					110		
Ser	Gly	Thr	Lys	Ala	Phe	Met	Glu	Ala	Leu	Gln	Ala	Gly	Ala	Asp	Ile
			115				120					125			
Ser	Met	Ile	Gly	Gln	Phe	Gly	Val	Gly	Phe	Tyr	Ser	Ala	Tyr	Leu	Val
		130				135					140				
Ala	Glu	Lys	Val	Thr	Val	Ile	Thr	Lys	His	Asn	Asp	Asp	Glu	Gln	Tyr

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145	150	155	160
Ala Trp Glu Ser Ser Ala Gly Gly Ser Phe Thr Val Arg Thr Asp Thr	165	170	175
Gly Glu Pro Met Gly Arg Gly Thr Lys Val Ile Leu His Leu Lys Glu	180	185	190
Asp Gln Thr Glu Tyr Leu Glu Glu Arg Arg Ile Lys Glu Ile Val Lys	195	200	205
Lys His Ser Gln Phe Ile Gly Tyr Pro Ile Thr Leu Phe Val Glu Lys	210	215	220
Glu Arg Asp Lys Glu Val Ser Asp Asp Glu Ala Glu Glu Lys Glu Asp	225	230	235
Lys Glu Glu Glu Lys Glu Lys Glu Glu Lys Glu Ser Glu Asp Lys Pro	245	250	255
Glu Ile Glu Asp Val Gly Ser Asp Glu Glu Glu Glu Lys Lys Asp Gly	260	265	270
Asp Lys Lys Lys Lys Lys Lys Ile Lys Glu Lys Tyr Ile Asp Gln Glu	275	280	285
Glu Leu Asn Lys Thr Lys Pro Ile Trp Thr Arg Asn Pro Asp Asp Ile	290	295	300
Thr Asn Glu Glu Tyr Gly Glu Phe Tyr Lys Ser Leu Thr Asn Asp Trp	305	310	315
Glu Asp His Leu Ala Val Lys His Phe Ser Val Glu Gly Gln Leu Glu	325	330	335
Phe Arg Ala Leu Leu Phe Val Pro Arg Arg Ala Pro Phe Asp Leu Phe	340	345	350
Glu Asn Arg Lys Lys Lys Asn Asn Ile Lys Leu Tyr Val Arg Arg Val	355	360	365
Phe Ile Met Asp Asn Cys Glu Glu Leu Ile Pro Glu Tyr Leu Asn Phe	370	375	380
Ile Arg Gly Val Val Asp Ser Glu Asp Leu Pro Leu Asn Ile Ser Arg	385	390	395
Glu Met Leu Gln Gln Ser Lys Ile Leu Lys Val Ile Arg Lys Asn Leu	405	410	415
Val Lys Lys Cys Leu Glu Leu Phe Thr Glu Leu Ala Glu Asp Lys Glu	420	425	430
Asn Tyr Lys Lys Phe Tyr Glu Gln Phe Ser Lys Asn Ile Lys Leu Gly	435	440	445
Ile His Glu Asp Ser Gln Asn Arg Lys Lys Leu Ser Glu Leu Leu Arg	450	455	460
Tyr Tyr Thr Ser Ala Ser Gly Asp Glu Met Val Ser Leu Lys Asp Tyr	465	470	475
Cys Thr Arg Met Lys Glu Asn Gln Lys His Ile Tyr Tyr Ile Thr Gly	485	490	495
Glu Thr Lys Asp Gln Val Ala Asn Ser Ala Phe Val Glu Arg Leu Arg	500	505	510
Lys His Gly Leu Glu Val Ile Tyr Met Ile Glu Pro Ile Asp Glu Tyr	515	520	525
Cys Val Gln Gln Leu Lys Glu Phe Glu Gly Lys Thr Leu Val Ser Val	530	535	540
Thr Lys Glu Gly Leu Glu Leu Pro Glu Asp Glu Glu Glu Lys Lys Lys	545	550	555
			560

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Gln Glu Glu Lys Lys Thr Lys Phe Glu Asn Leu Cys Lys Ile Met Lys
 565 570 575
 Asp Ile Leu Glu Lys Lys Val Glu Lys Val Val Val Ser Asn Arg Leu
 580 585 590
 Val Thr Ser Pro Cys Cys Ile Val Thr Ser Thr Tyr Gly Trp Thr Ala
 595 600 605
 Asn Met Glu Arg Ile Met Lys Ala Gln Ala Leu Arg Asp Asn Ser Thr
 610 615 620
 Met Gly Tyr Met Ala Ala Lys Lys His Leu Glu Ile Asn Pro Asp His
 625 630 635 640
 Ser Ile Ile Glu Thr Leu Arg Gln Lys Ala Glu Ala Asp Lys Asn Asp
 645 650 655
 Lys Ser Val Lys Asp Leu Val Ile Leu Leu Tyr Glu Thr Ala Leu Leu
 660 665 670
 Ser Ser Gly Phe Ser Leu Glu Asp Pro Gln Thr His Ala Asn Arg Ile
 675 680 685
 Tyr Arg Met Ile Lys Leu Gly Leu Gly Ile Asp Glu Asp Asp Pro Thr
 690 695 700
 Ala Asp Asp Thr Ser Ala Ala Val Thr Glu Glu Met Pro Pro Leu Glu
 705 710 715 720
 Gly Asp Asp Asp Thr Ser Arg Met Glu Glu Val Asp
 725 730

<210> SEQ ID NO 16
 <211> LENGTH: 573
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 16

Met Leu Arg Leu Pro Thr Val Phe Arg Gln Met Arg Pro Val Ser Arg
 1 5 10 15
 Val Leu Ala Pro His Leu Thr Arg Ala Tyr Ala Lys Asp Val Lys Phe
 20 25 30
 Gly Ala Asp Ala Arg Ala Leu Met Leu Gln Gly Val Asp Leu Leu Ala
 35 40 45
 Asp Ala Val Ala Val Thr Met Gly Pro Lys Gly Arg Thr Val Ile Ile
 50 55 60
 Glu Gln Ser Trp Gly Ser Pro Lys Val Thr Lys Asp Gly Val Thr Val
 65 70 75 80
 Ala Lys Ser Ile Asp Leu Lys Asp Lys Tyr Lys Asn Ile Gly Ala Lys
 85 90 95
 Leu Val Gln Asp Val Ala Asn Asn Thr Asn Glu Glu Ala Gly Asp Gly
 100 105 110
 Thr Thr Thr Ala Thr Val Leu Ala Arg Ser Ile Ala Lys Glu Gly Phe
 115 120 125
 Glu Lys Ile Ser Lys Gly Ala Asn Pro Val Glu Ile Arg Arg Gly Val
 130 135 140
 Met Leu Ala Val Asp Ala Val Ile Ala Glu Leu Lys Lys Gln Ser Lys
 145 150 155 160
 Pro Val Thr Thr Pro Glu Glu Ile Ala Gln Val Ala Thr Ile Ser Ala
 165 170 175
 Asn Gly Asp Lys Glu Ile Gly Asn Ile Ile Ser Asp Ala Met Lys Lys

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180				185				190			
Val Gly Arg Lys Gly Val Ile Thr	Val Lys Asp Gly Lys Thr Leu Asn										
195	200	205									
Asp Glu Leu Glu Ile Ile Glu Gly Met Lys Phe Asp Arg Gly Tyr Ile											
210	215	220									
Ser Pro Tyr Phe Ile Asn Thr Ser Lys Gly Gln Lys Cys Glu Phe Gln											
225	230	235									
Asp Ala Tyr Val Leu Leu Ser Glu Lys Lys Ile Ser Ser Ile Gln Ser											
245	250	255									
Ile Val Pro Ala Leu Glu Ile Ala Asn Ala His Arg Lys Pro Leu Val											
260	265	270									
Ile Ile Ala Glu Asp Val Asp Gly Glu Ala Leu Ser Thr Leu Val Leu											
275	280	285									
Asn Arg Leu Lys Val Gly Leu Gln Val Val Ala Val Lys Ala Pro Gly											
290	295	300									
Phe Gly Asp Asn Arg Lys Asn Gln Leu Lys Asp Met Ala Ile Ala Thr											
305	310	315									
Gly Gly Ala Val Phe Gly Glu Glu Gly Leu Thr Leu Asn Leu Glu Asp											
325	330	335									
Val Gln Pro His Asp Leu Gly Lys Val Gly Glu Val Ile Val Thr Lys											
340	345	350									
Asp Asp Ala Met Leu Leu Lys Gly Lys Gly Asp Lys Ala Gln Ile Glu											
355	360	365									
Lys Arg Ile Gln Glu Ile Ile Glu Gln Leu Asp Val Thr Thr Ser Glu											
370	375	380									
Tyr Glu Lys Glu Lys Leu Asn Glu Arg Leu Ala Lys Leu Ser Asp Gly											
385	390	395									
Val Ala Val Leu Lys Val Gly Gly Thr Ser Asp Val Glu Val Asn Glu											
405	410	415									
Lys Lys Asp Arg Val Thr Asp Ala Leu Asn Ala Thr Arg Ala Ala Val											
420	425	430									
Glu Glu Gly Ile Val Leu Gly Gly Gly Cys Ala Leu Leu Arg Cys Ile											
435	440	445									
Pro Ala Leu Asp Ser Leu Thr Pro Ala Asn Glu Asp Gln Lys Ile Gly											
450	455	460									
Ile Glu Ile Ile Lys Arg Thr Leu Lys Ile Pro Ala Met Thr Ile Ala											
465	470	475									
Lys Asn Ala Gly Val Glu Gly Ser Leu Ile Val Glu Lys Ile Met Gln											
485	490	495									
Ser Ser Ser Glu Val Gly Tyr Asp Ala Met Ala Gly Asp Phe Val Asn											
500	505	510									
Met Val Glu Lys Gly Ile Ile Asp Pro Thr Lys Val Val Arg Thr Ala											
515	520	525									
Leu Leu Asp Ala Ala Gly Val Ala Ser Leu Leu Thr Thr Ala Glu Val											
530	535	540									
Val Val Thr Glu Ile Pro Lys Glu Glu Lys Asp Pro Gly Met Gly Ala											
545	550	555									
Met Gly Gly Met Gly Gly Gly Met Gly Gly Gly Met Phe											
565	570										

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<211> LENGTH: 215

<212> TYPE: PRT

<213> ORGANISM: Human

<400> SEQUENCE: 17

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Met Gly Lys Gly Asp Pro Lys Lys Pro Arg Arg Lys Met Ser Ser Tyr
 1             5             10             15

Ala Phe Phe Val Gln Thr Cys Arg Glu Glu His Lys Lys Lys His Pro
      20             25             30

Asp Ala Ser Val Asn Phe Ser Glu Phe Ser Lys Lys Cys Ser Glu Arg
      35             40             45

Trp Lys Thr Met Ser Ala Lys Glu Lys Gly Lys Phe Glu Asp Met Ala
      50             55             60

Lys Ala Asp Lys Ala Arg Tyr Glu Arg Glu Met Lys Thr Tyr Ile Pro
      65             70             75             80

Pro Lys Gly Glu Thr Lys Lys Lys Phe Lys Asp Pro Asn Ala Pro Lys
      85             90             95

Arg Pro Pro Ser Ala Phe Phe Leu Phe Cys Ser Glu Tyr Arg Pro Lys
      100            105            110

Ile Lys Gly Glu His Pro Gly Leu Ser Ile Gly Asp Val Ala Lys Lys
      115            120            125

Leu Gly Glu Met Trp Asn Asn Thr Ala Ala Asp Asp Lys Gln Pro Tyr
      130            135            140

Glu Lys Lys Ala Glu Lys Leu Lys Glu Lys Tyr Glu Lys Asp Ile Ala
      145            150            155            160

Ala Tyr Arg Ala Lys Gly Lys Pro Asp Ala Ala Lys Lys Gly Val Val
      165            170            175

Lys Ala Glu Lys Ser Lys Lys Lys Lys Glu Glu Glu Glu Gly Glu Glu
      180            185            190

Asp Glu Glu Asp Glu Glu Glu Glu Glu Asp Glu Glu Asp Glu Asp Glu
      195            200            205

Glu Glu Asp Asp Asp Asp Glu
      210            215

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<210> SEQ ID NO 18

<211> LENGTH: 1087

<212> TYPE: PRT

<213> ORGANISM: Human

<400> SEQUENCE: 18

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Met Met Thr Ser Val Gly Thr Asn Arg Ala Arg Gly Asn Trp Glu Gln
 1             5             10             15

Pro Gln Asn Gln Asn Gln Thr Gln His Lys Gln Arg Pro Gln Ala Thr
      20             25             30

Ala Glu Gln Ile Arg Leu Ala Gln Met Ile Ser Asp His Asn Asp Ala
      35             40             45

Asp Phe Glu Glu Lys Val Lys Gln Leu Ile Asp Ile Thr Gly Lys Asn
      50             55             60

Gln Asp Glu Cys Val Ile Ala Leu His Asp Cys Asn Gly Asp Val Asn
      65             70             75             80

Arg Ala Ile Asn Val Leu Leu Glu Gly Asn Pro Asp Thr His Ser Trp
      85             90             95

Glu Met Val Gly Lys Lys Lys Gly Val Ser Gly Gln Lys Asp Gly Gly
      100            105            110

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Gln Thr Glu Ser Asn Glu Glu Gly Lys Glu Asn Arg Asp Arg Asp Arg	115	120	125
Asp Tyr Ser Arg Arg Arg Gly Gly Pro Pro Arg Arg Gly Arg Gly Ala	130	135	140
Ser Arg Gly Arg Glu Phe Arg Gly Gln Glu Asn Gly Leu Asp Gly Thr	145	150	155
Lys Ser Gly Gly Pro Ser Gly Arg Gly Thr Glu Arg Gly Arg Arg Gly	165	170	175
Arg Gly Arg Gly Arg Gly Gly Ser Gly Arg Arg Gly Gly Arg Phe Ser	180	185	190
Ala Gln Gly Met Gly Thr Phe Asn Pro Ala Asp Tyr Ala Glu Pro Ala	195	200	205
Asn Thr Asp Asp Asn Tyr Gly Asn Ser Ser Gly Asn Thr Trp Asn Asn	210	215	220
Thr Gly His Phe Glu Pro Asp Asp Gly Thr Ser Ala Trp Arg Thr Ala	225	230	235
Thr Glu Glu Trp Gly Thr Glu Asp Trp Asn Glu Asp Leu Ser Glu Thr	245	250	255
Lys Ile Phe Thr Ala Ser Asn Val Ser Ser Val Pro Leu Pro Ala Glu	260	265	270
Asn Val Thr Ile Thr Ala Gly Gln Arg Ile Asp Leu Ala Val Leu Leu	275	280	285
Gly Lys Thr Pro Ser Thr Met Glu Asn Asp Ser Ser Asn Leu Asp Pro	290	295	300
Ser Gln Ala Pro Ser Leu Ala Gln Pro Leu Val Phe Ser Asn Ser Lys	305	310	315
Gln Thr Ala Ile Ser Gln Pro Ala Ser Gly Asn Thr Phe Ser His His	325	330	335
Ser Met Val Ser Met Leu Gly Lys Gly Phe Gly Asp Val Gly Glu Ala	340	345	350
Lys Gly Gly Ser Thr Thr Gly Ser Gln Phe Leu Glu Gln Phe Lys Thr	355	360	365
Ala Gln Ala Leu Ala Gln Leu Ala Ala Gln His Ser Gln Ser Gly Ser	370	375	380
Thr Thr Thr Ser Ser Trp Asp Met Gly Ser Thr Thr Gln Ser Pro Ser	385	390	395
Leu Val Gln Tyr Asp Leu Lys Asn Pro Ser Asp Ser Ala Val His Ser	405	410	415
Pro Phe Thr Lys Arg Gln Ala Phe Thr Pro Ser Ser Thr Met Met Glu	420	425	430
Val Phe Leu Gln Glu Lys Ser Pro Ala Val Ala Thr Ser Thr Ala Ala	435	440	445
Pro Pro Pro Pro Ser Ser Pro Leu Pro Ser Lys Ser Thr Ser Ala Pro	450	455	460
Gln Met Ser Pro Gly Ser Ser Asp Asn Gln Ser Ser Ser Pro Gln Pro	465	470	475
Ala His Gln Lys Leu Lys Gln Gln Lys Lys Lys Ala Ser Leu Thr Ser	485	490	495
Lys Ile Pro Ala Leu Ala Val Glu Met Pro Gly Ser Ala Asp Ile Ser	500	505	510

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Gly	Leu	Asn	Leu	Gln	Phe	Gly	Ala	Leu	Gln	Phe	Gly	Ser	Glu	Pro	Val
	515						520					525			
Leu	Ser	Asp	Tyr	Glu	Ser	Thr	Pro	Thr	Thr	Ser	Ala	Ser	Ser	Ser	Gln
	530					535					540				
Ala	Pro	Ser	Ser	Leu	Tyr	Thr	Ser	Thr	Ala	Ser	Glu	Ser	Ser	Ser	Thr
	545				550					555					560
Ile	Ser	Ser	Asn	Gln	Ser	Gln	Glu	Ser	Gly	Tyr	Gln	Ser	Gly	Pro	Ile
			565						570					575	
Gln	Ser	Thr	Thr	Tyr	Thr	Ser	Gln	Asn	Asn	Ala	Gln	Gly	Pro	Leu	Tyr
			580					585					590		
Glu	Gln	Arg	Ser	Thr	Gln	Thr	Arg	Arg	Tyr	Pro	Ser	Ser	Ile	Ser	Ser
		595					600					605			
Ser	Pro	Gln	Lys	Asp	Leu	Thr	Gln	Ala	Lys	Asn	Gly	Phe	Ser	Ser	Val
	610					615					620				
Gln	Ala	Thr	Gln	Leu	Gln	Thr	Thr	Gln	Ser	Val	Glu	Gly	Ala	Thr	Gly
	625				630					635					640
Ser	Ala	Val	Lys	Ser	Asp	Ser	Pro	Ser	Thr	Ser	Ser	Ile	Pro	Pro	Leu
			645					650					655		
Asn	Glu	Thr	Val	Ser	Ala	Ala	Ser	Leu	Leu	Thr	Thr	Thr	Asn	Gln	His
		660						665					670		
Ser	Ser	Ser	Leu	Gly	Gly	Leu	Ser	His	Ser	Glu	Glu	Ile	Pro	Asn	Thr
		675					680					685			
Thr	Thr	Thr	Gln	His	Ser	Ser	Thr	Leu	Ser	Thr	Gln	Gln	Asn	Thr	Leu
	690					695					700				
Ser	Ser	Ser	Thr	Ser	Ser	Gly	Arg	Thr	Ser	Thr	Ser	Thr	Leu	Leu	His
	705				710				715						720
Thr	Ser	Val	Glu	Ser	Glu	Ala	Asn	Leu	His	Ser	Ser	Ser	Ser	Thr	Phe
			725					730						735	
Ser	Thr	Thr	Ser	Ser	Thr	Val	Ser	Ala	Pro	Pro	Pro	Val	Val	Ser	Val
		740					745					750			
Ser	Ser	Ser	Leu	Asn	Ser	Gly	Ser	Ser	Leu	Gly	Leu	Ser	Leu	Gly	Ser
		755				760					765				
Asn	Ser	Thr	Val	Thr	Ala	Ser	Thr	Arg	Ser	Ser	Val	Ala	Thr	Thr	Ser
	770				775						780				
Gly	Lys	Ala	Pro	Pro	Asn	Leu	Pro	Pro	Gly	Val	Pro	Pro	Leu	Leu	Pro
	785				790				795						800
Asn	Pro	Tyr	Ile	Met	Ala	Pro	Gly	Leu	Leu	His	Ala	Tyr	Pro	Pro	Gln
			805					810						815	
Val	Tyr	Gly	Tyr	Asp	Asp	Leu	Gln	Met	Leu	Gln	Thr	Arg	Phe	Pro	Leu
		820					825					830			
Asp	Tyr	Tyr	Ser	Ile	Pro	Phe	Pro	Thr	Pro	Thr	Thr	Pro	Leu	Thr	Gly
		835				840						845			
Arg	Asp	Gly	Ser	Leu	Ala	Ser	Asn	Pro	Tyr	Ser	Gly	Asp	Leu	Thr	Lys
		850				855					860				
Phe	Gly	Arg	Gly	Asp	Ala	Ser	Ser	Pro	Ala	Pro	Ala	Thr	Thr	Leu	Ala
	865				870					875					880
Gln	Pro	Gln	Gln	Asn	Gln	Thr	Gln	Thr	His	His	Thr	Thr	Gln	Gln	Thr
			885						890					895	
Phe	Leu	Asn	Pro	Ala	Leu	Pro	Pro	Gly	Tyr	Ser	Tyr	Thr	Ser	Leu	Pro
		900					905					910			
Tyr	Tyr	Thr	Gly	Val	Pro	Gly	Leu	Pro	Ser	Thr	Phe	Gln	Tyr	Gly	Pro

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915	920	925
Ala Val Phe Pro Val Ala Pro Thr Ser Ser Lys Gln His Gly Val Asn 930 935 940		
Val Ser Val Asn Ala Ser Ala Thr Pro Phe Gln Gln Pro Ser Gly Tyr 945 950 955 960		
Gly Ser His Gly Tyr Asn Thr Gly Val Ser Val Thr Ser Ser Asn Thr 965 970 975		
Gly Val Pro Asp Ile Ser Gly Ser Val Tyr Ser Lys Thr Gln Gln Ser 980 985 990		
Phe Glu Lys Gln Gly Phe His Ser Gly Thr Pro Ala Ala Ser Phe Asn 995 1000 1005		
Leu Pro Ser Ala Leu Gly Ser Gly Gly Pro Ile Asn Pro Ala Thr 1010 1015 1020		
Ala Ala Ala Tyr Pro Pro Ala Pro Phe Met His Ile Leu Thr Pro 1025 1030 1035		
His Gln Gln Pro His Ser Gln Ile Leu His His His Leu Gln Gln 1040 1045 1050		
Asp Gly Gln Thr Gly Ser Gly Gln Arg Ser Gln Thr Ser Ser Ile 1055 1060 1065		
Pro Gln Lys Pro Gln Thr Asn Lys Ser Ala Tyr Asn Ser Tyr Ser 1070 1075 1080		
Trp Gly Ala Asn 1085		
<210> SEQ ID NO 19		
<211> LENGTH: 806		
<212> TYPE: PRT		
<213> ORGANISM: Human		
<400> SEQUENCE: 19		
Met Ala Ser Gly Ala Asp Ser Lys Gly Asp Asp Leu Ser Thr Ala Ile 1 5 10 15		
Leu Lys Gln Lys Asn Arg Pro Asn Arg Leu Ile Val Asp Glu Ala Ile 20 25 30		
Asn Glu Asp Asn Ser Val Val Ser Leu Ser Gln Pro Lys Met Asp Glu 35 40 45		
Leu Gln Leu Phe Arg Gly Asp Thr Val Leu Leu Lys Gly Lys Lys Arg 50 55 60		
Arg Glu Ala Val Cys Ile Val Leu Ser Asp Asp Thr Cys Ser Asp Glu 65 70 75 80		
Lys Ile Arg Met Asn Arg Val Val Arg Asn Asn Leu Arg Val Arg Leu 85 90 95		
Gly Asp Val Ile Ser Ile Gln Pro Cys Pro Asp Val Lys Tyr Gly Lys 100 105 110		
Arg Ile His Val Leu Pro Ile Asp Asp Thr Val Glu Gly Ile Thr Gly 115 120 125		
Asn Leu Phe Glu Val Tyr Leu Lys Pro Tyr Phe Leu Glu Ala Tyr Arg 130 135 140		
Pro Ile Arg Lys Gly Asp Ile Phe Leu Val Arg Gly Gly Met Arg Ala 145 150 155 160		
Val Glu Phe Lys Val Val Glu Thr Asp Pro Ser Pro Tyr Cys Ile Val 165 170 175		

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Ala	Pro	Asp	Thr	Val	Ile	His	Cys	Glu	Gly	Glu	Pro	Ile	Lys	Arg	Glu
			180					185					190		
Asp	Glu	Glu	Glu	Ser	Leu	Asn	Glu	Val	Gly	Tyr	Asp	Asp	Ile	Gly	Gly
	195						200					205			
Cys	Arg	Lys	Gln	Leu	Ala	Gln	Ile	Lys	Glu	Met	Val	Glu	Leu	Pro	Leu
	210					215					220				
Arg	His	Pro	Ala	Leu	Phe	Lys	Ala	Ile	Gly	Val	Lys	Pro	Pro	Arg	Gly
225					230				235						240
Ile	Leu	Leu	Tyr	Gly	Pro	Pro	Gly	Thr	Gly	Lys	Thr	Leu	Ile	Ala	Arg
			245						250					255	
Ala	Val	Ala	Asn	Glu	Thr	Gly	Ala	Phe	Phe	Phe	Leu	Ile	Asn	Gly	Pro
			260					265					270		
Glu	Ile	Met	Ser	Lys	Leu	Ala	Gly	Glu	Ser	Glu	Ser	Asn	Leu	Arg	Lys
	275						280					285			
Ala	Phe	Glu	Glu	Ala	Glu	Lys	Asn	Ala	Pro	Ala	Ile	Ile	Phe	Ile	Asp
290						295					300				
Glu	Leu	Asp	Ala	Ile	Ala	Pro	Lys	Arg	Glu	Lys	Thr	His	Gly	Glu	Val
305					310					315					320
Glu	Arg	Arg	Ile	Val	Ser	Gln	Leu	Leu	Thr	Leu	Met	Asp	Gly	Leu	Lys
			325						330					335	
Gln	Arg	Ala	His	Val	Ile	Val	Met	Ala	Ala	Thr	Asn	Arg	Pro	Asn	Ser
			340					345					350		
Ile	Asp	Pro	Ala	Leu	Arg	Arg	Phe	Gly	Arg	Phe	Asp	Arg	Glu	Val	Asp
	355						360				365				
Ile	Gly	Ile	Pro	Asp	Ala	Thr	Gly	Arg	Leu	Glu	Ile	Leu	Gln	Ile	His
	370					375					380				
Thr	Lys	Asn	Met	Lys	Leu	Ala	Asp	Asp	Val	Asp	Leu	Glu	Gln	Val	Ala
385				390						395					400
Asn	Glu	Thr	His	Gly	His	Val	Gly	Ala	Asp	Leu	Ala	Ala	Leu	Cys	Ser
			405					410						415	
Glu	Ala	Ala	Leu	Gln	Ala	Ile	Arg	Lys	Lys	Met	Asp	Leu	Ile	Asp	Leu
			420					425					430		
Glu	Asp	Glu	Thr	Ile	Asp	Ala	Glu	Val	Met	Asn	Ser	Leu	Ala	Val	Thr
	435					440						445			
Met	Asp	Asp	Phe	Arg	Trp	Ala	Leu	Ser	Gln	Ser	Asn	Pro	Ser	Ala	Leu
	450					455					460				
Arg	Glu	Thr	Val	Val	Glu	Val	Pro	Gln	Val	Thr	Trp	Glu	Asp	Ile	Gly
465					470					475					480
Gly	Leu	Glu	Asp	Val	Lys	Arg	Glu	Leu	Gln	Glu	Leu	Val	Gln	Tyr	Pro
			485						490					495	
Val	Glu	His	Pro	Asp	Lys	Phe	Leu	Lys	Phe	Gly	Met	Thr	Pro	Ser	Lys
			500					505					510		
Gly	Val	Leu	Phe	Tyr	Gly	Pro	Pro	Gly	Cys	Gly	Lys	Thr	Leu	Leu	Ala
	515						520					525			
Lys	Ala	Ile	Ala	Asn	Glu	Cys	Gln	Ala	Asn	Phe	Ile	Ser	Ile	Lys	Gly
	530					535						540			
Pro	Glu	Leu	Leu	Thr	Met	Trp	Phe	Gly	Glu	Ser	Glu	Ala	Asn	Val	Arg
545					550					555					560
Glu	Ile	Phe	Asp	Lys	Ala	Arg	Gln	Ala	Ala	Pro	Cys	Val	Leu	Phe	Phe
			565					570						575	
Asp	Glu	Leu	Asp	Ser	Ile	Ala	Lys	Ala	Arg	Gly	Gly	Asn	Ile	Gly	Asp

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580					585					590					
Gly	Gly	Gly	Ala	Ala	Asp	Arg	Val	Ile	Asn	Gln	Ile	Leu	Thr	Glu	Met
	595						600					605			
Asp	Gly	Met	Ser	Thr	Lys	Lys	Asn	Val	Phe	Ile	Ile	Gly	Ala	Thr	Asn
610						615					620				
Arg	Pro	Asp	Ile	Ile	Asp	Pro	Ala	Ile	Leu	Arg	Pro	Gly	Arg	Leu	Asp
625					630					635					640
Gln	Leu	Ile	Tyr	Ile	Pro	Leu	Pro	Asp	Glu	Lys	Ser	Arg	Val	Ala	Ile
			645					650						655	
Leu	Lys	Ala	Asn	Leu	Arg	Lys	Ser	Pro	Val	Ala	Lys	Asp	Val	Asp	Leu
		660						665					670		
Glu	Phe	Leu	Ala	Lys	Met	Thr	Asn	Gly	Phe	Ser	Gly	Ala	Asp	Leu	Thr
	675						680					685			
Glu	Ile	Cys	Gln	Arg	Ala	Cys	Lys	Leu	Ala	Ile	Arg	Glu	Ser	Ile	Glu
	690					695						700			
Ser	Glu	Ile	Arg	Arg	Glu	Arg	Glu	Arg	Gln	Thr	Asn	Pro	Ser	Ala	Met
705					710					715					720
Glu	Val	Glu	Glu	Asp	Asp	Pro	Val	Pro	Glu	Ile	Arg	Arg	Asp	His	Phe
				725					730					735	
Glu	Glu	Ala	Met	Arg	Phe	Ala	Arg	Arg	Ser	Val	Ser	Asp	Asn	Asp	Ile
			740					745					750		
Arg	Lys	Tyr	Glu	Met	Phe	Ala	Gln	Thr	Leu	Gln	Gln	Ser	Arg	Gly	Phe
		755					760						765		
Gly	Ser	Phe	Arg	Phe	Pro	Ser	Gly	Asn	Gln	Gly	Gly	Ala	Gly	Pro	Ser
	770					775						780			
Gln	Gly	Ser	Gly	Gly	Gly	Thr	Gly	Gly	Ser	Val	Tyr	Thr	Glu	Asp	Asn
785					790					795					800
Asp	Asp	Asp	Leu	Tyr	Gly										
				805											

<210> SEQ ID NO 20
 <211> LENGTH: 260
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 20

Met	Val	Lys	Val	Lys	Val	Glu	Val	Asn	Gly	Phe	Gly	His	Thr	Gly	Arg
1				5					10					15	
Leu	Val	Thr	Arg	Ala	Ala	Phe	Asn	Ser	Gly	Lys	Val	Asp	Ile	Val	Thr
			20					25					30		
Ile	Asn	Asp	Pro	Phe	Ile	Asp	Leu	Asn	Tyr	Pro	Phe	Ile	Asp	Leu	Asn
		35					40						45		
Tyr	Met	Ile	Tyr	Met	Phe	Gln	Tyr	Asp	Ser	Met	Ala	Asn	Ser	Met	Ala
	50					55					60				
Pro	Ser	Arg	Leu	Arg	Met	Gly	Ser	Leu	Ser	Ser	Arg	Glu	Ile	Pro	Ser
65					70					75					80
Pro	Ser	Ser	Arg	Ser	Glu	Ile	Pro	Pro	Lys	Ser	Asn	Gly	Gly	Glu	Ala
				85					90					95	
Lys	Arg	Ile	Ile	Ile	Ser	Ala	Pro	Ser	Ala	Asp	Ala	Pro	Met	Phe	Met
			100					105					110		
Met	Gly	Ile	Asn	Arg	Glu	Lys	Tyr	Asp	Asn	Ser	Leu	Glu	Ile	Ile	Ser
			115				120					125			

-continued

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Asn Ala Ser Cys Thr Thr Asn Cys Leu Ala Pro Leu Ala Lys Val Ile
 130                      135                      140

His Asp Asn Phe Gly Ile Met Glu Gly Leu Met Thr Thr Val His Ala
145                      150                      155                      160

Ile Ala Ala Thr Gln Lys Thr Val Asp Ser Pro Ser Gly Lys Leu Trp
                      165                      170                      175

Cys Asp Gly Cys Arg Ala Leu Gln Asn Ile Ile Pro Ala Ser Thr Gly
                      180                      185                      190

Ser Ser Leu Ala Lys Pro Ser Val Val Pro Thr Thr Asn Val Ser Val
                      195                      200                      205

Val Asp Leu Thr Cys His Leu Glu Lys Pro Ala Lys Tyr Asp Asp Ile
210                      215                      220

Lys Lys Trp Cys Ser Arg His Gln Lys Ala Pro Ser Arg Ala Ser Trp
225                      230                      235                      240

Ala Thr Leu Ser Thr Cys Asn Arg Val Val Asp Leu Met Ala His Met
245                      250                      255

Ala Ser Lys Glu
260

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<210> SEQ ID NO 21
<211> LENGTH: 279
<212> TYPE: PRT
<213> ORGANISM: Human

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<400> SEQUENCE: 21

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Met Asn Lys Val Glu Leu Glu Ser Arg Leu Glu Gly Leu Thr Asp Glu
 1                      5                      10                      15

Ile Asn Phe Leu Arg Gln Leu Tyr Glu Glu Leu Arg Glu Leu Gln
20                      25                      30

Ser Gln Ile Ser Asp Thr Ser Val Val Leu Ser Met Asp Asn Ser Arg
35                      40                      45

Ser Leu Asp Met Asp Ser Ile Ile Ala Glu Val Lys Ala Gln Tyr Glu
50                      55                      60

Asp Ile Ala Asn Arg Ser Arg Ala Glu Ala Glu Ser Met Tyr Gln Ile
65                      70                      75                      80

Lys Tyr Glu Glu Leu Gln Ser Leu Ala Gly Lys His Gly Asp Asp Leu
85                      90                      95

Arg Arg Thr Lys Thr Glu Ile Ser Glu Met Asn Arg Asn Ile Ser Arg
100                      105                      110

Leu Gln Ala Glu Ile Glu Gly Leu Lys Gly Gln Arg Ala Ser Leu Glu
115                      120                      125

Ala Ala Ile Ala Asp Ala Glu Gln Arg Gly Glu Leu Ala Ile Lys Asp
130                      135                      140

Ala Asn Ala Lys Leu Ser Glu Leu Glu Ala Ala Leu Gln Arg Ala Lys
145                      150                      155                      160

Gln Asp Met Ala Arg Gln Leu Arg Glu Tyr Gln Glu Leu Met Asn Val
165                      170                      175

Lys Leu Ala Met Asp Ile Glu Ile Ala Thr Tyr Arg Lys Leu Leu Glu
180                      185                      190

Gly Glu Glu Ser Arg Leu Glu Ser Gly Met Gln Asn Met Ser Ile His
195                      200                      205

Thr Lys Thr Thr Gly Gly Tyr Ala Gly Gly Leu Ser Ser Ala Tyr Gly
210                      215                      220

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-continued

Gly Leu Ala Ser Pro Gly Leu Ser Tyr Ser Leu Gly Ser Ser Phe Gly
 225 230 235 240

Ser Gly Ala Gly Ser Ser Ser Phe Ser Arg Thr Ser Ser Ser Arg Ala
 245 250 255

Val Val Val Lys Lys Ile Glu Thr Arg Asp Gly Lys Leu Val Ser Glu
 260 265 270

Ser Ser Asp Val Leu Pro Lys
 275

<210> SEQ ID NO 22
 <211> LENGTH: 577
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 22

Met Asn Lys Leu Tyr Ile Gly Asn Leu Asn Glu Ser Val Thr Pro Ala
 1 5 10 15

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

Phe Leu Val Lys Ser Gly Tyr Ala Phe Val Asp Cys Pro Asp Glu His
 35 40 45

Trp Ala Met Lys Ala Ile Glu Thr Phe Ser Gly Lys Val Glu Leu Gln
 50 55 60

Gly Lys Arg Leu Glu Ile Glu His Ser Val Pro Lys Lys Gln Arg Ser
 65 70 75 80

Arg Lys Ile Gln Ile Arg Asn Ile Pro Pro Gln Leu Arg Trp Glu Val
 85 90 95

Leu Asp Ser Leu Leu Ala Gln Tyr Gly Thr Val Glu Asn Cys Glu Gln
 100 105 110

Val Asn Thr Glu Ser Glu Thr Ala Val Val Asn Val Thr Tyr Ser Asn
 115 120 125

Arg Glu Gln Thr Arg Gln Ala Ile Met Lys Leu Asn Gly His Gln Leu
 130 135 140

Glu Asn His Ala Leu Lys Val Ser Tyr Ile Pro Asp Glu Gln Ile Ala
 145 150 155 160

Gln Gly Pro Glu Asn Gly Arg Arg Gly Gly Phe Gly Ser Arg Gly Gln
 165 170 175

Pro Arg Gln Gly Ser Pro Val Ala Ala Gly Ala Pro Ala Lys Gln Gln
 180 185 190

Gln Val Asp Ile Pro Leu Arg Leu Leu Val Pro Thr Gln Tyr Val Gly
 195 200 205

Ala Ile Ile Gly Lys Glu Gly Ala Thr Ile Arg Asn Ile Thr Lys Gln
 210 215 220

Thr Gln Ser Lys Ile Asp Val His Arg Lys Glu Asn Ala Gly Ala Ala
 225 230 235 240

Glu Lys Ala Ile Ser Val His Ser Thr Pro Glu Gly Cys Ser Ser Ala
 245 250 255

Cys Lys Met Ile Leu Glu Ile Met His Lys Glu Ala Lys Asp Thr Lys
 260 265 270

Thr Ala Asp Glu Val Pro Leu Lys Ile Leu Ala His Asn Asn Phe Val
 275 280 285

Gly Arg Leu Ile Gly Lys Glu Gly Arg Asn Leu Lys Lys Val Glu Gln

-continued

290	295	300
Asp Thr Glu Thr Lys Ile Thr Ile Ser Ser Leu Gln Asp Leu Thr Leu 305 310 315 320		
Tyr Asn Pro Glu Arg Thr Ile Thr Val Lys Gly Ala Ile Glu Asn Cys 325 330 335		
Cys Arg Ala Glu Gln Glu Ile Met Lys Lys Val Arg Glu Ala Tyr Glu 340 345 350		
Asn Asp Val Ala Ala Met Ser Leu Gln Ser His Leu Ile Pro Gly Leu 355 360 365		
Asn Leu Ala Ala Val Gly Leu Phe Pro Ala Ser Ser Ser Ala Val Pro 370 375 380		
Pro Pro Pro Ser Ser Val Thr Gly Ala Ala Pro Tyr Ser Ser Phe Met 385 390 395 400		
Gln Ala Pro Glu Gln Glu Met Val Gln Val Phe Ile Pro Ala Gln Ala 405 410 415		
Val Gly Ala Ile Ile Gly Lys Lys Gly Gln His Ile Lys Gln Leu Ser 420 425 430		
Arg Phe Ala Ser Ala Ser Ile Lys Ile Ala Pro Pro Glu Thr Pro Asp 435 440 445		
Ser Lys Val Arg Met Val Ile Ile Thr Gly Pro Pro Glu Ala Gln Phe 450 455 460		
Lys Ala Gln Gly Arg Ile Tyr Gly Lys Leu Lys Glu Glu Asn Phe Phe 465 470 475 480		
Gly Pro Lys Glu Glu Val Lys Leu Glu Thr His Ile Arg Val Pro Ala 485 490 495		
Ser Ala Ala Gly Arg Val Ile Gly Lys Gly Gly Lys Thr Val Asn Glu 500 505 510		
Leu Gln Asn Leu Thr Ala Ala Glu Val Val Val Pro Arg Asp Gln Thr 515 520 525		
Pro Asp Glu Asn Asp Gln Val Ile Val Lys Ile Ile Gly His Phe Tyr 530 535 540		
Ala Ser Gln Met Ala Gln Arg Lys Ile Arg Asp Ile Leu Ala Gln Val 545 550 555 560		
Lys Gln Gln His Gln Lys Gly Gln Ser Asn Gln Ala Gln Ala Arg Arg 565 570 575		

Lys

<210> SEQ ID NO 23
 <211> LENGTH: 329
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 23

Met Ala Thr Gly Gln Lys Leu Met Arg Ala Val Arg Val Phe Glu Phe 1 5 10 15
Gly Gly Pro Glu Val Leu Lys Leu Arg Ser Asp Ile Ala Val Pro Ile 20 25 30
Pro Lys Asp His Gln Val Leu Ile Lys Val His Ala Cys Gly Val Asn 35 40 45
Pro Val Glu Thr Tyr Ile Arg Ser Gly Thr Tyr Ser Arg Lys Pro Leu 50 55 60
Leu Pro Tyr Thr Pro Gly Ser Asp Val Ala Gly Val Ile Glu Ala Val

-continued

65	70	75	80
Gly Asp Asn Ala Ser Ala Phe Lys Lys Gly Asp Arg Val Phe Thr Ser	85	90	95
Ser Thr Ile Ser Gly Gly Tyr Ala Glu Tyr Ala Leu Ala Ala Asp His	100	105	110
Thr Val Tyr Lys Leu Pro Glu Lys Leu Asp Phe Lys Gln Gly Ala Ala	115	120	125
Ile Gly Ile Pro Tyr Phe Thr Ala Tyr Arg Ala Leu Ile His Ser Ala	130	135	140
Cys Val Lys Ala Gly Glu Ser Val Leu Val His Gly Ala Ser Gly Gly	145	150	155
Val Gly Leu Ala Ala Cys Gln Ile Ala Arg Ala Tyr Gly Leu Lys Ile	165	170	175
Leu Gly Thr Ala Gly Thr Glu Glu Gly Gln Lys Ile Val Leu Gln Asn	180	185	190
Gly Ala His Glu Val Phe Asn His Arg Glu Val Asn Tyr Ile Asp Lys	195	200	205
Ile Lys Lys Tyr Val Gly Glu Lys Gly Ile Asp Ile Ile Ile Glu Met	210	215	220
Leu Ala Asn Val Asn Leu Ser Lys Asp Leu Ser Leu Leu Ser His Gly	225	230	235
Gly Arg Val Ile Val Val Gly Ser Arg Gly Thr Ile Glu Ile Asn Pro	245	250	255
Arg Asp Thr Met Ala Lys Glu Ser Ser Ile Ile Gly Val Thr Leu Phe	260	265	270
Ser Ser Thr Lys Glu Glu Phe Gln Gln Tyr Ala Ala Ala Leu Gln Ala	275	280	285
Gly Met Glu Ile Gly Trp Leu Lys Pro Val Ile Gly Ser Gln Tyr Pro	290	295	300
Leu Glu Lys Val Ala Glu Ala His Glu Asn Ile Ile His Gly Ser Gly	305	310	315
Ala Thr Gly Lys Met Ile Leu Leu Leu	325		

<210> SEQ ID NO 24
 <211> LENGTH: 125
 <212> TYPE: PRT
 <213> ORGANISM: Human

<400> SEQUENCE: 24

Met Gln Pro Ala Ser Ala Lys Trp Tyr Asp Arg Arg Asp Tyr Val Phe	1	5	10	15
Ile Glu Phe Cys Val Glu Asp Ser Lys Asp Val Asn Val Asn Phe Glu	20	25	30	
Lys Ser Lys Leu Thr Phe Ser Cys Leu Gly Gly Ser Asp Asn Phe Lys	35	40	45	
His Leu Asn Glu Ile Asp Leu Phe His Cys Ile Asp Pro Asn Asp Ser	50	55	60	
Lys His Lys Arg Thr Asp Arg Ser Ile Leu Cys Cys Leu Arg Lys Gly	65	70	75	80
Glu Ser Gly Gln Ser Trp Pro Arg Leu Thr Lys Glu Arg Ala Lys Leu	85	90	95	

-continued

Asn	Trp	Leu	Ser	Val	Asp	Phe	Asn	Asn	Trp	Lys	Asp	Trp	Glu	Asp	Asp
			100					105					110		
Ser	Asp	Glu	Asp	Met	Ser	Asn	Phe	Asp	Arg	Phe	Ser	Glu			
	115						120					125			

What is claimed is:

1. A Biomarker for liver diseases selected from any one of the amino acid sequences with SEQ ID NO:1 to SEQ ID NO:24 or derivatives or fragments or variants or the combination thereof or the antibodies against said amino acid sequences.

2. The biomarker according to claim 1, wherein said liver disease is liver cirrhosis or liver cancer.

3. The biomarker according to claim 1, wherein said variant and any one of the amino acid sequences with SEQ ID NO:1 to SEQ ID NO:24 show sequence homology greater than 80%.

4. A detection kit for liver diseases, comprising biomarkers selected from any one of the amino acid sequences with SEQ ID NO:1 to SEQ ID NO:24 or derivatives or fragments or variants or the combination thereof.

5. The detection kit according to claim 4, wherein said liver disease is liver cirrhosis or liver cancer.

6. The detection kit according to claim 4, wherein the detection kit can further include secondary antibodies that can recognize autoantibody against any one of the amino acid sequences with SEQ ID NO:1 to SEQ ID NO:24 or derivatives or fragments or variants or the combination thereof.

7. A method for screening liver diseases, comprising the steps of:

providing a specimen;

using a biomarker selected from any one of the amino acid sequences with SEQ ID NO:1 to SEQ ID NO:24 or derivatives or fragments or variants or the combination thereof to identify and capture autoantibodies in the specimen; and

detecting the autoantibodies.

8. The method according to claim 7, wherein said specimen includes whole blood or serum.

9. The method according to claim 8, wherein said specimen is serum.

10. The method according to claim 7, wherein said biomarker may be made into detection kits.

11. The method according to claim 7, wherein said biomarker is firstly immobilized on a substrate.

12. The method according to claim 11, wherein said substrate is an immunoassay plate or a biochip.

13. The method according to claim 7, wherein said specimen is firstly labeled with a fluorescence marker.

14. The method according to claim 7, wherein the method further include a step of using a secondary antibody to recognize and adsorb the autoantibody.

15. The method according to claim 14, wherein said secondary antibody is modified and has a special functional group detectable by means of color reaction, radioactivity or fluorescence.

16. The method according to claim 7, wherein the detection of the autoantibody is achieved by using a fluorescence scanner to detect a fluorescence-labeled autoantibody.

17. The method according to claim 7, wherein the detection of the autoantibody is achieved by detection of the secondary autoantibody with enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA) or immunofluorescence.

18. A detection kit for liver diseases, comprising a set of antibodies against any one of amino acid sequences with SEQ ID NO:1 to SEQ ID NO:24.

19. The detection kit according to claim 18, wherein said liver disease is liver cirrhosis or liver cancer.

20. A screening method for liver diseases, comprising the steps of:

providing a specimen;

using an antibody against any one of the amino acid sequences with SEQ ID NO:1 to SEQ ID NO:24 to capture an antigen in the specimen; and

detecting the antibody-antigen complex.

21. The screening method according to claim 20, wherein said specimen is whole blood or serum.

22. The screening method according to claim 21, wherein said specimen is serum.

* * * * *

专利名称(译)	用于肝脏疾病的生物标志物及其使用方法		
公开(公告)号	US20050136489A1	公开(公告)日	2005-06-23
申请号	US11/013684	申请日	2004-12-17
[标]申请(专利权)人(译)	财团法人工业技术研究院		
申请(专利权)人(译)	工业技术研究院		
当前申请(专利权)人(译)	工业技术研究院		
[标]发明人	TSENG TZU LING CHENG PING FU		
发明人	TSENG, TZU-LING CHENG, PING-FU		
IPC分类号	G01N33/53 C07K14/47 C07K16/18 G01N21/78 G01N33/543 G01N33/567 G01N33/574 G01N33/68		
CPC分类号	G01N33/57438 G01N2800/085 G01N2800/08 G01N33/6893		
优先权	092136309 2003-12-19 TW		
外部链接	Espacenet USPTO		

摘要(译)

提供了用于肝脏疾病的生物标志物及其使用方法。为了检测肝硬化和肝癌，生物标志物选自具有SEQ ID NO：1至SEQ ID NO：24的任一氨基酸序列或衍生物或片段或变体或其组合或针对氨基酸序列的抗体。。然后将生物标记物进一步开发成检测试剂盒，使得通过检测筛选的样品中自身抗体或自身抗原的存在，以更高的准确度和灵敏度检测肝脏疾病。

Use biomarker to detect
autoantibody in the specimen