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Sahin et al.

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(54) **AUTOANTIGENES FOR IMPROVED DIAGNOSIS, PROGNOSIS AND TREATMENT OF INFLAMMATORY NEUROLOGICAL DISEASES**

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(30) **Foreign Application Priority Data**

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(51) **Int. Cl.**
G01N 33/53 (2006.01)
G01N 33/537 (2006.01)
G01N 33/567 (2006.01)

(52) **U.S. Cl.** **435/7.92**; 435/7.1; 435/7.21; 435/7.8; 435/7.9; 436/501; 436/503

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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Primary Examiner — Olga N Chernyshev

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(57) **ABSTRACT**

According to the invention, autoantibodies, the appearance of which is characteristic of neurological autoimmune diseases, especially multiple sclerosis, are detected and the respective autoantigens identified. It can further be shown that many of these autoantigens are expressed specifically in the brain. The identification of the autoantigens and autoantibodies is useful for diagnosis and treatment. A brain-specific expression of the autoantigens further emphasizes an important role of the antigens and antibodies in the origin and development of neurological autoimmune diseases.

9 Claims, 10 Drawing Sheets

Fig. 1

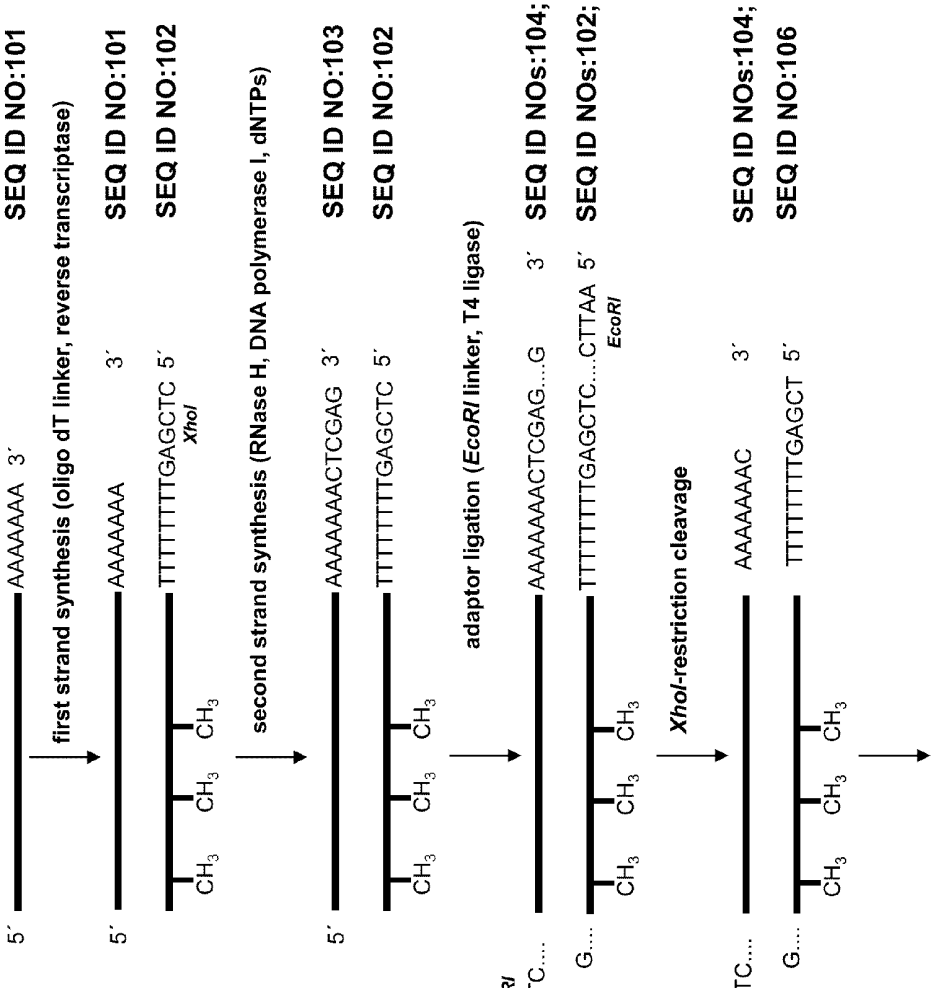

mRNA
5′ AAAAAAA 3′
SEQ ID NO:101
first strand synthesis (oligo dT linker, reverse transcriptase)
mRNA
5′ AAAAAAA 3′
SEQ ID NO:101
Methyl-cDNA
TTTTTTTTGAGCTC 5′
XhoI
SEQ ID NO:102
second strand synthesis (RNase H, DNA polymerase I, dNTPs)
DNA
5′ AAAAAAACTCGAG 3′
SEQ ID NO:103
Methyl-cDNA
TTTTTTTTGAGCTC 5′
SEQ ID NO:102
adaptor ligation (EcoRI linker, T4 ligase)
EcoRI
DNA
5′ AATTC.... AAAAAAACTCGAG....G 3′
SEQ ID NOs:104; 103
Methyl-cDNA
G.... TTTTTTTTGAGCTC....CTTAA 5′
EcoRI
SEQ ID NOs:102; 104
XhoI-restriction cleavage
DNA
5′ AATTC.... AAAAAAAC 3′
SEQ ID NOs:104; 105
G.... TTTTTTTTGAGCT 5′
SEQ ID NO:106
Cloning into XhoI/EcoRI cleaved Uni-ZAP
XR insertion vector

Fig. 2

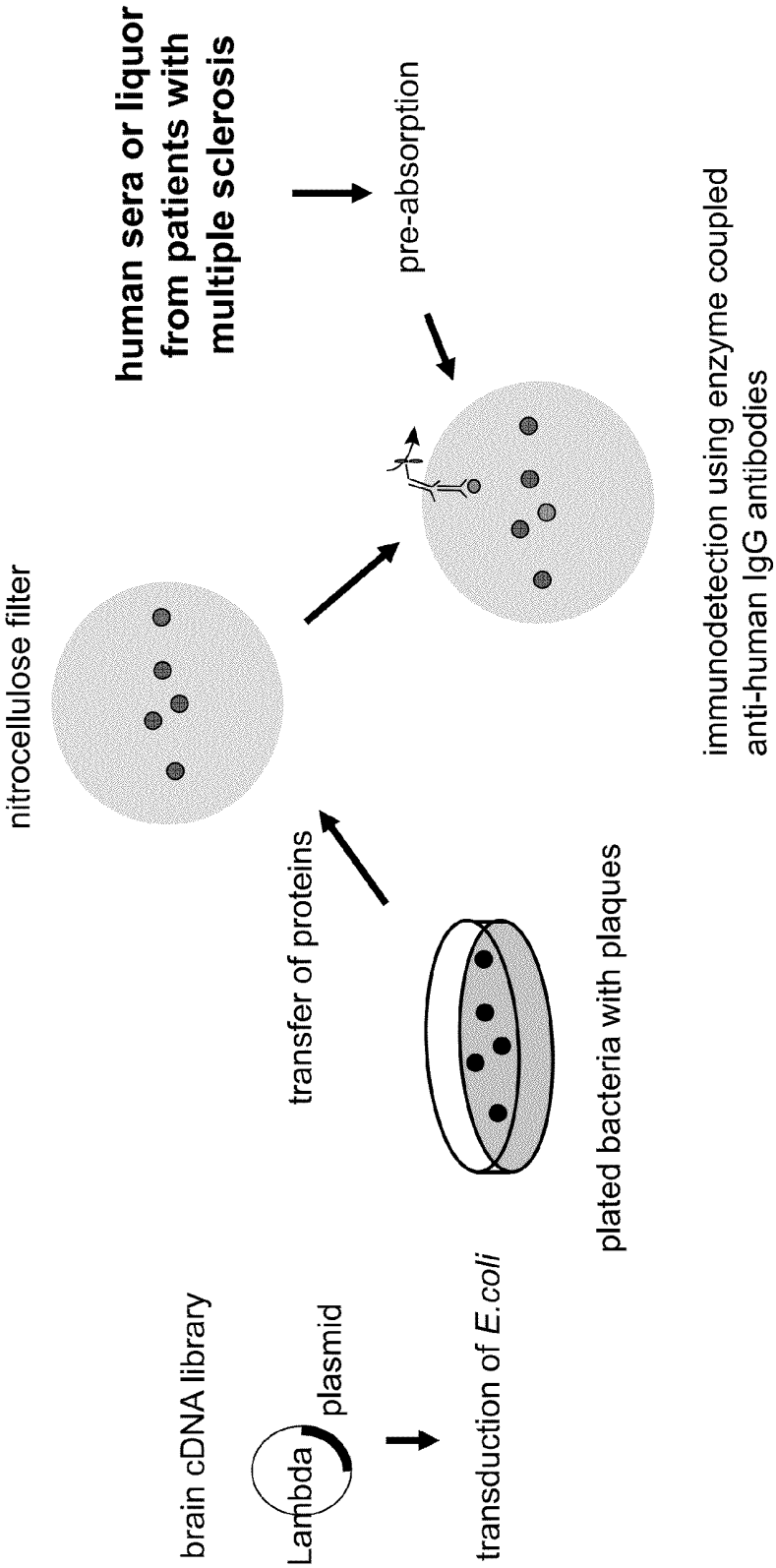
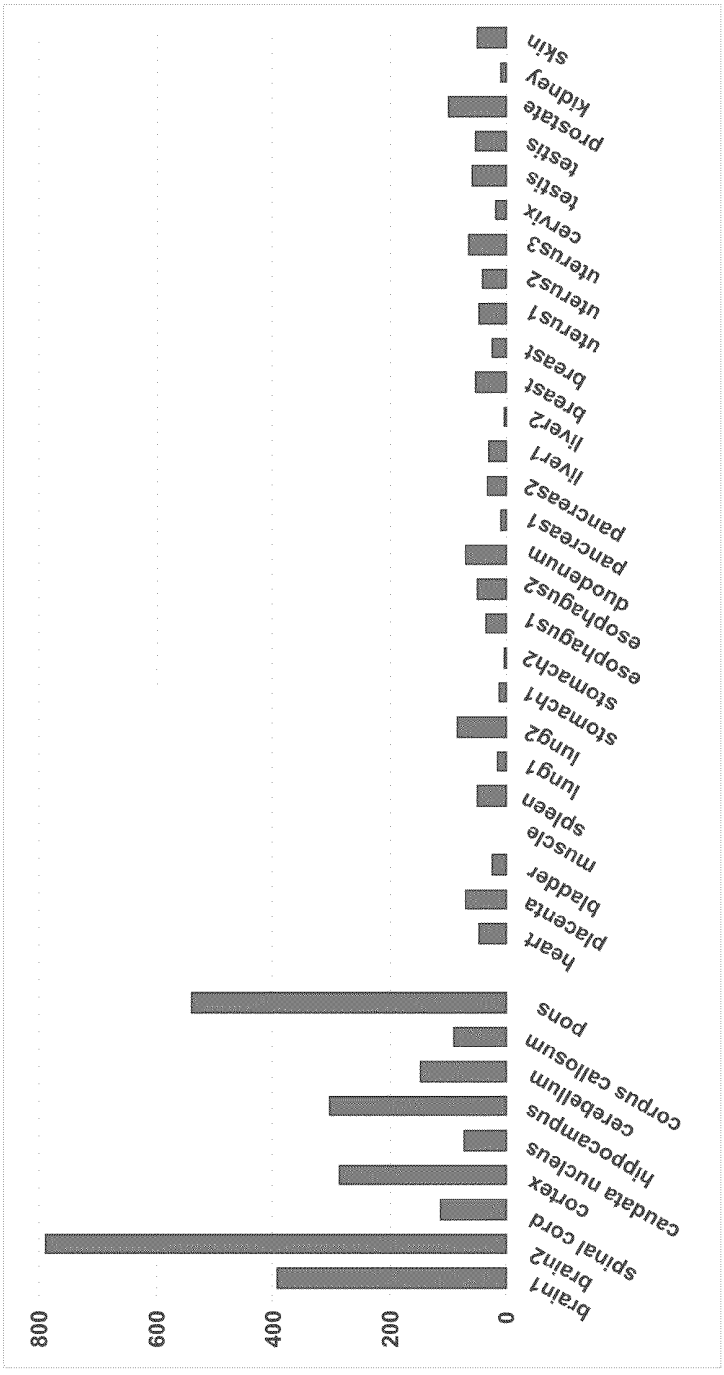

brain cDNA library
Lambda
plasmid
transduction of E.coli
plated bacteria with plaques
transfer of proteins
nitrocellulose filter
human sera or liquor from patients with multiple sclerosis
pre-absorption
immunodetection using enzyme coupled anti-human IgG antibodies

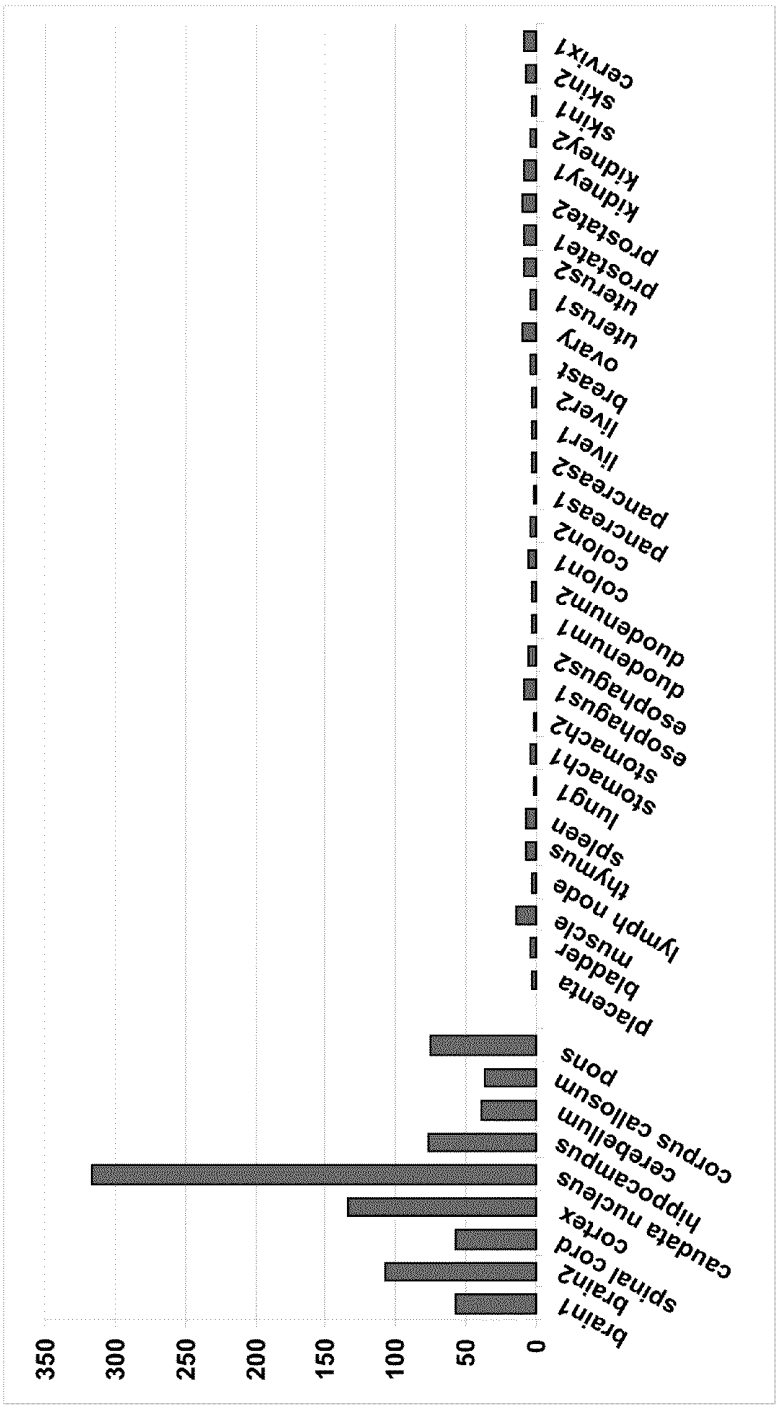
Fig. 3

class	number	gene
brain specific antigens	8	ARPP-19, NAP1L3, CLSTN1, CMTM2, CPE, LITAF, ENO2, TUBG1
other autoantigens	4	SDCCAG8, HSP90B1, SAT, EXOSC5
unknown antigens	10	chromosome 20 sequence; CEP63; LOC115648; chromosome 18 sequence; chromosome 14 sequence 1; chromosome 14 sequence 2; IQWD1; c6ORF199; chromosome 22 sequence; LOC400843
other cellular antigens	17	IRF2BP2, SREBF1, XPO4, ZFP64, FNPB1, CCL4, COPA, GHITM, NGLY1, KTN1, SFRS11, NME1-NME2, RPS15, APC2, GLS2, TECAL8, PPIF
mitochondrial antigens	5	ND4; ATP5H; COX1; COX2; COX3
summary	**44 autoantigens**	

Fig. 4


CLSTN1
800
600
400
200
0
brain1
brain2
spinal cord
cortex
caudata nucleus
hippocampus
cerebellum
corpus callosum
pons
heart
placenta
bladder
muscle
spleen
lung1
lung2
stomach1
stomach2
esophagus1
esophagus2
duodenum
pancreas1
pancreas2
liver1
liver2
breast
breast
uterus1
uterus2
uterus3
cervix
testis
testis
prostate
kidney
skin

ARPP-19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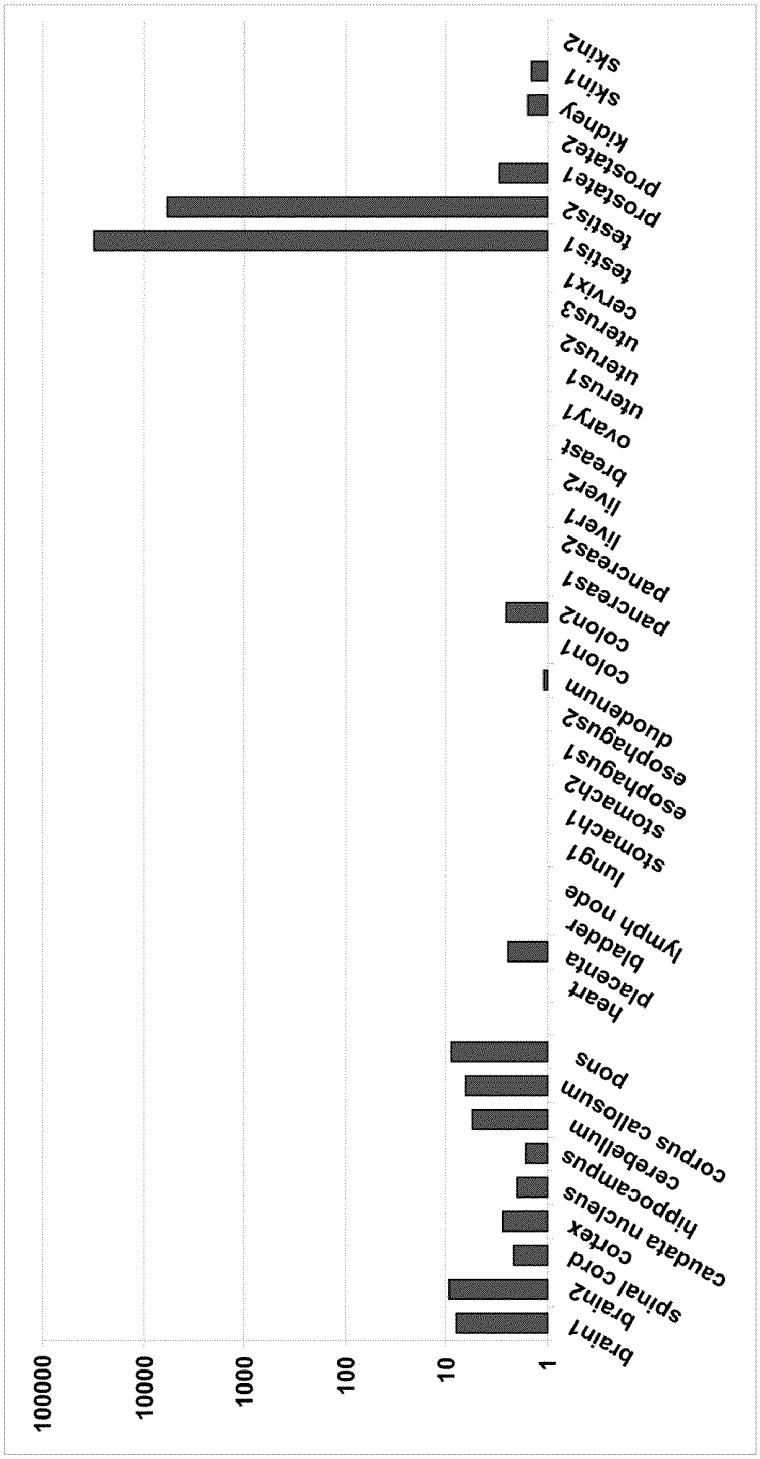
brain2
spinal cord
cortex
caudata nucleus
hippocampus
cerebellum
corpus callosum
pons
placenta
bladder
muscle
lymph node
thymus
spleen
lung1
stomach1
stomach2
esophagus1
esophagus2
duodenum1
duodenum2
colon1
colon2
pancreas1
pancreas2
liver1
liver2
breast
ovary
uterus1
uterus2
prostate1
prostate2
kidney1
kidney2
skin1
skin2
cervix1
0
50
100
150
200
250
300
350

Fig. 5

Fig. 6

CMTM2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10000
1000
100
10
1
brain1
brain2
spinal cord
cortex
caudata nucleus
hippocampus
cerebellum
corpus callosum
pons
heart
placenta
bladder
lymph node
lung1
stomach1
stomach2
esophagus1
esophagus2
duodenum
colon1
colon2
pancreas1
pancreas2
liver1
liver2
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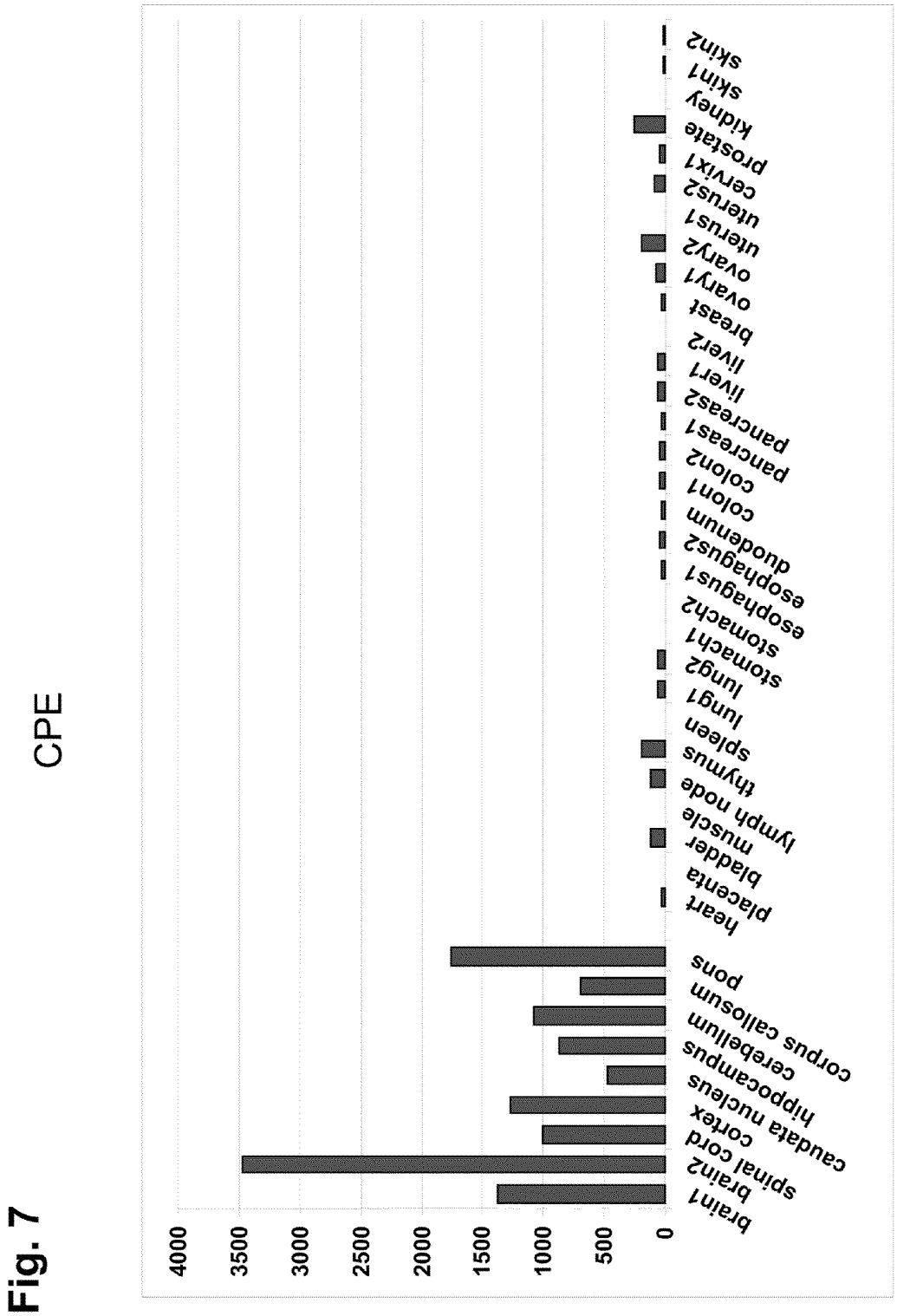
testis1
testis2
prostate1
prostate2
kidney
skin1
skin2


CPE
4000
3500
3000
2500
2000
1500
1000
500
0
brain1
brain2
spinal cord
cortex
caudata nucleus
hippocampus
cerebellum
corpus callosum
pons
heart
placenta
bladder
muscle
lymph node
thymus
spleen
lung1
lung2
stomach1
stomach2
esophagus1
esophagus2
duodenum
colon1
colon2
pancreas1
pancreas2
liver1
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ovary1
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uterus1
uterus2
cervix1
prostate
kidney
skin1
skin2

Fig. 7

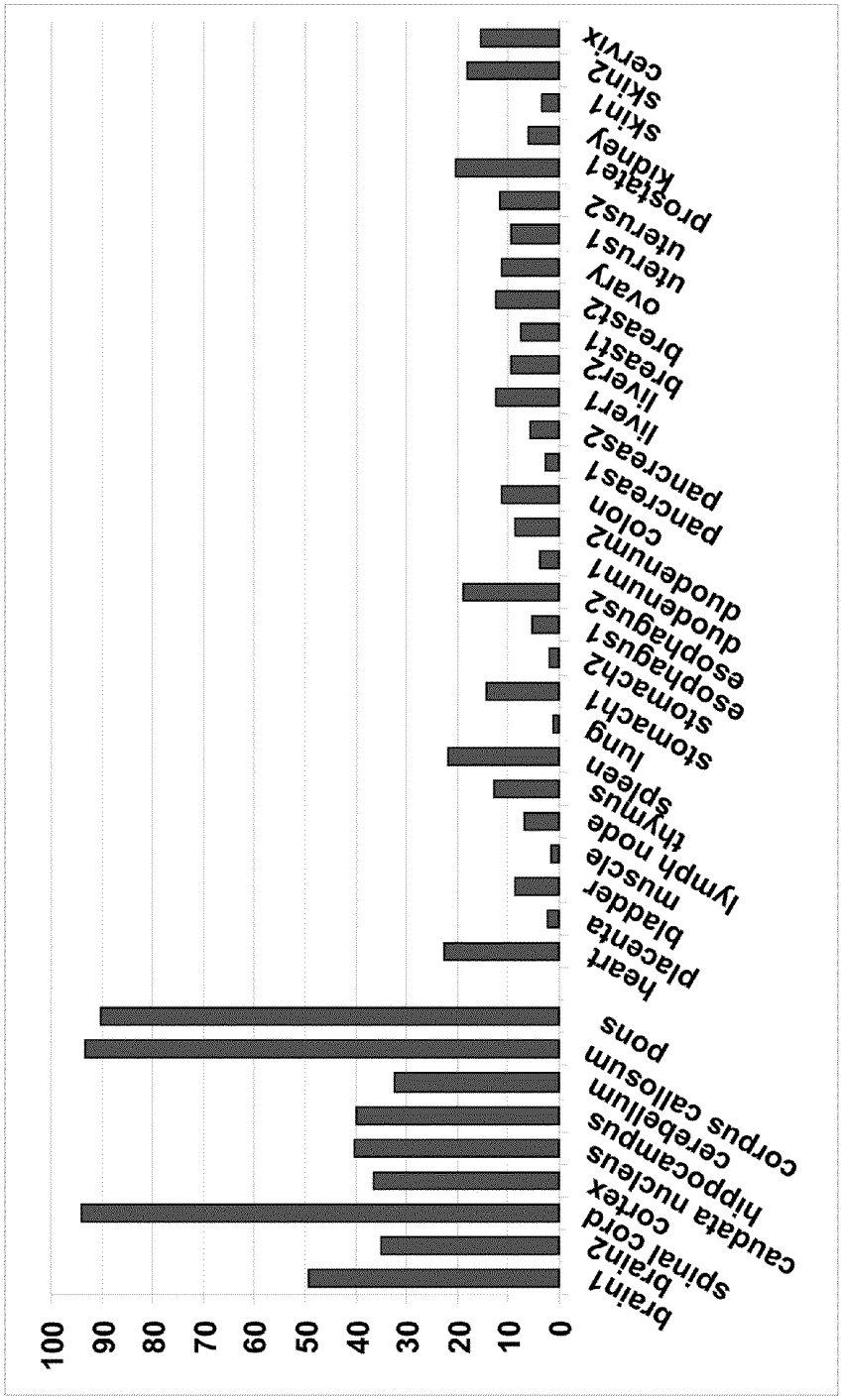

LITAF
100
90
80
70
60
50
40
30
20
10
0
brain1
brain2
spinal cord
cortex
caudata nucleus
hippocampus
cerebellum
corpus callosum
pons
heart
placenta
bladder
muscle
lymph node
thymus
spleen
lung
stomach1
stomach2
esophagus1
esophagus2
duodenum1
duodenum2
colon
pancreas1
pancreas2
liver1
liver2
breast1
breast2
ovary
uterus1
uterus2
prostate1
kidney
skin1
skin2
cervix

Fig. 8

Fig. 9

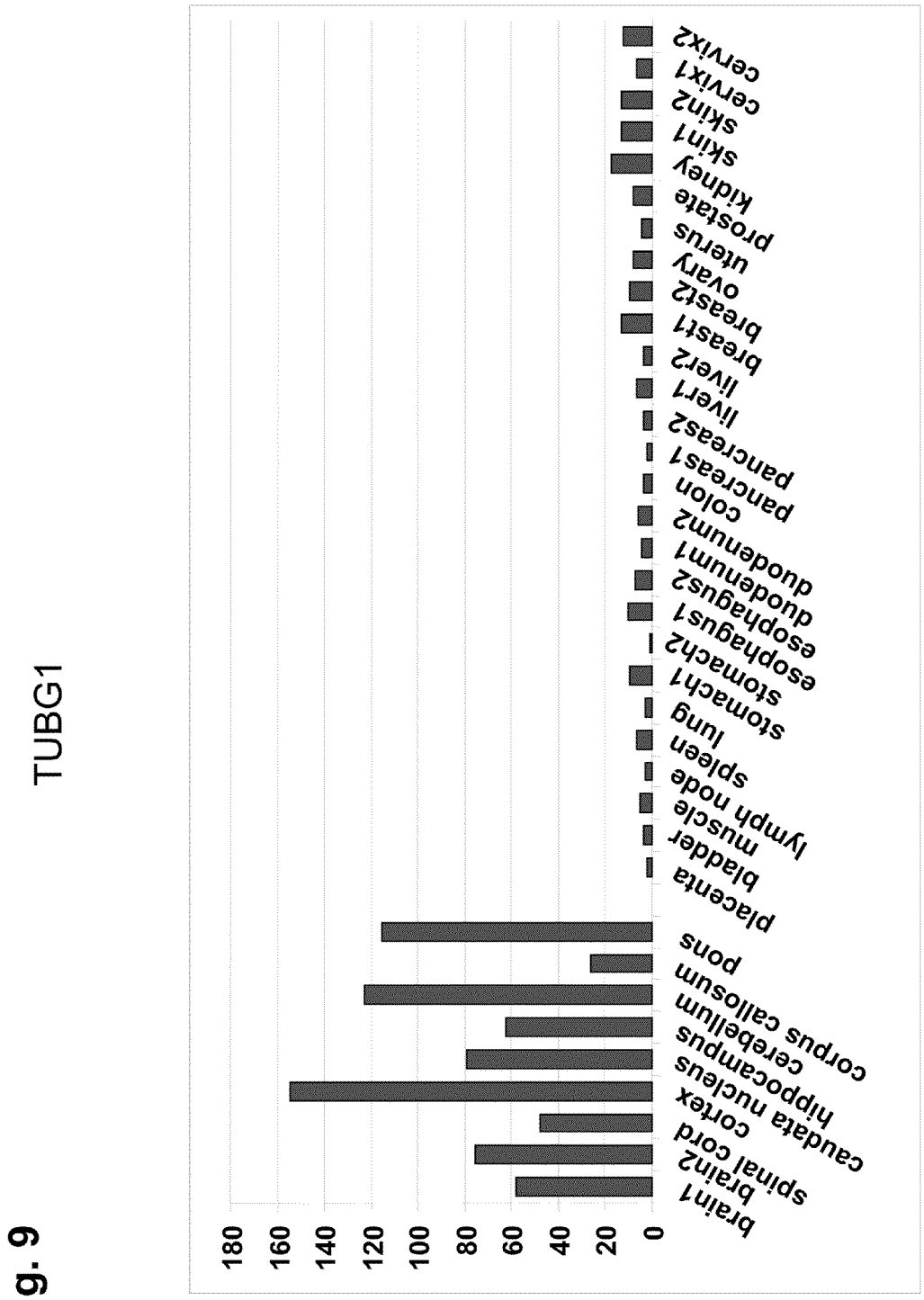
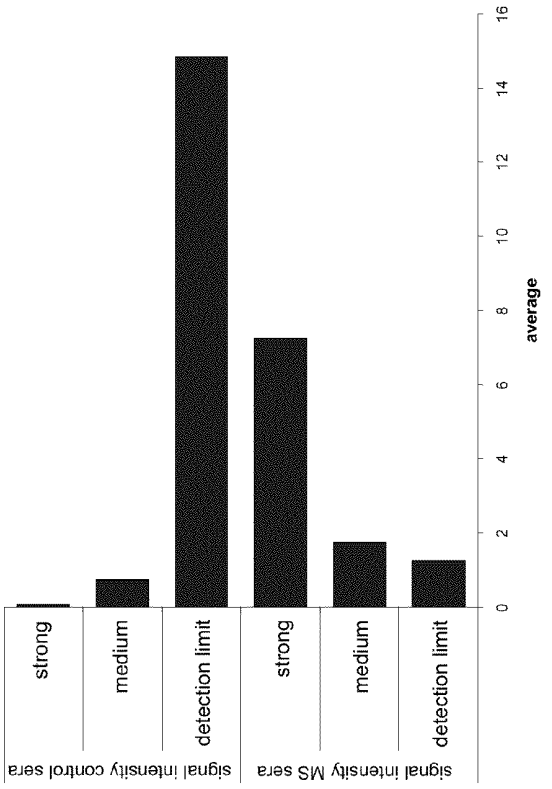

TUBG1
180
160
140
120
100
80
60
40
20
0
brain1
brain2
spinal cord
cortex
caudata nucleus
hippocampus
cerebellum
corpus callosum
pons
placenta
bladder
muscle
lymph node
spleen
lung
stomach1
stomach2
esophagus1
esophagus2
duodenum1
duodenum2
colon
pancreas1
pancreas2
liver1
liver2
breast1
breast2
ovary
uterus
prostate
kidney
skin1
skin2
cervix1
cervix2

Fig. 10

A

clone	signal intensity MS sera			signal intensity control sera			MS	control
	detection limit	medium	strong	detection limit	medium	strong	n	n
SREBF1	1	3	6	18	0	0	10	18
TUBG1	0	1	9	18	0	0	10	18
ARPP-19	0	1	9	17	1	0	10	18
XPO4	0	2	8	16	2	0	10	18
CMTM2	0	2	10	15	2	0	12	17
PPIF	0	2	8	18	0	0	10	18
LITAF	0	1	9	16	2	0	10	18
Chrom. 14 seq. 1	0	2	8	18	0	0	10	18
SDCCAG8	0	2	8	18	0	0	10	18
ZFP64	0	1	6	12	0	0	7	12
EXOSC5	0	1	6	12	0	0	7	12
NAP1L3	0	1	11	17	0	0	12	17
HSP90B1	0	2	10	16	2	0	12	18
CCL4	0	1	11	16	1	0	12	17
CLSTN1	0	4	9	16	1	0	13	17
IRF2BP2	0	6	6	17	0	0	12	17
TCEAL8	0	1	11	17	0	0	12	17
Chrom. 20 Seq.	0	1	11	18	0	0	12	18
CEP61	1	2	9	18	0	0	12	18
LOC400843	9	1	0	12	0	0	10	12
NGLY1	0	4	6	9	2	1	10	12
ENO2	8	1	1	9	2	0	10	11
GLS2	10	0	0	11	0	0	10	11
Chrom. 14 seq. 2	1	0	2	2	3	1	3	6
average	1,25	1,75	7,25	14,83	0,75	0,08		

B



AUTOANTIGENES FOR IMPROVED DIAGNOSIS, PROGNOSIS AND TREATMENT OF INFLAMMATORY NEUROLOGICAL DISEASES

RELATED APPLICATIONS

This application is a Continuation Application of International Application Number PCT/EP2007/008776, filed Oct. 9, 2007, and claiming priority benefit of German Patent Application Number 10 2008 048 201.8, filed on Oct. 11, 2006, the contents of which are incorporated herein by reference in their entireties.

FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[Not Applicable]

BACKGROUND OF THE INVENTION

A maximally comprehensive analysis of the autoimmune response of the immune system is necessary for developing efficient serodiagnostic agents and therapeutic agents for neurological autoimmune diseases. The serodiagnosis of autoimmune diseases is based on detection of autoantibodies which circulate in the blood and are specifically directed against immunogenic constituents (antigens) of autologous proteins. These antigens are also the sites of action of preventive and therapeutic strategies for autoimmune diseases. Knowledge of these antigens therefore permits the development of methods for the specific diagnosis and therapy of inflammatory neurological diseases.

Inflammatory neurological diseases, and especially multiple sclerosis (MS), are widespread diseases. According to statements by the WHO, multiple sclerosis is the commonest neurological disease in young adults around the world, with a prevalence of about 1:800 in Europe and North America. The chronic inflammatory disease of the nervous system, which appears for the first time in patients between 15 and 40 years of age, leads to a demyelinization of dendrites of the central nervous system (CNS). This results in a progressive paralysis of the muscles, losses of sensitivity and psychological disorders. Both the clinical course and the pathology of the cerebral disease are extremely heterogeneous (Lucchinetti et al., 2000 Ann Neurol 47, 707), The disease has either a chronic progressive or episodic course. General neurological symptoms appear initially and can be differentiated only with difficulty from other neurological diseases.

The etiology of the neurological autoimmune diseases and especially of MS has not been completely elucidated as yet, despite intensive research. An important role is ascribed to genetic and immunological and viral/bacterial factors (Kalman et al., 1999, Biomed Pharmac 53, 358; Lucchinetti et al., 2001, Curr Opin Neurol 14, 259; Kurtzke, 2001, J Clin Epidemiol 54, 1). A crucial role is, however, played by autoimmune processes, and various hypotheses concerning the immune dysregulation have been suggested. Thus, for example, the loss of regulatory mechanisms of autoreactive T cells has been described. The pathogenesis of MS lesions (Lucchinetti et al., 2000, Ann Neurol 47, 707) additionally supports the importance of autoimmune processes in the course of the disease. The reasons for the autoimmunity might be for example the similarity of viral antigens to encephalitogenic antigens ("Molecular mimicry") or traumatic tissue death (Levin et al., 2002, Nat Med 8, 509; Ludewig et al., 2004, J Exp Med 200, 837) as underlying

mechanism. The significance of the immune dysregulation in inflammatory neurological diseases is additionally supported by numerous experiments in model organisms in which an "experimental autoimmune encephalitis" (EAE) can be induced by autoimmunological processes ('t Hart et al., 2003, Curr Opin Neurol 18, 375).

The diagnosis of neurological autoimmune diseases and of MS in particular is currently a great problem. The first symptoms such as, for example, vision or coordination impairments and signs of paralysis and deafness apply to numerous neurological diseases, and differential diagnosis from autoimmune diseases is scarcely possible (Schmitt, 2003, Biomed Pharmacother 57, 261). A reliable diagnosis of MS is ultimately obtained only by combination with other criteria such as, for example, the number of inflammatory brain lesions which are obtained with the aid of MRI spectroscopy (magnetic resonance imaging), or analysis of oligoclonal IgG bands in the CSF. A rapid and reliable diagnosis using serum or urine is not at present possible, although various markers have been analyzed for their diagnostic power (Berger et al., 2003, New Engl J Med 349, 139; Chamczuk et al., 2002, J Imm Methods 262, 21; Vojdani et al., 2003, J Int Med 254, 383) and immunological tests in the form of ELISA and RIA are commercially available (e.g. from Diagnostics Systems Laboratory, Dakocytomation). There is as yet furthermore no laboratory diagnostic method which characterizes the course of MS in relation to imminent pathological episodes, and characterizes the course of pathological episodes and determines whether the disease is about to take a more active or aggressive course in patients (e.g. episodic course of the disease to chronic progressive). Ultimately, there is no diagnostic method which gives prognostic indications of possible MS and/or a diagnostic method which characterizes the course of treatment of MS.

A disease-specific treatment of MS has not been established to date. The treatment of MS is currently predominantly symptomatic using antiinflammatory medicaments. Steroids and various interferons are employed in particular (Jacobs et al., 2003, J Exp Med 343, 598; EP1289541). In principle, these medicaments reduce the inflammatory immune response through toxic effects on lymphocytes, but do not prevent the further episodic or chronic progressive course of the disease. Other substances currently being tested are statins (US2002159974) and glatiramer acetate, which is said to inhibit T-cell proliferation by competition (Duda et al., 1999, J Clin Invest 105, 987; EP1487783; WO2004078145). In addition, some antigen-specific approaches are currently being analyzed. Attempts to treat MS by T-cell vaccinations are still in the early stages (WO9115225). Therapeutic approaches with various monoclonal antibodies directed against the antigens α_4-integrin (Bielekova et al. 2000, Nat Med 6, 1145), CD40 (patent publication: WO03045978) and CD52 (patent publication: EP1455826) are moreover in different clinical phases. It has moreover been possible to test successfully an antigen-specific tolerance therapy in EAE models (Robinson et al., 2003, Nat Biotechn 21, 1033).

It has not been possible to utilize the information obtained to date in order to provide maximally sensitive and specific test methods enabling reliable and generally accepted diagnostic methods using serum for neurological autoimmune diseases, especially multiple sclerosis. Nor has it been possible on the basis of the antigens known to date to establish either an effective preventive or a therapeutic vaccination, although a wide variety of methods have been published, and some substances are still being tested.

There is thus a need for an effective diagnosis, prognosis and therapy of neurological autoimmune diseases, and especially multiple sclerosis.

It was the object of the present invention to provide target structures for a diagnosis, prognosis and therapy of neurological autoimmune diseases such as multiple sclerosis. It was the particular object of the present invention to identify molecular markers which enable differential diagnosis between neurological autoimmune diseases such as multiple sclerosis and other neurological diseases.

This object is achieved according to the invention by the subject matter of the claims.

BRIEF SUMMARY OF THE INVENTION

According to the invention, autoantibodies whose occurrence is characteristic of neurological autoimmune diseases, especially multiple sclerosis, are detected and the respective autoantigens are identified. It has further been possible to show according to the invention that some of these autoantigens are specifically expressed in the brain. Identification of the autoantigens and autoantibodies is of diagnostic and therapeutic use, with brain-specific expression of the autoantigens further underlining an important role of the antigens and antibodies in the development and course of neurological autoimmune diseases.

Accordingly, the invention relates to methods which enable assessment and/or prognosis of a neurological autoimmune disease. The methods of the invention preferably make it possible to state whether a neurological autoimmune disease has been contracted or will be contracted. The methods of the invention preferably allow a distinction to be made between a neurological disease which is not an autoimmune disease, and a neurological autoimmune disease, especially between a neurological disease which is not multiple sclerosis, and multiple sclerosis. The methods of the invention may also give information about the success of a treatment of a neurological autoimmune disease. In this embodiment, success of a treatment of a neurological autoimmune disease is preferably indicated by a decrease in one or more of the auto-antibodies or T lymphocytes described herein. The methods of the invention also make it possible to monitor the course of the disease, and if the disease deteriorates, as indicated for example by an increase in one or more of the autoantibodies or T lymphocytes described herein, the planning of a more aggressive therapy such as a treatment by immunosuppression is made possible.

In one aspect, the invention relates to a method for the diagnosis, prognosis and/or monitoring, i.e. determination of the regression, progression and/or course, of a neurological autoimmune disease in a patient, comprising the detection and/or determination of the amount of an antibody which is specific for a protein or peptide which is encoded by a nucleic acid which is selected from the group consisting of:

(a) a nucleic acid which comprises a nucleic acid sequence which is selected from the group consisting of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, a part and a derivative thereof,

(b) a nucleic acid which hybridizes under stringent conditions with the nucleic acid of (a), (c) a nucleic acid which is degenerate in relation to the nucleic acid of (a) or (b), and (d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c), or is specific for a part or a derivative of the protein or peptide, in a biological sample isolated from a patient. The protein or peptide for which the antibody is specific preferably comprises a sequence which is selected from the group consisting of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, a part and derivative thereof.

In one embodiment of the invention, the method of the invention further comprises the detection and/or determination of the amount of the antibody in a biological sample isolated from a patient without the autoimmune disease and/or without a risk of the autoimmune disease.

Presence of the antibody and/or an amount of the antibody which is increased by comparison with a patient without the autoimmune disease and/or without a risk of the autoimmune disease in the biological sample indicates preferentially the presence of the autoimmune disease or a risk of the development of the autoimmune disease.

In a preferred embodiment, the detection and/or determination of the amount of the antibody takes place with an immunoassay. The detection and/or determination of the amount of the antibody preferably comprises (i) contacting the biological sample with an agent which specifically binds to the antibody, and (ii) detecting the formation of a complex between the agent and the antibody. The agent which specifically binds to the antibody is preferably immobilized on a support material and/or is preferably a protein or peptide or derivative thereof which specifically binds to the antibody. In a preferred embodiment, the protein or peptide which specifically binds to the antibody comprises a sequence which is encoded by a nucleic acid which is selected from the group consisting of: (a) a nucleic acid which comprises a nucleic acid sequence selected from the group consisting of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 89, 71, 73, 75, 77, 79, 81, 83, 85, 87, a part and a derivative thereof, (b) a nucleic acid which hybridizes under stringent conditions with the nucleic acid of (a), (c) a nucleic acid which is degenerate in relation to the nucleic acid of (a) or (b), and (d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c). The protein or peptide which specifically binds to the antibody preferably comprises a sequence which is selected from the group consisting of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 18, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 84, 68, 68, 70, 72, 74, 78, 78, 80, 82, 84, 88, 88, and a part thereof. A derivative of the protein or peptide is accordingly preferably derived from such a protein or peptide.

In a further aspect, the invention relates to a method for the diagnosis, prognosis and/or monitoring of a neurological autoimmune disease in a patient, comprising the detection and/or determination of the amount of a T lymphocyte which is specific for a protein or peptide which is encoded by a nucleic acid which is selected from the group consisting of: (a) a nucleic acid which comprises a nucleic acid sequence which is selected from the group consisting of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, a part and a derivative thereof, (b) a nucleic acid which hybridizes under stringent conditions with the nucleic acid of (a), (c) a nucleic acid which is degenerate in relation to the nucleic acid of (a) or (b), and (d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c), or is specific for a part or a derivative of the protein or peptide, in a biological sample isolated from a patient. The protein or peptide for which the T lymphocyte is specific preferably comprises a sequence selected from the group consisting of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52,

54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, a part and derivative thereof.

In one embodiment of the invention, the method of the invention further comprises the detection and/or determination of the amount of the T lymphocyte in a biological sample isolated from a patient without the autoimmune disease and/or without a risk of the autoimmune disease.

Presence of the T lymphocyte and/or an amount of the T lymphocyte which is increased by comparison with a patient without the autoimmune disease and/or without a risk of the autoimmune disease in the biological sample indicates preferentially the presence of the autoimmune disease or a risk of the development of the autoimmune disease.

In a preferred embodiment, the detection and/or determination of the amount of the T lymphocyte takes place with a lymphocyte proliferation test. The detection and/or determination of the amount of the T lymphocyte preferably comprises (i) contacting the biological sample with an agent which specifically binds to the T lymphocyte, and (ii) detecting the formation of a complex between the agent and the T lymphocyte. The agent which specifically binds to the T lymphocyte is preferably immobilized on a support material. In one embodiment, the agent which specifically binds to the T lymphocyte is a protein or peptide or a derivative thereof which specifically binds to the T lymphocyte. In a further embodiment, the agent which specifically binds to the T lymphocyte is a complex which comprises an MHC molecule or a part thereof and a protein or peptide or derivative thereof and which specifically binds to the T lymphocyte. In one embodiment, the complex is presented by a cell such as an antigen-presenting cell.

The protein or peptide which specifically binds to the T lymphocyte, or which is comprised in the complex which specifically binds to the T lymphocyte, preferably comprises a sequence which is encoded by a nucleic acid which is selected from the group consisting of: (a) a nucleic acid which comprises a nucleic acid sequence selected from the group consisting of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 81, 83, 65, 87, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, a part and a derivative thereof, (b) a nucleic acid which hybridizes under stringent conditions with the nucleic acid of (a), (c) a nucleic acid which is degenerate in relation to the nucleic acid of (a) or (b), and (d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c). The protein or peptide which specifically binds to the T lymphocyte, or which is comprised in the complex which specifically binds to the T lymphocyte, preferably comprises a sequence selected from the group consisting of SEQ ID NO: 2, 4, 8, 8, 10, 12, 14, 18, 18, 20, 22, 24, 28, 28, 30, 32, 34, 36, 38, 40, 42, 44, 48, 48, 50, 52, 54, 56, 58, 60, 82, 64, 68, 88, 70, 72, 74, 78, 78, 80, 82, 84, 86, 88, and a part thereof. A derivative of the protein or peptide is accordingly preferably derived from such a protein or peptide.

In one embodiment, the methods of the invention for monitoring a neurological autoimmune disease comprise a determination of the regression, the course or the onset of the disease in a sample from the patient. In particular embodiments, the methods of the invention for monitoring a neurological autoimmune disease serve to monitor a successful therapy of the neurological autoimmune disease, in which case a decrease in the level of antibodies and/or T lymphocytes which are detected and/or determined according to the invention indicates a successful therapy.

In particular embodiments, the methods of the invention for the diagnosis, prognosis and/or monitoring of a neurological autoimmune disease comprise a detection or determination of the amount in a first sample at a first time and in a further sample at a second time and comparison of the two samples.

A biological sample comprises according to the invention preferably body fluid and/or body tissue, where the body fluid is preferably selected from serum, plasma, urine and cerebrospinal fluid.

The neurological autoimmune disease is preferably according to the invention multiple sclerosis.

In a particularly preferred embodiment, the invention in the foregoing aspects relates to a method for the diagnosis of a neurological autoimmune disease, especially multiple sclerosis.

In particular embodiments of the methods of the invention for the diagnosis, prognosis and/or monitoring of a neurological autoimmune disease, the patent is suffering from a neurological disease, in particular from a neurological autoimmune disease, and displays in particular symptoms of such a disease, is suspected of suffering from a neurological disease, in particular from a neurological autoimmune disease, or of developing such a disease, or exhibits a risk of a neurological disease, in particular a neurological autoimmune disease.

In a preferred embodiment, the biological sample isolated from a patient is compared with a comparable normal biological sample such as a sample from a healthy individual.

The agent used for a detection or determination of the amount of antibodies or T lymphocytes, in particular the protein, peptide or derivative thereof, or the agent which binds to a complex formed between an antibody or T lymphocyte and an agent binding thereto, in particular an anti-immunoglobulin antibody or an antibody directed against T lymphocytes, are preferably detectably labeled. In particular embodiments, the detectable marker is a radioactive marker, fluorescent marker or enzyme marker.

In particular embodiments, the methods of the invention comprise a detection of a plurality of the autoantibodies and/or T lymphocytes described herein.

In a further aspect, the invention relates to a kit which comprises one or more agents which make it possible to detect and/or determine the amount of the antibodies or T lymphocytes described herein in a biological sample isolated from a patient. Such agents are described herein and known to the person skilled in the art.

The invention in this aspect relates in particular to a kit for the diagnosis, prognosis and/or monitoring of a neurological autoimmune disease in a patient, comprising a protein or peptide which comprises a sequence selected from the group consisting of SEQ ID NO: 2, 4, 8, 8, 10, 12, 14, 18, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 48, 48, 50, 52, 54, 56, 58, 60, 82, 64, 68, 88, 70, 72, 74, 78, 78, 80, 82, 84, 86, 88, and a part thereof or a derivative of the protein or peptide. The protein or peptide or the derivative thereof is preferably immobilized on a support.

The kit of the invention preferably further comprises instructions for use of the kit in a method for the diagnosis, prognosis and/or monitoring of a neurological autoimmune disease in a patient, where the method is preferably a method of the invention.

In one embodiment, the kit further comprises a reagent for detecting a binding of an antibody to the protein or peptide contained therein, or the derivative thereof, where the reagent preferably comprises a detectably labeled binding partner for the antibody. The binding partner for the antibody is preferably an anti-immunoglobulin antibody, in particular an anti-human immunoglobulin antibody coupled to a detectable

marker such as an enzyme. The kit of the invention may further also comprise an enzyme substrate, and positive controls and negative controls.

In a further aspect, the invention relates to a pharmaceutical composition comprising one or more components which are selected from the group consisting of (i) a protein or peptide which comprises a sequence which is selected from the group consisting of SEQ ID NO: 2, 4, 8, 8, 10, 12, 14, 18, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 58, 58, 80, 62, 64, 86, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, and a part thereof or a derivative of the protein or peptide, (ii) a nucleic acid which expresses the protein or peptide or the derivative thereof in (i), and (iii) a host cell which comprises the nucleic acid in (ii). The nucleic acid may be present in an expression vector. The host cell will preferably express the peptide or protein or derivative thereof.

A host cell present in the pharmaceutical composition of the invention may secrete the protein or peptide or derivative thereof, express it on the surface or may additionally express an MHC molecule which binds to the protein or peptide or derivative thereof or to a processed form thereof. In one embodiment, the host cell expresses the MHC molecule endogenously. In a further embodiment, the host cell expresses the MHC molecule and/or the protein or peptide or derivative thereof recombinantly. The host cell is preferably non-proliferative. In a preferred embodiment, the host cell is an antigen-presenting cell.

A pharmaceutical composition of the invention may comprise a pharmaceutically acceptable carrier and/or an adjuvant, and is preferably suitable for the treatment of a neurological autoimmune disease, especially for the treatment of multiple sclerosis.

The invention further relates to a method for the treatment of a neurological autoimmune disease, especially multiple sclerosis, comprising the administration of a pharmaceutical composition of the invention.

BRIEF DESCRIPTION OF SEVERAL VIEWS OF THE DRAWINGS

FIG. **1**. Diagrammatic representation of the strategy for producing a brain-specific cDNA expression library.

FIG. **2**. Immunoscreening with sera from MS patients and identification of a reactive antigen.

FIG. **3**. Classification of the antigens identified according to the invention.

FIG. **4**: Analysis of CLSTN1-specific expression. Quantitative analysis of CLSTN1-specific expression in healthy tissue samples. The relative expression (-fold activation) is shown.

FIG. **5**: Analysis of ARPP19-specific expression, Quantitative analysis of ARPP19-specific expression in healthy tissue samples. The relative expression (-fold activation) is shown.

FIG. **6**: Analysis of CMTM2-specific expression. Quantitative analysis of CMTM2-specific expression in healthy tissue samples. The relative expression (-fold activation) is shown.

FIG. **7**: Analysis of CPE-specific expression. Quantitative analysis of CPE-specific expression in healthy tissue samples. The relative expression (-fold activation) is shown.

FIG. **8**: Analysis of LITAF-specific expression. Quantitative analysis of LITAF-specific expression in healthy tissue samples. The relative expression (-fold activation) is shown.

FIG. **9**: Analysis of TUBG1-specific expression. Quantitative analysis of TUBG1-specific expression in healthy tissue samples. The relative expression (-fold activation) is shown.

FIG. **10**, Differential serology of selected antigens. A: Representation of the qualitative analysis of the signal intensity for selected antigens after incubation with sera from MS patients compared with healthy control sera.

B: Summary of the signal intensities of all the antigens depicted in FIG. **10** A after incubation with sera from MS patients compared with healthy control sera.

DETAILED DESCRIPTION OF THE INVENTION

The term "autoantigen" relates according to the invention to a substance which generates an immune response such as the production of antibodies in the creature from which it is derived. In particular, the term "autoantigen" relates according to the invention to a protein or peptide which is encoded by a nucleic acid which is selected from the group consisting of:

(a) a nucleic acid which comprises a nucleic acid sequence selected from the group consisting of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 83, 65, 67, 89, 71, 73, 75, 77, 79, 81, 83, 85, 87, a part and a derivative thereof, (b) a nucleic acid which hybridizes under stringent conditions with the nucleic acid of (a), (c) a nucleic acid which is degenerate in relation to the nucleic acid of (a) or (b), and (d) a nucleic acid which is complementary to the nucleic acid of (a), (b) or (c), or a part or a derivative of the protein or peptide. The term "autoantigen" refers according to the invention in particular to a protein or peptide which comprises a sequence which is selected from the group consisting of SEQ ID NO: 2, 4, 8, 8, 10, 12, 14, 18, 18, 20, 22, 24, 26, 28, 30, 32, 34, 38, 38, 40, 42, 44, 48, 48, 50, 52, 54, 58, 58, 80, 82, 84, 86, 88, 70, 72, 74, 76, 78, 80, 82, 84, 88, 88, a part and derivative thereof.

The term "autoantibody" relates according to the invention to antibodies which are directed against an autoantigen. Autoantibodies recognize an endogenous antigen and occur inter alia in association with autoimmune diseases. In particular, the term "autoantibody" relates according to the invention to an antibody which is directed against an autoantigen described above and in particular specifically binds thereto.

The term "detection and/or determination of the amount" in relation to a substance relates according to the invention to the determination of the occurrence or absence and/or the absolute and/or relative amount of the substance. The term also includes situations in which no substance is detected, either because it is not present, or its amount is below the limit of detection of the detection system.

It is generally possible according to the invention to employ all methods suitable for a detection and analysis of antibodies or T lymphocytes for a detection and/or determination of the amount thereof. Possibilities for carrying out a detection and/or determination of the amount of antibodies and T lymphocytes in the methods of the invention are known to the person skilled in the art.

It is possible in particular to use according to the invention any direct or indirect method for detecting antibodies.

In the direct methods, the binding of the antibodies to be detected to the antigen is determined via a change in the chemical or physical properties, so that subsequent detection steps with labeled binding partners are unnecessary.

It is preferred according to the invention for antibodies to be detected in an immunoassay, preferably in a solid-phase immunoassay, with direct or indirect coupling of a binding partner.

The detection can particularly preferably take place in an ELISA, an RIA or a fluorescence immunoassay. The procedure for these detection methods is known to the person skilled in the art.

It is possible to use as solid phase for example any support able to bind to antigen or antibody. Such supports include materials such as glass, polystyrene, polypropylene, polyethylene, dextran, nylon, natural or modified celluloses, polyacrylamides, agaroses and magnetite. The support may have any possible structural configuration as long as the molecule bound thereto, such as antigen or antibody, is able to bind to its binding partner. Suitable configurations include a spherical configuration, a cylindrical configuration such as the inside of a test vessel, or a flat configuration such as test strips etc.

In an ELISA for example antigen is bound directly or indirectly to a support substance such as polystyrene. Incubation with the antibodies to be detected is followed by detection of antigen-bound antibodies directly or indirectly by means of enzyme-coupled substances. These substances may be antibodies, fragments of antibodies or high-affinity ligands. Examples of suitable enzymes are peroxidase, alkaline phosphatase, β-galactosidase, urease or glucose oxidase. It is possible by adding a chromogenic substrate for the bound enzymes, and thus for example the bound antibodies, to be quantified.

In a radioimmunoassay, the antigen is bound directly or indirectly to a support substance such as polystyrene. Incubation with the antibodies to be detected is followed by detection of antigen-bound antibodies by means of substances having a radioactive label such as ^{125}I. These substances may be antibodies, fragments of antibodies or high-affinity ligands. The bound radioactivity can be quantified by means of a suitable measuring instrument.

By the same principle, in a fluorescence immunoassay the antigen-bound antibodies are detected by means of substances which have a fluorescent label such as fluorescein isothiocyanate (FITC). These substances may be antibodies, fragments of antibodies or high-affinity ligands. The bound amount of fluorescent dye is then quantified by means of a suitable measuring instrument.

It is also possible according to the invention to detect antibodies in an agglutination test or gel diffusion test. These detection methods are also known to the person skilled in the art.

In the gel diffusion test, the antigen solutions or antibody solutions are preferably put into neighboring, adjacent wells of agar or agarose plates. If the substances diffuse out of their wells, concentration gradients form, starting from the wells. If the overlapping antigen and antibody concentrations in the gel are within certain proportions, and the antibody solution contains antibodies against the antigen, visible precipitates are formed in the gel.

In the agglutination test, antigen-carrying particles such as particles of latex or polystyrene are crosslinked by antibodies. The aggregates formed can be detected for example by turbodimetry.

A detection or determination of the amount of a T lymphocyte can take place according to the invention with a cell which presents a complex, for which the T lymphocyte is specific, between a protein, peptide or derivative thereof and an MHC molecule, where the cell is preferably an antigen-presenting cell. Detection or determination of the amount of a T lymphocyte takes place where appropriate through detection of its proliferation, cytokine production and/or cytotoxic activity which is induced by the specific stimulation with the complex between the protein, peptide or derivatives thereof and an MHC molecule. A detection or determination of the amount of a T lymphocyte can moreover take place through a recombinant MHC molecule or a complex of two or more MHC molecules which are loaded with one or more proteins, peptides, or derivatives thereof.

In one embodiment, the cell expresses the MHC molecule endogenously. In a further embodiment, the cell expresses the MHC molecule and/or the protein or peptide or derivative thereof recombinantly. The host cell is preferably non-proliferative. In a preferred embodiment, the host cell is an antigen-presenting cell.

A binding agent such as antibody is specific for its target, such as an antigen, if it binds thereto. The term "binding" relates according to the invention preferably to a specific binding. "Specific binding" means that a binding to a target such as an epitope for which a binding agent such as an antibody is specific is stronger by comparison with the binding to another target. A "stronger binding" can be characterized for example by a lower dissociation constant.

It is possible according to the invention to use a "reference" such as a reference sample or a reference organism in order to correlate or compare the results obtained in the methods of the invention. A reference organism is typically a healthy organism, especially an organism which is not suffering from a neurological autoimmune disease, especially from multiple sclerosis.

A "reference value" can be determined on the basis of a reference empirically by measuring a sufficient number of references.

A nucleic acid is according to the invention preferably deoxyribonucleic acid (DNA) or ribonucleic acid (RNA). Nucleic acids include according to the invention genomic DNA, cDNA, mRNA, recombinantly prepared and chemically synthesized molecules. A nucleic acid may according to the invention be in the form of a single-stranded or double-stranded and linear or covalently circularly closed molecule.

The nucleic acids described according to the invention are preferably isolated. The term "isolated nucleic acid" means according to the invention that the nucleic acid (i) has been amplified in vitro, for example by polymerase chain reaction (PCR), (ii) has been produced recombinantly by cloning, (iii) has been purified, for example by cleavage and fractionation by gel electrophoresis, or (iv) has been synthesized, for example by chemical synthesis. An isolated nucleic acid is a nucleic acid which is available for manipulation by recombinant DNA techniques.

A degenerate nucleic acid is according to the invention a nucleic acid which differs from a reference nucleic acid in terms of the codon sequence on the basis of the degeneracy of the genetic code.

The term "nucleic acid" also includes according to the invention derivatives of nucleic acids. By "derivative" of a nucleic acid is meant according to the invention that single or multiple, preferably at least 2, at least 4, at least 6 and preferably up to 3, up to 4, up to 5, up to 6, up to 10, up to 15 or up to 20, substitutions, deletions and/or additions of nucleotides are present in the nucleic acid.

The term "derivative" of a nucleic acid further includes also a chemical derivatization of a nucleic acid on a nucleotide base, on the sugar or on the phosphate and nucleic acids which contain non-naturally occurring nucleotides and nucleotide analogs.

The degree of identity between a nucleic acid and a nucleic acid which is a derivative of the first nucleic acid, which hybridizes with the first nucleic acid and/or which is degenerate in relation to the first nucleic acid is preferably according to the invention at least 70%, in particular at least 75%, at

least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 97%, at least 98%, and preferably at least 99%. The degree of identity is preferably indicated for a region of at least about 30, at least about 50, at least about 70, at least about 90, at least about 100, at least about 150, at least about 200, at least about 300, at least about 400, at least about 500, at least about 1000, or at least about 2000 consecutive nucleotides. In preferred embodiments, the degree of identity is indicated for the complete length of the reference nucleic acid like the nucleic acid sequences indicated in the sequence listing.

A nucleic acid is "complementary" to another nucleic acid if the two sequences are able to hybridize together and enter into a stable duplex, the hybridization preferably taking place under conditions which permit a specific hybridization between polynucleotides (stringent conditions). Stringent conditions are described for example in Molecular Cloning: A Laboratory Manual, J. Sambrook et al., editors, 2nd edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989 or Current Protocols in Molecular Biology, F. M. Ausubel et al., editors, John Wiley & Sons, Inc., New York, and relate for example to hybridization at 65° C. in hybridization buffer (3.5×SSC, 0.02% Ficoll, 0.02% polyvinylpyrrolidone, 0.02% bovine serum albumin, 2.5 mM NaH_2PO_4 (pH 7), 0.5% SDS, 2 mM EDTA). SSC is 0.15 M sodium chloride/0.15 M sodium citrate, pH 7. After the hybridization, the membrane to which the DNA has been transferred is washed for example in 2×SSC at room temperature and then in 0.1-0.5×SSC/0.1×SDS at temperatures up to 68° C.

Percent complementarity indicates the percentage of consecutive nucleotides in a nucleic acid which are able to form hydrogen bonds (e.g. by Watson-Crick base pairing) with a second nucleic acid. Complementary nucleic acids preferably exhibit according to the invention at least 40%, in particular at least 50%, at least 80%, at least 70%, at least 80%, at least 90% and preferably at least 95%, at least 98% or at least 99% complementary nucleotides. Complementary nucleic acids are preferably completely complementary, meaning that all consecutive nucleotides can enter into hydrogen bonds with the same number of consecutive nucleotides in a second nucleic acid.

"Sequence similarity" indicates the percentage of amino acids which either are identical or represent conservative amino acid substitutions. "Sequence identity" between two polypeptides or nucleic acids indicates the percentage of amino acids or nucleotides which are identical between the sequences.

The term "% identity" is intended to refer to a percentage of nucleotides which are identical between two sequences to be compared with an optimal alignment, this percentage being purely statistical, it being possible for the differences between the two sequences to be distributed at random and over the complete sequence length, and it being possible for the sequence to be compared to include additions or deletions by comparison with the reference sequence in order to achieve an optimal alignment between two sequences. Sequence comparisons between two sequences are generally carried out by comparing the sequences after an optimal alignment in relation to a segment or "comparison window" in order to identify local regions of sequence agreement. The optimal alignment for a comparison can be carried out manually or with the aid of the local homology algorithm of Smith and Waterman, 1981, Ads App. Math. 2, 482, with the aid of the local homology algorithm of Neddleman and Wunsch, 1970, J. Mol. Biol. 48, 443, and with the aid of the similarity search algorithm of Pearson and Lipman, 1988, Proc. Natl. Acad. Sci. USA 85, 2444, or with the aid of computer programs which use these algorithms (GAP, BESTFIT, FASTA, BLAST P, BLAST N and TFASTA in Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Drive, Madison, Wis.).

The percent identity is obtained by determining the number of identical positions in which the sequences to be compared agree, dividing this number by the compared positions and multiplying this result by 100.

It is for example possible to use the program BLAST "BLAST 2 sequences" which is obtainable from the website http://www.ncbi.nlm.nih.gov/blast/bl2seq/wblast2.cgi.

Derivatives of a particular nucleic acid relate in particular to variants of the nucleic acid, especially splice variants, isoforms and species homologs of the nucleic acid, especially those which are expressed naturally.

Nucleic acids can be analyzed in relation to variants such as splice variants according to the invention in a manner known per se. Techniques for analyzing splice variants include reverse transcription polymerase chain reaction (RT-PCR), Northern blotting and in situ hybridization.

A technique called "RNAse protection" can also be used in order to identify alternatively spliced mRNAs. RNAse protection includes transcription of a gene sequence into synthetic RNA, which is hybridized onto RNA derived for example from other cells. The hybridized RNA is then incubated with enzymes which recognize RNA:RNA hybrid mismatches. Fragments which are smaller than expected indicate the presence of alternatively spliced mRNAs. The putative alternatively spliced mRNAs can be cloned and sequenced in a manner known per se.

RT-PCR can also be used in order to identify alternatively spliced mRNAs. In RT-PCR, mRNA is converted into cDNA by the enzyme reverse transcriptase in a manner known per se. The complete coding sequence of the cDNA is then amplified by means of PCR using a forward primer which is located in the 3'-nontranslated region, and a reverse primer which is located in the 5'-nontranslated region. The amplification products can be analyzed for alternative splice forms for example by comparing the size of the amplified products with the size of the expected product from normally spliced mRNA for example by means of agarose gel electrophoresis. Any changes in the size of the amplification products may indicate alternative splicing.

mRNA derived from mutated genes can also be easily identified with the aid of the techniques described above for identifying alternative splice forms. Thus, for example, allelic forms of genes, and the mRNA produced thereby, which are considered according to the invention to be "mutants", can be identified.

Nucleic acids may according to the invention be present alone or in combination with other nucleic acids, which may be homologous or heterologous. In particular embodiments, a nucleic acid is present according to the invention functionally connected to expression control sequences which may be homologous or heterologous in relation to the nucleic acid, where the term "homologous" here indicates that a nucleic acid is also naturally functionally connected to the expression control sequence, and the term "heterologous" indicates that a nucleic acid is not naturally functionally connected to the expression control sequence.

A nucleic acid, preferably a transcribable nucleic acid, and especially one which codes for a peptide or protein, and an expression control sequence are "functionally" connected together if they are covalently linked together in such a way that transcription or expression of the nucleic acid is under the control or under the influence of the expression control sequence. If the nucleic acid is to be translated into a func-

tional peptide or protein, when an expression control sequence is functionally connected to the coding sequence an induction of the expression control sequence leads to a transcription of the coding sequence without there being a shift in the reading frame in the coding sequence or an inability of the coding sequence to be translated into the desired peptide or protein.

The term "expression control sequence" includes according to the invention promoters, ribosome binding sequences, enhancers and other control elements which control the transcription of a gene or the translation of mRNA. In particular embodiments of the invention, the expression control sequences are regulatable. The exact structure of expression control sequences may vary depending on species or depending on cell type, but generally includes 5'-nontranscribed and 5'- and 3'-nontranslated sequences which are involved in the initiation of transcription or translation, such as TATA box, capping sequence, CAAT sequence and the like. 5'-Nontranscribed expression control sequences include in particular a promoter region which includes a promoter sequence for transcriptional control of the functionally connected nucleic acid. Expression control sequences may also include enhancer sequences or activator sequences located upstream.

The term "promoter" or "promoter region" relates to a nucleic acid sequence which is located upstream (5') of the sequence to be expressed and controls the expression of the sequence by providing a recognition and binding site for RNA polymerase. The promoter region may include further recognition or binding sites for further factors involved in regulating the transcription of a gene. A promoter can control the transcription of a prokaryotic or eukaryotic gene. A promoter may be "inducible" and initiate transcription in response to an inducer, or it may be "constitutive" if the transcription is not controlled by an inducer. An inducible promoter is not expressed or is expressed to only a very small extent if an inducer is absent. In the presence of the inducer, the gene is "switched on" or the transcription level is raised. This is ordinarily mediated by binding of a specific transcription factor.

Promoters preferred according to the invention are for example promoters for SP6, T3 or T7 polymerase, human U6 RNA promoter and CMV promoter.

The term "expression" is used according to the invention in its most general meaning and includes the production of RNA or of RNA and protein/peptide. It also includes partial expression of nucleic acids. The expression may furthermore take place transiently or stably.

It is further possible for a nucleic acid which codes for a protein or peptide to be present according to the invention in conjunction with another nucleic acid which codes for a peptide sequence which controls secretion of the protein or peptide encoded by the nucleic acid from a host cell. It is also possible for a nucleic acid to be present according to the invention in conjunction with another nucleic acid which codes for a peptide sequence which brings about anchoring of the encoded protein or peptide on the cell membrane of a host cell or its compartmentalization in particular organelles of this cell. Conjunction with a nucleic acid which represents a reporter gene or any type of "tag" is equally possible.

In a preferred embodiment, a nucleic acid is present according to the invention in a vector, where appropriate with a promoter which controls the expression of the nucleic acid. The term "vector" is used in this connection in its most general meaning and includes all intermediate vehicles for a nucleic acid which make it possible for example for the nucleic acid to be introduced into prokaryotic and/or into eukaryotic cells and, where appropriate, be integrated into a genome. Such vectors are preferably replicated and/or expressed in the cell. Vectors include plasmids, phagemids, bacteriophages or viral genomes. The term "plasmid" as used herein relates generally to a construct of extrachromosomal genetic material, usually a circular DNA duplex, which can replicate independently of chromosomal DNA.

The term "host cell" relates according to the invention to any cell which can be transformed or transfected with an exogenous nucleic acid, preferably DNA or RNA. The term "host cell" includes according to the invention prokaryotic (e.g. *E. coli*) or eukaryotic cells (e.g. mammalian cells, especially human cells, yeast cells and insect cells). Mammalian cells such as human cells, mouse cells, hamster cells, pig cells, goat cells and primate cells are particularly preferred. The cells can be derived from a large number of tissue types and include primary cells and cell lines. Specific examples include keratinocytes, peripheral blood leukocytes, bone marrow stem cells and embryonic stem cells. In further embodiments, the host cell is an antigen-presenting cell, where the term "antigen-presenting cell" includes according to the invention dendritic cells, monocytes and macrophages. A nucleic acid may be present in the host cell in a single or in a plurality of copies and is expressed in one embodiment in the host cell.

In the cases of the invention in which an MHC molecule presents a protein or peptide, it is possible for an expression vector also to include a nucleic acid sequence which codes for the MHC molecule. The nucleic acid sequence which codes for the MHC molecule may be present on the same expression vector as the nucleic acid which codes for the protein or peptide, or the two nucleic acids may be present on different expression vectors. In the latter case, the two expression vectors may be cotransfected into a cell. If a host cell expresses neither the protein or peptide nor the MHC molecule, the two nucleic acids coding therefor may be transfected either on the same expression vector or on different expression vectors into the cell. If the cell already expresses the MHC molecule, it is possible for only the nucleic acid sequence which codes for the protein or peptide to be transfected into the cell.

The term "peptide" relates according to the invention to substances which include at least 2, at least 3, at least 4, at least 8, at least 8, at least 10, at least 13, at least 16, at least 20 and preferably up to 8, 10, 20, 30, 50, or 100 consecutive amino acids which are connected together by peptide linkages. The term "protein" relates to large peptides, preferably peptides having more than 100 amino acids, but the terms "peptide" and "protein" are generally used exchangeably herein. The term "protein or peptide" is also intended to include, unless indicated otherwise, derivatives thereof.

The proteins and peptides described according to the invention are preferably isolated. The terms "isolated protein" or "isolated peptide" mean that the protein or peptide is separated from its natural environment. An isolated protein or peptide may be in an essentially purified state. The term "essentially purified" means that the protein or peptide is essentially free of other substances with which it is present in nature or in vivo.

Proteins and peptides are used according to the invention for example for preparing antibodies and can be employed in immunological or diagnostic assays or as therapeutic agents. Proteins and peptides described according to the invention can be isolated from biological samples such as tissue or cell homogenates and can also be expressed recombinantly in a large number of prokaryotic or eukaryotic expression systems. It is further possible according to the invention for

proteins and peptides to be synthesized on solid or liquid phase in a manner known per se.

The proteins, peptides or derivatives thereof described herein can be used in their free or bound form for the diagnosis or treatment of patients with a neurological autoimmune disease, where the proteins, peptides or derivatives thereof have the ability in particular to bind, neutralize and/or selectively remove autoantibodies.

"Derivatives" of a protein or peptide or of an amino acid sequence in the context of this invention include amino acid insertion variants, amino acid deletion variants and/or amino acid substitution variants.

Amino acid insertion variants include amino- and/or carboxy-terminal fusions, and insertions of individual or a plurality of amino acids in a particular amino acid sequence. In amino acid sequence variants with an insertion, one or more amino acid residues are introduced into a predetermined position in an amino acid sequence, although random insertion with suitable screening of the resulting product is also possible.

Amino acid deletion variants are characterized by the removal of one or more amino acids from the sequence.

Amino acid substitution variants are distinguished by at least one residue in the sequence being removed and another residue being inserted in its place. The modifications are preferably located at positions in the amino acid sequence which are not conserved between homologous proteins or peptides, and/or amino acids are replaced by others having similar properties, such as hydrophobicity, hydrophilicity, electronegativity, volume of the side chain and the like (conservative substitution). Conservative substitutions relate for example to the exchange of one amino acid by another amino acid mentioned below in the same group as the substituted amino acid:

1. mall aliphatic, nonpolar or slightly polar residues: Ala, Ser, Thr (Pro, Gly)
2. egatively charged residues and their amides: Asn, Asp, Glu, Gln
3. ositively charged residues: His, Arg, Lys
4. arge aliphatic, nonpolar residues: Met, Leu, Ile, Val (Cys)
5. arge aromatic residues: Phe, Tyr, Trp.

Three residues are placed in parentheses because of their particular role for protein architecture. Gly is the only residue without a side chain and thus confers flexibility on the chain. Pro has an unusual geometry which greatly restricts the chain. Cys can form a disulfide bridge.

The degree of similarity, preferably identity, between one amino acid sequence and an amino acid sequence which is a derivative of the former amino acid sequence is preferably at least 70%, in particular at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 97%, at least 98%, and preferably at least 99%. The degree of identity is preferably indicated for a range of at least about 10, at least about 30, at least about 50, at least about 70, at least about 90, at least about 100, at least about 150, at least about 200, at least about 300, at least about 400, or at least about 500 consecutive amino acids. In preferred embodiments, the degree of identity is indicated for the complete length of the reference amino acid sequence like the amino acid sequences indicated in the sequence listing.

The amino acid variants described above can easily be prepared with the aid of known peptide synthesis techniques such as, for example, by "solid-phase synthesis" (Merrifield, 1964) and similar methods or by recombinant DNA manipulation. The manipulation of DNA sequences for preparing proteins and peptides with substitutions, insertions or deletions is described in detail for example in Sambrook et al. (1989).

"Derivatives" of proteins or peptides include according to the invention also single or multiple substitutions, deletions and/or additions of any molecules associated with the protein or peptide, such as carbohydrates, lipids and/or proteins or peptides. The term "derivative" also extends further to all functional chemical equivalents of the proteins and peptides and substances which comprise not only amino acid constituents but also non-amino acid constituents such as sugars and phosphate structures and also include substances which comprise linkages such as ester linkages, thioether linkages and disulfide linkages. A derivative of a protein or peptide preferably has a better stability, preferably a longer in vivo half-life, than the protein or peptide from which it is derived.

Derivatives of a particular protein or peptide also relate to post-translationally modified variants, isoforms and species homologs of the protein or peptide, especially those which are expressed naturally.

A part, i.e. fragment, or derivative of a protein or peptide preferably displays according to the invention a functional property of the protein or peptide from which it is derived. Such functional properties include for example immunoreactivity, especially the interaction with antibodies or the interaction with other peptides or proteins. An important property is the ability to enter into a complex with MHC molecules and where appropriate to generate or prevent an immune response for example by stimulating or inhibiting cytotoxic or helper T cells. A part of a protein or peptide preferably includes a sequence of at least 6, at least 8, at least 1, at least 1, at least 1, at least 2, at least 30 and preferably up to , up to 1, up to 1, up to 1, up to 2, up to 30 or up to 50 consecutive amino acids from the protein or peptide. In one embodiment, a part of a protein or peptide relates according to the invention to one or a plurality of epitopes from the complete peptide or protein, where the plurality of epitopes may be present in their natural connection or may have an artificial, i.e. non-naturally occurring connection, i.e. the epitopes may be separated from one another for example by an artificial linker. A part of a protein or peptide preferably relates according to the invention to a sequence which is a target, in particular an epitope, for an immune response in a patient, for example in a patient with a neurological autoimmune disease. In preferred embodiments, the sequence is the target for an antibody- and/or T-cell-mediated immune response. A peptide, protein or derivative used according to the invention may also include a plurality of sequences which represent epitopes for antibodies or T cells.

A part, i.e. fragment, of a nucleic acid which codes for a protein or peptide relates according to the invention preferably to the part of the nucleic acid which codes at least for the protein or peptide and/or for a part of the protein or peptide as defined above. A part of a nucleic acid which codes for a protein or peptide preferably relates to the part of the nucleic acid which corresponds to the open reading frame. In a further embodiment, a part of a nucleic acid is the part of a nucleic acid which codes only for one or more epitopes of the protein or peptide which is encoded by the complete nucleic acid, in particular by the complete open reading frame.

The proteins, peptides or derivatives thereof which are employed for a therapeutic use are preferably those which inhibit a binding of the autoantibodies described herein to the autoantigens described herein, or compete therefor and/or inhibit the stimulation of T lymphocytes which recognize the autoantigens or parts thereof described herein, and thus protect a patient from an autoimmune disease of the nervous

system such as multiple sclerosis. Proteins, peptides or derivatives which can be employed therapeutically are in particular those which interact with the binding of T cells via their T-cell receptor to the MHC/antigen complex which is necessary for initiating or propagating an immune recognition or an inflammatory course.

A protein or peptide which includes an antibody epitope and/or a T-cell epitope and is administered according to the invention to a patient may be able to modify the patient's response to an autoantigen, leading to inhibition of an autoimmune response. In particular, therefore, proteins, peptides or derivatives thereof able to compete with the autoantigens or fragments thereof for recognition by T lymphocytes or autoantibodies are used according to the invention. Peptides particularly preferred according to the invention are those which include or represent a modified version of the T-cell epitope from the naturally occurring autoantigen which can bind to MHC molecules but, in contrast to the naturally occurring epitope, does not activate specific T cells. The proteins, peptides or derivatives employed for a therapeutic use preferably compete for the binding of autoantigens to antibodies and/or MHC molecules and do not initiate proliferation and/or induction of a T cell which reacts with the autoantigen or parts thereof.

Candidate proteins, peptides, or derivatives can be screened in a test which measures a binding, in particular a competitive binding to antibodies and/or MHC molecules, and/or a test which measures a T-cell proliferation.

"MHC-binding peptides" relates according to the invention to peptides which bind to an MHC class I and/or an MHC class II molecule. In the case of class I MHC/peptide complexes, the binding peptides are typically 8-10 amino acids long, although longer or shorter peptides may be active. In the case of class II MHC/peptide complexes, the binding peptides are typically 10-25 amino acids long and in particular 13-18 amino acids long, although longer and shorter peptides may be active. It is possible according to the invention to administer an MHC-binding peptide for a direct binding to MHC molecules, or an MCH-binding peptide may result after suitable processing, especially in vivo after administration, from an administered protein, peptide or derivative thereof. It is also possible for an MHC-binding peptide to result through processing of an autoantigen. In particular embodiments, therefore, an MHC-binding peptide is a part of an administered protein, peptide or derivative thereof or of an autoantigen. Such cases are included when reference is made according to the invention to proteins, peptides or derivatives employed for a therapeutic use, or to T cells which react with an autoantigen.

The ability of a peptide to bind to an antibody can be determined for example with one of the immunoassays described herein.

The ability to bind competitively to MHC molecules can be determined according to the invention for example with known binding tests which measure the displacement of a labeled binding molecule.

Autoantigens described according to the invention can be employed in peptide libraries, including phage display libraries, in order for example to identify and select peptide binding partners of antibodies or MHC molecules. Such molecules can be used for example for screening assays, purification protocols, for interference with the function of the antibodies or MHC molecules and for other purposes known to the person skilled in the art.

Phage display may be particularly effective for identifying binding peptides. In this case, for example, a phage library which presents inserts of a length of from 4 to about 80 amino acid residues is prepared (by using for example the m13, fd or lambda phage). Phages which harbor inserts which bind to the target are then selected. This process can be repeated over a plurality of cycles of back-selection of phages which bind to the target. Repeated rounds lead to an enrichment of phages which harbor particular sequences. It is possible to analyze DNA sequences in order to identify the sequences of the expressed peptides. The smallest linear portion of the sequence which binds to the target can be determined.

The yeast "two-hybrid system" can also be employed for identifying peptides which bind to a target.

The ability to initiate a proliferation and/or induction of T cells can be determined simply by an in vitro test. Typically, T cells are provided for the tests by transformed T-cell lines, such as T-cell hybridomas or T cells which are isolated from a mammal such as a human or a rodent such as a mouse. Suitable T-cell hybridomas are freely available or can be prepared in a manner known per se. T cells can be isolated from a mammal in a manner known per se; cf., for example, Shimonkevitz, R. et al., 1983, J. Exp. Med. 158:303.

A suitable test for determining whether a peptide is capable of modulating the activity of T cells takes place as follows by steps 1-4 below. T cells express in a suitable manner a marker which can be tested and indicates T-cell activation or modulation of T-cell activity after activation. Thus, the mouse T-cell hybridoma DO11.10which expresses interleukin-2 (IL-2) on activation can be used. IL-2 concentrations can be measured in order to determine whether a specific presented peptide is capable of modulating the activity of this T-cell hybridoma. A suitable test of this type takes place by the following steps:

1. T cells are obtained for example from an interesting T-cell hybridoma or by isolation from a mammal.
2. The T cells are cultured under conditions permitting proliferation.
3. The growing T cells are contacted with antigen-presenting cells which in turn have been contacted with a peptide to be presented or with a nucleic acid coding therefor.
4. The T cells are tested for a marker, e.g. IL-2 production is measured.

The T cells used in the tests are incubated under conditions suitable for proliferation. For example, a DO11.10 T-cell hybridoma is suitably incubated at about 37° C. and 5% CO_2 in complete medium (RPMI 1640, supplemented with 10% FBS, penicillin/streptomycin, L-glutamine and 5×10^{-5} M 2-mercaptoethanol). Serial dilutions of the investigated peptide can be tested. T-cell activation signals are provided by antigen-presenting cells which have been loaded with the peptide.

As an alternative to measuring an expressed protein such as IL-2, it is possible to determine the modulation of T-cell activation in a suitable manner through alterations in the proliferation of T cells as measured by known radiolabeling methods. For example, a labeled (such as tritiated) nucleotide can be introduced into a test culture medium. The introduction of such a labeled nucleotide into the DNA serves as quantity for measuring T-cell proliferation.

Identification of modified and substituted proteins or peptides which are suitable in the diagnostic and therapeutic methods of the invention can also easily be tested through their ability to inhibit proliferative responses in vitro of the patient's T cells or of T-cell lines or clones which are specific for an autoantigen, or a binding of the autoantigen to autoantibodies specific therefor. Epitopes in autoantigens against which antibodies and T cells in patients with multiple sclerosis are directed are identified by using truncated and/or

mutagenized recombinant proteins and peptides. These peptide epitopes are tested for their antigenicity in generating a T-cell response or in binding to antibodies.

What has been stated above about therapeutically employed proteins, peptides or derivatives applies analogously to therapeutically employed nucleic acids which encode such proteins, peptides or derivatives.

Proteins, peptides or derivatives thereof described herein, where appropriate coupled to a polymer such as PEG which makes the protein, peptide or derivative tolerogenic, and/or in conjunction with an adjuvant, can also be employed therapeutically in order to generate tolerance. The proteins, peptides or derivatives are preferably employed in high doses in this embodiment. The method of tolerization is described for example in WO 94/06828. Thus, in one embodiment, a pharmaceutical composition of the invention is used to tolerize a patient to one or more autoantigens described herein. In this embodiment, the pharmaceutical composition preferably includes a peptide or protein which comprises an amino acid sequence which corresponds to a sequence motif of an autoantigen described herein, which is associated with a neurological autoimmune disease described herein, or is derived therefrom. Such peptides or proteins preferably bind to MHC molecules to form a complex which activates autoreactive T cells in patients with the autoimmune disease. The use of such a tolerization in relation to autoimmune diseases is known and need not therefore be explained in more detail.

Antibodies directed against the autoantigens described herein can be used to identify antigenic epitopes on the autoantigen. As soon as such epitopes have been identified, it is possible for synthetic peptides to be prepared and be employed for example as antigens in diagnostic tests or kits or for developing therapeutic agents.

Antisera containing antibodies which bind specifically to a target can be prepared by various standard methods; cf. for example "Monoclonal Antibodies: A Practical Approach" by Philip Shepherd, Christopher Dean ISBN 0-19-983722-9, "Antibodies: A Laboratory Manual" by Ed Harlow, David Lane ISBN: 0879893142 and "Using Antibodies: A Laboratory Manual: Portable protocol NO" by Edward Harlow, David Lane, Ed Harlow ISBN: 0879895447. It is also possible in this connection to generate antibodies which have affinity and specificity and which recognize complex membrane proteins in their native form (Azorsa et al., *J. Immunol. Methods* 229: 35-48, 1999; Anderson et al., *J. Immunol.* 143: 1899-1904, 1989; Gardsvoll, *J. Immunol. Methods,* 234: 107-116, 2000). This is important in particular for the production of antibodies which are to be employed therapeutically, but also for many diagnostic applications. It is possible for this purpose to use the complete protein, extracellular partial sequences as well as cells which express the target molecule in a physiologically folded form for immunization.

Monoclonal antibodies are traditionally produced with the aid of hybridoma technology (for technical details: see "Monoclonal Antibodies: A Practical Approach" by Philip Shepherd, Christopher Dean ISBN 0-19-963722-9, "Antibodies: A Laboratory Manual" by Ed Harlow, David Lane ISBN: 0879893142, "Using Antibodies: A Laboratory Manual: Portable protocol NO" by Edward Harlow, David Lane, Ed Harlow ISBN: 0879695447).

It is known that only a small part of an antibody molecule, the paratope, is involved in binding of the antibody to its epitope (cf. Clark, W. R. (1988), *The Experimental Foundations of Modern Immunology*, Wiley & Sons, Inc., New York; Roitt, I. (1991), *Essential Immunology,* 7th edition, Blackwell Scientific Publications, Oxford). The pFc' and Fc regions are for example effectors of the complement cascade, but are not involved in antigen binding. An antibody from which the pFc' region has been eliminated enzymatically or which has been prepared without the pFc' region, referred to as $F(ab')_2$ fragment, carries both antigen binding sites of a complete antibody. In a similar way, an antibody from which the Fc region has been eliminated enzymatically, or which has been produced without the Fc region, referred to as Fab fragment, carries one antigen binding site of an intact antibody molecule. In addition, Fab fragments consist of a covalently bonded light chain of an antibody and a part of the heavy chain of the antibody, referred as Fd. The Fd fragments are the principal determinants of antibody specificity (a single Fd fragment can be associated with up to ten different light chains without altering the specificity of the antibody) and Fd fragments retain on isolation the ability to bind to an epitope.

Within the antigen-binding part of an antibody there are complementarity-determining regions (CDRs) which interact directly with the epitope of the antigen, and framework regions (FRs) which maintain the tertiary structure of the paratope. Four framework regions (FR1 to FR4) are located both in the Fd fragment of the heavy chain and in the light chain of IgG immunoglobulins and are in each case separated by three complementarity-determining regions (CDR1 to CDR3). The CDRs and especially the CDRS regions, and even more the CDRS region of the heavy chain, are mostly responsible for antibody specificity.

It is known that the non-CDR regions of a mammalian antibody can be replaced by similar regions of antibodies with the same or a different specificity, with the specificity for the epitope of the original antibody being retained. This made it possible to develop so-called "humanized" antibodies in which non-human CDRs are covalently connected to human FR regions and/or Fc/pFc' regions to produce a functional antibody.

As another example, WO 92/04381 describes the preparation and use of humanized mouse RSV antibodies in which at least one part of the mouse FR regions have been replaced by FR regions of a human origin. Such antibodies, including fragments of intact antibodies with an antigen-binding capability, are often referred to as "chimeric" antibodies.

The term "antibody" includes according to the invention also $F(ab')_2$, Fab, Fv and Fd fragments of antibodies, chimeric antibodies in which the Fc and/or FR and/or CDR1 and/or CDR2 and/or light chain CDRS regions have been replaced by homologous human or non-human sequences, chimeric $F(ab')_2$ fragment antibodies in which the FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences, chimeric Fab fragment antibodies in which the FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences, and chimeric Fd fragment antibodies in which the FR and/or CDR1 and/or CDR2 regions have been replaced by homologous human or non-human sequences. The term "antibody" also includes according to the invention single-chain antibodies.

Antibodies can also be coupled to specific diagnostic agents in order for example to demonstrate cells and tissues which express particular proteins or peptides like the autoantigens described herein. They can further be coupled to therapeutic agents.

Diagnostic agents include any type of label which is suitable: (i) for providing a detectable signal, (ii) for interacting with a second label in order to modify the detectable signal provided by the first or second label, e.g. FRET (fluorescence resonance energy transfer), (iii) for influencing the mobility such as electrophoretic mobility through charge, hydropho-

bicity, shape or other physical parameters, or (iv) for providing a capture group, e.g. affinity, antibody/antigen or ionic complexation.

Suitable labels are structures such as fluorescent labels, luminescent labels, chromophore labels, radioisotope labels, isotope labels, preferably stable isotope labels, enzyme labels, particle labels, especially metal particle labels, magnetic particle labels, polymer particle labels, small organic molecules such as biotin, ligands of receptors or binding molecules such as cell adhesion proteins or lectins, and label sequences which include nucleic acid sequences and/or amino acid sequences. Diagnostic agents include in a non-limiting manner barium sulfate, iocetamic acid, iopanoic acid, calcium ipodate, sodium diatrizoate, meglumine diatrizoate, metrizamide, sodium tyropanoate and radiodiagnostic agents, including positron emitters such as fluorine-18 and carbon-11, gamma emitters such as iodine-123, technetium-99m, iodine-131 and indium-111, and nuclides for magnetic nuclear resonance such as fluorine and gadolinium.

The term "therapeutic agent" relates according to the invention to any substance which may have a therapeutic effect.

The term "major histocompatibility complex" or "MHC" relates to a complex of genes which is present in all vertebrates. MHC proteins or molecules are involved in the signaling between lymphocytes and antigen-presenting cells in normal immune responses, in which case they bind peptides and present them for recognition by T-cell receptors. MHC molecules bind peptides within an intracellular processing compartment and present these peptides on the surface of antigen-presenting cells for recognition by T cells. The human MHC region, also called HLA, is located on chromosome 6 and includes the class I and class II regions. In a preferred embodiment in all aspects of the invention, an MHC molecule is an HLA molecule.

The term "patient", "creature" or "organism" includes according to the invention humans, non-human primates or another animal, especially mammal such as cow, horse, pig, sheep, goat, dog, cat or rodent such as mouse and rat. In a particularly preferred embodiment, the patient is a human.

The term "disease" relates according to the invention to a pathological condition. The term "autoimmune disease" relates according to the invention to a disease caused by an excessive reaction of the immune system to endogenous tissue. The immune system erroneously recognizes endogenous tissue as a foreign body against which defence is necessary. This results in severe inflammatory reactions which lead to damage to the affected organs. The term "neurological autoimmune disease" relates according to the invention to an autoimmune disease of the nervous system. If the immune system in the CNS gets out of control in a neurological autoimmune disease it is possible for inflammatory cascades of damage to trigger nerve cell death and a neuropathological state associated therewith. Inflammatory processes and networks are involved in the development and progression of many neurodegenerative diseases such as multiple sclerosis, stroke, Parkinson's disease and Alzheimer's disease.

In a preferred embodiment, the term "neurological autoimmune disease" relates according to the invention to multiple sclerosis. Multiple sclerosis is an inflammatory, demyelinizing disease of the central nervous system which causes motor, sensory and cognitive deficits. Multiple sclerosis arises if T lymphocytes and other cells of the immune system infiltrate the white matter of the CNS. Inflammatory messengers block conduction at the Ranvier's nodes and soluble and cellular effectors bring about breakdown of the myelin layer. This results in so-called demyelinization or demyelination. This brings about progressive paralysis and other neurological symptoms such as, for example, muscle tremor, numbness, itching, color blindness, double vision, blindness, loss of coordination and balance, acute paralysis and a deterioration in cognitive abilities.

The term "increased amount" preferably relates to an increase of at least 10%, in particular at least 20%, at least 50% or at least 100%. The amount of a substance is also increased in a test object such as a biological sample in relation to a reference if it is detectable in the test object but not present and/or not detectable in the reference.

"Reduce" or "inhibit" relates here to the ability to bring about a decrease, such as a decrease of 20% or more, more preferably of 50% or more, most preferably of 75% or more.

A biological sample may according to the invention be a tissue sample, including body fluids, and/or a cellular sample and can be obtained in a conventional way, such as by tissue biopsy, including punch biopsy, and removal of blood, bronchial aspirate, sputum, urine, feces or other body fluids. The term "biological sample" also includes according to the invention fractions of biological samples.

The terms "T cell" and "T lymphocyte" are used here exchangeably and include T-helper cells and cytolytic T cells such as cytotoxic T cells.

The pharmaceutical compositions described according to the invention may also be employed preventively, i.e. as vaccines, in order to prevent the diseases described herein.

Proteins and peptides can be administered according to the invention in a manner known per se.

It is possible according to the invention to administer nucleic acids either as naked nucleic acid or in conjunction with an administration reagent. For example, the invention also provides for administration of nucleic acids in vivo by means of targeted liposomes.

It is possible to employ for administering nucleic acids vectors which are derived from adenovirus (AV), adeno-associated virus (AAV), retroviruses (such as Antiviruses (LV), rhabdoviruses, murine leukemia virus), or herpesvirus, and the like. The tropism of the viral vectors can be suitably modified by pseudotyping the vectors with envelope proteins or other surface antigens of other viruses or by replacing various viral capsid proteins.

Liposomes can assist delivery of the nucleic acid to a particular tissue and may also increase the half-life of the nucleic acid. Liposomes suitable according to the invention are formed from standard vesicle-forming lipids which generally include neutral or negatively charged phospholipids, and a sterol such as cholesterol. The selection of lipids is generally determined by factors such as the desired size of the liposomes and the half-life of the liposomes. A large number of methods for preparing liposomes is known; cf., for example, Szoka et al. (1980), Ann. Rev. Biophys. Bioeng. 9: 467; and U.S. Pat. Nos. 4,235,871, 4,501,728, 4,837,028 and 5,019,389.

In particular embodiments, direction of the nucleic acid to particular cells is preferred. In such embodiments, a carrier which is employed for administering a nucleic acid to a cell (e.g. a retrovirus or a liposome) may have a bound targeting molecule. For example, a molecule such as an antibody which is specific for a surface membrane protein on the target cell, or a ligand for a receptor on the target cell, can be incorporated in the nucleic acid carrier or bound thereto. If administration of a nucleic acid by liposomes is desired, it is possible to incorporate proteins which bind to a surface membrane protein which is associated with endocytosis into the liposome formulation in order to make targeting and/or uptake possible. Such proteins include capsid proteins or fragments

thereof which are specific for a particular cell type, antibodies against proteins which are internalized, proteins which aim at an intracellular site, and the like.

The pharmaceutical compositions of the invention can be administered in pharmaceutically acceptable preparations. Such preparations may comprise usual pharmaceutically acceptable concentrations of salts, buffer substances, preservatives, carriers, supplementary immunity-enhancing substances such as adjuvants, CpG oligo-nucleotides, cytokines, chemokines, saponin, GM-CSF and/or RNA and, where appropriate, other therapeutic active ingredients.

The therapeutic active ingredients of the invention can be administered in any conventional way, including by injection or by infusion. Administration is possible for example orally, intravenously, intraperitoneally, intramuscularly, subcutaneously or transdermally.

Suitable methods for administering nucleic acids to cells include administration of the nucleic acid to a creature by means of a gene gun, electroporation, nanoparticles, microencapsulation and the like, or by parenteral and enteral delivery.

The compositions of the invention are administered in effective amounts. An "effective amount" relates to the amount which, alone or together with further doses, achieves a desired response or a desired effect. In the case of treatment of a particular disease or of a particular condition, the desired response preferably relates to inhibition of the course of the disease. This includes slowing the progression of the disease and in particular stopping or reversing progression of the disease. The desired response on treatment of a disease or of a condition may also be delaying the onset or preventing the onset of the disease or condition.

An effective amount of a composition of the invention will depend on the condition to be treated, the severity of the disease, the individual parameters of a patient, including age, physiological condition, height and weight, the duration of the treatment, the nature of a concomitant therapy (if present), the specific route of administration and similar factors.

The pharmaceutical compositions of the invention are preferably sterile and comprise an effective amount of the therapeutically effective substance for generating the desired response or the desired effect.

The doses of the compositions of the invention which are administered may depend on various parameters such as the mode of administration, the patient's condition, the desired period of administration etc. In the case where a response of a patient is inadequate with an initial dose, it is possible to employ higher doses (or effectively higher doses which are achieved by a different, more localized administration route).

The pharmaceutical compositions of the invention are generally administered in pharmaceutically acceptable amounts and in pharmaceutically acceptable compositions. The term "pharmaceutically acceptable" relates to a non-toxic material which does not interact with the effect of the active ingredient of the pharmaceutical composition. Such preparations may usually comprise salts, buffer substances, preservatives, carriers and, where appropriate, other therapeutic active ingredients. For use in medicine, the salts should be pharmaceutically acceptable. Non-pharmaceutically acceptable salts can, however, be used to prepare pharmaceutically acceptable salts and are included by the invention. Such pharmacologically and pharmaceutically acceptable salts include in a non-limiting manner those prepared from the following acids: hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, maleic, acetic, salicylic, citric, formic, malonic, succinic acids and the like. Pharmaceutically suitable salts can also be prepared as alkali metal or alkaline earth metal salts such as sodium, potassium or calcium salts.

A pharmaceutical composition of the invention may include a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" relates according to the invention to one or more compatible solid or liquid fillers, diluents, or capsule substances which are suitable for administration in particular to a human. The term "carrier" relates to an organic or inorganic ingredient, natural or synthetic in nature, in which the active ingredient is combined in order to facilitate use. The ingredients of the pharmaceutical composition of the invention are ordinarily of such a nature that no interaction which substantially impairs the desired pharmaceutical efficacy occurs.

The pharmaceutical compositions of the invention may comprise suitable buffer substances such as acetic acid in a salt, citric acid in a salt, boric acid in a salt and phosphoric acid in a salt.

The pharmaceutical compositions may also include where appropriate suitable preservatives such as benzalkonium chloride, chlorobutanol, parabens and thimerosal.

The pharmaceutical compositions are ordinarily supplied in a standard dose form and can be produced in a manner known per se. Pharmaceutical compositions of the invention may for example be in the form of capsules, tablets, pastilles, suspensions, syrups, elixirs or as emulsion.

Compositions suitable for parenteral administration include ordinarily a sterile aqueous or nonaqueous preparation of the active ingredient, which is preferably isotonic with the recipient's blood. Suitable carriers and solvents are for example Ringer's solution and isotonic sodium chloride solution. Ordinarily employed additionally as dissolving or suspending medium are sterile, fixed oils.

The present invention is described in detail by the following figures and examples which serve exclusively for illustration and are not to be understood as limiting. Further embodiments which are likewise encompassed by the invention are accessible to the person skilled in the art on the basis of the description and the examples.

EXAMPLES

Example 1

Production of a Brain-Specific cDNA Library

A brain-specific cDNA expression library was produced in lambda phages (FIG. **1**). In this system, a complete pBluescript plasmid is present in a lambda phage genome and thus combines the properties of a phage and of a plasmid. Human mRNA isolated from brain tissue was transcribed into methylated cDNA in a first-strand synthesis using a reverse transcriptase and an oligo-dT linker on whose 5' end an XhoI cleavage site was attached. After targeted degradation of the mRNA, the DNA was made double-stranded in a second-strand synthesis. An EcoRI linker was ligated onto the double-stranded DNA, and the construct was then cleaved with the restriction endonuclease XhoI. The use of methylated dCTPs in the first-strand synthesis protects the cDNA first strand from XhoI cleavage. The cDNA fragments obtained in this way were cloned into vector previously cleaved with XhoI/EcoRI. Over 1×10^6 recombinant clones were obtained.

Example 2

Immunoscreening Methods and Antigen Identification

The immunoscreening was carried out as described in Molecular Cloning: A Laboratory Manual, J. Sambrook et al.,

editors, 2nd edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989 or Current Protocols in Molecular Biology, F. M. Ausubel et al., editors, John Wiley & Sons, Inc., New York. The method is depicted diagrammatically in FIG. **2**. Bacteria of the strain XL1 MRF derived from *E. coli* K12 were harvested in the exponential phase of growth, adjusted to an OD_{600} of 0.5 and infected with the lambda phages of the described expression library. The number of plaque-forming units (pfu) was adjusted so that the plaques were subconfluent (e.g. ~5000 pfu/145 mm Petri dish). With addition of TOP agar and IPTG, the infection mixture was plated out on agar plates with tetracycline. Phage plaques formed on the bacterial lawn in an overnight culture at 37° C. Each individual plaque represents a lambda phage clone with the nucleic acid inserted into this clone and simultaneously comprises the recombinantly expressed protein encoded by the nucleic acid.

Nitrocellulose membranes were put on in order to produce plaque-lift preparations of the recombinant proteins. Washing steps in TBS-Tween and blocking of nonspecific binding sites in TBS+10% milk powder were followed by incubation in serum overnight. Serum diluted 1:100-1:1000 was used for this purpose. After further washing steps, the nitrocellulose membranes were incubated with a secondary AP-conjugated antibody directed against human IgG. It was possible to visualize bindings of serum antibodies to proteins expressed recombinantly in phage plaques by a color reaction in this way. It was possible to trace clones identified as reacting with sera back to the culture plate and to isolate therefrom the corresponding phage construct monoclonally. Such positive clones were confirmed after renewed plating out. The lambda phage clone was recircularized to the phagemid by in vivo excision.

To analyze the brain-specific phage library, in total about 1 000 000 clones were analyzed, using a total of 17 different sera. Pooled sera were used in some cases, initially identified clones were firstly isolated oligoclonally augmented by adjacent non-reactive phage plaques and were monoclonalized after confirmation. The integrated human DNA was amplified from the monoclonal clones by PCR with the T7/T3 standard primers of the integrated plasmid vector, and the amplicon was then sequenced by standard methods. The sequences found in this way were compared with known sequences in the gene library by BLAST analysis. It was possible through the analysis to isolate in total 44 different clones which reacted with serum from MS patients. The antigens were assigned to different groups according to their properties (FIG. **3**).

Example 3

Molecular Biological and Serological Validation of the Autoantigens

Validation of the antigens identified according to the invention is of central importance for utilization of the autoantigens for immunotherapeutic purposes (antibody therapy using monoclonal antibodies, vaccination to induce an improved autoantigen tolerance, T-cell receptor-mediated therapeutic approaches; cf. EP-B 0 879 282) or other targeted approaches (small compounds, siRNA etc.) in the treatment of autoimmune diseases and for diagnostic questions. In this case, validation takes place by expression analysis at the RNA level and by serological analyses.

1. Investigation of RNA Expression

The first validation of the identified autoantigens takes place with the aid of RNA obtained from various tissues or from tissue-specific cell lines. Brain-specific expression of the autoantigens associated with the neurological diseases is of decisive importance in this connection for the later therapeutic use. Isolation of total RNA from native tissue samples or from cell lines takes place with standard methods of molecular biology. For example, isolation is possible with the aid of the RNeasy Maxi Kit (Qiagen, cat. No. 75162) according to the manufacturer's instructions. This isolation method is based on the use of guanidinium isothiocyanate as chaotropic reagent. Isolation can be carried out alternatively with acidic phenol (Chomczynski & Sacchi, Anal. Biochem. 162: 156-159, 1987). After the tissue has been worked up with guanidinium isothiocyanate, the RNA is extracted with acidic phenol, and then the RNA is precipitated with isopropanol and taken up in DEPC-treated water.

2-4 μg of the RNA isolated in this way are then transcribed into cDNA, e.g. using Superscript II (Invitrogen) in accordance with the manufacturers protocol. The cDNA synthesis is in this case primed with the aid of random hexamers (e.g. Roche Diagnostics) according to the standard protocols of the respective manufacturer. For quality control, the cDNAs are amplified in 30 cycles with primers which are specific for the only slightly expressed p53 gene. Only p53-positive cDNA samples are used for further reaction steps.

For detailed analysis, the target candidates are investigated by PCR or quantitative PCR (qPCR) for their expression in a comprehensive set of normal tissues. For this purpose, 0.5 μl of cDNA from the above batch is amplified with a DNA polymerase (e.g. 1 U of HotStarTaq DNA polymerase, Qiagen) in analogy to the protocols of the respective manufacturer (total volume of the mixture: 25-50 μl). Besides the polymerase, the amplification mixture contains 0.3 mM dNTPs, reaction buffer (final concentration 1×, depending on the manufacturer of the DNA polymerase) and 0.3 mM each of the gene-specific forward and reverse primer.

The specific primers of the target gene are selected, where possible, so that they are located in two different exons and thus genomic contamination does not lead to any false-positive results. In a non-quantitative endpoint PCR, the cDNA is typically incubated at 95° C. for 15 minutes in order to denature the DNA and activate the Hot-Start enzyme. The DNA is then amplified in 35 cycles (1 min 95° C., 1 min primer-specific hybridization temperature (about 55-65° C.), 1 min 72° C. for elongation of the amplicons). 10 μl of the PCR mixture are then loaded onto agarose gels and fractionated in an electrical field. The DNA in the gels is visualized by staining with ethidium bromide, and the result of the PCR is documented by photograph.

As alternative to conventional PCR, the expression analysis of a target gene can also take place by quantitative real time PCR. Various analysis systems are now obtainable for this analysis, the best-known being the ABI PRISM sequence detection system (TaqMan, Applied Biosystems), the iCycler (Biorad) and the Light cycler (Roche Diagnostics). As described above, a specific PCR mixture is subjected to a run in the real time apparatuses. The newly synthesized DNA is visualized by addition of a DNA-intercalating dye (e.g. ethidium bromide, CybrGreen) by specific photoexcitation (according to information from the dye manufacturers). The complete process can be followed by a large number of measurement points during the amplification, and a quantitative determination of the nucleic acid concentration of the target gene can be carried out. Normalization of the PCR mixture takes place by measuring a housekeeping gene (e.g. 18S RNA, β-actin). Alternative strategies with fluorescence-labeled DNA probes likewise permit quantitative determina-

tion of the target gene from a specific tissue sample (see TaqMan applications of Applied Biosystems).

2. Cloning

The complete target gene is cloned, as is necessary for further characterization of the antigen, by conventional methods of molecular biology (e.g. in "Current Protocols in Molecular Biology", John Wiley & Sons Ltd., Wiley InterScience). For cloning and sequence analysis of the target gene, the latter is initially amplified with a DNA polymerase with proofreading function (e.g. pfu, Roche Diagnostics). The amplicon is then ligated into a cloning vector by standard methods. Positive clones are identified by sequence analysis and then characterized with the aid of prediction programs and known algorithms.

3. Expression and Purification

For detailed characterization and for product development it is necessary for the identified antigens to be synthesized in an expression system and then purified.

Very diverse systems are well established and commercially available for antigen expression, some examples of commercial suppliers are indicated, and detailed protocols are published by the suppliers. The commonest expression systems are in vitro transcription/translation (Roche Diagnostics, Invitrogen), antigen expression in *E. coli* (Qiagen, Invitrogen), in yeast (Invitrogen, Stratagene, RCT) and in eukaryotic cells after transfection of the cells or after infection with viral expression vectors such as, for example, with recombinant baculoviruses or vacciniaviruses (Invitrogen, Roche Diagnostics). Very diverse methods (e.g. electroporation, liposome-based transfection, calcium phosphate precipitation) are well established (e.g. Lemoine et al., *Methods Mol. Biol.* 75: 441-7, 1997) for transfecting cells with DNA for antigen expression.

Antigen expression is followed by purification of the antigen by commercially available methods. A wide selection of chromatographic methods in particular is established (Biorad, Amersham Biosciences). Affinity chromatography is particularly suitable for antigen purification. It is possible to employ for this purpose on the one hand short, universally employable protein anchors such as, for example, the His tag, the FLAG tag or glutatione S-transferase (GST) (Biorad, Amersham Biosciences, Qiagen). Purification then takes place via the specific properties of the anchor molecule. Affinity chromatography can, however, also take place using an antigen-specific antibody. A large number of protocols are to be found with the commercial suppliers or in the literature, e.g. in "Current Protocols of Proteinsciences" (John Wiley & Sons Ltd., Wiley InterScience).

4. Serological Analysis of the Identified Antigens

In order to detect disease-associated antigens, all the antigens found are investigated for the presence of specific immune responses (antibodies) in patients with MS, and in control groups without the disease. This allows antigens of clinical relevance to be determined. It is possible to employ for this purpose several detection and measurement methods such as protein arrays based on proteomic analyses or mostly immunological analytical methods such as, for example, ELISA, CrELISA or Western blotting. Direct serological detection with the aid of the expression system used in the immunoscreening is also possible.

The most widely used serological detection method is the enzyme-linked immune sorbent assay (ELiSA) which is published in very diverse embodiments. In principle, a protein (peptide, antigen or antibody) is bound to a surface for this purpose. The sample to be analyzed is analyzed with this bound protein. The next step is incubation, usually with a further antibody which is coupled to a dye (e.g. FITC, Cy3) or an enzyme (e.g. peroxidase, alkaline phosphatase). The antigen detection then takes place depending on the coupled substance, e.g. by a color reaction or by fluorescence. ELISA for detecting very diverse antigens are commercially available (Amersham Bioscience, Biorad etc), and detailed protocols are for example in the "Short Protocols in Molecular Biology" (Asubel, 2003; Wiley & Sons, ISBN: 047132938X) or in the "Current Protocols of Proteinsciences" (John Wiley & Sons Ltd., Wiley InterScience). In analogy to the ELISA, the crude lysate enzyme-linked immune sorbent assay (CrELISA) is based on the binding of lysates of the antigen-expressing bacteria on a surface (Türeci et al., 2004, J Imm Methods 289, 191). The sample to be analyzed is then analyzed with this bound protein. The next step is incubation, usually with a further antibody which is coupled to a dye (e.g. FITC, Cy3) or an enzyme (e.g. peroxidase, alkaline phosphatase). The antigen detection then takes place depending on the coupled substance, e.g. by a color reaction or by fluorescence. Direct detection using the expression system used for the antigen screening is possible with the SEROGRID method (Krause et al., 2003, J Imm Methods 283, 261). For this purpose, *E. coli* bacteria are harvested in the exponential growth phase and infected subconfluently with antigen-specific, monoclonal lambda phages. The infection mixture is plated out, with addition of TOP agar and IPTG, on large-area agar plates with tetracycline. The individual clones are in this case separated from one another with the aid of spacers. Phage plaques form on the bacterial lawn on overnight culture at 37° C., each individual plaque representing a specific lambda phage clone with the inserted nucleic acid of the antigen which is to be analyzed and which is expressed recombinantly. The antigens are then blotted as in a normal immunoscreening method onto a nitrocellulose membrane and then incubated with the human sera. The advantage of the SEROGRID method is the parallelized analysis of numerous identified antigens in one test mixture.

Further validation of the identified antigens permits the use of protein arrays which makes simultaneous analysis of a plurality of antigens in one mixture possible. In this case, the antigen molecules are bound at defined positions in wells or on planar surfaces such as, for example, on filter membranes such as nitrocellulose or modified glass surfaces. The antigens can be bound covalently through chemical linkers or non-covalently via hydrophobic van der Waals, ionic or other interactions. The directed binding of the antigens onto the surface can be facilitated for example via a tag (e.g. histidine tag). Spotting of the protein arrays mostly takes place by pin-based systems which transfer solutions in the nanoliter range. Antigen detection is frequently based on fluorescence. One application of protein arrays is investigation of antigen-antibody interactions. Protein array technology can also be employed as clinical diagnostic tests.

Example 4

Obtaining Antibodies

Antibodies can be used for example for characterizing the peptides and/or proteins of the invention and in the diagnostic and therapeutic methods of the invention. It is possible for antibodies to recognize proteins in native and/or denatured state (Anderson et al., *J. Immunol.* 143: 1899-1904, 1989: Gardsvoll, *J. Immunol. Methods* 234: 107-116, 2000; Kayyem et al., *Eur. J. Biochem.* 208: 1-8, 1992; Spiller et al., *J. Immunol. Methods* 224: 51-60, 1999).

Antisera containing specific antibodies which bind specifically to the target protein can be prepared by various standard

methods; cf. for example "Monoclonal Antibodies: A Practical Approach" by Philip Shepherd, Christopher Dean ISBN 0-19-963722-9, "Antibodies: A Laboratory Manual" by Ed Harlow, David Lane ISBN: 0879893142 and "Using Antibodies: A Laboratory Manual: Portable protocol NO" by Edward Harlow, David Lane, Ed Harlow ISBN: 0879695447. It is also possible in this connection to generate antibodies which have affinity and specificity and which recognize complex membrane proteins in their native form (Azorsa et al., *J. Immunol. Methods* 229: 35-48, 1999; Anderson et al., *J. Immunol.* 143: 1899-1904, 1989; Gardsvoll, *J. Immunol. Methods,* 234: 107-118, 2000). This is important in particular for the production of antibodies which are to be employed therapeutically, but also for many diagnostic applications. It is possible for this purpose to use the complete protein as well as extracellular partial sequences for immunization.

Immunization and Obtaining Polyclonal Antibodies

A species (e.g. rabbits, mice) is immunized by a first injection of the desired target protein. The immune response of the animal to the immunogen can be enhanced by a second or third immunization within a defined period (e.g. about 2-4 weeks after the last immunization). Again after various defined time intervals (e.g. 1st bleed after 4 weeks, subsequently every 2-3 weeks up to 5 removals) blood is taken from the animals, and immune serum is obtained. The immune sera taken in this way contain polyclonal antibodies with which the target protein can be detected and characterized in Western blotting, by flow cytometry, immunofluorescence or immunohistochemistry.

The animals are usually immunized by one of four well-established methods, although other methods exist. Immunization is possible in this connection with the peptides specific for the target protein, with the complete protein, with extracellular partial sequences of a protein which are identifiable by experiment or via prediction programs. Since the prediction programs do not always operate error-free, in some circumstances two domains separated from one another by a transmembrane domain are also used. One of the two domains must then be extracellular, which can then be demonstrated experimentally (see below).

(1) In the first case, peptides (with a length of, for example, 8-12 amino acids) are synthesized by in vitro methods (possible by a commercial service) and these peptides are used for the immunization. Usually 3 immunizations take place (e.g. with a concentration of 5-100 μg/immunization). The immunization can also be carried out as a service by service providers.

(2) Alternatively, immunization is possible with recombinant proteins. For this purpose, the cloned DNA of the target gene is cloned into an expression vector, and the target protein is synthesized in analogy to the conditions of the respective manufacturer (e.g. Roche Diagnostics, Invitrogen, Clontech, Qiagen), e.g. cell-free in vitro, in bacteria (e.g. *E. coli*), in yeast (e.g. *S. pombe*), in insect cells or in mammalian cells. It is also possible in this connection for the target protein to be synthesized with the aid of viral expression systems (e.g. baculovirus, vacciniavirus, adenovirus). After synthesis in one of the systems, the target protein is purified. The purification in this case usually takes place by chromatographic methods. It is also possible in this connection to use for the immunization proteins which have a molecular anchor as aid to purification (e.g. His tag, Qiagen; FLAG tag, Roche Diagnostics; GST fusion proteins). A large number of protocols are to be found for example in "Current Protocols in Molecular Biology", John Wiley & Sons Ltd., Wiley InterScience. Purification of the target protein is followed by immunization as described above.

(3) If a cell line which synthesizes the desired protein endogenously is available, this cell line can also be used directly for producing the specific antiserum. The immunization takes place in this case in 1-3 injections with in each case about 1-5×10^7 cells.

(4) The immunization can also take place by injecting DNA (DNA immunization). For this purpose, the target gene is initially cloned into an expression vector so that the target sequence is under the control of a strong eukaryotic promoter (e.g. CMV promoter). DNA (e.g. 1-10 μg per injection) is then transferred as immunogen using a gene gun into capillary regions with a strong blood flow in an organism (e.g. mouse, rabbit). The transferred DNA is taken up by the animal's cells, the target gene is expressed, and the animal finally develops an immune response to the target protein (Jung et al., *Mol. Cells* 12: 41-49, 2001; Kasinrerk et al., *Hybrid Hybridomics* 21: 287-293, 2002).

Obtaining Monoclonal Antibodies

Monoclonal antibodies are traditionally produced with the aid of hybridoma technology (for technical details: see "Monoclonal Antibodies: A Practical Approach" by Philip Shepherd, Christopher Dean ISBN 0-19-983722-9, "Antibodies: A Laboratory Manual" by Ed Harlow, David Lane ISBN: 0879893142 and "Using Antibodies: A Laboratory Manual: Portable protocol NO" by Edward Harlow, David Lane, Ed Harlow ISBN: 0879695447). A new method also employed is the so-called SLAM technology. This entails B cells being isolated from whole blood, and the cells being monoclonalized. The supernatant of the isolated B cell is then analyzed for its antibody specificity. In contrast to hybridoma technology, the variable region of the antibody gene is then amplified by a single-cell PCR and cloned into a suitable vector. The obtaining of monoclonal antibodies is expedited in this manner (de Wildt et al. J. Immunol. Methods 207: 81-67, 1997).

Example 5

Construction of a Test System for Diagnosing Autoimmune Diseases

The identified autoantigens form the basis for a diagnostic system which is specific for the diagnosis of autoimmune diseases and/or specific for the diagnosis or prognosis of multiple sclerosis. Diagnosis involves in this case the detection of the presence or quantification of one or more human autoantibodies which are specific for an epitope or specific for a plurality of epitopes of the identified autoantigens. The presence or the increased concentration of one or more of these autoantibodies in this case indicates a particular stage of the MS disease or a possible more aggressive stage of the disease.

A test system for diagnosis can in this case be based on the use of one or on the use of a combination of the identified autoantigens. This includes specific antigens as markers of autoimmune diseases and/or multiple sclerosis and/or polyclonal/monoclonal antibodies specific for antigens whose prevalence is associated with autoimmune diseases. The test system for diagnosis is based on the use of the antigens or antibodies for example immunoassays such as, for example, ELISA assays or protein arrays (see Example 3). Detection includes the removal of a biological sample such as, for example, serum or CSF from MS patients.

Example 6

Identification of CLSTN1 as Autoantigen

Calsyntenin 1 or CLSTN1 (SEQ ID NO: 1) is a gene which is located on chromosome 1 (1p36.22). The gene encodes a

type I transmembrane protein with a size of about 110 kDa (SEQ ID NO: 2). The protein contains two cadherin domains and might, according to analyses of homology, be a calcium-dependent neurotransmitter.

It was possible according to the invention to identify CLSTN1 as an autoantigen in the autoimmunoscreening. To analyze the tissue-specific expression of CLSTN1, establishment of a gene-specific quantitative RT-PCR (primer pair SEQ ID NO: 89 and 90) was followed by analysis of the amount of the specific transcripts in various regions of the brain and in other healthy tissues. CLSTN1 is distinctly overexpressed in all the investigated regions of the brain by comparison with the other tissues investigated (FIG. **4**) and can thus be regarded as brain-specific. Expression in the analyzed tissues might be attributable to expression in peripheral nerve tissue.

Example 7

Identification of ARPP-19 as Autoantigen

Cyclic AMP phosphoprotein 19 or ARPP-19 (SEQ ID NO: 3) is a gene located on chromosome 15 (15q21). The gene encodes a protein which is probably localized in the cytoplasm and has a size of about 12 kDa (SEQ ID NO: 4). Analyses of homology indicate that ARPP-19 is a phosphoprotein and belongs to the endosulfine family. ARPP-19 might thus be a substrate for a cAMP-dependent kinase.

It was possible according to the invention to identify ARPP-19 as an autoantigen in autoimmunoscreening. To analyze the tissue-specific expression of ARPP-19, establishment of a gene-specific quantitative RT-PCR (primer pair SEQ ID NO: 91 and 92) was followed by analysis of the amount of the specific transcripts in various regions of the brain and in other healthy tissues. ARPP-19 is at least 10-fold overexpressed in all the regions of the brain investigated by comparison with the other tissues investigated (FIG. **5**) and is thus to be regarded as brain-specific. Expression in the analyzed tissues might be attributable to expression in peripheral nerve tissue.

Example 8

Identification of CMTM2 as Autoantigen

CMTM2 (SEQ ID NO: 5) is a gene which is located on chromosome 16 (16q22.1). The gene encodes an integral membrane protein with a size of about 27 kDa (SEQ ID NO: 6). The protein belongs to the family of chemokine-like factors and has in addition significant homologies with the family of signal molecules with four transmembrane domains. CMTM2 might thus be an important molecule in cellular signal transduction. It was possible according to the invention to identify CMTM2 as an autoantigen in autoimmunoscreening. To analyze the tissue-specific expression of CMTM2, establishment of a gene-specific quantitative RT-PCR (primer pair SEQ ID NO: 93 and 94) was followed by analysis of the amount of the specific transcripts in various regions of the brain and in other healthy tissues. CMTM2 is highly overexpressed in the immunoprivileged testis (FIG. **6**). In the other tissues investigated, CMTM2 was very selectively expressed especially in the various regions of the brain, so that the autoimmune response is to be regarded as brain-specific.

Example 9

Identification of CPE as Autoantigen

Carboxypeptidase E or CPE (SEQ ID NO: **7**) is a gene which is located on chromosome 4 (4q32). The gene encodes a soluble protein with a size of about 53 kDa (SEQ ID NO: 8) which is localized in the cytoplasm. CPE is a carboxypeptidase which activates prohormones and neurotransmitters through its enzymatic function and is thus involved in the biosynthesis of these biological regulators.

It was possible according to the invention to identify CPE as an autoantigen in autoimmunoscreening. To analyze the tissue-specific expression of CPE, establishment of a gene-specific quantitative RT-PCR (primer pair SEQ ID NO: 95 and 96) was followed by analysis of the amount of the specific transcripts in various regions of the brain and in other healthy tissues. It was possible to detect in a quantitative RT-PCR an at least 5-fold overexpression in the brain by comparison with all the other tissues investigated (FIG. **7**).

Example 10

Identification of LITAF as Autoantigen

LPS-induced TNF-alpha factor or LITAF (SEQ ID NO: 9) is a gene which is located on chromosome 16 (16p13). The gene encodes a soluble protein with a size of about 24 kDa (SEQ ID NO: 10) which is localized in the nucleus. LITAF has an important role in the regulation of transcription of the cytokine TNF-alpha and is thought to be associated with the neurological Charcot-Marie-tooth disease (Street, 2003. *Neurology* 60: 22-26).

It was possible according to the invention to identify LITAF as an autoantigen in autoimmunoscreening. To analyze the tissue-specific expression of LITAF, establishment of a gene-specific quantitative RT-PCR (primer pair SEQ ID NO: 97 and 98) was followed by analysis of the amount of the specific transcripts in various regions of the brain and in other healthy tissues. It was possible to detect an at least 2- to 5-fold overexpression in the brain by comparison with all the other tissues investigated (FIG. **8**).

Example 11

Identification of TUBG1 as Autoantigen

Tubulin gamma 1 or TUBG1 (SEQ ID NO: 11) is a gene which is located on chromosome 17 (16q21). The gene encodes a soluble protein with a size of about 51 kDa (SEQ ID NO: 12) which is localized in the nucleus. TUBG1 is a member of the tubulin family and constituent of the microtubules in the cell nucleus. The protein plays an important part in regulating division of the cell nucleus.

It was possible according to the invention to identify TUBG1 as an autoantigen in autoimmunoscreening. To analyze the tissue-specific expression of TUBG1, establishment of a gene-specific quantative RT-PCR (primer pair SEQ ID NO: 99 and 100) was followed by analysis of the amount of the specific transcripts in various regions of the brain and in other healthy tissues. It was possible to detect an at least 2- to 5-fold overexpression in the brain by comparison with all the other tissues investigated (FIG. **9**).

Example 12

Identification of NAP1L3 as Autoantigen

Nucleosome assembly protein 1-like 3 or NAP1L3 (SEQ ID NO: 13) is a gene which is located on chromosome X (Xq21-22). The gene encodes a soluble protein with a size of about 58 kDa (SEQ ID NO: 14) which is localized in the

nucleus. NAP1L3 is a member of the nucleosome assembly family and plays an important role in regulating the cell nucleus.

Example 13

Identification of ENO2 as Autoantigen

Enolase 2 or ENO2 (SEQ ID NO: 15) is a gene which is located on chromosome 12 (12q13). The gene encodes a soluble protein with a size of about 47 kDa (SEQ ID NO: 16) which is localized in the cytoplasm. The ENO2 gene codes for an enzyme of the glycolytic metabolic pathway which is mainly expressed in neurons and cells of neuronal origin.

Example 14

Identification of Autoantigens Already Associated With Other Autoimmune Diseases

It was surprisingly possible by the immunoscreening to identify a total of four autoantigens which have previously been described in connection with other autoimmune responses.

The gene SDCCAG8 (SEQ ID NO: 17) is located on chromosome 1 (1q43-44). The gene codes for a protein with a size of about 49 kDa (SEQ ID NO: 18) with as yet unknown function. SDCCAG8 has been described as a colon-specific tumor autoantigen.

The gene HSP90B1 (SEQ ID NO: 19) is located on chromosome 12 (12q24) and codes for a protein having a size of about 92 kDa (SEQ ID NO: 20). The gene belongs to the family of chaperones which have an important function in the genesis and transport of secreted proteins in the lumen of the ER. HSP90B1 is upregulated in myelomas.

The gene SAT (SEQ ID NO: 21) is located on the X chromosome (Xp22) and codes for a protein about 20 kDa in size (SEQ ID NO: 22). The soluble enzyme is present in the cytoplasm as a homotetramer and fulfills a catalytic function in the regulation of polyamines.

The gene EXOSC5 (SEQ ID NO: 23) is located on chromosome 19 (19q13) and codes for a nuclear protein about 25 kDa in size (SEQ ID NO: 24). The enzyme has exonuclease activity and is a constituent of the nuclear exosome. EXOSC5-specific autoantibodies were detectable in patients with myopathies and skin diseases.

Example 15

Identification of Autoantigens of as Yet Unknown Function

It was surprisingly possible to identify by the immunoscreening a total of ten novel, previously hypothetical genes and some chromosomal regions to which no gene has yet been assignable to date. Accordingly, the function and properties of their gene products are unknown. These genes and the relevant gene products are as follows: chromosome 20 sequence: SEQ ID NO: 25, 26; CEP63: SEQ ID NO: 27, 28; LOC115648: SEQ ID NO: 29, 30; chromsome 18 sequence: SEQ ID NO: 31, 32; chromosome 14 sequence 1: SEQ ID NO: 33, 34; chromosome 14 sequence 2: SEQ ID NO: 35, 36; IQWD1: SEQ ID NO: 37, 38; C60ORF199: SEQ ID NO: 39, 40; chromosome 22 sequence: SEQ ID NO: 41, 42; LOC400843: SEQ ID NO: 43, 44. The gene product with SEQ ID NO: 28 is a soluble centrosomally located protein of unknown function. IQWD1 codes for a nuclear protein with a size of about 96 kDa (SEQ ID NO: 38) with several WD40 domains and a nuclear translocation sequence. WD40 domains probably have a function in protein-protein interactions. The gene with SEQ ID NO: 39 codes for a protein with a size of about 48 kDa, which is possibly localized in mitochondria and has an adenylate kinase function.

Example 16

Identification of Further Human Autoantigens

It was surprisingly possible to identify by the immunoscreening a total of 17 cellular antigens not previously known to be involved in autoimmune responses.

Interferon regulatory factor 2 binding protein 2 or IRF2BP2 (SEQ ID NO: 45) is a gene which is located on chromosome 1 (1p42). The gene encodes a soluble protein with a size of about 61 kDa (SEQ ID NO: 46) which is probably localized in the nucleus. The exact function of IRF2BP2 is not yet known. The protein binds to the transcription factor IRF2 and influences IRF2-specific gene regulation.

Sterol regulatory element binding factor 1 or SREBF1 (SEQ ID NO: 47) is a gene which is located on chromosome 17 (17p11). The gene encodes a protein with a size of about 122 kDa (SEQ ID NO: 48). SREBF1 has a transmembrane domain and plays a role in the regulation of transcription and in sterol transport. In the unactivated state, SREBF1 is localized in the ER but, after activation, it is translocated into the nucleus where the protein regulates the transcription of various genes by direct DNA binding.

Exportin4 or XP04 (SEQ ID NO: 49) is a gene which is located on chromosome 1 (13q11). The gene encodes a soluble protein with a size of about 130 kDa (SEQ ID NO: 50). XPO4 binds to the elongation factor elF-5A and mediates the transport of the elongation factor from the nucleus into the cytoplasm.

Zinc finger protein 64 or ZFP64 (SEQ ID NO: 51) is a gene which is located on chromosome 1 (20q13). The gene encodes a soluble protein with a size of about 75 kDa (SEQ ID NO: 52) which is localized in the nucleus. ZFP64 probably binds to DNA and has the function of a transcription factor.

Formin binding protein 1 or FNBP1 (SEQ ID NO: 53) is a gene which is located on chromosome 9 (9q34). The gene encodes a soluble protein with a size of about 70 kDa (SEQ ID NO: 54) which is probably localized in the cytoplasm. The protein is assigned a function in cellular growth regulation.

CCL4 (SEQ ID NO: 55) is a gene which is located on chromosome 17 (17q24). The gene encodes a soluble protein with a size of about 10.5 kDa (SEQ ID NO: 56) which is secreted. The protein binds to cytokine receptors and belongs to the family of chemokines.

COPA (SEQ ID NO: 57) is a gene which is located on chromosome 1 (1q23-25). The gene encodes a soluble protein with a size of about 138 kDa (SEQ ID NO: 58) which is localized in the cytoplasm. The protein is involved in regulating secretory vesicles and is also secreted during this.

GHITM (SEQ ID NO: 59) is a gene which is located on chromosome 10 (10q23.1). The gene encodes an integral membrane protein with a size of about 34 kDa (SEQ ID NO: 60) whose expression is probably chemokine-dependent. The protein is assigned a function in the interferon signaling system and a potential receptor function.

NGLY1 (SEQ ID NO: 61) is a gene which is located on chromosome 3 (3q24.2). The gene encodes an integral membrane protein with a size of about 55 kDa (SEQ ID NO: 62). The protein is assigned a function in the degradation of incorrectly folded proteins.

KTN1 (SEQ ID NO: 63) is a gene which is located on chromosome 14 (14q22.1). The gene encodes a membrane protein with a size of about 156 kDa (SEQ ID NO: 64). The protein is assigned a function as kinesin receptor and thus in kinesin-driven vesicle motility.

SFRS11 (SEQ ID NO: 65) is a gene which is located on chromosome 1 (1q31). The gene encodes a soluble protein with a size of about 54 kDa (SEQ ID NO: 66) which is probably localized in the nucleus. The protein is assigned a function in pre-mRNA splicing.

NME1-NME2 (SEQ ID NO: 67) is a gene which is located on chromosome 17 (17q21.3). The gene encodes a soluble protein with a size of about 17 kDa (SEQ ID NO: 68) which is probably localized in the cytoplasm and nucleus. The protein has, as nucleoside-diphosphate kinase, a function in the synthesis of non-ATP nucleoside triphosphates.

RPS15 (SEQ ID NO: 69) is a gene which is located on chromsome 19 (19q13.3). The gene encodes a soluble protein with a size of about 17 kDa (SEQ ID NO: 70) which is probably localized in the cytoplasm. RPS15 is a member of the S19P family of ribosomal proteins and plays a part in protein synthesis.

APC2 (SEQ ID NO: 71) is a gene which is located on chromosome 19 (19q13.3). The gene encodes a soluble protein with a size of about 245 kDa (SEQ ID NO: 72) which is localized in the cytoplasm and possibly colocalized with tubular structures and the golgi apparatus. The protein is assigned a function as tumor suppressor.

GLS2 (SEQ ID NO: 73) is a gene which is located on chromosome 12 (12q13). The gene encodes a soluble protein with a size of about 68 kDa (SEQ ID NO: 74) which is localized in mitochondria. The protein is assigned an enzymatic function as glutaminase in the hydrolysis of glutamine.

TECAL8 (SEQ ID NO: 75) is a gene which is located on chromosome X (Xq22.1). The gene codes for a soluble protein with a size of about 14 kDa (SEQ ID NO: 76). The protein is assigned a function as transcription elongation factor.

PPIF (SEQ ID NO: 77) is a gene which is located on chromosome 10 (10q22-q23). The gene codes for a protein with a size of about 22 kDa (SEQ ID NO: 78) which is localized in the mitochondria. The protein is assigned an enzymatic function in protein folding and a possible function in the induction of apoptotic and necrotic cell death.

Example 17

Identification of Mitochondrial Autoantigens

It was possible by the immunoscreening to identify a total of five mitochondrial genes against whose gene products autoantibodies are formed in patients with multiple sclerosis. These genes and relevant gene products are as follows: ND4: SEQ ID NO: 79, 80; ATP5H: SEQ ID NO: 81, 82; COX1: SEQ ID NO: 83, 84; COX2: SEQ ID NO: 85, 88; COX3: SEQ ID NO: 87, 88.

Example 18

Serological Analysis of Selected Autoimmune Antigens

In order to investigate the prevalence of the identified antigens in patients with multiple sclerosis, 24 of the 44 identified antigens were investigated with up to 12 sera from MS patients and up to 18 sera from control patients in a Serogrid analysis (Krause et al., 2003, *J Imm Methods* 283, 261) (see Example 3). The result of the analysis is depicted in FIG. **10**. The identified antigens were moderately to strongly positive in almost all the samples investigated originating from patients with an MS disease and thus demonstrated a high prevalence of the identified autoantibodies in patients with multiple sclerosis. It was by contrast possible to identify at the most only a weak reactivity close to the limit of detection in the control samples (n=18) derived from healthy subjects.

SEQUENCE LISTING

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<211> LENGTH: 5209
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

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gaaggatgag tcctcggggt ggagaaggag gagcgggtcc ccgggtaccg ctcacccggc 180

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<211> LENGTH: 981
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

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

Glu Gly Glu Ile Cys Gly Phe Lys Ile His Gly Gln Asn Val Pro Phe
                85                  90                  95

Asp Ala Val Val Val Asp Lys Ser Thr Gly Glu Gly Val Ile Arg Ser
            100                 105                 110

Lys Glu Lys Leu Asp Cys Glu Leu Gln Lys Asp Tyr Ser Phe Thr Ile
        115                 120                 125

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

Ala Pro Val Phe Lys Glu Lys Ser Tyr Lys Ala Thr Val Ile Glu Gly
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Lys Gln Tyr Asp Ser Ile Leu Arg Val Glu Ala Val Asp Ala Asp Cys
            180                 185                 190

Ser Pro Gln Phe Ser Gln Ile Cys Ser Tyr Glu Ile Ile Thr Pro Asp
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Val Pro Phe Thr Val Asp Lys Asp Gly Tyr Ile Lys Asn Thr Glu Lys
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Leu Asn Tyr Gly Lys Glu His Gln Tyr Lys Leu Thr Val Thr Ala Tyr
225                 230                 235                 240

Asp Cys Gly Lys Lys Arg Ala Thr Glu Asp Val Leu Val Lys Ile Ser
                245                 250                 255

Ile Lys Pro Thr Cys Thr Pro Gly Trp Gln Gly Trp Asn Asn Arg Ile
            260                 265                 270

Glu Tyr Glu Pro Gly Thr Gly Ala Leu Ala Val Phe Pro Asn Ile His
        275                 280                 285

Leu Glu Thr Cys Asp Glu Pro Val Ala Ser Val Gln Ala Thr Val Glu
    290                 295                 300

Leu Glu Thr Ser His Ile Gly Lys Gly Cys Asp Arg Asp Thr Tyr Ser
305                 310                 315                 320

Glu Lys Ser Leu His Arg Leu Cys Gly Ala Ala Ala Gly Thr Ala Glu
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Leu Leu Pro Ser Pro Ser Gly Ser Leu Asn Trp Thr Met Gly Leu Pro
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Thr Asp Asn Gly His Asp Ser Asp Gln Val Phe Glu Phe Asn Gly Thr
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Gln Ala Val Arg Ile Pro Asp Gly Val Val Ser Val Ser Pro Lys Glu
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Pro Phe Thr Ile Ser Val Trp Met Arg His Gly Pro Phe Gly Arg Lys
385                 390                 395                 400

Lys Glu Thr Ile Leu Cys Ser Ser Asp Lys Thr Asp Met Asn Arg His
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His Tyr Ser Leu Tyr Val His Gly Cys Arg Leu Ile Phe Leu Phe Arg
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Gln Asp Pro Ser Glu Glu Lys Lys Tyr Arg Pro Ala Glu Phe His Trp
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Val Glu Phe Pro Ser Val Thr Leu Tyr Val Asp Gly Thr Ser His Glu
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Pro Phe Ser Val Thr Glu Asp Tyr Pro Leu His Pro Ser Lys Ile Glu
                485                 490                 495

Thr Gln Leu Val Val Gly Ala Cys Trp Gln Glu Phe Ser Gly Val Glu
            500                 505                 510

Asn Asp Asn Glu Thr Glu Pro Val Thr Val Ala Ser Ala Gly Gly Asp
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Leu His Met Thr Gln Phe Phe Arg Gly Asn Leu Ala Gly Leu Thr Leu
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Arg Ser Gly Lys Leu Ala Asp Lys Lys Val Ile Asp Cys Leu Tyr Thr
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Cys Lys Glu Gly Leu Asp Leu Gln Val Leu Glu Asp Ser Gly Arg Gly
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Val Gln Ile Gln Ala His Pro Ser Gln Leu Val Leu Thr Leu Glu Gly
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Glu Asp Leu Gly Glu Leu Asp Lys Ala Met Gln His Ile Ser Tyr Leu
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Asn Ser Arg Gln Phe Pro Thr Pro Gly Ile Arg Arg Leu Lys Ile Thr
    610                 615                 620

Ser Thr Ile Lys Cys Phe Asn Glu Ala Thr Cys Ile Ser Val Pro Pro
625                 630                 635                 640

Val Asp Gly Tyr Val Met Val Leu Gln Pro Glu Glu Pro Lys Ile Ser
                645                 650                 655

Leu Ser Gly Val His His Phe Ala Arg Ala Ala Ser Glu Phe Glu Ser
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Ser Glu Gly Val Phe Leu Phe Pro Glu Leu Arg Ile Ile Ser Thr Ile
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Thr Arg Glu Val Glu Pro Glu Gly Asp Gly Ala Glu Asp Pro Thr Val
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Gln Glu Ser Leu Val Ser Glu Glu Ile Val His Asp Leu Asp Thr Cys
705                 710                 715                 720

Glu Val Thr Val Glu Gly Glu Glu Leu Asn His Glu Gln Glu Ser Leu
                725                 730                 735

Glu Val Asp Met Ala Arg Leu Gln Gln Lys Gly Ile Glu Val Ser Ser
            740                 745                 750

Ser Glu Leu Gly Met Thr Phe Thr Gly Val Asp Thr Met Ala Ser Tyr
        755                 760                 765

Glu Glu Val Leu His Leu Leu Arg Tyr Arg Asn Trp His Ala Arg Ser
    770                 775                 780

Leu Leu Asp Arg Lys Phe Lys Leu Ile Cys Ser Glu Leu Asn Gly Arg
785                 790                 795                 800

Tyr Ile Ser Asn Glu Phe Lys Val Glu Val Asn Val Ile His Thr Ala
                805                 810                 815

Asn Pro Met Glu His Ala Asn His Met Ala Ala Gln Pro Gln Phe Val
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His Pro Glu His Arg Ser Phe Val Asp Leu Ser Gly His Asn Leu Ala
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Asn Pro His Pro Phe Ala Val Val Pro Ser Thr Ala Thr Val Val Ile
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Val Val Cys Val Ser Phe Leu Val Phe Met Ile Ile Leu Gly Val Phe
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Arg Ile Arg Ala Ala His Arg Arg Thr Met Arg Asp Gln Asp Thr Gly
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Lys Glu Asn Glu Met Asp Trp Asp Asp Ser Ala Leu Thr Ile Thr Val
            900                 905                 910

Asn Pro Met Glu Thr Tyr Glu Asp Gln His Ser Ser Glu Glu Glu Glu
        915                 920                 925

Glu Glu Glu Glu Glu Glu Glu Ser Glu Asp Gly Glu Glu Glu Asp Asp
    930                 935                 940

Ile Thr Ser Ala Glu Ser Glu Ser Ser Glu Glu Glu Glu Gly Glu Gln
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Gly Asp Pro Gln Asn Ala Thr Arg Gln Gln Gln Leu Glu Trp Asp Asp
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Ser Thr Leu Ser Tyr
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<210> SEQ ID NO 3
<211> LENGTH: 5162
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

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<210> SEQ ID NO 4
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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

Met Ser Ala Glu Val Pro Glu Ala Ala Ser Ala Glu Glu Gln Lys Glu
1 5 10 15

Met Glu Asp Lys Val Thr Ser Pro Glu Lys Ala Glu Glu Ala Lys Leu
20 25 30

Lys Ala Arg Tyr Pro His Leu Gly Gln Lys Pro Gly Gly Ser Asp Phe
35 40 45

Leu Arg Lys Arg Leu Gln Lys Gly Gln Lys Tyr Phe Asp Ser Gly Asp
50 55 60

Tyr Asn Met Ala Lys Ala Lys Met Lys Asn Lys Gln Leu Pro Thr Ala
65 70 75 80

Ala Pro Asp Lys Thr Glu Val Thr Gly Asp His Ile Pro Thr Pro Gln
85 90 95

Asp Leu Pro Gln Arg Lys Pro Ser Leu Val Ala Ser Lys Leu Ala Gly
100 105 110

<210> SEQ ID NO 5
<211> LENGTH: 1073
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 5

ggcgcgggag ttggcattcg gtggtcctgg cagttagctg agcacgccct ctgagccgct 60

cggtggacac caggcactct agtaggcctg gcctacccag aaacagcagg agagagaaga 120

aacaggccag ctgtgagaag ccaaggacac cgagtcagtc atggcaccta aggcggcaaa 180

gggggccaag ccagagccag caccagctcc acctccaccc ggggccaaac ccgaggaaga 240

caagaaggac ggtaaggagc catcggacaa acctcaaaag gcggtgcagg accataagga 300

gccatcggac aaacctcaaa aggcggtgca gcccaagcac gaagtgggca cgaggagggg 360

gtgtcgccgc taccggtggg aattaaaaga cagcaataaa gagttctggc tcttggggca 420

cgctgagatc aagattcgga gtttgggctg cctaatagct gcaatgatac tgttgtcctc 480

actcaccgtg caccccatct tgaggcttat catcaccatg gagatatcct tcttcagctt 540

cttcatctta ctgtacagct ttgccattca tagatacata cccttcatcc tgtggcccat 600

ttctgacctc ttcaacgacc tgattgcttg tgcgttcctt gtgggagccg tggtctttgc 660

tgtgagaagt cggcgatcca tgaatctcca ctacttactt gctgtgatcc ttattggtgc 720

ggctggagtt tttgctttta tcgatgtgtg tcttcaaaga aaccacttca gaggcaagaa 780

ggccaaaaag catatgctgg ttcctcctcc aggaaaggaa aaaggacccc agcagggcaa 840

gggaccagaa cccgccaagc caccagaacc tggcaagcca ccagggccag caaagggaaa 900

gaaatgactt ggaggaggct cctggtgtct gaaacggcag tgtattttac agcaatatgt 960

ttccactctc ttccttgtct tctttctgga atggttttct tttccatttt cattaccacc 1020

tttgcttgga aaagaatgga ttaatggatt ctaaaagcct aaaaaaaaaa aaa 1073

<210> SEQ ID NO 6
<211> LENGTH: 248
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

Met Ala Pro Lys Ala Ala Lys Gly Ala Lys Pro Glu Pro Ala Pro Ala
1 5 10 15

Pro Pro Pro Pro Gly Ala Lys Pro Glu Glu Asp Lys Lys Asp Gly Lys
20 25 30

Glu Pro Ser Asp Lys Pro Gln Lys Ala Val Gln Asp His Lys Glu Pro
35 40 45

Ser Asp Lys Pro Gln Lys Ala Val Gln Pro Lys His Glu Val Gly Thr
50 55 60

Arg Arg Gly Cys Arg Arg Tyr Arg Trp Glu Leu Lys Asp Ser Asn Lys
65 70 75 80

Glu Phe Trp Leu Leu Gly His Ala Glu Ile Lys Ile Arg Ser Leu Gly
85 90 95

Cys Leu Ile Ala Ala Met Ile Leu Leu Ser Ser Leu Thr Val His Pro
100 105 110

Ile Leu Arg Leu Ile Ile Thr Met Glu Ile Ser Phe Phe Ser Phe Phe
115 120 125

Ile Leu Leu Tyr Ser Phe Ala Ile His Arg Tyr Ile Pro Phe Ile Leu
130 135 140

Trp Pro Ile Ser Asp Leu Phe Asn Asp Leu Ile Ala Cys Ala Phe Leu
145 150 155 160

Val Gly Ala Val Val Phe Ala Val Arg Ser Arg Arg Ser Met Asn Leu
165 170 175

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His Tyr Leu Leu Ala Val Ile Leu Ile Gly Ala Ala Gly Val Phe Ala
            180                 185                 190

Phe Ile Asp Val Cys Leu Gln Arg Asn His Phe Arg Gly Lys Lys Ala
        195                 200                 205

Lys Lys His Met Leu Val Pro Pro Pro Gly Lys Glu Lys Gly Pro Gln
    210                 215                 220

Gln Gly Lys Gly Pro Glu Pro Ala Lys Pro Pro Glu Pro Gly Lys Pro
225                 230                 235                 240

Pro Gly Pro Ala Lys Gly Lys Lys
                245
```

<210> SEQ ID NO 7
<211> LENGTH: 2443
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

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aaatggcgtg cccgtctctc cgccggcccc ctgcctcgca gtggtttctc ctgcagctcc     60

cctgggctcc gcggccagta gtgcagcccg tggagccgcg gctttgcccg tctcctctgg    120

gtggccccag tgcgcgggct gacactcatt cagccgggga aggtgaggcg agtagaggct    180

ggtgcggaac ttgccgcccc cagcagcgcc ggcgggctaa gcccagggcc gggcagacaa    240

aagaggccgc ccgcgtagga aggcacggcc ggcggcggcg gagcgcagcg atggccgggc    300

gagggggcag cgcgctgctg gctctgtgcg gggcactggc tgcctgcggg tggctcctgg    360

gcgccgaagc ccaggagccc ggggcgcccg cggcgggcat gaggcggcgc cggcggctgc    420

agcaagagga cggcatctcc ttcgagtacc accgctaccc cgagctgcgc gaggcgctcg    480

tgtccgtgtg gctgcagtgc accgccatca gcaggattta cacggtgggg cgcagcttcg    540

agggccggga gctcctggtc atcgagctgt ccgacaaccc tggcgtccat gagcctggtg    600

agcctgaatt taaatacatt gggaatatgc atgggaatga ggctgttgga cgagaactgc    660

tcattttctt ggcccagtac ctatgcaacg aataccagaa ggggaacgag acaattgtca    720

acctgatcca cagtacccgc attcacatca tgccttccct gaacccagat ggctttgaga    780

aggcagcgtc tcagcctggt gaactcaagg actggtttgt gggtcgaagc aatgcccagg    840

gaatagatct gaaccggaac tttccagacc tggataggat agtgtacgtg aatgagaaag    900

aaggtggtcc aaataatcat ctgttgaaaa atatgaagaa aattgtggat caaaacacaa    960

agcttgctcc tgagaccaag gctgtcattc attggattat ggatattcct tttgtgcttt   1020

ctgccaatct ccatggagga gaccttgtgg ccaattatcc atatgatgag acgcggagtg   1080

gtagtgctca cgaatacagc tcctccccag atgacgccat tttccaaagc ttggcccggg   1140

catactcttc tttcaacccg gccatgtctg accccaatcg gccaccatgt cgcaagaatg   1200

atgatgacag cagctttgta gatggaacca ccaacggtgg tgcttggtac agcgtacctg   1260

gagggatgca agacttcaat taccttagca gcaactgttt tgagatcacc gtggagctta   1320

gctgtgagaa gttcccacct gaagagactc tgaagaccta ctgggaggat aacaaaaact   1380

ccctcattag ctaccttgag cagatacacc gaggagttaa aggatttgtc cgagaccttc   1440

aaggtaaccc aattgcgaat gccaccatct ccgtggaagg aatagaccac gatgttacat   1500

ccgcaaagga tggtgattac tggagattgc ttatacctgg aaactataaa cttacagcct   1560

cagctccagg ctatctggca ataacaaaga aagtggcagt tccttacagc cctgctgctg   1620

gggttgattt tgaactggag tcattttctg aaaggaaaga agaggagaag gaagaattga   1680

tggaatggtg gaaaatgatg tcagaaactt taaattttta aaaaggcttc tagttagctg   1740
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ctttaaatct atctatataa tgtagtatga tgtaatgtgg tctttttttt agattttgtg 1800

cagttaatac ttaacattga tttatttttt aatcatttaa atattaatca actttcctta 1860

aaataaatag cctcttaggt aaaaatataa gaacttgata tatttcattc tcttatatag 1920

tattcatttt cctacctata ttacacaaaa aagtatagaa aagatttaag taattttgcc 1980

atcctaggct taaatgcaat attcctggta ttatttacaa tgcagaattt tttgagtaat 2040

tctagctttc aaaaattagt gaagttcttt tactgtaatt ggtgacaatg tcacataatg 2100

aatgctattg aaaaggttaa cagatacagc tcggagttgt gagcactcta ctgcaagact 2160

taaatagttc agtataaatt gtcgtttttt tcttgtgctg actaactata agcatgatct 2220

tgttaatgca tttttgatgg gaagaaaagg tacatgttta caaagaggtt ttatgaaaag 2280

aataaaaatt gacttcttgc ttgtacatat aggagcaata ctattatatt atgtagtccg 2340

ttaacactac ttaaaagttt agggttttct cttggttgta gagtggccca gaattgcatt 2400

ctgaatgaat aaaggttaaa aaaaaatccc cagtgaaaaa aaa 2443

<210> SEQ ID NO 8
<211> LENGTH: 476
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

Met Ala Gly Arg Gly Gly Ser Ala Leu Leu Ala Leu Cys Gly Ala Leu
1 5 10 15

Ala Ala Cys Gly Trp Leu Leu Gly Ala Glu Ala Gln Glu Pro Gly Ala
20 25 30

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

Ile Ser Phe Glu Tyr His Arg Tyr Pro Glu Leu Arg Glu Ala Leu Val
50 55 60

Ser Val Trp Leu Gln Cys Thr Ala Ile Ser Arg Ile Tyr Thr Val Gly
65 70 75 80

Arg Ser Phe Glu Gly Arg Glu Leu Leu Val Ile Glu Leu Ser Asp Asn
85 90 95

Pro Gly Val His Glu Pro Gly Glu Pro Glu Phe Lys Tyr Ile Gly Asn
100 105 110

Met His Gly Asn Glu Ala Val Gly Arg Glu Leu Leu Ile Phe Leu Ala
115 120 125

Gln Tyr Leu Cys Asn Glu Tyr Gln Lys Gly Asn Glu Thr Ile Val Asn
130 135 140

Leu Ile His Ser Thr Arg Ile His Ile Met Pro Ser Leu Asn Pro Asp
145 150 155 160

Gly Phe Glu Lys Ala Ala Ser Gln Pro Gly Glu Leu Lys Asp Trp Phe
165 170 175

Val Gly Arg Ser Asn Ala Gln Gly Ile Asp Leu Asn Arg Asn Phe Pro
180 185 190

Asp Leu Asp Arg Ile Val Tyr Val Asn Glu Lys Glu Gly Gly Pro Asn
195 200 205

Asn His Leu Leu Lys Asn Met Lys Lys Ile Val Asp Gln Asn Thr Lys
210 215 220

Leu Ala Pro Glu Thr Lys Ala Val Ile His Trp Ile Met Asp Ile Pro
225 230 235 240

Phe Val Leu Ser Ala Asn Leu His Gly Gly Asp Leu Val Ala Asn Tyr
245 250 255

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```
Pro Tyr Asp Glu Thr Arg Ser Gly Ser Ala His Glu Tyr Ser Ser Ser
            260                 265                 270

Pro Asp Asp Ala Ile Phe Gln Ser Leu Ala Arg Ala Tyr Ser Ser Phe
        275                 280                 285

Asn Pro Ala Met Ser Asp Pro Asn Arg Pro Pro Cys Arg Lys Asn Asp
    290                 295                 300

Asp Asp Ser Ser Phe Val Asp Gly Thr Thr Asn Gly Gly Ala Trp Tyr
305                 310                 315                 320

Ser Val Pro Gly Gly Met Gln Asp Phe Asn Tyr Leu Ser Ser Asn Cys
                325                 330                 335

Phe Glu Ile Thr Val Glu Leu Ser Cys Glu Lys Phe Pro Pro Glu Glu
            340                 345                 350

Thr Leu Lys Thr Tyr Trp Glu Asp Asn Lys Asn Ser Leu Ile Ser Tyr
        355                 360                 365

Leu Glu Gln Ile His Arg Gly Val Lys Gly Phe Val Arg Asp Leu Gln
    370                 375                 380

Gly Asn Pro Ile Ala Asn Ala Thr Ile Ser Val Glu Gly Ile Asp His
385                 390                 395                 400

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

Gly Asn Tyr Lys Leu Thr Ala Ser Ala Pro Gly Tyr Leu Ala Ile Thr
            420                 425                 430

Lys Lys Val Ala Val Pro Tyr Ser Pro Ala Ala Gly Val Asp Phe Glu
        435                 440                 445

Leu Glu Ser Phe Ser Glu Arg Lys Glu Glu Glu Lys Glu Glu Leu Met
    450                 455                 460

Glu Trp Trp Lys Met Met Ser Glu Thr Leu Asn Phe
465                 470                 475
```

<210> SEQ ID NO 9
<211> LENGTH: 2368
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

```
gtttctctcc ctgcccccgc gacttcgcgc aagatccggg aaggacaccc gaggcccctg     60

ggagaccctg gggaggtgaa agtcagagag cgaagcgggc cgtggcccct aggcctgacc    120

cctccccgcg gggtaaggcg ggcaccccgc gagcgcaggg gtcctcttac tgctgatggc    180

acccagctct gggcccagac gccgctcacc gtccaccgcc ggtgctgggt aaaatgtcgg    240

ttccaggacc ttaccaggcg gccactgggc cttcctcagc accatccgca cctccatcct    300

atgaagagac agtggctgtt aacagttatt accccacacc tccagctccc atgcctgggc    360

caactacggg gcttgtgacg gggcctgatg ggaagggcat gaatcctcct tcgtattata    420

cccagccagc gcccatcccc aataacaatc caattaccgt gcagacggtc tacgtgcagc    480

accccatcac ctttttggac cgccctatcc aaatgtgttg tccttcctgc aacaagatga    540

tcgtgagtca gctgtcctat aacgccggtg ctctgacctg gctgtcctgc gggagcctgt    600

gcctgctggg gtgcatagcg ggctgctgct tcatcccctt ctgcgtggat gccctgcagg    660

acgtggacca ttactgtccc aactgcagag ctctcctggg cacctacaag cgtttgtagg    720

actcagccag acgtggaggg agccgggtgc cgcaggaagt cctttccacc tctcatccag    780

cttcacgcct ggtggaggtt ctgccctggt ggtctcacct ctccaggggg cccaccttca    840

tgtcttcttt tgggggggaat acgtcgcaaa actaacaaat ctccaaaccc cagaaattgc    900
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tgcttggagt cgtgcatagg acttgcaaag acattcccct tgagtgtcag ttccacggtt 960

tcctgcctcc ctgagaccct gagtcctgcc atctaactgt gatcattgcc ctatccgaat 1020

atcttcctgt gatctgccat cagtggctct tttttcctgc ttccatgggc ctttctggtg 1080

gcagtctcaa actgagaagc cacagttgcc ttatttttga ggctgttctg cccagagctc 1140

ggctgaacca gcctttagtg cctaccatta tcttatccgt ctcttcccgt ccctgatgac 1200

aaagatcttg ccttacagac tttacaggct tggctttgag attctgtaac tgcagacttc 1260

attagcacac agattcactt taatttctta attttttttt taaatacaag gaggggggcta 1320

ttaacaccca gtacagacat atccacaagg tcgtaaatgc atgctagaaa aatagggctg 1380

gatcttatca ctgccctgtc tccccttgtt tctctgtgcc agatcttcag tgccccctttc 1440

catacaggga ttttttttctc atagagtaat tatatgaaca gtttttatga cctccttttg 1500

gtctgaaata cttttgaaca gaatttcttt tttttaaaaa aaaacagaga tggggtctta 1560

ctatgttgcc caggctggtg tcgaactcct gggctcaagc gatccttctg ccttggcctc 1620

ccgaagtgct gggattgcag gcataagcta ccatgctggg cctgaacata atttcaagag 1680

gaggatttat aaaaccattt tctgtaatca aatgattggt gtcattttcc catttgccaa 1740

tgtagtctca cttaaaaaaa aaaaaaagaa aaagaaatgg ataatttcat ctactgcctt 1800

tacttggggt taatgtgatt cttaaacacc ttcatcatgg aactctcaga gtggggtccg 1860

ttttggtttc ctggtggtgg gttttgaaag ataagggaaa gcacattttg agcatgtctg 1920

ggtaccatgg tgcggatgct tgggaaccag aactgtttca gaggaatcta aagtctgatt 1980

ttagttttca gagacacagc ttgttgtaaa acatgagaag acatgatttc taggactcaa 2040

gcagcaagcc aggattctag gttggctgct gtgtcatctt tgaagtcaag acaaagctgg 2100

gctcgacctt caagggtcct cgttttgata atacttcaga atagggaact catgtgaata 2160

ctactatgta gaaataaaac ctagaccttg agcgaacatc tgtatattgg ttgaaaacga 2220

tagtggtaac cattgatccc ccttcatttg atgtttggaa aattccagta attatcattt 2280

ttgcaacgaa tatggatacc acatagtact ttggtgttac ctgcttttga aaaataaagt 2340

ctttggttca cccggtaaaa aaaaaaaa 2368

<210> SEQ ID NO 10
<211> LENGTH: 161
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

Met Ser Val Pro Gly Pro Tyr Gln Ala Ala Thr Gly Pro Ser Ser Ala
1 5 10 15

Pro Ser Ala Pro Pro Ser Tyr Glu Glu Thr Val Ala Val Asn Ser Tyr
20 25 30

Tyr Pro Thr Pro Pro Ala Pro Met Pro Gly Pro Thr Thr Gly Leu Val
35 40 45

Thr Gly Pro Asp Gly Lys Gly Met Asn Pro Pro Ser Tyr Tyr Thr Gln
50 55 60

Pro Ala Pro Ile Pro Asn Asn Asn Pro Ile Thr Val Gln Thr Val Tyr
65 70 75 80

Val Gln His Pro Ile Thr Phe Leu Asp Arg Pro Ile Gln Met Cys Cys
85 90 95

Pro Ser Cys Asn Lys Met Ile Val Ser Gln Leu Ser Tyr Asn Ala Gly
100 105 110

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```
Ala Leu Thr Trp Leu Ser Cys Gly Ser Leu Cys Leu Leu Gly Cys Ile
        115                 120                 125

Ala Gly Cys Cys Phe Ile Pro Phe Cys Val Asp Ala Leu Gln Asp Val
    130                 135                 140

Asp His Tyr Cys Pro Asn Cys Arg Ala Leu Leu Gly Thr Tyr Lys Arg
145                 150                 155                 160

Leu
```

<210> SEQ ID NO 11
<211> LENGTH: 1645
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

```
gcgggctggc gtgcggcgcc gttgcgggcg ggagcggctg caacgccggt gcctgaggag     60

cgatgccgag ggaaatcatc accctacagt tgggccagtg cggcaatcag attgggttcg    120

agttctggaa acagctgtgc gccgagcatg gtatcagccc cgagggcatc gtggaggagt    180

tcgccaccga gggcactgac cgcaaggacg tctttttcta ccaggcagac gatgagcact    240

acatcccccg ggccgtgctg ctggacttgg aaccccgggt gatccactcc atcctcaact    300

ccccctatgc caagctctac aacccagaga acatctacct gtcggaacat ggaggaggag    360

ctggcaacaa ctgggccagc ggattctccc agggagaaaa gatccatgag gacatttttg    420

acatcataga ccgggaggca gatggtagtg acagtctaga gggctttgtg ctgtgtcact    480

ccattgctgg ggggacaggc tctggactgg gttcctacct cttagaacgg ctgaatgaca    540

ggtatcctaa gaagctggtg cagacatact cagtgtttcc caaccaggac gagatgagcg    600

atgtggtggt ccagccttac aattcactcc tcacactcaa gaggctgacg cagaatgcag    660

actgtgtggt ggtgctggac aacacagccc tgaaccggat tgccacagac cgcctgcaca    720

tccagaaccc atccttctcc cagatcaacc agctggtgtc taccatcatg tcagccagca    780

ccaccaccct gcgctaccct ggctacatga acaatgacct catcggcctc atcgcctcgc    840

tcattcccac cccacggctc cacttcctca tgaccggcta cacccctctc actacggacc    900

agtcagtggc cagcgtgagg aagaccacgg tcctggatgt catgaggcgg ctgctgcagc    960

ccaagaacgt gatggtgtcc acaggccgag accgccagac caaccactgc tacatcgcca   1020

tcctcaacat catccaggga gaggtggacc ccacccaggt ccacaagagc ttgcagagga   1080

tccgggaacg caagttggcc aacttcatcc cgtggggccc cgccagcatc caggtggccc   1140

tgtcgaggaa gtctccctac ctgccctcgg cccaccgggt cagcgggctc atgatggcca   1200

accacaccag catctcctcg ctcttcgaga gaacctgtcg ccagtatgac aagctgcgta   1260

agcgggaggc cttcctggag cagttccgca aggaggacat gttcaaggac aactttgatg   1320

agatggacac atccagggag attgtgcagc agctcatcga tgagtaccat gcggccacac   1380

ggccagacta catctcctgg ggcacccagg agcagtgagt cccccaggac agggaccctc   1440

atctgcctta ctggttggcc caagccctgc ctgactgacc acccctcag agcacagatc   1500

agggacctca cgcatctctt tctcatatac atggactctc tgttggcctg caaacacatt   1560

tacttctcct cttatgagac tatttatctt taataaagca ctggatataa aaaaaaaaaa   1620

aaaaaaaaaa aaaaaaaaaa aaaaa                                         1645
```

<210> SEQ ID NO 12
<211> LENGTH: 451
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 12

```
Met Pro Arg Glu Ile Ile Thr Leu Gln Leu Gly Gln Cys Gly Asn Gln
1               5                  10                  15

Ile Gly Phe Glu Phe Trp Lys Gln Leu Cys Ala Glu His Gly Ile Ser
            20                  25                  30

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

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

Val Leu Leu Asp Leu Glu Pro Arg Val Ile His Ser Ile Leu Asn Ser
65                  70                  75                  80

Pro Tyr Ala Lys Leu Tyr Asn Pro Glu Asn Ile Tyr Leu Ser Glu His
                85                  90                  95

Gly Gly Gly Ala Gly Asn Asn Trp Ala Ser Gly Phe Ser Gln Gly Glu
            100                 105                 110

Lys Ile His Glu Asp Ile Phe Asp Ile Ile Asp Arg Glu Ala Asp Gly
        115                 120                 125

Ser Asp Ser Leu Glu Gly Phe Val Leu Cys His Ser Ile Ala Gly Gly
    130                 135                 140

Thr Gly Ser Gly Leu Gly Ser Tyr Leu Leu Glu Arg Leu Asn Asp Arg
145                 150                 155                 160

Tyr Pro Lys Lys Leu Val Gln Thr Tyr Ser Val Phe Pro Asn Gln Asp
                165                 170                 175

Glu Met Ser Asp Val Val Val Gln Pro Tyr Asn Ser Leu Leu Thr Leu
            180                 185                 190

Lys Arg Leu Thr Gln Asn Ala Asp Cys Val Val Val Leu Asp Asn Thr
        195                 200                 205

Ala Leu Asn Arg Ile Ala Thr Asp Arg Leu His Ile Gln Asn Pro Ser
    210                 215                 220

Phe Ser Gln Ile Asn Gln Leu Val Ser Thr Ile Met Ser Ala Ser Thr
225                 230                 235                 240

Thr Thr Leu Arg Tyr Pro Gly Tyr Met Asn Asn Asp Leu Ile Gly Leu
                245                 250                 255

Ile Ala Ser Leu Ile Pro Thr Pro Arg Leu His Phe Leu Met Thr Gly
            260                 265                 270

Tyr Thr Pro Leu Thr Thr Asp Gln Ser Val Ala Ser Val Arg Lys Thr
        275                 280                 285

Thr Val Leu Asp Val Met Arg Arg Leu Leu Gln Pro Lys Asn Val Met
    290                 295                 300

Val Ser Thr Gly Arg Asp Arg Gln Thr Asn His Cys Tyr Ile Ala Ile
305                 310                 315                 320

Leu Asn Ile Ile Gln Gly Glu Val Asp Pro Thr Gln Val His Lys Ser
                325                 330                 335

Leu Gln Arg Ile Arg Glu Arg Lys Leu Ala Asn Phe Ile Pro Trp Gly
            340                 345                 350

Pro Ala Ser Ile Gln Val Ala Leu Ser Arg Lys Ser Pro Tyr Leu Pro
        355                 360                 365

Ser Ala His Arg Val Ser Gly Leu Met Met Ala Asn His Thr Ser Ile
    370                 375                 380

Ser Ser Leu Phe Glu Arg Thr Cys Arg Gln Tyr Asp Lys Leu Arg Lys
385                 390                 395                 400

Arg Glu Ala Phe Leu Glu Gln Phe Arg Lys Glu Asp Met Phe Lys Asp
                405                 410                 415
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Asn Phe Asp Glu Met Asp Thr Ser Arg Glu Ile Val Gln Gln Leu Ile
420 425 430

Asp Glu Tyr His Ala Ala Thr Arg Pro Asp Tyr Ile Ser Trp Gly Thr
435 440 445

Gln Glu Gln
450

<210> SEQ ID NO 13
<211> LENGTH: 2687
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

gatctaaaac gagaagagat ctcggggtct catactgcgc cattcggctg cggtacatct 60

cggcactcta gctgcagccg ggagaggcct tgccgccacc gctgtcgccc aagcctccac 120

tgccgctgcc acctcagcgc cggcctctgc atccccagct ccagctccgc tctgcgccgc 180

tgctgccatc gccgctgcca cctccgcagc ccgggcctcc gccgccgcca ctcaagcatc 240

cgtgagtcat tttctgccca tctctggtcg cgcggtctcc ctggtagagt ttgtaggctt 300

gcaagatggc agaagcagat tttaaaatgg tctcggaacc tgtcgcccat ggggttgccg 360

aagaggagat ggctagctcg actagtgatt ctggggaaga atctgacagc agtagctcta 420

gcagcagcac tagtgacagc agcagcagca gcagcactag tggcagcagc agcggcagcg 480

gcagcagcag cagcagcagc ggcagcacta gcagccgcag ccgcttgtat agaaagaaga 540

gggtacctga gccttccaga agggcgcggc gggccccgtt gggaacaaat ttcgtggata 600

ggctgcctca ggcagttaga aatcgtgtgc aagcgcttag aaacattcaa gatgaatgtg 660

acaaggtaga taccctgttc ttaaaagcaa ttcatgatct tgaaagaaaa tatgctgaac 720

tcaacaagcc tctgtatgat aggcggtttc aaatcatcaa tgcagaatac gagcctacag 780

aagaagaatg tgaatggaat tcagaggatg aggagttcag cagtgatgag gaggtgcagg 840

ataacacccc tagtgaaatg cctcccttag agggtgagga agaagaaaac cctaaagaaa 900

acccagaggt gaaagctgaa gagaaggaag ttcctaaaga aattcctgag gtgaaggatg 960

aagaaaagga agttcctaaa gaaattcctg aggtaaaggc tgaagaaaaa gcagattcta 1020

aagactgtat ggaggcaacc cctgaagtaa aagaagatcc taaagaagtc ccccaggtaa 1080

aggcagatga taaagaacag cctaaagcaa cagaggctaa ggcaagggct gcagtaagag 1140

agactcataa aagagttcct gaggaaaggc ttcaggacag tgtagatctt aaaagagcta 1200

ggaagggaaa gcctaaaaga gaagacccta aaggcattcc tgactattgg ctgattgttt 1260

taaagaatgt tgacaagctc gggcctatga ttcagaagta tgatgagccc attctgaagt 1320

tcttgtcgga tgttagcctg aagttctcaa aacctggcca gcctgtaagt tacacctttg 1380

aatttcattt tctacccaac ccatacttca gaaatgaggt gctggtgaag acatatataa 1440

taaaggcaaa accagatcac aatgatccct tcttttcttg gggatgggaa attgaagatt 1500

gcaaaggctg caagatagac tggagaagag gaaaagatgt tactgtgaca actacccaga 1560

gtcgcacaac tgctactgga gaaattgaaa tccagccaag agtggttcct aatgcatcat 1620

tcttcaactt ctttagtcct cctgagattc ctatgattgg gaagctggaa ccacgagaag 1680

atgctatcct ggatgaggac tttgaaattg ggcagatttt acatgataat gtcatcctga 1740

aatcaatcta ttactatact ggagaagtca atggtaccta ctatcaattt ggcaaacatt 1800

atggaaacaa gaaatacaga aaataagtca atctgaaaga tttttcaaga atcttaaaat 1860

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ctcaagaagt gaagcagatt catacagcct tgaaaaaagt aaaaccctga cctgtaacct   1920

gaacactatt attccttata gtcaagtttt tgtggtttct tggtagtcta tattttaaaa   1980

atagtcctaa aaagtgtcta agtgccagtt tattctatct aggctgttgt agtataatat   2040

tcttcaaaat atgtaagctg ttgtcaatta tctaaagcat gttagtttgg tgctacacag   2100

tgttgatttt tgtgatgtcc tttggtcatg tttctgttag actgtagctg tgaaactgtc   2160

agaattgtta actgaaacaa atatttgctt gaaaaaaaaa gttcatgaag taccaatgca   2220

agtgttttat ttttttcttt tttccagccc ataagactaa gggtttaaat ctgcttgcac   2280

tagctgtgcc ttcattagtt tgctatagaa atccagtact tatagtaaat aaaacagtgt   2340

attttgaagt ttgactgctt gaaaaagatt agcatacatc taatgtgaaa agaccacatt   2400

tgattcaact gagaccttgt gtatgtgaca tatagtggcc tataaattta atcataatga   2460

tgttattgtt taccactgag gtgttaatat aacatagtat ttttgaaaaa gtttcttcat   2520

cttatattgt gtaattgtaa actaaagata ccgtgttttc tttgtattgt gttctacctt   2580

ccctttcact gaaaatgatc acttcatttg atactgtttt tcatgttctt gtattgcaac   2640

ctaaaataaa taaatattaa agtgtgttat actataaaaa aaaaaaa                 2687
```

<210> SEQ ID NO 14
<211> LENGTH: 506
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

```
Met Ala Glu Ala Asp Phe Lys Met Val Ser Glu Pro Val Ala His Gly
1               5                   10                  15

Val Ala Glu Glu Glu Met Ala Ser Ser Thr Ser Asp Ser Gly Glu Glu
            20                  25                  30

Ser Asp Ser Ser Ser Ser Ser Ser Ser Thr Ser Asp Ser Ser Ser Ser
        35                  40                  45

Ser Ser Thr Ser Gly Ser Ser Ser Gly Ser Gly Ser Ser Ser Ser Ser
    50                  55                  60

Ser Gly Ser Thr Ser Ser Arg Ser Arg Leu Tyr Arg Lys Lys Arg Val
65                  70                  75                  80

Pro Glu Pro Ser Arg Arg Ala Arg Arg Ala Pro Leu Gly Thr Asn Phe
                85                  90                  95

Val Asp Arg Leu Pro Gln Ala Val Arg Asn Arg Val Gln Ala Leu Arg
            100                 105                 110

Asn Ile Gln Asp Glu Cys Asp Lys Val Asp Thr Leu Phe Leu Lys Ala
        115                 120                 125

Ile His Asp Leu Glu Arg Lys Tyr Ala Glu Leu Asn Lys Pro Leu Tyr
    130                 135                 140

Asp Arg Arg Phe Gln Ile Ile Asn Ala Glu Tyr Glu Pro Thr Glu Glu
145                 150                 155                 160

Glu Cys Glu Trp Asn Ser Glu Asp Glu Glu Phe Ser Ser Asp Glu Glu
                165                 170                 175

Val Gln Asp Asn Thr Pro Ser Glu Met Pro Pro Leu Glu Gly Glu Glu
            180                 185                 190

Glu Glu Asn Pro Lys Glu Asn Pro Glu Val Lys Ala Glu Glu Lys Glu
        195                 200                 205

Val Pro Lys Glu Ile Pro Glu Val Lys Asp Glu Glu Lys Glu Val Pro
    210                 215                 220

Lys Glu Ile Pro Glu Val Lys Ala Glu Glu Lys Ala Asp Ser Lys Asp
225                 230                 235                 240
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```
Cys Met Glu Ala Thr Pro Glu Val Lys Glu Asp Pro Lys Glu Val Pro
                245                 250                 255

Gln Val Lys Ala Asp Asp Lys Glu Gln Pro Lys Ala Thr Glu Ala Lys
            260                 265                 270

Ala Arg Ala Ala Val Arg Glu Thr His Lys Arg Val Pro Glu Glu Arg
        275                 280                 285

Leu Gln Asp Ser Val Asp Leu Lys Arg Ala Arg Lys Gly Lys Pro Lys
    290                 295                 300

Arg Glu Asp Pro Lys Gly Ile Pro Asp Tyr Trp Leu Ile Val Leu Lys
305                 310                 315                 320

Asn Val Asp Lys Leu Gly Pro Met Ile Gln Lys Tyr Asp Glu Pro Ile
                325                 330                 335

Leu Lys Phe Leu Ser Asp Val Ser Leu Lys Phe Ser Lys Pro Gly Gln
            340                 345                 350

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

Arg Asn Glu Val Leu Val Lys Thr Tyr Ile Ile Lys Ala Lys Pro Asp
    370                 375                 380

His Asn Asp Pro Phe Phe Ser Trp Gly Trp Glu Ile Glu Asp Cys Lys
385                 390                 395                 400

Gly Cys Lys Ile Asp Trp Arg Arg Gly Lys Asp Val Thr Val Thr Thr
                405                 410                 415

Thr Gln Ser Arg Thr Thr Ala Thr Gly Glu Ile Glu Ile Gln Pro Arg
            420                 425                 430

Val Val Pro Asn Ala Ser Phe Phe Asn Phe Phe Ser Pro Pro Glu Ile
        435                 440                 445

Pro Met Ile Gly Lys Leu Glu Pro Arg Glu Asp Ala Ile Leu Asp Glu
    450                 455                 460

Asp Phe Glu Ile Gly Gln Ile Leu His Asp Asn Val Ile Leu Lys Ser
465                 470                 475                 480

Ile Tyr Tyr Tyr Thr Gly Glu Val Asn Gly Thr Tyr Tyr Gln Phe Gly
                485                 490                 495

Lys His Tyr Gly Asn Lys Lys Tyr Arg Lys
            500                 505


<210> SEQ ID NO 15
<211> LENGTH: 2423
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

acccgcgctc gtacgtgcgc ctccgccggc agctcctgac tcatcggggg ctccgggtca     60

catgcgcccg cgcggcccta taggcgcctc ctccgcccgc cgcccgggag ccgcagccgc    120

cgccgccact gccactcccg ctctctcagc gccgccgtcg ccaccgccac cgccaccgcc    180

actaccaccg tctgagtctg cagtcccgag atcccagcca tcatgtccat agagaagatc    240

tgggcccggg agatcctgga ctcccgcggg aaccccacag tggaggtgga tctctatact    300

gccaaaggtc ttttccgggc tgcagtgccc agtggagcct ctacgggcat ctatgaggcc    360

ctggagctga gggatggaga caaacagcgt tacttaggca aaggtgtcct gaaggcagtg    420

gaccacatca actccaccat cgcgccagcc ctcatcagct caggtctctc tgtggtggag    480

caagagaaac tggacaacct gatgctggag ttggatggga ctgagaacaa atccaagttt    540

ggggccaatg ccatcctggg tgtgtctctg gccgtgtgta aggcaggggc agctgagcgg    600
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gaactgcccc tgtatcgcca cattgctcag ctggccggga actcagacct catcctgcct 660

gtgccggcct tcaacgtgat caatggtggc tctcatgctg gcaacaagct ggccatgcag 720

gagttcatga tcctcccagt gggagctgag agctttcggg atgccatgcg actaggtgca 780

gaggtctacc atacactcaa gggagtcatc aaggacaaat acggcaagga tgccaccaat 840

gtgggggatg aaggtggctt tgcccccaat atcctggaga acagtgaagc cttggagctg 900

gtgaaggaag ccatcgacaa ggctggctac acggaaaaga tcgttattgg catggatgtt 960

gctgcctcag agttttatcg tgatggcaaa tatgacttgg acttcaagtc tcccactgat 1020

ccttcccgat acatcactgg ggaccagctg ggggcactct accaggactt tgtcagggac 1080

tatcctgtgg tctccattga ggacccattt gaccaggatg attgggctgc ctggtccaag 1140

ttcacagcca atgtagggat ccagattgtg ggtgatgacc tgacagtgac caacccaaaa 1200

cgtattgagc gggcagtgga agaaaaggcc tgcaactgtc tgctgctcaa ggtcaaccag 1260

atcggctcgg tcactgaagc catccaagcg tgcaagctgg cccaggagaa tggctggggg 1320

gtcatggtga gtcatcgctc aggagagact gaggacacat tcattgctga cctggtggtg 1380

gggctgtgca caggccagat caagactggt gccccgtgcc gttctgaacg tctggctaaa 1440

tacaaccagc tcatgagaat tgaggaagag ctgggggatg aagctcgctt tgccggacat 1500

aacttccgta atcccagtgt gctgtgattc ctctgcttgc ctggagacgt ggaacctctg 1560

tctcatcctc ctggaacctt gctgtcctga tctgtgatag ttcacccccc gagatccccc 1620

gagccccagg gtgcccagaa cttccctgat tgacctgctc cgctgctcct tggcttacct 1680

gacctcttgc tgtctctgct cgccctcctt tctgtgccct actcattggg gttccgcact 1740

ttccacttct tcctttctct ttctctcttc cctcagaaac tagaaatgtg aatgaggatt 1800

attataaaag ggggtccgtg gaagaatgat cagcatctgt gatgggagcg tcagggttgg 1860

tgtgctgagg tgttagagag ggaccatgtg tcacttgtgc tttgctcttg tcccacgtgt 1920

cttccacttt gcatatgagc cgtgaactgt gcatagtgct gggatggagg ggagtgttgg 1980

gcatgtgatc acgcctggct aataaggctt tagtgtattt atttatttat ttattttatt 2040

tgtttttcat tcatcccatt aatcatttcc ccataactca atggcctaaa actggcctga 2100

cttgggggaa cgatgtgtct gtatttcatg tggctgtaga tcccaagatg actggggtgg 2160

gaggtcttgc tagaatggga agggtcatag aaagggcctt gacatcagtt cctttgtgtg 2220

tactcactga agcctgcgtt ggtccagagc ggaggctgtg tgcctggggg agttttcctc 2280

tatacatctc tccccaaccc taggttccct gttcttcctc cagctgcacc agagcaacct 2340

ctcactcccc atgccacgtt ccacagttgc caccacctct gtggcattga aatgagcacc 2400

tccattaaag tctgaatcag tgc 2423

<210> SEQ ID NO 16
<211> LENGTH: 434
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

Met Ser Ile Glu Lys Ile Trp Ala Arg Glu Ile Leu Asp Ser Arg Gly
1 5 10 15

Asn Pro Thr Val Glu Val Asp Leu Tyr Thr Ala Lys Gly Leu Phe Arg
20 25 30

Ala Ala Val Pro Ser Gly Ala Ser Thr Gly Ile Tyr Glu Ala Leu Glu
35 40 45

Leu Arg Asp Gly Asp Lys Gln Arg Tyr Leu Gly Lys Gly Val Leu Lys

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    50                  55                  60

Ala Val Asp His Ile Asn Ser Thr Ile Ala Pro Ala Leu Ile Ser Ser
65                  70                  75                  80

Gly Leu Ser Val Val Glu Gln Glu Lys Leu Asp Asn Leu Met Leu Glu
                85                  90                  95

Leu Asp Gly Thr Glu Asn Lys Ser Lys Phe Gly Ala Asn Ala Ile Leu
            100                 105                 110

Gly Val Ser Leu Ala Val Cys Lys Ala Gly Ala Ala Glu Arg Glu Leu
        115                 120                 125

Pro Leu Tyr Arg His Ile Ala Gln Leu Ala Gly Asn Ser Asp Leu Ile
    130                 135                 140

Leu Pro Val Pro Ala Phe Asn Val Ile Asn Gly Gly Ser His Ala Gly
145                 150                 155                 160

Asn Lys Leu Ala Met Gln Glu Phe Met Ile Leu Pro Val Gly Ala Glu
                165                 170                 175

Ser Phe Arg Asp Ala Met Arg Leu Gly Ala Glu Val Tyr His Thr Leu
            180                 185                 190

Lys Gly Val Ile Lys Asp Lys Tyr Gly Lys Asp Ala Thr Asn Val Gly
        195                 200                 205

Asp Glu Gly Gly Phe Ala Pro Asn Ile Leu Glu Asn Ser Glu Ala Leu
    210                 215                 220

Glu Leu Val Lys Glu Ala Ile Asp Lys Ala Gly Tyr Thr Glu Lys Ile
225                 230                 235                 240

Val Ile Gly Met Asp Val Ala Ala Ser Glu Phe Tyr Arg Asp Gly Lys
                245                 250                 255

Tyr Asp Leu Asp Phe Lys Ser Pro Thr Asp Pro Ser Arg Tyr Ile Thr
            260                 265                 270

Gly Asp Gln Leu Gly Ala Leu Tyr Gln Asp Phe Val Arg Asp Tyr Pro
        275                 280                 285

Val Val Ser Ile Glu Asp Pro Phe Asp Gln Asp Asp Trp Ala Ala Trp
    290                 295                 300

Ser Lys Phe Thr Ala Asn Val Gly Ile Gln Ile Val Gly Asp Asp Leu
305                 310                 315                 320

Thr Val Thr Asn Pro Lys Arg Ile Glu Arg Ala Val Glu Glu Lys Ala
                325                 330                 335

Cys Asn Cys Leu Leu Leu Lys Val Asn Gln Ile Gly Ser Val Thr Glu
            340                 345                 350

Ala Ile Gln Ala Cys Lys Leu Ala Gln Glu Asn Gly Trp Gly Val Met
        355                 360                 365

Val Ser His Arg Ser Gly Glu Thr Glu Asp Thr Phe Ile Ala Asp Leu
    370                 375                 380

Val Val Gly Leu Cys Thr Gly Gln Ile Lys Thr Gly Ala Pro Cys Arg
385                 390                 395                 400

Ser Glu Arg Leu Ala Lys Tyr Asn Gln Leu Met Arg Ile Glu Glu Glu
                405                 410                 415

Leu Gly Asp Glu Ala Arg Phe Ala Gly His Asn Phe Arg Asn Pro Ser
            420                 425                 430

Val Leu


<210> SEQ ID NO 17
<211> LENGTH: 2142
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17
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ctccgggaac atgccagcag aagcattcac caactgacat gtgccctgaa agaaggcgat 120

gtcactattg gagaagatgc accaaatctt tcttttagca ccagtgtggg aaatgaggac 180

gccaggacag cctggcccga attacaacag agccatgctg ttaatcagct caaagatttg 240

ttgcgccaac aagcagataa ggaaagtgaa gtatctccgt caagaagaag aaaaatgtcc 300

cccttgaggt cattagaaca tgaggaaacc aatatgccta ctatgcacga ccttgttcat 360

actattaatg accagtctca atatattcat catttagagg cagaagttaa gttctgcaag 420

gaggaactct ctggaatgaa aaataaaata caagtagttg tgcttgaaaa cgaagggctc 480

cagcaacagc taaaatctca aagacaagag gagacactga gggaacaaac acttctggat 540

gcatccggaa acatgcacaa ttcttggatt acaacaggtg aagattctgg ggtgggcgaa 600

acctccaaaa gaccattttc ccatgacaat gcagattttg gcaaagctgc atctgctggt 660

gagcagctag aactggagaa gctaaaactt acttatgagg aaaagtgtga aattgaggaa 720

tcccaattga agtttttgag gaacgactta gctgaatatc agagaacttg tgaagatctt 780

aaagagcaac taaagcataa agaatttctt ctggctgcta atacttgtaa ccgtgttggt 840

ggtctttgtt tgaaatgtgc tcagcatgaa gctgttcttt cccaaaccca tactaatgtt 900

catatgcaga ccatcgaaag actggttaaa gaaagagatg acttgatgtc tgcactagtt 960

tccgtaagga gcagcttggc agatacgcag caaagagaag caagtgctta tgaacaggtg 1020

aaacaagttt tgcaaatatc tgaggaagcc aattttgaaa aaaccaaggc tttaatccag 1080

tgtgaccagt tgaggaagga gctggagagg caggcggagc gacttgaaaa agaacttgca 1140

tctcagcaag agaaaagggc cattgagaaa gacatgatga aaaaggaaat aacgaaagaa 1200

agggagtaca tgggatcaaa gatgttgatc ttgtctcaga atattgccca actggaggcc 1260

caggtggaaa aggttacaaa ggaaaagatt tcagctatta atcaactgga ggaaattcaa 1320

agccagctgg cttctcggga aatggatgtc acaaaggtgt gtggagaaat gcgctatcag 1380

ctgaataaaa ccaacatgga gaaggatgag gcagaaaagg agcacagaga gttcagagca 1440

aaaactaaca gggatcttga aattaaagat caggaaatag agaaattgag aatagaactg 1500

gatgaaagca aacaacactt ggaacaggag cagcagaagg cagccctggc cagagaggag 1560

tgcctgagac taacagaact gctgggcgaa tctgagcacc aactgcacct caccagacag 1620

gaaaaagata gcattcagca gagctttagc aaggaagcaa aggcccaagc ccttcaggcc 1680

cagcaaagag agcaggagct gacacagaag atacagcaaa tggaagccca gcatgacaaa 1740

actgaaaatg aacagtattt gttgctgacc tcccagaata catttttgac aaagttaaag 1800

gaagaatgct gtacattagc caagaaactg gaacaaatct ctcaaaaaac cagatctgaa 1860

atagctcaac tcagtcaaga aaaaaggtat acatatgata aattgggaaa gttacagaga 1920

agaaatgaag aattggagga acagtgtgtc cagcatggga gagtacatga gacgatgaag 1980

caaaggctaa ggcagctgga taagcacagc caggccacag cccagcagct ggtgcagctc 2040

ctcagcaagc agaaccagct tctcctggag aggcagagcc tgtcggaaga ggtggaccgg 2100

ctgcggaccc agttacccag catgccacaa tctgattgct ga 2142

<210> SEQ ID NO 18
<211> LENGTH: 713
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

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```
Met Ala Lys Ser Pro Glu Asn Ser Thr Leu Glu Glu Ile Leu Gly Gln
1               5                  10                  15

Tyr Gln Arg Ser Leu Arg Glu His Ala Ser Arg Ser Ile His Gln Leu
            20                  25                  30

Thr Cys Ala Leu Lys Glu Gly Asp Val Thr Ile Gly Glu Asp Ala Pro
        35                  40                  45

Asn Leu Ser Phe Ser Thr Ser Val Gly Asn Glu Asp Ala Arg Thr Ala
    50                  55                  60

Trp Pro Glu Leu Gln Gln Ser His Ala Val Asn Gln Leu Lys Asp Leu
65                  70                  75                  80

Leu Arg Gln Gln Ala Asp Lys Glu Ser Glu Val Ser Pro Ser Arg Arg
                85                  90                  95

Arg Lys Met Ser Pro Leu Arg Ser Leu Glu His Glu Glu Thr Asn Met
            100                 105                 110

Pro Thr Met His Asp Leu Val His Thr Ile Asn Asp Gln Ser Gln Tyr
        115                 120                 125

Ile His His Leu Glu Ala Glu Val Lys Phe Cys Lys Glu Glu Leu Ser
    130                 135                 140

Gly Met Lys Asn Lys Ile Gln Val Val Val Leu Glu Asn Glu Gly Leu
145                 150                 155                 160

Gln Gln Gln Leu Lys Ser Gln Arg Gln Glu Glu Thr Leu Arg Glu Gln
                165                 170                 175

Thr Leu Leu Asp Ala Ser Gly Asn Met His Asn Ser Trp Ile Thr Thr
            180                 185                 190

Gly Glu Asp Ser Gly Val Gly Glu Thr Ser Lys Arg Pro Phe Ser His
        195                 200                 205

Asp Asn Ala Asp Phe Gly Lys Ala Ala Ser Ala Gly Glu Gln Leu Glu
    210                 215                 220

Leu Glu Lys Leu Lys Leu Thr Tyr Glu Glu Lys Cys Glu Ile Glu Glu
225                 230                 235                 240

Ser Gln Leu Lys Phe Leu Arg Asn Asp Leu Ala Glu Tyr Gln Arg Thr
                245                 250                 255

Cys Glu Asp Leu Lys Glu Gln Leu Lys His Lys Glu Phe Leu Leu Ala
            260                 265                 270

Ala Asn Thr Cys Asn Arg Val Gly Gly Leu Cys Leu Lys Cys Ala Gln
        275                 280                 285

His Glu Ala Val Leu Ser Gln Thr His Thr Asn Val His Met Gln Thr
    290                 295                 300

Ile Glu Arg Leu Val Lys Glu Arg Asp Asp Leu Met Ser Ala Leu Val
305                 310                 315                 320

Ser Val Arg Ser Ser Leu Ala Asp Thr Gln Gln Arg Glu Ala Ser Ala
                325                 330                 335

Tyr Glu Gln Val Lys Gln Val Leu Gln Ile Ser Glu Glu Ala Asn Phe
            340                 345                 350

Glu Lys Thr Lys Ala Leu Ile Gln Cys Asp Gln Leu Arg Lys Glu Leu
        355                 360                 365

Glu Arg Gln Ala Glu Arg Leu Glu Lys Glu Leu Ala Ser Gln Gln Glu
    370                 375                 380

Lys Arg Ala Ile Glu Lys Asp Met Met Lys Lys Glu Ile Thr Lys Glu
385                 390                 395                 400

Arg Glu Tyr Met Gly Ser Lys Met Leu Ile Leu Ser Gln Asn Ile Ala
                405                 410                 415

Gln Leu Glu Ala Gln Val Glu Lys Val Thr Lys Glu Lys Ile Ser Ala
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            420                 425                 430

Ile Asn Gln Leu Glu Glu Ile Gln Ser Gln Leu Ala Ser Arg Glu Met
        435                 440                 445

Asp Val Thr Lys Val Cys Gly Glu Met Arg Tyr Gln Leu Asn Lys Thr
    450                 455                 460

Asn Met Glu Lys Asp Glu Ala Glu Lys Glu His Arg Glu Phe Arg Ala
465                 470                 475                 480

Lys Thr Asn Arg Asp Leu Glu Ile Lys Asp Gln Glu Ile Glu Lys Leu
                485                 490                 495

Arg Ile Glu Leu Asp Glu Ser Lys Gln His Leu Glu Gln Glu Gln Gln
            500                 505                 510

Lys Ala Ala Leu Ala Arg Glu Glu Cys Leu Arg Leu Thr Glu Leu Leu
        515                 520                 525

Gly Glu Ser Glu His Gln Leu His Leu Thr Arg Gln Glu Lys Asp Ser
    530                 535                 540

Ile Gln Gln Ser Phe Ser Lys Glu Ala Lys Ala Gln Ala Leu Gln Ala
545                 550                 555                 560

Gln Gln Arg Glu Gln Glu Leu Thr Gln Lys Ile Gln Gln Met Glu Ala
                565                 570                 575

Gln His Asp Lys Thr Glu Asn Glu Gln Tyr Leu Leu Leu Thr Ser Gln
            580                 585                 590

Asn Thr Phe Leu Thr Lys Leu Lys Glu Glu Cys Cys Thr Leu Ala Lys
        595                 600                 605

Lys Leu Glu Gln Ile Ser Gln Lys Thr Arg Ser Glu Ile Ala Gln Leu
    610                 615                 620

Ser Gln Glu Lys Arg Tyr Thr Tyr Asp Lys Leu Gly Lys Leu Gln Arg
625                 630                 635                 640

Arg Asn Glu Glu Leu Glu Glu Gln Cys Val Gln His Gly Arg Val His
                645                 650                 655

Glu Thr Met Lys Gln Arg Leu Arg Gln Leu Asp Lys His Ser Gln Ala
            660                 665                 670

Thr Ala Gln Gln Leu Val Gln Leu Leu Ser Lys Gln Asn Gln Leu Leu
        675                 680                 685

Leu Glu Arg Gln Ser Leu Ser Glu Glu Val Asp Arg Leu Arg Thr Gln
    690                 695                 700

Leu Pro Ser Met Pro Gln Ser Asp Cys
705                 710


<210> SEQ ID NO 19
<211> LENGTH: 2780
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

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ggctcctgcg atcgaagggg acttgagact caccggccgc acgccatgag ggccctgtgg    120

gtgctgggcc tctgctgcgt cctgctgacc ttcgggtcgg tcagagctga cgatgaagtt    180

gatgtggatg gtacagtaga agaggatctg ggtaaaagta gagaaggatc aaggacggat    240

gatgaagtag tacagagaga ggaagaagct attcagttgg atggattaaa tgcatcacaa    300

ataagagaac ttagagagaa gtcggaaaag tttgccttcc aagccgaagt taacagaatg    360

atgaaactta tcatcaattc attgtataaa aataaagaga ttttcctgag agaactgatt    420

tcaaatgctt ctgatgcttt agataagata aggctaatat cactgactga tgaaaatgct    480
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ctttctggaa atgaggaact aacagtcaaa attaagtgtg ataaggagaa gaacctgctg 540

catgtcacag acaccggtgt aggaatgacc agagaagagt tggttaaaaa ccttggtacc 600

atagccaaat ctgggacaag cgagttttta aacaaaatga ctgaagcaca ggaagatggc 660

cagtcaactt ctgaattgat tggccagttt ggtgtcggtt tctattccgc cttccttgta 720

gcagataagg ttattgtcac ttcaaaacac aacaacgata cccagcacat ctgggagtct 780

gactccaatg aattttctgt aattgctgac ccaagaggaa acactctagg acggggaacg 840

acaattaccc ttgtcttaaa agaagaagca tctgattacc ttgaattgga tacaattaaa 900

aatctcgtca aaaaatattc acagttcata aactttccta tttatgtatg gagcagcaag 960

actgaaactg ttgaggagcc catggaggaa gaagaagcag ccaaagaaga gaaagaagaa 1020

tctgatgatg aagctgcagt agaggaagaa gaagaagaaa agaaaccaaa gactaaaaaa 1080

gttgaaaaaa ctgtctggga ctgggaactt atgaatgata tcaaaccaat atggcagaga 1140

ccatcaaaag aagtagaaga agatgaatac aaagctttct acaaatcatt ttcaaaggaa 1200

agtgatgacc ccatggctta tattcacttt actgctgaag gggaagttac cttcaaatca 1260

attttatttg tacccacatc tgctccacgt ggtctgtttg acgaatatgg atctaaaaag 1320

agcgattaca ttaagctcta tgtgcgccgt gtattcatca cagacgactt ccatgatatg 1380

atgcctaaat acctcaattt tgtcaagggt gtggtggact cagatgatct ccccttgaat 1440

gtttcccgcg agactcttca gcaacataaa ctgcttaagg tgattaggaa gaagcttgtt 1500

cgtaaaacgc tggacatgat caagaagatt gctgatgata aatacaatga tacttttttgg 1560

aaagaatttg gtaccaacat caagcttggt gtgattgaag accactcgaa tcgaacacgt 1620

cttgctaaac ttcttaggtt ccagtcttct catcatccaa ctgacattac tagcctagac 1680

cagtatgtgg aaagaatgaa ggaaaaacaa gacaaaatct acttcatggc tgggtccagc 1740

agaaaagagg ctgaatcttc tccatttgtt gagcgacttc tgaaaaaggg ctatgaagtt 1800

atttacctca cagaacctgt ggatgaatac tgtattcagg cccttcccga atttgatggg 1860

aagaggttcc agaatgttgc caaggaagga gtgaagttcg atgaaagtga gaaaactaag 1920

gagagtcgtg aagcagttga gaaagaattt gagcctctgc tgaattggat gaaagataaa 1980

gcccttaagg acaagattga aaaggctgtg gtgtctcagc gcctgacaga atctccgtgt 2040

gctttggtgg ccagccagta cggatggtct ggcaacatgg agagaatcat gaaagcacaa 2100

gcgtaccaaa cgggcaagga catctctaca aattactatg cgagtcagaa gaaaacattt 2160

gaaattaatc ccagacaccc gctgatcaga gacatgcttc gacgaattaa ggaagatgaa 2220

gatgataaaa cagttttgga tcttgctgtg gttttgtttg aaacagcaac gcttcggtca 2280

gggtatcttt taccagacac taaagcatat ggagatagaa tagaaagaat gcttcgcctc 2340

agtttgaaca ttgaccctga tgcaaaggtg gaagaagagc ccgaagaaga acctgaagag 2400

acagcagaag acacaacaga agacacagag caagacgaag atgaagaaat ggatgtggga 2460

acagatgaag aagaagaaac agcaaaggaa tctacagctg aaaaagatga attgtaaatt 2520

atactctcac catttggatc ctgtgtggag agggaatgtg aaatttacat catttctttt 2580

tgggagagac ttgttttgga tgccccctaa tccccttctc ccctgcactg taaaatgtgg 2640

gattatgggt cacaggaaaa agtgggtttt ttagttgaat ttttttttaac attcctcatg 2700

aatgtaaatt tgtactattt aactgactat tcttgatgta aaatcttgtc atgtgtataa 2760

aaataaaaaa gatcccaaat 2780

<210> SEQ ID NO 20

-continued

<211> LENGTH: 803
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

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

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
225 230 235 240

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 Glu Ala Ala Lys Glu Glu Lys Glu
290 295 300

Glu Ser Asp Asp Glu Ala Ala Val Glu Glu Glu Glu Glu Glu Lys Lys
305 310 315 320

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
385 390 395 400

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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                 480

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                 560

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
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<210> SEQ ID NO 21

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<211> LENGTH: 1060
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

cgcgggccga ctggtgttta tccgtcactc gccgaggttc cttgggtcat ggtgccagcc 60

tgactgagaa gaggacgctc ccgggagacg aatgaggaac cacctcctcc tactgttcaa 120

gtacaggggc ctggtccgca aagggaagaa aagcaaaaga cgaaaatggc taaattcgtg 180

atccgcccag ccactgccgc cgactgcagt gacatactgc ggctgatcaa ggagctggct 240

aaatatgaat acatggaaga acaagtaatc ttaactgaaa aagatctgct agaagatggt 300

tttggagagc acccctttta ccactgcctg gttgcagaag tgccgaaaga gcactggact 360

ccggaaggac acagcattgt tggttttgcc atgtactatt ttacctatga cccgtggatt 420

ggcaagttat tgtatcttga ggacttcttc gtgatgagtg attatagagg ctttggcata 480

ggatcagaaa ttctgaagaa tctaagccag gttgcaatga ggtgtcgctg cagcagcatg 540

cacttcttgg tagcagaatg gaatgaacca tccatcaact tctataaaag aagaggtgct 600

tctgatctgt ccagtgaaga gggttggaga ctgttcaaga tcgacaagga gtacttgcta 660

aaaatggcaa cagaggagtg aggagtgctg ctgtagatga caacctccat tctattttag 720

aataaattcc caacttctct tgctttctat gctgtttgta gtgaaataat agaatgagca 780

cccattccaa agctttatta ccagtggcgt tgttgcatgt ttgaaatgag gtctgtttaa 840

agtggcaatc tcagatgcag tttggagagt cagatctttc tccttgaata tctttcgata 900

aacaacaagg tggtgtgatc ttaatatatt tgaaaaaaac ttcattctcg tgagtcattt 960

aaatgtgtac aatgtacaca ctggtactta gagtttctgt ttgattcttt tttaataaac 1020

tactctttga tttaaaaaaa aaaaaaaaaa aaaaaaaaaa 1060

<210> SEQ ID NO 22
<211> LENGTH: 171
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

Met Ala Lys Phe Val Ile Arg Pro Ala Thr Ala Ala Asp Cys Ser Asp
1 5 10 15

Ile Leu Arg Leu Ile Lys Glu Leu Ala Lys Tyr Glu Tyr Met Glu Glu
20 25 30

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

His Pro Phe Tyr His Cys Leu Val Ala Glu Val Pro Lys Glu His Trp
50 55 60

Thr Pro Glu Gly His Ser Ile Val Gly Phe Ala Met Tyr Tyr Phe Thr
65 70 75 80

Tyr Asp Pro Trp Ile Gly Lys Leu Leu Tyr Leu Glu Asp Phe Phe Val
85 90 95

Met Ser Asp Tyr Arg Gly Phe Gly Ile Gly Ser Glu Ile Leu Lys Asn
100 105 110

Leu Ser Gln Val Ala Met Arg Cys Arg Cys Ser Ser Met His Phe Leu
115 120 125

Val Ala Glu Trp Asn Glu Pro Ser Ile Asn Phe Tyr Lys Arg Arg Gly
130 135 140

Ala Ser Asp Leu Ser Ser Glu Glu Gly Trp Arg Leu Phe Lys Ile Asp
145 150 155 160

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Lys Glu Tyr Leu Leu Lys Met Ala Thr Glu Glu
165 170

<210> SEQ ID NO 23
<211> LENGTH: 1006
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

cagccgcacg tgggctcggc gcgatggagg aggagacgca tactgacgcc aaaatccgtg 60

ctgaaaatgg aacagggtcc agccctcggg gtcctggctg cagcctccgg cactttgcct 120

gcgaacagaa cctgctgtcg cggccagatg gctctgcttc cttcctgcaa ggtgacacct 180

ctgtcctggc gggtgtgtac gggccggccg aggtgaaggt cagcaaagag attttcaaca 240

aggccacact cgaagtgatc ctgaggccga agattgggct gcctggtgtt gcagagaaga 300

gccgggagcg gctgatcagg aacacgtgcg aggcggtggt gctgggcacg ttgcaccccc 360

gcacctccat caccgtggtg ctgcaggttg tcagcgatgc cggctctctc ctggcctgtt 420

gtctgaatgc cgcctgcatg gcattggtgg atgcaggtgt gcccatgcgg gctctcttct 480

gtggggtcgc ctgcgccctg gactctgatg ggaccctcgt gctggatcct acatccaagc 540

aagaaaagga ggcccgggca gtcctgacct ttgccctgga cagcgtggaa cggaagctgc 600

tgatgtccag caccaagggg ctctactcag acactgagct ccagcagtgc ctggctgcgg 660

cccaggccgc ttcgcaacac gtcttccgtt tctaccggga atcgctgcag aggcgttact 720

ccaagagctg aggcaagctg gggcaagggg ccgctcccat tgcctccacc cactcacccc 780

ctacagcctg aagcaaacca gcagcccagc cttgcctctc tgacccatgg gctccttgag 840

cctgcagctc tgtaaccaca gggctcctgt ggggaggcct tggcctgtga cagcccccag 900

gcctgggggc acagatcccc ccagcaagga taacattcaa aggagctcac atttatggaa 960

tggatgaatc aataaattaa ttcactttaa caaaaaaaaa aaaaaa 1006

<210> SEQ ID NO 24
<211> LENGTH: 235
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

Met Glu Glu Glu Thr His Thr Asp Ala Lys Ile Arg Ala Glu Asn Gly
1 5 10 15

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

Cys Glu Gln Asn Leu Leu Ser Arg Pro Asp Gly Ser Ala Ser Phe Leu
35 40 45

Gln Gly Asp Thr Ser Val Leu Ala Gly Val Tyr Gly Pro Ala Glu Val
50 55 60

Lys Val Ser Lys Glu Ile Phe Asn Lys Ala Thr Leu Glu Val Ile Leu
65 70 75 80

Arg Pro Lys Ile Gly Leu Pro Gly Val Ala Glu Lys Ser Arg Glu Arg
85 90 95

Leu Ile Arg Asn Thr Cys Glu Ala Val Val Leu Gly Thr Leu His Pro
100 105 110

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

Leu Leu Ala Cys Cys Leu Asn Ala Ala Cys Met Ala Leu Val Asp Ala
130 135 140

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Gly Val Pro Met Arg Ala Leu Phe Cys Gly Val Ala Cys Ala Leu Asp
145                 150                 155                 160

Ser Asp Gly Thr Leu Val Leu Asp Pro Thr Ser Lys Gln Glu Lys Glu
                165                 170                 175

Ala Arg Ala Val Leu Thr Phe Ala Leu Asp Ser Val Glu Arg Lys Leu
            180                 185                 190

Leu Met Ser Ser Thr Lys Gly Leu Tyr Ser Asp Thr Glu Leu Gln Gln
        195                 200                 205

Cys Leu Ala Ala Ala Gln Ala Ala Ser Gln His Val Phe Arg Phe Tyr
    210                 215                 220

Arg Glu Ser Leu Gln Arg Arg Tyr Ser Lys Ser
225                 230                 235


<210> SEQ ID NO 25
<211> LENGTH: 315
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

gctctctata aaaattattt gtgttctata tagtgagttt taccagtaaa tgtggcttaa     60

tattttaatt cttagaatgt gtcttctcta cgtgatgtga ctaaattctg ttttgtttgt    120

ggaatgacta gcacaggccg actccctctc tccctcactt aacaaaagac caatgagctg    180

ttaatcgagc tgttatctcc atggtattac ttgctaaatg cactgatttc ataagtatgt    240

ggaatccttt tccttttgaa tctgtatatc atatataaga ctgaatctac ttaataaaca    300

ctgaacaaca aaccg                                                     315


<210> SEQ ID NO 26
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

Ala Leu Tyr Lys Asn Tyr Leu Cys Ser Ile
1               5                   10


<210> SEQ ID NO 27
<211> LENGTH: 1970
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

caaacgcgcc gactacagag gctggacgta agcttagcgg tggcgcgcgt gcgcagcgcc     60

ggcccgagtt gccaaaacaa aggggatttg gtgatggagg ctttgttaga aggaatacaa    120

aatcgagggc atggtggggg atttttgaca tcttgtgaag cagaactaca ggagctcatg    180

aaacagattg acataatggt ggctcataaa aaatctgaat gggaaggacg tacacatgct    240

ctagaaactt gcttgaaaat ccgtgaacag gaacttaaga gtcttaggag tcagttggat    300

gtgacacata aggaggttgg aatgttgcat cagcaggtag aagaacatga aaaaatcaag    360

caagagatga ccatggaata taagcaggag ttgaagaaac tacatgaaga attatgcata    420

ctgaagagaa gctatgaaaa gcttcagaaa aagcaaatga gggaattcag aggaaatacc    480

aaaaatcaca gggaagatcg gtctgaaatt gagaggttaa ctgcaaaaat agaggaattc    540

cgtcagaaat cgctggactg ggagaagcaa cgcttgattt atcagcaaca ggtatcttca    600

ctggaggcac aaaggaaggc tctggctgaa caatcagaga taattcaggc tcagcttgtc    660

aatcggaaac agaaattaga gtctgtggaa ctttctagcc aatcagaaat tcaacactta    720
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agcagtaaac tggagcgggc taatgacact atctgtgcca atgagttgga aatagagcgc 780

ctcaccatga gggtcaatga cttggttgga accagtatga ctgtcctaca ggagcagcag 840

caaaaagaag aaaaattgag ggaatctgaa aaactattag aggctctgca ggaagaaaag 900

agagaattga aggcagctct tcagtctcaa gaaaatctca tacatgaggc cagaatacaa 960

aaggagaagt tacaagaaaa agtaaaggca actaacactc aacatgctgt agaagctata 1020

aggccacggg aagaatctct ggcagaaaag aagtacacct ctcaagggca gggggactta 1080

gacagtgtgc tctcccagtt gaattttacc catactagtg aggaccttct gcaggcagag 1140

gtgacttgtc ttgaaggcag tttggaatct gtgagtgcaa cgtgtaaaca gctgagccaa 1200

gaactaatgg aaaaatatga agaactgaag aggatggaag cacataacaa tgaatacaaa 1260

gcagagatta agaagttgaa agaacagatt ttacagggtg aacaaagtta cagttctgca 1320

ctagaaggaa tgaagatgga aatctcccat ctaactcagg agttacatca gcgagatatc 1380

actattgctt ccaccaaagg ttcttcctca gacatggaaa agcgactcag agcagagatg 1440

caaaaggcag aagacaaagc agtagagcat aaggagattt tggatcagct ggagtcactc 1500

aaattagaaa atcgtcatct ttctgaaatg gtgatgaaat tggaattggg tttacatgag 1560

tgttccttgc ctgtatctcc ccttggttca atagctacca gatttttgga agaggaggaa 1620

ctgaggtctc atcacattct agagcgcttg gatgcccata ttgaagaact aaaaagagag 1680

agtgaaaaga cagtgagaca attcacagcc ttaaagtagc ctcttaaaaa aatcacaatc 1740

ttggaaataa aaataaacac caaagagtta ctgtcatctg aagtagcagc tctttaaaaa 1800

catgaagaga taaaattata aaaatgatac atctaaagca gtggtgaaga aagctgaaaa 1860

actgatactt ttgataggca ttttctctgc actggtttgt ttaaaggact tcttccagca 1920

ataagttgaa agaataaacc actttgctag acaaaaaaaa aaaaaaaaaa 1970

<210> SEQ ID NO 28
<211> LENGTH: 541
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

Met Glu Ala Leu Leu Glu Gly Ile Gln Asn Arg Gly His Gly Gly Gly
1 5 10 15

Phe Leu Thr Ser Cys Glu Ala Glu Leu Gln Glu Leu Met Lys Gln Ile
20 25 30

Asp Ile Met Val Ala His Lys Lys Ser Glu Trp Glu Gly Arg Thr His
35 40 45

Ala Leu Glu Thr Cys Leu Lys Ile Arg Glu Gln Glu Leu Lys Ser Leu
50 55 60

Arg Ser Gln Leu Asp Val Thr His Lys Glu Val Gly Met Leu His Gln
65 70 75 80

Gln Val Glu Glu His Glu Lys Ile Lys Gln Glu Met Thr Met Glu Tyr
85 90 95

Lys Gln Glu Leu Lys Lys Leu His Glu Glu Leu Cys Ile Leu Lys Arg
100 105 110

Ser Tyr Glu Lys Leu Gln Lys Lys Gln Met Arg Glu Phe Arg Gly Asn
115 120 125

Thr Lys Asn His Arg Glu Asp Arg Ser Glu Ile Glu Arg Leu Thr Ala
130 135 140

Lys Ile Glu Glu Phe Arg Gln Lys Ser Leu Asp Trp Glu Lys Gln Arg
145 150 155 160

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Leu Ile Tyr Gln Gln Gln Val Ser Ser Leu Glu Ala Gln Arg Lys Ala
                165                 170                 175

Leu Ala Glu Gln Ser Glu Ile Ile Gln Ala Gln Leu Val Asn Arg Lys
            180                 185                 190

Gln Lys Leu Glu Ser Val Glu Leu Ser Ser Gln Ser Glu Ile Gln His
        195                 200                 205

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

Leu Glu Ile Glu Arg Leu Thr Met Arg Val Asn Asp Leu Val Gly Thr
225                 230                 235                 240

Ser Met Thr Val Leu Gln Glu Gln Gln Gln Lys Glu Glu Lys Leu Arg
                245                 250                 255

Glu Ser Glu Lys Leu Leu Glu Ala Leu Gln Glu Glu Lys Arg Glu Leu
            260                 265                 270

Lys Ala Ala Leu Gln Ser Gln Glu Asn Leu Ile His Glu Ala Arg Ile
        275                 280                 285

Gln Lys Glu Lys Leu Gln Glu Lys Val Lys Ala Thr Asn Thr Gln His
    290                 295                 300

Ala Val Glu Ala Ile Arg Pro Arg Glu Glu Ser Leu Ala Glu Lys Lys
305                 310                 315                 320

Tyr Thr Ser Gln Gly Gln Gly Asp Leu Asp Ser Val Leu Ser Gln Leu
                325                 330                 335

Asn Phe Thr His Thr Ser Glu Asp Leu Leu Gln Ala Glu Val Thr Cys
            340                 345                 350

Leu Glu Gly Ser Leu Glu Ser Val Ser Ala Thr Cys Lys Gln Leu Ser
        355                 360                 365

Gln Glu Leu Met Glu Lys Tyr Glu Glu Leu Lys Arg Met Glu Ala His
    370                 375                 380

Asn Asn Glu Tyr Lys Ala Glu Ile Lys Lys Leu Lys Glu Gln Ile Leu
385                 390                 395                 400

Gln Gly Glu Gln Ser Tyr Ser Ser Ala Leu Glu Gly Met Lys Met Glu
                405                 410                 415

Ile Ser His Leu Thr Gln Glu Leu His Gln Arg Asp Ile Thr Ile Ala
            420                 425                 430

Ser Thr Lys Gly Ser Ser Ser Asp Met Glu Lys Arg Leu Arg Ala Glu
        435                 440                 445

Met Gln Lys Ala Glu Asp Lys Ala Val Glu His Lys Glu Ile Leu Asp
    450                 455                 460

Gln Leu Glu Ser Leu Lys Leu Glu Asn Arg His Leu Ser Glu Met Val
465                 470                 475                 480

Met Lys Leu Glu Leu Gly Leu His Glu Cys Ser Leu Pro Val Ser Pro
                485                 490                 495

Leu Gly Ser Ile Ala Thr Arg Phe Leu Glu Glu Glu Glu Leu Arg Ser
            500                 505                 510

His His Ile Leu Glu Arg Leu Asp Ala His Ile Glu Glu Leu Lys Arg
        515                 520                 525

Glu Ser Glu Lys Thr Val Arg Gln Phe Thr Ala Leu Lys
    530                 535                 540


<210> SEQ ID NO 29
<211> LENGTH: 1733
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29
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ctccaggtct acccttcact gctctgtgtc ctcagcgtgt gtggcttcgt gacctgaaga     60

tactgggaaa tccatagcta agatgccagg acccccctgaa agcctagaca tggggccgtt    120

gacatttagg gatgtggcca tagaattctc tctggaggag tggcaatgcc tggacactgc    180

tcagcaggat ttgtatagga aagtgatgtt agagaactac agaaacctgg tcttcttggc    240

aggtattgct gtctctaagc cagatctggt cacctgtctg gagcaaggaa aagatccctg    300

gaatatgaag ggacacagta cggtagtcaa acccccagta gagacggggt ttcaccgttt    360

tggccaggat ggtctctatc tcctgacctc gtgatccgcc cgcctcagtc tcccaaagtg    420

ctggtattac aggcgtgagc caccatgccc agcctaataa aaatttttttt atttctattg    480

tatccaatag cttgttttaa gtgtgtagaa caataactta cacttttatg ttaattttat    540

attttgttaa tttactgact gtattattag tttagacaaa tttcaatgta ctgtggtttt    600

ttatgtgtaa gattatatat tcctcaaaca gcaacttttt acttatttgt cttcagtttc    660

aatggcttta aaaagaattc ttttttcatt attctgccac atgcttccag tgctatgtta    720

aaatagaaac attgacaaag ggcacaatag agtttactat tggtgtctgt gaatttgaaa    780

tggcaaacaa ctccttaagt ttttataagc tgatttcagg aggtaaagat cttcttttct    840

tgtgttcccc agggttttgg gatgccctct gggtttgtag tggagtgggg ttgtaacttg    900

gttgcaaggc tgctggttct acattagggt ccatatttag ttgtcatgtt acaagaggct    960

tgggtagttg tacttcccaa ttttttttttt ttttttttttt ttttttgag acaggagtct   1020

cgctctgtcg cctggctgga gtgcagtggt gtgatctcag ctcatcaaaa cctttgcctc   1080

cctagttcaa gcgattttcc tacctcagcc tcctgagtag ctgggattac aggtgcccac   1140

cagcacgccc agctaatttt ttgtgtgttt ttagtggaga cggggtttca ccatgttggc   1200

taagctgggt ctcgaactcc tgacctcagg tgatccaccc gccttggcct cctgggtgct   1260

gggattacag acgtgagcca ccacccccgg ccacttgttt cttttaaatg cttattaaaa   1320

gtttctcatc agaatatttt atttataatt atactgcata ttctctgaaa ttttactgcc   1380

aatttttcaa aatacctgct tttgatgagt acagttacag tcaaatactg tagttagaca   1440

aattcttttt taatggtata ttaatgttgc ataccaaatt gtatgagtta aacgtctctt   1500

cctgtgcagt ttcatattag tggtgttttc agtgtaggta tcttaatatc agcttatcgt   1560

ggtttttggt tatgtattat aattttagtc aatttgcaat tctgtctgta tactttatgt   1620

caatgtgagg ttgaattaaa agatagccat atgtctatca caaaaaaaaa aaaaaaaaaa   1680

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaacctc ggg          1733


<210> SEQ ID NO 30
<211> LENGTH: 103
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

Met Pro Gly Pro Pro Glu Ser Leu Asp Met Gly Pro Leu Thr Phe Arg
1               5                   10                  15

Asp Val Ala Ile Glu Phe Ser Leu Glu Glu Trp Gln Cys Leu Asp Thr
            20                  25                  30

Ala Gln Gln Asp Leu Tyr Arg Lys Val Met Leu Glu Asn Tyr Arg Asn
        35                  40                  45

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

Cys Leu Glu Gln Gly Lys Asp Pro Trp Asn Met Lys Gly His Ser Thr
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65 70 75 80

Val Val Lys Pro Pro Val Glu Thr Gly Phe His Arg Phe Gly Gln Asp
85 90 95

Gly Leu Tyr Leu Leu Thr Ser
100

<210> SEQ ID NO 31
<211> LENGTH: 285
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

cttctgtctc agcctcctga gtagctggga ctacaggcat gcccgtgccc agctaatttt 60

tttttattt ttagtggaga cggggtttca caatgttggc caggctggtc tcgaactcct 120

tacctcaagt gatctgcctg cctcagcctc ctaaagtgct agcattacca ctgtggctag 180

cgtgagccac tgtgctgggt ctgtagaata tatttggatt attatgatca caaaactagt 240

tttttgttgt tgagaaatgg gctttgaaaa gatccgagga ccaga 285

<210> SEQ ID NO 32
<211> LENGTH: 50
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

Phe Cys Leu Ser Leu Leu Ser Ser Trp Asp Tyr Arg His Ala Arg Ala
1 5 10 15

Gln Leu Ile Phe Phe Leu Phe Leu Val Glu Thr Gly Phe His Asn Val
20 25 30

Gly Gln Ala Gly Leu Glu Leu Leu Thr Ser Ser Asp Leu Pro Ala Ser
35 40 45

Ala Ser
50

<210> SEQ ID NO 33
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

ttgattgttt aactcttatt ctgaaatgca ctggttactg gcataaagta aattatatta 60

gtaaatatta tgacaaaaat tttcgaatat gtatttatag tgtaaaaatt tttgagcagt 120

tgcctcttat tttctcaact attaaaaata acaaattatt gaagaataat aagacctgtt 180

catatctttt gacatagtaa tcttttatca tagaatctat cataataaaa ttttaaaaat 240

taaaagtatt atttgcatag agctgtttat tgcagcatta ttataactct ggaaaaatta 300

aaaccaacct gaatgatcat tcaggttaac tctacaaaag atattaaaca cctgtgcatc 360

agatacact 369

<210> SEQ ID NO 34
<211> LENGTH: 64
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

Asp Cys Leu Thr Leu Ile Leu Lys Cys Thr Gly Tyr Trp His Lys Val
1 5 10 15

Asn Tyr Ile Ser Lys Tyr Tyr Asp Lys Asn Phe Arg Ile Cys Ile Tyr

-continued

20 25 30

Ser Val Lys Ile Phe Glu Gln Leu Pro Leu Ile Phe Ser Thr Ile Lys
35 40 45

Asn Asn Lys Leu Leu Lys Asn Asn Lys Thr Cys Ser Tyr Leu Leu Thr
50 55 60

<210> SEQ ID NO 35
<211> LENGTH: 799
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

cctctgatca acagcccgga agaaagagat atcttttctc agcaagtagc agttcttttc 60

tacagtcaag cctcagttca tcctatttcc aactgtctgg aagaatggtc cacaaaggag 120

ccacgataag atgactgaaa agaaacctcc agtgatcatc cccccacagg gggaaaacaa 180

aattgaacaa ctattcatgc aagaaagcac cttcataaga actaaaaatc aggtggagtc 240

tcactctgtc gcccaagctg gaatgcaggg gcgtgatctt ggctcactgc aagctccacc 300

tcctgggttc acgcggtttt tctgcttcgg catcccgagt agctgggatt acaggatttt 360

ttgctgtttt tccaatgaga agatgagcgg ggagcagagc aggtgacaga gttatcttgg 420

aagtcccact gaaactcagt ctgtactagc ggtctctggg agccctagct ttggaccaga 480

tgtattgccc acaggaggcc tcttgtgcct tgctgctctc agcttgcaga gttgctacct 540

gtgaggtttc atctatgtaa ccagatcacc tttgctagct atgcctcctc ttccccctct 600

cccatcacct gccttgccat taaagcctga tataccacta taacctgttt gtagccatac 660

tttgagcctg cattctttct gtagcctcaa gatggtatgt tagtttccta ttgggggtcg 720

ggctttcttt ctaaaggctc ttatgtataa gaattaaata aatttatgtg ccttttctcc 780

tgttaaaaaa aaaaaaaaa 799

<210> SEQ ID NO 36
<211> LENGTH: 91
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

Met Thr Glu Lys Lys Pro Pro Val Ile Ile Pro Pro Gln Gly Glu Asn
1 5 10 15

Lys Ile Glu Gln Leu Phe Met Gln Glu Ser Thr Phe Ile Arg Thr Lys
20 25 30

Asn Gln Val Glu Ser His Ser Val Ala Gln Ala Gly Met Gln Gly Arg
35 40 45

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

Cys Phe Gly Ile Pro Ser Ser Trp Asp Tyr Arg Ile Phe Cys Cys Phe
65 70 75 80

Ser Asn Glu Lys Met Ser Gly Glu Gln Ser Arg
85 90

<210> SEQ ID NO 37
<211> LENGTH: 3243
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

gttgctgatc tttggatgtt ctggttagtc taagaaggag agtatgaggc gagctccggc 60

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```
ccgggtgcgg ccgggcttca ggggcccagg cgccgctgct gccaccgcca tctaacgctg    120
cgccctggag gcccggcgcg cggatggtgc cggtgcggct cgggtgttga aacgggtgtc    180
ccctccccct cctcccctcc cccacgcggt ggtctcccct cccacccggc tcaggcagag    240
ccatgtctcg gggtggctcc tacccacacc tgttgtggga cgtgaggaaa aggtccctcg    300
ggctggagga cccgtcccgg ctgcggagtc gctacctggg aagaagagaa tttatccaaa    360
gattaaaact tgaagcaacc cttaatgtgc atgatggttg tgttaataca atctgttgga    420
atgacactgg agaatatatt ttatctggct cagatgacac caaattagta attagtaatc    480
cttacagcag aaaggttttg acaacaattc gttcagggca ccgagcaaac atatttagtg    540
caaagttctt accttgtaca aatgataaac agattgtatc ctgctctgga gatggagtaa    600
tattttatac caacgttgag caagatgcag aaaccaacag acaatgccaa tttacgtgtc    660
attatggaac tacttatgag attatgactg tacccaatga cccttacact tttctctctt    720
gtggtgaaga tggaactgtt aggtggtttg atacacgcat caaaactagc tgcacaaaag    780
aagattgtaa agatgatatt ttaattaact gtcgacgtgc tgccacgtct gttgctattt    840
gcccaccaat accatattac cttgctgttg gttgttctga cagctcagta cgaatatatg    900
atcggcgaat gctgggcaca agagctacag ggaattatgc aggtcgaggg actactggaa    960
tggttgcccg ttttattcct tcccatctta ataataagtc ctgcagagtg acatctctgt   1020
gttacagtga agatggtcaa gagattctcg ttagttactc ttcagattac atatatcttt   1080
ttgacccgaa agatgataca gcacgagaac ttaaaactcc ttctgcggaa gagagaagag   1140
aagagttgcg acaaccacca gttaagcgtt tgagacttcg tggtgattgg tcagatactg   1200
gacccagagc aaggccggag agtgaacgag aacgagatgg agagcagagt cccaatgtgt   1260
cattgatgca gagaatgtct gatatgttat caagatggtt tgaagaagca agtgaggttg   1320
cacaaagcaa tagaggacga ggaagatctc gacccagagg tggaacaagt caatcagata   1380
tttcaactct tcctacggtc ccatcaagtc ctgatttgga agtgagtgaa actgcaatgg   1440
aagtagatac tccagctgaa caatttcttc agccttctac atcctctaca atgtcagctc   1500
aggctcattc gacatcatct cccacagaaa gccctcattc tactcctttg ctatcttctc   1560
cagacagtga acaaaggcag tctgttgagg catctggaca ccacacacat catcagtctg   1620
ataacaataa tgaaaagctg agccccaaac cagggacagg tgaaccagtt ttaagtttgc   1680
actacagcac agaaggaaca actacaagca caataaaact gaactttaca gatgaatgga   1740
gcagtatagc atcaagttct agaggaattg ggagccattg caaatctgag ggtcaggagg   1800
aatctttcgt cccacagagc tcagtgcaac caccagaagg agacagtgaa acaaaagctc   1860
ctgaagaatc atcagaggat gtgacaaaat atcaggaagg agtatctgca gaaaacccag   1920
ttgagaacca tatcaatata acacaatcag ataagttcac agccaagcca ttggattcca   1980
actcaggaga aagaaatgac ctcaatcttg atcgctcttg tggggttcca gaagaatctg   2040
cttcatctga aaaagccaag gaaccagaaa cttcagatca gactagcact gagagtgcta   2100
ccaatgaaaa taacaccaat cctgagcctc agttccaaac agaagccact gggccttcag   2160
ctcatgaaga aacatccacc agggactctg ctcttcagga cacagatgac agtgatgatg   2220
acccagtcct gatcccaggt gcaaggtatc gagcaggacc tggtgataga cgctctgctg   2280
ttgcccgtat tcaggagttc ttcagacgga gaaaagaaag gaaagaaatg gaagaattgg   2340
atactttgaa cattagaagg ccgctagtaa aaatggttta taaaggccat cgcaactcca   2400
ggacaatgat aaaagaagcc aatttctggg gtgctaactt tgtaatgagt ggttctgact   2460
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gtggccacat tttcatctgg gatcggcaca ctgctgagca tttgatgctt ctggaagctg 2520

ataatcatgt ggtaaactgc ctgcagccac atccgtttga cccaatttta gcctcatctg 2580

gcatagatta tgacataaag atctggtcac cattagaaga gtcaaggatt tttaaccgaa 2640

aacttgctga tgaagttata actcgaaacg aactcatgct ggaagaaact agaaacacca 2700

ttacagttcc agcctctttc atgttgagga tgttggcttc acttaatcat atccgagctg 2760

accggttgga gggtgacaga tcagaaggct ctggtcaaga gaatgaaaat gaggatgagg 2820

aataataaac tctttttggc aagcacttaa atgttctgaa atttgtataa gacatttatt 2880

atatttttt ctttacagag ctttagtgca attttaaggt tatggttttt ggagtttttc 2940

cctttttttg ggataaccta acattggttt ggaatgattg tgtgcatgaa tttgggagat 3000

tgtataaaac aaaactagca gaatgttttt aaaacttttt gccgtgtatg aggagtgcta 3060

gaaaatgcaa agtgcaatat tttccctaac cttcaaatgt gggagcttgg atcaatgttg 3120

aagaataatt ttcatcatag tgaaaatgtt ggttcaaata aatttctaca cttgccattt 3180

gcatgtttgt tgctttctaa ttaaagaaac tggttgtttt aagataccct gaaaaaaaaa 3240

aaa 3243

<210> SEQ ID NO 38
<211> LENGTH: 860
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

Met Ser Arg Gly Gly Ser Tyr Pro His Leu Leu Trp Asp Val Arg Lys
1 5 10 15

Arg Ser Leu Gly Leu Glu Asp Pro Ser Arg Leu Arg Ser Arg Tyr Leu
20 25 30

Gly Arg Arg Glu Phe Ile Gln Arg Leu Lys Leu Glu Ala Thr Leu Asn
35 40 45

Val His Asp Gly Cys Val Asn Thr Ile Cys Trp Asn Asp Thr Gly Glu
50 55 60

Tyr Ile Leu Ser Gly Ser Asp Asp Thr Lys Leu Val Ile Ser Asn Pro
65 70 75 80

Tyr Ser Arg Lys Val Leu Thr Thr Ile Arg Ser Gly His Arg Ala Asn
85 90 95

Ile Phe Ser Ala Lys Phe Leu Pro Cys Thr Asn Asp Lys Gln Ile Val
100 105 110

Ser Cys Ser Gly Asp Gly Val Ile Phe Tyr Thr Asn Val Glu Gln Asp
115 120 125

Ala Glu Thr Asn Arg Gln Cys Gln Phe Thr Cys His Tyr Gly Thr Thr
130 135 140

Tyr Glu Ile Met Thr Val Pro Asn Asp Pro Tyr Thr Phe Leu Ser Cys
145 150 155 160

Gly Glu Asp Gly Thr Val Arg Trp Phe Asp Thr Arg Ile Lys Thr Ser
165 170 175

Cys Thr Lys Glu Asp Cys Lys Asp Asp Ile Leu Ile Asn Cys Arg Arg
180 185 190

Ala Ala Thr Ser Val Ala Ile Cys Pro Pro Ile Pro Tyr Tyr Leu Ala
195 200 205

Val Gly Cys Ser Asp Ser Ser Val Arg Ile Tyr Asp Arg Arg Met Leu
210 215 220

Gly Thr Arg Ala Thr Gly Asn Tyr Ala Gly Arg Gly Thr Thr Gly Met
225 230 235 240

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Val Ala Arg Phe Ile Pro Ser His Leu Asn Asn Lys Ser Cys Arg Val
                245                 250                 255

Thr Ser Leu Cys Tyr Ser Glu Asp Gly Gln Glu Ile Leu Val Ser Tyr
            260                 265                 270

Ser Ser Asp Tyr Ile Tyr Leu Phe Asp Pro Lys Asp Asp Thr Ala Arg
        275                 280                 285

Glu Leu Lys Thr Pro Ser Ala Glu Glu Arg Arg Glu Glu Leu Arg Gln
    290                 295                 300

Pro Pro Val Lys Arg Leu Arg Leu Arg Gly Asp Trp Ser Asp Thr Gly
305                 310                 315                 320

Pro Arg Ala Arg Pro Glu Ser Glu Arg Glu Arg Asp Gly Glu Gln Ser
                325                 330                 335

Pro Asn Val Ser Leu Met Gln Arg Met Ser Asp Met Leu Ser Arg Trp
            340                 345                 350

Phe Glu Glu Ala Ser Glu Val Ala Gln Ser Asn Arg Gly Arg Gly Arg
        355                 360                 365

Ser Arg Pro Arg Gly Gly Thr Ser Gln Ser Asp Ile Ser Thr Leu Pro
    370                 375                 380

Thr Val Pro Ser Ser Pro Asp Leu Glu Val Ser Glu Thr Ala Met Glu
385                 390                 395                 400

Val Asp Thr Pro Ala Glu Gln Phe Leu Gln Pro Ser Thr Ser Ser Thr
                405                 410                 415

Met Ser Ala Gln Ala His Ser Thr Ser Ser Pro Thr Glu Ser Pro His
            420                 425                 430

Ser Thr Pro Leu Leu Ser Ser Pro Asp Ser Glu Gln Arg Gln Ser Val
        435                 440                 445

Glu Ala Ser Gly His His Thr His His Gln Ser Asp Asn Asn Asn Glu
    450                 455                 460

Lys Leu Ser Pro Lys Pro Gly Thr Gly Glu Pro Val Leu Ser Leu His
465                 470                 475                 480

Tyr Ser Thr Glu Gly Thr Thr Thr Ser Thr Ile Lys Leu Asn Phe Thr
                485                 490                 495

Asp Glu Trp Ser Ser Ile Ala Ser Ser Ser Arg Gly Ile Gly Ser His
            500                 505                 510

Cys Lys Ser Glu Gly Gln Glu Glu Ser Phe Val Pro Gln Ser Ser Val
        515                 520                 525

Gln Pro Pro Glu Gly Asp Ser Glu Thr Lys Ala Pro Glu Glu Ser Ser
    530                 535                 540

Glu Asp Val Thr Lys Tyr Gln Glu Gly Val Ser Ala Glu Asn Pro Val
545                 550                 555                 560

Glu Asn His Ile Asn Ile Thr Gln Ser Asp Lys Phe Thr Ala Lys Pro
                565                 570                 575

Leu Asp Ser Asn Ser Gly Glu Arg Asn Asp Leu Asn Leu Asp Arg Ser
            580                 585                 590

Cys Gly Val Pro Glu Glu Ser Ala Ser Ser Glu Lys Ala Lys Glu Pro
        595                 600                 605

Glu Thr Ser Asp Gln Thr Ser Thr Glu Ser Ala Thr Asn Glu Asn Asn
    610                 615                 620

Thr Asn Pro Glu Pro Gln Phe Gln Thr Glu Ala Thr Gly Pro Ser Ala
625                 630                 635                 640

His Glu Glu Thr Ser Thr Arg Asp Ser Ala Leu Gln Asp Thr Asp Asp
                645                 650                 655

Ser Asp Asp Asp Pro Val Leu Ile Pro Gly Ala Arg Tyr Arg Ala Gly
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           660                 665                 670

Pro Gly Asp Arg Arg Ser Ala Val Ala Arg Ile Gln Glu Phe Phe Arg
        675                 680                 685

Arg Arg Lys Glu Arg Lys Glu Met Glu Glu Leu Asp Thr Leu Asn Ile
    690                 695                 700

Arg Arg Pro Leu Val Lys Met Val Tyr Lys Gly His Arg Asn Ser Arg
705                 710                 715                 720

Thr Met Ile Lys Glu Ala Asn Phe Trp Gly Ala Asn Phe Val Met Ser
                725                 730                 735

Gly Ser Asp Cys Gly His Ile Phe Ile Trp Asp Arg His Thr Ala Glu
            740                 745                 750

His Leu Met Leu Leu Glu Ala Asp Asn His Val Val Asn Cys Leu Gln
        755                 760                 765

Pro His Pro Phe Asp Pro Ile Leu Ala Ser Ser Gly Ile Asp Tyr Asp
    770                 775                 780

Ile Lys Ile Trp Ser Pro Leu Glu Glu Ser Arg Ile Phe Asn Arg Lys
785                 790                 795                 800

Leu Ala Asp Glu Val Ile Thr Arg Asn Glu Leu Met Leu Glu Glu Thr
                805                 810                 815

Arg Asn Thr Ile Thr Val Pro Ala Ser Phe Met Leu Arg Met Leu Ala
            820                 825                 830

Ser Leu Asn His Ile Arg Ala Asp Arg Leu Glu Gly Asp Arg Ser Glu
        835                 840                 845

Gly Ser Gly Gln Glu Asn Glu Asn Glu Asp Glu Glu
    850                 855                 860


<210> SEQ ID NO 39
<211> LENGTH: 2584
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

atagggaggt cgggtagagg ctcccgggac ctgcgtgctg ccgagagagg aagcgaaggg     60

caccatcttt gtattttgtg tcatgacttc tcaagagaag acagaagagt atccttttgc    120

agatatattt gatgaagatg aaactgaaag gaatttttg ttgtccaaac ctgtttgctt    180

tgttgtattt gggaaaccag gtgttgggaa aacaacatta gcccgttaca taacacaggc    240

atggaaatgt attcgtgttg aagctttgcc aattttagaa gaacagattg ctgctgaaac    300

cgaatcagga gttatgttgc aatcaatgtt gatcagcggt caaagcattc cagatgaact    360

tgtcataaag ctaatgttgg agaagctcaa ctccccagaa gtctgtcact ttggttatat    420

tatcactgaa ataccatcac tttcacagga tgccatgact accttacagc aaatagaatt    480

aattaaaaac ttaaacctga aacctgatgt tataatcaat ataaagtgtc ctgactatga    540

tttgtgccag agaatttctg ggcaaagaca gcacaataat acgggataca tatacagtag    600

agaccagtgg gatcctgaag tcattgagaa tcataggaaa aagaagaaag aagcccaaaa    660

ggacggaaaa ggagaagagg aagaagagga agaagagcaa gaagaagaag aggcatttat    720

tgccgaaatg cagatggtgg ctgaaattct tcatcatcta gtccagaggc ctgaagatta    780

tttggaaaat gttgaaaaca ttgttaagct ttataaggaa acaattctcc aaactttaga    840

agaagtaatg gctgaacaca atccccagta tctcattgag ctaaatggaa ataaaccagc    900

agaggagctc tttatgattg ttatggatcg acttaaatat ctgaacctaa aaagagcagc    960

tattctaacc aaacttcagg gtgcagagga agaaattaat gacacaatgg aaaatgatga   1020
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gctatttcgt actcttgcat cttataaact tattgcacca agatacagat ggcaaagaag 1080

taaatgggga cgtacatgtc ctgtgaattt aaaagatggt aacatttatt caggattacc 1140

agattattct gtgagttttc taggtaaaat ctactgtctt tcatcagaag aagcattaaa 1200

accatttttg ttgaacccac gtccctatct gcttccacct atgccaggac caccatgtaa 1260

agtattcata cttggacctc aatattcagg gaaaacaaca ctttgcaata tgcttgcaga 1320

aaattacaaa ggaaaggtga ctaactaact atctgtctat ctatctatct atctatctat 1380

ctatctatct atctatctat gtctatctgt catgtatcta tactcgatta taatttgtag 1440

gattttattt gtactcagtt tttaaaattt catgttttaa ttgaataatt gttccactgg 1500

gcttggggta gggtaggcat tctttttgtt gtttattgct gcttccagac cagagtccct 1560

ccctgcttcc caaaagctcc cacatgtgaa tatcgtgtca ttcagactct gccacctatt 1620

agctttcttg gttctactca tcttctgtcc cctgggtttc acttctcctg gctcactctc 1680

actctcccca tataatcact cctgtcctaa ttcttggtga tttcagtatt acaaagatga 1740

tcctcccaac accttgacac ctccctcagt aatcttgttc tccactctca gtaaatgaaa 1800

ttatttttag cttagacaag agtgatagca gtaaaagtgg tatgaaacaa gcatatttgg 1860

gatataattt gaagacaaag ctgaaagatt tgatgaggga ttggaatgtg gaggaattct 1920

agaaggggca atgtggcttg aggattgcct atgcaagaag gaatggcaca agatcatggc 1980

taaagacaga gcaattcagg ccacagaaag gtgttagaag ttgttcaaag tgctgttgca 2040

ttcttttaag cgccggagta tcattttcta tttgctttta acttttttcat tgtgaaacat 2100

gacaaacata cagaaaagtg aagcccactg agttaccgca aaatgaaccc ccatgtaacc 2160

accaaccagg tcaaatctgg aatgttgcca gcacccagac gccctctcat gtttcttctc 2220

aataccagtc tcctcactct ccacacaaag gtaaccactg cccagaattt tatggcattc 2280

acttccatac ttctcctatg gttttgccgt ggaagcatac atccaaatac cataggctag 2340

ttttgcatgg tttttttgaa ttttatagac ctaaacaatt tatcttcttt gtgcctggct 2400

tctttcactt aacattataa ttatgatatt tgtccagact attgaatgta gctgtagttt 2460

attcattttt attgttttat tgtattctgt tgattgactt ataccataat gtatttatcc 2520

acatttgagc actaataaaa cttggattga ttccagattg gagtaaacaa aaaaaaaaaa 2580

aaaa 2584

<210> SEQ ID NO 40
<211> LENGTH: 421
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

Met Thr Ser Gln Glu Lys Thr Glu Glu Tyr Pro Phe Ala Asp Ile Phe
1 5 10 15

Asp Glu Asp Glu Thr Glu Arg Asn Phe Leu Leu Ser Lys Pro Val Cys
20 25 30

Phe Val Val Phe Gly Lys Pro Gly Val Gly Lys Thr Thr Leu Ala Arg
35 40 45

Tyr Ile Thr Gln Ala Trp Lys Cys Ile Arg Val Glu Ala Leu Pro Ile
50 55 60

Leu Glu Glu Gln Ile Ala Ala Glu Thr Glu Ser Gly Val Met Leu Gln
65 70 75 80

Ser Met Leu Ile Ser Gly Gln Ser Ile Pro Asp Glu Leu Val Ile Lys
85 90 95

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Leu Met Leu Glu Lys Leu Asn Ser Pro Glu Val Cys His Phe Gly Tyr
            100                 105                 110

Ile Ile Thr Glu Ile Pro Ser Leu Ser Gln Asp Ala Met Thr Thr Leu
        115                 120                 125

Gln Gln Ile Glu Leu Ile Lys Asn Leu Asn Leu Lys Pro Asp Val Ile
    130                 135                 140

Ile Asn Ile Lys Cys Pro Asp Tyr Asp Leu Cys Gln Arg Ile Ser Gly
145                 150                 155                 160

Gln Arg Gln His Asn Asn Thr Gly Tyr Ile Tyr Ser Arg Asp Gln Trp
                165                 170                 175

Asp Pro Glu Val Ile Glu Asn His Arg Lys Lys Lys Lys Glu Ala Gln
            180                 185                 190

Lys Asp Gly Lys Gly Glu Glu Glu Glu Glu Glu Glu Glu Gln Glu Glu
        195                 200                 205

Glu Glu Ala Phe Ile Ala Glu Met Gln Met Val Ala Glu Ile Leu His
    210                 215                 220

His Leu Val Gln Arg Pro Glu Asp Tyr Leu Glu Asn Val Glu Asn Ile
225                 230                 235                 240

Val Lys Leu Tyr Lys Glu Thr Ile Leu Gln Thr Leu Glu Glu Val Met
                245                 250                 255

Ala Glu His Asn Pro Gln Tyr Leu Ile Glu Leu Asn Gly Asn Lys Pro
            260                 265                 270

Ala Glu Glu Leu Phe Met Ile Val Met Asp Arg Leu Lys Tyr Leu Asn
        275                 280                 285

Leu Lys Arg Ala Ala Ile Leu Thr Lys Leu Gln Gly Ala Glu Glu Glu
    290                 295                 300

Ile Asn Asp Thr Met Glu Asn Asp Glu Leu Phe Arg Thr Leu Ala Ser
305                 310                 315                 320

Tyr Lys Leu Ile Ala Pro Arg Tyr Arg Trp Gln Arg Ser Lys Trp Gly
                325                 330                 335

Arg Thr Cys Pro Val Asn Leu Lys Asp Gly Asn Ile Tyr Ser Gly Leu
            340                 345                 350

Pro Asp Tyr Ser Val Ser Phe Leu Gly Lys Ile Tyr Cys Leu Ser Ser
        355                 360                 365

Glu Glu Ala Leu Lys Pro Phe Leu Leu Asn Pro Arg Pro Tyr Leu Leu
    370                 375                 380

Pro Pro Met Pro Gly Pro Pro Cys Lys Val Phe Ile Leu Gly Pro Gln
385                 390                 395                 400

Tyr Ser Gly Lys Thr Thr Leu Cys Asn Met Leu Ala Glu Asn Tyr Lys
                405                 410                 415

Gly Lys Val Thr Asn
            420


<210> SEQ ID NO 41
<211> LENGTH: 212
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

tgcccctccc cctgtggaga agacgcttag ttgggggtgt gggtttgggc tccattctgg     60

attcggcggt tccgggggag gggtgggtct gtgccgatta ctctgtcttg tacgtttgtt    120

ctgctgctct tcaatattgt atcaacgcca ggaaaggggg gtgaaaagcc tcttttaccc    180

cccaaataaa ttgtcacatt ccgaagctga aa                                  212
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<210> SEQ ID NO 42
<211> LENGTH: 71
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (71)..(71)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 42

Ala Pro Pro Pro Val Glu Lys Thr Leu Ser Trp Gly Cys Gly Phe Gly
1 5 10 15

Leu His Ser Gly Phe Gly Gly Ser Gly Gly Gly Val Gly Leu Cys Arg
20 25 30

Leu Leu Cys Leu Val Arg Leu Phe Cys Cys Ser Ser Ile Leu Tyr Gln
35 40 45

Arg Gln Glu Arg Gly Val Lys Ser Leu Phe Tyr Pro Pro Asn Lys Leu
50 55 60

Ser His Ser Glu Ala Glu Xaa
65 70

<210> SEQ ID NO 43
<211> LENGTH: 1882
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

atggaggttg caggtctttt cctgggtggg cgtggggcgg ggcagcgggt tcccagcgtc 60

ctcctggcct gggcgtcttg gaggctgttg gggtgcattc cgtccccttg cgcggggcgg 120

ggccttgagg cgctggggcg ggattggcgg gggacggtcg cggagccccg ccccgaagca 180

cagggtcgag tcccttcttt ccgctccaac gcacggaggg tgaggtcggt acgcggtggt 240

ggcgtcacgg cgccagctcc tcccgacgcc gaggtgggtt ccgggagacc cgcgggtctg 300

gctgcgagag accatggggg ctcagctaag cggcggccgc ggcgccccgg agcctgcgca 360

aacccagccc cagccccagc cccagcctgc ggcgccggag ggcccggaac agccccggca 420

tccgccccag ccccagcccc agccccagcc ccagccccag cccgagccca gcccgtgggg 480

gccgctggac gacgtgcgct tcctcatcgc ctgcacttcc tggtactgac ggcgtcctcc 540

gcaggatgtc gcccgtctgt ccgccgtccc ctgtggttct tgcctgcctt gtctcctctc 600

cccacgtccc tgcgtctctt acacccccctc ccacccgagg ctccccagag atagcagaga 660

attcgaagag gtcgccgggg actggaaaga agtcccggca gggccgcctt cgcagtctac 720

accccagcct gcttcccagc ctacacccag acccagctca gaccttcgtg accaccccat 780

ccctttctcc ggctggctgg gtcgggggca tccctctctg tcgctggctt ccagaggcag 840

gacaggcctc ctggtaagcc cgcaaagttg ctgacctcct gacttcgtct gccttttatt 900

aatatctgta ttgctgataa ccgtgctctt gactatgtgt cccaggtcat gtcccaggtc 960

atggagaagc ccgtgccaca gtgaccctcc ccatactcct gggggggctg ctctccatcc 1020

tggatcgtaa ggaggcatca tcaggctgtg ttcctggaac cccaataacc ctgggccccc 1080

agggccagcc tgttgtagag ggaggctatc tgaccgccgg tctggcagag gagatgggtg 1140

ggcagctccc agacacccca aaggacccgg ttctcttccc agagcgtcct aaggttactc 1200

ttggaacctg atctttgttc cctcatccca gggaaatgac acactctgta tttctgtttt 1260

atttagaaat gatttaaaaa acattataca aaggctgatc agtttaaaat gtgactgaca 1320

ctgaaatgct gtgatgtccc ccaggctgag gggaagctag gctctggggc ccccagtgct 1380

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ttgcccctct gtctgccctg tcctggggtg atggacaaac agatgaccac aggcaggaga   1440

atctgagatt ggaagcctct aggctgagcc ctctgggcct ggccccacat ccctcacctc   1500

tgcagcctgg gctgcctgcc tccatctcct gttcattctc agctggcctg ccaggagcca   1560

atggggagcc tggcgggagg cgggggtgcc tagagctttc aagaagtgag agcaccaacc   1620

tgaggagtgg acagggacca ggaagtgggg gaagggaggc caggaagagg tggatacagg   1680

agacacttct catctcatct cagaccctag aggggtccac agatggggac acaagaccca   1740

gccagcccac tggatggccc gggcaagtaa caacctctct gtgcttcatc tgagggcacg   1800

gtgagagtta ccgtcggcct cccagggcct aacacgagtt tcatgtgagt ggacaggtgt   1860

gagctaataa agtgctttgc aa                                            1882


<210> SEQ ID NO 44
<211> LENGTH: 217
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

Met Glu Val Ala Gly Leu Phe Leu Gly Gly Arg Gly Ala Gly Gln Arg
1               5                   10                  15

Val Pro Ser Val Leu Leu Ala Trp Ala Ser Trp Arg Leu Leu Gly Cys
            20                  25                  30

Ile Pro Ser Pro Cys Ala Gly Arg Gly Leu Glu Ala Leu Gly Arg Asp
        35                  40                  45

Trp Arg Gly Thr Val Ala Glu Pro Arg Pro Glu Ala Gln Gly Arg Val
    50                  55                  60

Pro Ser Phe Arg Ser Asn Ala Arg Arg Val Arg Ser Val Arg Gly Gly
65                  70                  75                  80

Gly Val Thr Ala Pro Ala Pro Pro Asp Ala Glu Val Gly Ser Gly Arg
                85                  90                  95

Pro Ala Gly Leu Ala Ala Arg Asp His Gly Gly Ser Ala Lys Arg Arg
            100                 105                 110

Pro Arg Arg Pro Gly Ala Cys Ala Asn Pro Ala Pro Ala Pro Ala Pro
        115                 120                 125

Ala Cys Gly Ala Gly Gly Pro Gly Thr Ala Pro Ala Ser Ala Pro Ala
    130                 135                 140

Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Arg Ala Gln Pro Val Gly
145                 150                 155                 160

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

Thr Ala Ser Ser Ala Gly Cys Arg Pro Ser Val Arg Arg Pro Leu Trp
            180                 185                 190

Phe Leu Pro Ala Leu Ser Pro Leu Pro Thr Ser Leu Arg Leu Leu His
        195                 200                 205

Pro Leu Pro Pro Glu Ala Pro Gln Arg
    210                 215


<210> SEQ ID NO 45
<211> LENGTH: 1900
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

ctcctcctcc ggcgtcgcgg gctcctcgga catggccgcg gcggtggcgg tggcggccgc     60

gtcccggcgg cagtcgtgct acctgtgtga cctgccccgc atgccctggg ccatgatctg    120
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ggacttcacc gaacccgtct gccgcggctg cgtcaactac gagggcgccg accgcgtcga 180

gttcgtcatc gagacggcgc ggcagctcaa gcgggcgcac ggctgcttcc cggagggtcg 240

ctccccaccc ggcgccgcgg cctcggccgc cgccaagccg ccgccgctct ccgccaagga 300

catccttttg cagcagcagc agcagcttgg ccacggcggc cccgaggcgg ccccgcgcgc 360

gccgcaggcc ttggagcgct acccgttggc ggccgcggcc gagaggcccc cgcgcctcgg 420

ctctgacttc ggcagcagcc gcccggcagc gagcctggcc cagccgccga cgccgcagcc 480

gccgcccgtg aacggcatcc tggtgcccaa cggcttctcc aagctagagg aaccgcccga 540

gctgaatcgc cagagcccga aaccacggcg cggccacacg gtgccgccca ccctggtgcc 600

gctcatgaac ggctcggcca cgccgctgcc caccgcgctc ggcctcggcg gccgcgctgc 660

cgcctcctta gccgcggtgt ccggaaccgc ggccgccagc ctgggctccg cgcagcccac 720

cgatctgggc gcccacaagc ggccggcatc cgtgtcgagc agcgctaccg tggagcacga 780

gcagcgtgag gcggcagcca aggagaaaca accgccgccg cctgcgcacc ggggcccggc 840

cgacagcctg tccaccgcgg ccggggccgc cgagctgagc gcggaaggtg cgggcaagag 900

ccgcgggtct ggagagcagg actgggtcaa caggcccaag accgtgcgcg acacgctgct 960

ggcgctgcac cagcacggcc actcggggcc cttcgagagc aagtttaaga aggagccggc 1020

cctgactgca ggcaggttgt tgggtttcga ggccaacggg gccaacgggt ctaaagcagt 1080

tgcaagaaca gcaaggaaaa ggaagccctc tccagaacca gaaggtgaag tcgggccccc 1140

taagatcaac ggagaggccc agccgtggct gtccacatcc acagaggggc tcaagatccc 1200

catgactcct acatcctctt ttgtgtctcc gccaccaccc actgcctcac ctcattccaa 1260

ccggaccaca ccgcctgaag cggcccagaa tggccagtcc cccatggcag ccctgatctt 1320

agtagcagac aatgcagggg gcagtcatgc ctcaaaagat gccaaccagg ttcactccac 1380

taccaggagg aatagcaaca gtccgccctc tccgtcctct atgaaccaaa gaaggctggg 1440

ccccagagag gtgggggggcc agggagcagg caacacagga ggactggagc cagtgcaccc 1500

tgccagcctc ccggactcct ctctggcaac cagtgccccg ctgtgctgca ccctctgcca 1560

cgagcggctg gaggacaccc attttgtgca gtgcccgtcc gtcccttcgc acaagttctg 1620

cttcccttgc tccagacaaa gcatcaaaca gcagggagct agtggagagg tctattgtcc 1680

cagtggggaa aaatgccctc ttgtgggctc caatgtcccc tgggccttta tgcaagggga 1740

aattgcaacc atccttgctg gagatgtgaa agtgaaaaaa gagagagact cgtgactttt 1800

ccggtttcag aaaaacccaa tgattaccct taattaaaac tgcttgaatt gtatatatat 1860

ctccatatat atatatatcc aagacaaggg aaatgtagac 1900

<210> SEQ ID NO 46
<211> LENGTH: 587
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

Met Ala Ala Ala Val Ala Val Ala Ala Ala Ser Arg Arg Gln Ser Cys
1 5 10 15

Tyr Leu Cys Asp Leu Pro Arg Met Pro Trp Ala Met Ile Trp Asp Phe
20 25 30

Thr Glu Pro Val Cys Arg Gly Cys Val Asn Tyr Glu Gly Ala Asp Arg
35 40 45

Val Glu Phe Val Ile Glu Thr Ala Arg Gln Leu Lys Arg Ala His Gly
50 55 60

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Cys Phe Pro Glu Gly Arg Ser Pro Pro Gly Ala Ala Ala Ser Ala Ala
65                  70                  75                  80

Ala Lys Pro Pro Pro Leu Ser Ala Lys Asp Ile Leu Leu Gln Gln Gln
                85                  90                  95

Gln Gln Leu Gly His Gly Gly Pro Glu Ala Ala Pro Arg Ala Pro Gln
            100                 105                 110

Ala Leu Glu Arg Tyr Pro Leu Ala Ala Ala Ala Glu Arg Pro Pro Arg
        115                 120                 125

Leu Gly Ser Asp Phe Gly Ser Ser Arg Pro Ala Ala Ser Leu Ala Gln
    130                 135                 140

Pro Pro Thr Pro Gln Pro Pro Pro Val Asn Gly Ile Leu Val Pro Asn
145                 150                 155                 160

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

Lys Pro Arg Arg Gly His Thr Val Pro Pro Thr Leu Val Pro Leu Met
            180                 185                 190

Asn Gly Ser Ala Thr Pro Leu Pro Thr Ala Leu Gly Leu Gly Gly Arg
        195                 200                 205

Ala Ala Ala Ser Leu Ala Ala Val Ser Gly Thr Ala Ala Ala Ser Leu
    210                 215                 220

Gly Ser Ala Gln Pro Thr Asp Leu Gly Ala His Lys Arg Pro Ala Ser
225                 230                 235                 240

Val Ser Ser Ser Ala Thr Val Glu His Glu Gln Arg Glu Ala Ala Ala
                245                 250                 255

Lys Glu Lys Gln Pro Pro Pro Pro Ala His Arg Gly Pro Ala Asp Ser
            260                 265                 270

Leu Ser Thr Ala Ala Gly Ala Ala Glu Leu Ser Ala Glu Gly Ala Gly
        275                 280                 285

Lys Ser Arg Gly Ser Gly Glu Gln Asp Trp Val Asn Arg Pro Lys Thr
    290                 295                 300

Val Arg Asp Thr Leu Leu Ala Leu His Gln His Gly His Ser Gly Pro
305                 310                 315                 320

Phe Glu Ser Lys Phe Lys Lys Glu Pro Ala Leu Thr Ala Gly Arg Leu
                325                 330                 335

Leu Gly Phe Glu Ala Asn Gly Ala Asn Gly Ser Lys Ala Val Ala Arg
            340                 345                 350

Thr Ala Arg Lys Arg Lys Pro Ser Pro Glu Pro Glu Gly Glu Val Gly
        355                 360                 365

Pro Pro Lys Ile Asn Gly Glu Ala Gln Pro Trp Leu Ser Thr Ser Thr
    370                 375                 380

Glu Gly Leu Lys Ile Pro Met Thr Pro Thr Ser Ser Phe Val Ser Pro
385                 390                 395                 400

Pro Pro Pro Thr Ala Ser Pro His Ser Asn Arg Thr Thr Pro Pro Glu
                405                 410                 415

Ala Ala Gln Asn Gly Gln Ser Pro Met Ala Ala Leu Ile Leu Val Ala
            420                 425                 430

Asp Asn Ala Gly Gly Ser His Ala Ser Lys Asp Ala Asn Gln Val His
        435                 440                 445

Ser Thr Thr Arg Arg Asn Ser Asn Ser Pro Pro Ser Pro Ser Ser Met
    450                 455                 460

Asn Gln Arg Arg Leu Gly Pro Arg Glu Val Gly Gly Gln Gly Ala Gly
465                 470                 475                 480

Asn Thr Gly Gly Leu Glu Pro Val His Pro Ala Ser Leu Pro Asp Ser
                485                 490                 495
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Ser Leu Ala Thr Ser Ala Pro Leu Cys Cys Thr Leu Cys His Glu Arg
            500                 505                 510

Leu Glu Asp Thr His Phe Val Gln Cys Pro Ser Val Pro Ser His Lys
        515                 520                 525

Phe Cys Phe Pro Cys Ser Arg Gln Ser Ile Lys Gln Gln Gly Ala Ser
    530                 535                 540

Gly Glu Val Tyr Cys Pro Ser Gly Glu Lys Cys Pro Leu Val Gly Ser
545                 550                 555                 560

Asn Val Pro Trp Ala Phe Met Gln Gly Glu Ile Ala Thr Ile Leu Ala
                565                 570                 575

Gly Asp Val Lys Val Lys Lys Glu Arg Asp Ser
            580                 585


<210> SEQ ID NO 47
<211> LENGTH: 4284
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

agcagagctg cggccggggg aacccagttt ccgaggaact tttcgccggc gccgggccgc     60

ctctgaggcc agggcaggac acgaacgcgc ggagcggcgg cggcgactga gagccggggc    120

cgcggcggcg ctccctagga agggccgtac gaggcggcgg gcccggcggg cctcccggag    180

gaggcggctg cgccatggac gagccaccct tcagcgaggc ggctttggag caggcgctgg    240

gcgagccgtg cgatctggac gcggcgctgc tgaccgacat cgaaggtgaa gtcggcgcgg    300

ggaggggtag ggccaacggc ctggacgccc caagggcggg cgcagatcgc ggagccatgg    360

attgcacttt cgaagacatg cttcagctta tcaacaacca agacagtgac ttccctggcc    420

tatttgaccc accctatgct gggagtgggg caggggcac agaccctgcc agccccgata    480

ccagctcccc aggcagcttg tctccacctc ctgccacatt gagctcctct cttgaagcct    540

tcctgagcgg gccgcaggca gcgccctcac ccctgtcccc tccccagcct gcacccactc    600

cattgaagat gtacccgtcc atgcccgctt tctcccctgg gcctggtatc aaggaagagt    660

cagtgccact gagcatcctg cagaccccca ccccacagcc cctgccaggg gccctcctgc    720

cacagagctt cccagcccca gccccaccgc agttcagctc cacccctgtg ttaggctacc    780

ccagccctcc gggaggcttc tctacaggaa gccctcccgg gaacacccag cagccgctgc    840

ctggcctgcc actggcttcc ccgccagggg tcccgcccgt ctccttgcac acccaggtcc    900

agagtgtggt cccccagcag ctactgacag tcacagctgc ccccacggca gcccctgtaa    960

cgaccactgt gacctcgcag atccagcagg tcccggtcct gctgcagccc cacttcatca   1020

aggcagactc gctgcttctg acagccatga agacagacgg agccactgtg aaggcggcag   1080

gtctcagtcc cctggtctct ggcaccactg tgcagacagg gcctttgccg accctggtga   1140

gtggcggaac catcttggca acagtcccac tggtcgtaga tgcggagaag ctgcctatca   1200

accggctcgc agctggcagc aaggccccgg cctctgccca gagccgtgga gagaagcgca   1260

cagcccacaa cgccattgag aagcgctacc gctcctccat caatgacaaa atcattgagc   1320

tcaaggatct ggtggtgggc actgaggcaa agctgaataa atctgctgtc ttgcgcaagg   1380

ccatcgacta cattcgcttt ctgcaacaca gcaaccagaa actcaagcag gagaacctaa   1440

gtctgcgcac tgctgtccac aaaagcaaat ctctgaagga tctggtgtcg gcctgtggca   1500

gtggagggaa cacagacgtg ctcatggagg gcgtgaagac tgaggtggag gacacactga   1560

ccccaccccc ctcggatgct ggctcacctt tccagagcag ccccttgtcc cttggcagca   1620
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ggggcagtgg cagcggtggc agtggcagtg actcggagcc tgacagccca gtctttgagg 1680

acagcaaggc aaagccagag cagcggccgt ctctgcacag ccggggcatg ctggaccgct 1740

cccgcctggc cctgtgcacg ctcgtcttcc tctgcctgtc ctgcaacccc ttggcctcct 1800

tgctgggggc ccgggggctt cccagcccct cagataccac cagcgtctac catagccctg 1860

ggcgcaacgt gctgggcacc gagagcagag atggccctgg ctgggcccag tggctgctgc 1920

ccccagtggt ctggctgctc aatgggctgt tggtgctcgt ctccttggtg cttctctttg 1980

tctacggtga gccagtcaca cggccccact caggccccgc cgtgtacttc tggaggcatc 2040

gcaagcaggc tgacctggac ctggcccggg gagactttgc ccaggctgcc cagcagctgt 2100

ggctggccct gcgggcactg ggccggcccc tgcccacctc ccacctggac ctggcttgta 2160

gcctcctctg gaacctcatc cgtcacctgc tgcagcgtct ctgggtgggc cgctggctgg 2220

caggccgggc aggggcctg cagcaggact gtgctctgcg agtggatgct agcgccagcg 2280

cccgagacgc agccctggtc taccataagc tgcaccagct gcacaccatg gggaagcaca 2340

caggcgggca cctcactgcc accaacctgg cgctgagtgc cctgaacctg gcagagtgtg 2400

caggggatgc cgtgtctgtg gcgacgctgg ccgagatcta tgtggcggct gcattgagag 2460

tgaagaccag tctcccacgg gccttgcatt ttctgacacg cttcttcctg agcagtgccc 2520

gccaggcctg cctggcacag agtggctcag tgcctcctgc catgcagtgg ctctgccacc 2580

ccgtgggcca ccgtttcttc gtggatgggg actggtccgt gctcagtacc ccatgggaga 2640

gcctgtacag cttggccggg aacccagtgg acccctggc ccaggtgact cagctattcc 2700

gggaacatct cttagagcga gcactgaact gtgtgaccca gcccaacccc agccctgggt 2760

cagctgatgg ggacaaggaa ttctcggatg ccctcgggta cctgcagctg ctgaacagct 2820

gttctgatgc tgcgggggct cctgcctaca gcttctccat cagttccagc atggccacca 2880

ccaccggcgt agacccggtg gccaagtggt gggcctctct gacagctgtg gtgatccact 2940

ggctgcggcg ggatgaggag gcggctgagc ggctgtgccc gctggtggag cacctgcccc 3000

gggtgctgca ggagtctgag agacccctgc ccagggcagc tctgcactcc ttcaaggctg 3060

cccgggccct gctgggctgt gccaaggcag agtctggtcc agccagcctg accatctgtg 3120

agaaggccag tgggtacctg caggacagcc tggctaccac accagccagc agctccattg 3180

acaaggccgt gcagctgttc ctgtgtgacc tgcttcttgt ggtgcgcacc agcctgtggc 3240

ggcagcagca gccccggcc ccggccccag cagcccaggg caccagcagc aggccccagg 3300

cttccgccct tgagctgcgt ggcttccaac gggacctgag cagcctgagg cggctggcac 3360

agagcttccg gcccgccatg cggagggtgt tcctacatga ggccacggcc cggctgatgg 3420

cgggggccag ccccacacgg acacaccagc tcctcgaccg cagtctgagg cggcgggcag 3480

gccccggtgg caaaggaggc gcggtggcgg agctggagcc gcggcccacg cggcgggagc 3540

acgcggaggc cttgctgctg gcctcctgct acctgccccc cggcttcctg tcggcgcccg 3600

ggcagcgcgt gggcatgctg gctgaggcgg cgcgcacact cgagaagctt ggcgatcgcc 3660

ggctgctgca cgactgtcag cagatgctca tgcgcctggg cggtgggacc actgtcactt 3720

ccagctagac cccgtgtccc cggcctcagc acccctgtct ctagccactt tggtcccgtg 3780

cagcttctgt cctgcgtcga agctttgaag gccgaaggca gtgcaagaga ctctggcctc 3840

cacagttcga cctgcggctg ctgtgtgcct tcgcggtgga aggcccgagg ggcgcgatct 3900

tgaccctaag accggcggcc atgatggtgc tgacctctgg tggccgatcg gggcactgca 3960

ggggccgagc cattttgggg ggccccccctc cttgctctgc aggcacctta gtggcttttt 4020

-continued

tcctcctgtg tacagggaag agaggggtac atttccctgt gctgacggaa gccaacttgg 4080

ctttcccgga ctgcaagcag ggctctgccc cagaggcctc tctctccgtc gtgggagaga 4140

gacgtgtaca tagtgtaggt cagcgtgctt agcctcctga cctgaggctc ctgtgctact 4200

ttgccttttg caaactttat tttcatagat tgagaagttt tgtacagaga attaaaaatg 4260

aaattattta taatctggaa aaaa 4284

<210> SEQ ID NO 48
<211> LENGTH: 1177
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 48

Met Asp Glu Pro Pro Phe Ser Glu Ala Ala Leu Glu Gln Ala Leu Gly
1 5 10 15

Glu Pro Cys Asp Leu Asp Ala Ala Leu Leu Thr Asp Ile Glu Gly Glu
20 25 30

Val Gly Ala Gly Arg Gly Arg Ala Asn Gly Leu Asp Ala Pro Arg Ala
35 40 45

Gly Ala Asp Arg Gly Ala Met Asp Cys Thr Phe Glu Asp Met Leu Gln
50 55 60

Leu Ile Asn Asn Gln Asp Ser Asp Phe Pro Gly Leu Phe Asp Pro Pro
65 70 75 80

Tyr Ala Gly Ser Gly Ala Gly Gly Thr Asp Pro Ala Ser Pro Asp Thr
85 90 95

Ser Ser Pro Gly Ser Leu Ser Pro Pro Pro Ala Thr Leu Ser Ser Ser
100 105 110

Leu Glu Ala Phe Leu Ser Gly Pro Gln Ala Ala Pro Ser Pro Leu Ser
115 120 125

Pro Pro Gln Pro Ala Pro Thr Pro Leu Lys Met Tyr Pro Ser Met Pro
130 135 140

Ala Phe Ser Pro Gly Pro Gly Ile Lys Glu Glu Ser Val Pro Leu Ser
145 150 155 160

Ile Leu Gln Thr Pro Thr Pro Gln Pro Leu Pro Gly Ala Leu Leu Pro
165 170 175

Gln Ser Phe Pro Ala Pro Ala Pro Pro Gln Phe Ser Ser Thr Pro Val
180 185 190

Leu Gly Tyr Pro Ser Pro Pro Gly Gly Phe Ser Thr Gly Ser Pro Pro
195 200 205

Gly Asn Thr Gln Gln Pro Leu Pro Gly Leu Pro Leu Ala Ser Pro Pro
210 215 220

Gly Val Pro Pro Val Ser Leu His Thr Gln Val Gln Ser Val Val Pro
225 230 235 240

Gln Gln Leu Leu Thr Val Thr Ala Ala Pro Thr Ala Ala Pro Val Thr
245 250 255

Thr Thr Val Thr Ser Gln Ile Gln Gln Val Pro Val Leu Leu Gln Pro
260 265 270

His Phe Ile Lys Ala Asp Ser Leu Leu Leu Thr Ala Met Lys Thr Asp
275 280 285

Gly Ala Thr Val Lys Ala Ala Gly Leu Ser Pro Leu Val Ser Gly Thr
290 295 300

Thr Val Gln Thr Gly Pro Leu Pro Thr Leu Val Ser Gly Gly Thr Ile
305 310 315 320

Leu Ala Thr Val Pro Leu Val Val Asp Ala Glu Lys Leu Pro Ile Asn

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               325                 330                 335

Arg Leu Ala Ala Gly Ser Lys Ala Pro Ala Ser Ala Gln Ser Arg Gly
            340                 345                 350

Glu Lys Arg Thr Ala His Asn Ala Ile Glu Lys Arg Tyr Arg Ser Ser
        355                 360                 365

Ile Asn Asp Lys Ile Ile Glu Leu Lys Asp Leu Val Val Gly Thr Glu
    370                 375                 380

Ala Lys Leu Asn Lys Ser Ala Val Leu Arg Lys Ala Ile Asp Tyr Ile
385                 390                 395                 400

Arg Phe Leu Gln His Ser Asn Gln Lys Leu Lys Gln Glu Asn Leu Ser
                405                 410                 415

Leu Arg Thr Ala Val His Lys Ser Lys Ser Leu Lys Asp Leu Val Ser
            420                 425                 430

Ala Cys Gly Ser Gly Gly Asn Thr Asp Val Leu Met Glu Gly Val Lys
        435                 440                 445

Thr Glu Val Glu Asp Thr Leu Thr Pro Pro Pro Ser Asp Ala Gly Ser
    450                 455                 460

Pro Phe Gln Ser Ser Pro Leu Ser Leu Gly Ser Arg Gly Ser Gly Ser
465                 470                 475                 480

Gly Gly Ser Gly Ser Asp Ser Glu Pro Asp Ser Pro Val Phe Glu Asp
                485                 490                 495

Ser Lys Ala Lys Pro Glu Gln Arg Pro Ser Leu His Ser Arg Gly Met
            500                 505                 510

Leu Asp Arg Ser Arg Leu Ala Leu Cys Thr Leu Val Phe Leu Cys Leu
        515                 520                 525

Ser Cys Asn Pro Leu Ala Ser Leu Leu Gly Ala Arg Gly Leu Pro Ser
    530                 535                 540

Pro Ser Asp Thr Thr Ser Val Tyr His Ser Pro Gly Arg Asn Val Leu
545                 550                 555                 560

Gly Thr Glu Ser Arg Asp Gly Pro Gly Trp Ala Gln Trp Leu Leu Pro
                565                 570                 575

Pro Val Val Trp Leu Leu Asn Gly Leu Leu Val Leu Val Ser Leu Val
            580                 585                 590

Leu Leu Phe Val Tyr Gly Glu Pro Val Thr Arg Pro His Ser Gly Pro
        595                 600                 605

Ala Val Tyr Phe Trp Arg His Arg Lys Gln Ala Asp Leu Asp Leu Ala
    610                 615                 620

Arg Gly Asp Phe Ala Gln Ala Ala Gln Gln Leu Trp Leu Ala Leu Arg
625                 630                 635                 640

Ala Leu Gly Arg Pro Leu Pro Thr Ser His Leu Asp Leu Ala Cys Ser
                645                 650                 655

Leu Leu Trp Asn Leu Ile Arg His Leu Leu Gln Arg Leu Trp Val Gly
            660                 665                 670

Arg Trp Leu Ala Gly Arg Ala Gly Gly Leu Gln Gln Asp Cys Ala Leu
        675                 680                 685

Arg Val Asp Ala Ser Ala Ser Ala Arg Asp Ala Ala Leu Val Tyr His
    690                 695                 700

Lys Leu His Gln Leu His Thr Met Gly Lys His Thr Gly Gly His Leu
705                 710                 715                 720

Thr Ala Thr Asn Leu Ala Leu Ser Ala Leu Asn Leu Ala Glu Cys Ala
                725                 730                 735

Gly Asp Ala Val Ser Val Ala Thr Leu Ala Glu Ile Tyr Val Ala Ala
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Arg Phe Phe Leu Ser Ser Ala Arg Gln Ala Cys Leu Ala Gln Ser Gly
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Ser Val Pro Pro Ala Met Gln Trp Leu Cys His Pro Val Gly His Arg
785                 790                 795                 800

Phe Phe Val Asp Gly Asp Trp Ser Val Leu Ser Thr Pro Trp Glu Ser
                805                 810                 815

Leu Tyr Ser Leu Ala Gly Asn Pro Val Asp Pro Leu Ala Gln Val Thr
            820                 825                 830

Gln Leu Phe Arg Glu His Leu Leu Glu Arg Ala Leu Asn Cys Val Thr
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Gln Pro Asn Pro Ser Pro Gly Ser Ala Asp Gly Asp Lys Glu Phe Ser
    850                 855                 860

Asp Ala Leu Gly Tyr Leu Gln Leu Leu Asn Ser Cys Ser Asp Ala Ala
865                 870                 875                 880

Gly Ala Pro Ala Tyr Ser Phe Ser Ile Ser Ser Ser Met Ala Thr Thr
                885                 890                 895

Thr Gly Val Asp Pro Val Ala Lys Trp Trp Ala Ser Leu Thr Ala Val
            900                 905                 910

Val Ile His Trp Leu Arg Arg Asp Glu Glu Ala Ala Glu Arg Leu Cys
        915                 920                 925

Pro Leu Val Glu His Leu Pro Arg Val Leu Gln Glu Ser Glu Arg Pro
    930                 935                 940

Leu Pro Arg Ala Ala Leu His Ser Phe Lys Ala Ala Arg Ala Leu Leu
945                 950                 955                 960

Gly Cys Ala Lys Ala Glu Ser Gly Pro Ala Ser Leu Thr Ile Cys Glu
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Lys Ala Ser Gly Tyr Leu Gln Asp Ser Leu Ala Thr Thr Pro Ala Ser
            980                 985                 990

Ser Ser Ile Asp Lys Ala Val Gln  Leu Phe Leu Cys Asp  Leu Leu Leu
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Val Val  Arg Thr Ser Leu Trp  Arg Gln Gln Gln Pro  Pro Ala Pro
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Ala Pro  Ala Ala Gln Gly Thr  Ser Ser Arg Pro Gln  Ala Ser Ala
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Leu Glu  Leu Arg Gly Phe Gln  Arg Asp Leu Ser Ser  Leu Arg Arg
    1040                1045                1050

Leu Ala  Gln Ser Phe Arg Pro  Ala Met Arg Arg Val  Phe Leu His
    1055                1060                1065

Glu Ala  Thr Ala Arg Leu Met  Ala Gly Ala Ser Pro  Thr Arg Thr
    1070                1075                1080

His Gln  Leu Leu Asp Arg Ser  Leu Arg Arg Arg Ala  Gly Pro Gly
    1085                1090                1095

Gly Lys  Gly Gly Ala Val Ala  Glu Leu Glu Pro Arg  Pro Thr Arg
    1100                1105                1110

Arg Glu  His Ala Glu Ala Leu  Leu Leu Ala Ser Cys  Tyr Leu Pro
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Pro Gly  Phe Leu Ser Ala Pro  Gly Gln Arg Val Gly  Met Leu Ala
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Glu Ala  Ala Arg Thr Leu Glu  Lys Leu Gly Asp Arg  Arg Leu Leu
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His Asp  Cys Gln Gln Met Leu  Met Arg Leu Gly Gly  Gly Thr Thr
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Val Thr Ser Ser
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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<211> LENGTH: 1124
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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Thr Ser Lys Val Asp Tyr Val Leu Phe Gln Ala Ala Thr Ala Ile Met
35 40 45

Glu Ala Val Val Arg Glu Trp Ile Leu Leu Glu Lys Gly Ser Ile Glu
50 55 60

Ser Leu Arg Thr Phe Leu Leu Thr Tyr Val Leu Gln Arg Pro Asn Leu
65 70 75 80

Gln Lys Tyr Val Arg Glu Gln Ile Leu Leu Ala Val Ala Val Ile Val
85 90 95

Lys Arg Gly Ser Leu Asp Lys Ser Ile Asp Cys Lys Ser Ile Phe His
100 105 110

Glu Val Ser Gln Leu Ile Ser Ser Gly Asn Pro Thr Val Gln Thr Leu
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Arg Val Phe Gln Glu Glu Asp Leu Arg Gln Ile Phe Met Leu Thr Val
                165                 170                 175

Glu Val Leu Gln Glu Phe Ser Arg Arg Glu Asn Leu Asn Ala Gln Met
            180                 185                 190

Ser Ser Val Phe Gln Arg Tyr Leu Ala Leu Ala Asn Gln Val Leu Ser
        195                 200                 205

Trp Asn Phe Leu Pro Pro Asn Leu Gly Arg His Tyr Ile Ala Met Phe
    210                 215                 220

Glu Ser Ser Gln Asn Val Leu Leu Lys Pro Thr Glu Ser Trp Arg Glu
225                 230                 235                 240

Thr Leu Leu Asp Ser Arg Val Met Glu Leu Phe Phe Thr Val His Arg
                245                 250                 255

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

Ala Gln Leu Ala Ser Leu His Gly Pro Ile Phe Pro Asp Glu Gly Ser
        275                 280                 285

Gln Val Asp Tyr Leu Ala His Phe Ile Glu Gly Leu Leu Asn Thr Ile
    290                 295                 300

Asn Gly Ile Glu Ile Glu Asp Ser Glu Ala Val Gly Ile Ser Ser Ile
305                 310                 315                 320

Ile Ser Asn Leu Ile Thr Val Phe Pro Arg Asn Val Leu Thr Ala Ile
                325                 330                 335

Pro Ser Glu Leu Phe Ser Ser Phe Val Asn Cys Leu Thr His Leu Thr
            340                 345                 350

Cys Ser Phe Gly Arg Ser Ala Ala Leu Glu Glu Val Leu Asp Lys Asp
        355                 360                 365

Asp Met Val Tyr Met Glu Ala Tyr Asp Lys Leu Leu Glu Ser Trp Leu
    370                 375                 380

Thr Leu Val Gln Asp Asp Lys His Phe His Lys Gly Phe Phe Thr Gln
385                 390                 395                 400

His Ala Val Gln Val Phe Asn Ser Tyr Ile Gln Cys His Leu Ala Ala
                405                 410                 415

Pro Asp Gly Thr Arg Asn Leu Thr Ala Asn Gly Val Ala Ser Arg Glu
            420                 425                 430

Glu Glu Glu Ile Ser Glu Leu Gln Glu Asp Asp Arg Asp Gln Phe Ser
        435                 440                 445

Asp Gln Leu Ala Ser Val Gly Met Leu Gly Arg Ile Ala Ala Glu His
    450                 455                 460

Cys Ile Pro Leu Leu Thr Ser Leu Leu Glu Glu Arg Val Thr Arg Leu
465                 470                 475                 480

His Gly Gln Leu Gln Arg His Gln Gln Gln Leu Leu Ala Ser Pro Gly
                485                 490                 495

Ser Ser Thr Val Asp Asn Lys Met Leu Asp Asp Leu Tyr Glu Asp Ile
            500                 505                 510

His Trp Leu Ile Leu Val Thr Gly Tyr Leu Leu Ala Asp Asp Thr Gln
        515                 520                 525

Gly Glu Thr Pro Leu Ile Pro Pro Glu Ile Met Glu Tyr Ser Ile Lys
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His Ser Ser Glu Val Asp Ile Asn Thr Thr Leu Gln Ile Leu Gly Ser
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Val Ile Arg Leu Leu Ser Ala Ile Leu Arg Val Ser Glu Val Glu Ser
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Arg Ala Ile Arg Ala Asp Leu Thr His Leu Leu Ser Pro Gln Met Gly
        595                 600                 605

Lys Asp Ile Val Trp Phe Leu Lys Arg Trp Ala Lys Thr Tyr Leu Leu
    610                 615                 620

Val Asp Glu Lys Leu Tyr Asp Gln Ile Ser Leu Pro Phe Ser Thr Ala
625                 630                 635                 640

Phe Gly Ala Asp Thr Glu Gly Ser Gln Trp Ile Ile Gly Tyr Leu Leu
                645                 650                 655

Gln Lys Val Ile Ser Asn Leu Ser Val Trp Ser Ser Glu Gln Asp Leu
            660                 665                 670

Ala Asn Asp Thr Val Gln Leu Leu Val Thr Leu Val Glu Arg Arg Glu
        675                 680                 685

Arg Ala Asn Leu Val Ile Gln Cys Glu Asn Trp Trp Asn Leu Ala Lys
    690                 695                 700

Gln Phe Ala Ser Arg Ser Pro Pro Leu Asn Phe Leu Ser Ser Pro Val
705                 710                 715                 720

Gln Arg Thr Leu Met Lys Ala Leu Val Leu Gly Gly Phe Ala His Met
                725                 730                 735

Asp Thr Glu Thr Lys Gln Gln Tyr Trp Thr Glu Val Leu Gln Pro Leu
            740                 745                 750

Gln Gln Arg Phe Leu Arg Val Ile Asn Gln Glu Asn Phe Gln Gln Met
        755                 760                 765

Cys Gln Gln Glu Glu Val Lys Gln Glu Ile Thr Ala Thr Leu Glu Ala
    770                 775                 780

Leu Cys Gly Ile Ala Glu Ala Thr Gln Ile Asp Asn Val Ala Ile Leu
785                 790                 795                 800

Phe Asn Phe Leu Met Asp Phe Leu Thr Asn Cys Ile Gly Leu Met Glu
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Val Tyr Lys Asn Thr Pro Glu Thr Val Asn Leu Ile Ile Glu Val Phe
            820                 825                 830

Val Glu Val Ala His Lys Gln Ile Cys Tyr Leu Gly Glu Ser Lys Ala
        835                 840                 845

Met Asn Leu Tyr Glu Ala Cys Leu Thr Leu Leu Gln Val Tyr Ser Lys
    850                 855                 860

Asn Asn Leu Gly Arg Gln Arg Ile Asp Val Thr Ala Glu Glu Glu Gln
865                 870                 875                 880

Tyr Gln Asp Leu Leu Leu Ile Met Glu Leu Leu Thr Asn Leu Leu Ser
                885                 890                 895

Lys Glu Phe Ile Asp Phe Ser Asp Thr Asp Glu Val Phe Arg Gly His
            900                 905                 910

Glu Pro Gly Gln Ala Ala Asn Arg Ser Val Ser Ala Ala Asp Val Val
        915                 920                 925

Leu Tyr Gly Val Asn Leu Ile Leu Pro Leu Met Ser Gln Asp Leu Leu
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Lys Phe Pro Thr Leu Cys Asn Gln Tyr Tyr Lys Leu Ile Thr Phe Ile
945                 950                 955                 960

Cys Glu Ile Phe Pro Glu Lys Ile Pro Gln Leu Pro Glu Asp Leu Phe
                965                 970                 975

Lys Ser Leu Met Tyr Ser Leu Glu Leu Gly Met Thr Ser Met Ser Ser
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            980                 985                 990

Glu Val Cys Gln Leu Cys Leu Glu  Ala Leu Thr Pro Leu  Ala Glu Gln
        995                1000                1005

Cys Ala  Lys Ala Gln Glu Thr  Asp Ser Pro Leu Phe  Leu Ala Thr
    1010                1015                1020

Arg His  Phe Leu Lys Leu Val  Phe Asp Met Leu Val  Leu Gln Lys
    1025                1030                1035

His Asn  Thr Glu Met Thr Thr  Ala Ala Gly Glu Ala  Phe Tyr Thr
    1040                1045                1050

Leu Val  Cys Leu His Gln Ala  Glu Tyr Ser Glu Leu  Val Glu Thr
    1055                1060                1065

Leu Leu  Ser Ser Gln Gln Asp  Pro Val Ile Tyr Gln  Arg Leu Ala
    1070                1075                1080

Asp Ala  Phe Asn Lys Leu Thr  Ala Ser Ser Thr Pro  Pro Thr Leu
    1085                1090                1095

Asp Arg  Lys Gln Lys Met Ala  Phe Leu Lys Ser Leu  Glu Glu Phe
    1100                1105                1110

Met Ala  Asn Val Gly Gly Leu  Leu Cys Val Lys
    1115                1120


<210> SEQ ID NO 51
<211> LENGTH: 3281
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 51

ggcaggggcg catccctcgc cacccgcggt cgcccagcac gccgggacgc gcgtggccat     60

ccagctcccc gggggcgttg gggggctccg cgggcctggg cctcgggatt cgcccgccgc    120

ttccccgggg agccgctgct gcaaagccag gttggggcgc cgggcccggc cagcgccctc    180

taggcagcgg aagtgcagct tgctttacat ccgtcctccc cgcctcgcag agttgggaga    240

aggcagggtg gggggtgtgg aaaaataaaa ggaaaagtcc ttgcaccatg tagatcagcg    300

tcccccactt tggcatcccg gccggccggg gacctcccag tctgcggcca tgaacgcgag    360

cagcgagggc gagagcttcg cgggctcggt gcaaattcca ggtggcacaa cggtgctggt    420

ggagctgact cccgacatcc atatctgcgg catctgcaag cagcagttta acaacctgga    480

tgcctttgta gctcacaagc aaagtggctg ccagctgaca ggcacatccg cagcagcccc    540

cagcacggtc cagtttgtat cggaggaaac agtgcctgcc acccagactc agaccaccac    600

cagaaccatc acctcggaga cccagacaat cacagtttca gctccagaat ttgtttttga    660

acatggctat caaacttacc tgcccacgga aagtaatgaa aaccagacag ccactgtcat    720

ctctctccct gccaagtcac gcaccaaaaa gcccacaaca ccacctgctc agaaaaggct    780

taactgttgc tatccaggtt gccaattcaa gactgcttat ggcatgaagg acatggagcg    840

gcatttaaaa attcacacgg gagacaaacc ccataagtgt gaagtctgtg gcaagtgctt    900

tagccggaaa gacaagctga aaactcacat gcggtgccac acgggcgtga agccctacaa    960

gtgtaagacg tgtgactacg ccgctgccga cagcagcagc ctcaacaagc acctgaggat   1020

ccactcggac gagcggccct tcaaatgcca gatctgcccc tacgccagcc gcaactccag   1080

ccagctcact gtccacctgc gatcccacac gggggacgcc cccttccagt gctggctctg   1140

tagcgccaag ttcaaaatca gctcggactt gaaaaggcac atgcgggtgc actcgggggа   1200

gaagcctttc aagtgcgagt tctgcaatgt ccgctgcacc atgaagggga acctcaagtc   1260

gcacatccgt atcaagcaca gcgggaataa cttcaagtgt cctcattgcg acttcctggg   1320
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tgacagcaaa gccaccctcc ggaagcacag ccgcgtgcac cagtcggagc atcctgagaa 1380

gtgctcggaa tgcagctact cctgctccag caaggccgcc ctgcgcatcc acgagcgtat 1440

ccactgcacc gaccgccctt tcaagtgcaa ctactgcagc ttcgacacca aacagcccag 1500

caacctgagc aagcacatga agaagttcca tggggacatg gttaagactg aggctctaga 1560

gaggaaggac accggcaggc agagcagccg gcaggtggcc aagctggatg ccaagaagag 1620

tttccactgc gatatatgcg atgcctcctt catgcgggag gactcgctcc gcagccacaa 1680

gagacagcac agtgagtaca gtgagagtaa gaactcggac gtgaccgttc tccagtttca 1740

gatcgacccc agcaagcagc ccgccacgcc cctcactgtg ggacacctcc aggtgcccct 1800

ccagcccagc caagtgcccc agttcagcga gggaagagtc aaaatcatcg ttgggcatca 1860

ggtgccccag gcgaacacca tcgtccaggc tgccgccgct gcagtgaaca tcgtcccgcc 1920

tgccttggtg gcccagaacc cagaggaact cccagggaac agccggctgc agatcctgcg 1980

ccaggtcagt ctgatcgccc cccctcagtc ctcgcggtgt ccgagcgagg cgggcgcaat 2040

gacccagccg gctgtcctgc tgaccaccca cgagcagacg gacggagcca ctctgcacca 2100

gactctcatc cccacggcct caggtggccc ccaggaaggc tctggcaatc aaactttcat 2160

taccagttcg ggtattactt gcactgactt tgaaggccta aacgccttga ttcaggaggg 2220

gacagcagaa gtgacagtgg tgagcgatgg aggccagaac atcgcagtgg ccaccacagc 2280

gccaccggtc ttctcctcct cttcccagca agaactaccc aagcagacct actccatcat 2340

tcaaggggca gcccatccag ctttgctctg tcccgccgac tccattccag attagtgctt 2400

aaaaaaacaa aaggagtggg ggaaaggaat tgagaaaaag aaatcttaag tagaattctc 2460

taaaaggttt gctcttaatg ttttctttgt tttgttttgt ttttgagacg gagtctcgct 2520

ctgtttccca ggctggagtg cagtggcgct atcttggctc actgcaacgt ccgcctccca 2580

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catgactggc taatttttgt atatttagta gagacggggt ttcatcatgt tgaactcctg 2700

acctcaagtg atctgcccac ctcagcctcc caaagtgctg ggattacagg tgtgagccac 2760

catgcctggc cgtggtttgc tcttaatgtt tttaaggatg gttgtgaatc cccctggccc 2820

cataataaat tgtaatttta tactgcttac tataattttt ttaacactgt aacaactttg 2880

agaccacctc tgaatcgtcg cattataact gttgtagaat cttaaatgtt accaagatga 2940

ttccaatgag gggttggaat taaatgcatt aagtagtgaa ttcatgtgtt tgtttccaac 3000

ttgattttcc aactctaata aaggtttctg tccatcttat tacatttgtg tagtaaatgg 3060

tacttcccag cctctctttt gccccattct ggaatactcc ccagagtttg ggggtgttca 3120

tgttttatac atgtaagtct gttggcatga aggaccattt tctacataat atgacatgga 3180

tacttgaccc aaaaaaaaat gtttagtgct aatgagcaga aaatgaatgg ttccataata 3240

aattgatatc tgattaaaat ataaaaaaaa aaaaaaaaaa a 3281

<210> SEQ ID NO 52
<211> LENGTH: 681
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 52

Met Asn Ala Ser Ser Glu Gly Glu Ser Phe Ala Gly Ser Val Gln Ile
1 5 10 15

Pro Gly Gly Thr Thr Val Leu Val Glu Leu Thr Pro Asp Ile His Ile
20 25 30

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```
Cys Gly Ile Cys Lys Gln Gln Phe Asn Asn Leu Asp Ala Phe Val Ala
        35                  40                  45

His Lys Gln Ser Gly Cys Gln Leu Thr Gly Thr Ser Ala Ala Ala Pro
    50                  55                  60

Ser Thr Val Gln Phe Val Ser Glu Glu Thr Val Pro Ala Thr Gln Thr
65                  70                  75                  80

Gln Thr Thr Thr Arg Thr Ile Thr Ser Glu Thr Gln Thr Ile Thr Val
                85                  90                  95

Ser Ala Pro Glu Phe Val Phe Glu His Gly Tyr Gln Thr Tyr Leu Pro
            100                 105                 110

Thr Glu Ser Asn Glu Asn Gln Thr Ala Thr Val Ile Ser Leu Pro Ala
        115                 120                 125

Lys Ser Arg Thr Lys Lys Pro Thr Thr Pro Pro Ala Gln Lys Arg Leu
    130                 135                 140

Asn Cys Cys Tyr Pro Gly Cys Gln Phe Lys Thr Ala Tyr Gly Met Lys
145                 150                 155                 160

Asp Met Glu Arg His Leu Lys Ile His Thr Gly Asp Lys Pro His Lys
                165                 170                 175

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

His Met Arg Cys His Thr Gly Val Lys Pro Tyr Lys Cys Lys Thr Cys
        195                 200                 205

Asp Tyr Ala Ala Ala Asp Ser Ser Ser Leu Asn Lys His Leu Arg Ile
    210                 215                 220

His Ser Asp Glu Arg Pro Phe Lys Cys Gln Ile Cys Pro Tyr Ala Ser
225                 230                 235                 240

Arg Asn Ser Ser Gln Leu Thr Val His Leu Arg Ser His Thr Gly Asp
                245                 250                 255

Ala Pro Phe Gln Cys Trp Leu Cys Ser Ala Lys Phe Lys Ile Ser Ser
            260                 265                 270

Asp Leu Lys Arg His Met Arg Val His Ser Gly Glu Lys Pro Phe Lys
        275                 280                 285

Cys Glu Phe Cys Asn Val Arg Cys Thr Met Lys Gly Asn Leu Lys Ser
    290                 295                 300

His Ile Arg Ile Lys His Ser Gly Asn Asn Phe Lys Cys Pro His Cys
305                 310                 315                 320

Asp Phe Leu Gly Asp Ser Lys Ala Thr Leu Arg Lys His Ser Arg Val
                325                 330                 335

His Gln Ser Glu His Pro Glu Lys Cys Ser Glu Cys Ser Tyr Ser Cys
            340                 345                 350

Ser Ser Lys Ala Ala Leu Arg Ile His Glu Arg Ile His Cys Thr Asp
        355                 360                 365

Arg Pro Phe Lys Cys Asn Tyr Cys Ser Phe Asp Thr Lys Gln Pro Ser
    370                 375                 380

Asn Leu Ser Lys His Met Lys Lys Phe His Gly Asp Met Val Lys Thr
385                 390                 395                 400

Glu Ala Leu Glu Arg Lys Asp Thr Gly Arg Gln Ser Ser Arg Gln Val
                405                 410                 415

Ala Lys Leu Asp Ala Lys Lys Ser Phe His Cys Asp Ile Cys Asp Ala
            420                 425                 430

Ser Phe Met Arg Glu Asp Ser Leu Arg Ser His Lys Arg Gln His Ser
        435                 440                 445

Glu Tyr Ser Glu Ser Lys Asn Ser Asp Val Thr Val Leu Gln Phe Gln
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    450                 455                 460

Ile Asp Pro Ser Lys Gln Pro Ala Thr Pro Leu Thr Val Gly His Leu
465                 470                 475                 480

Gln Val Pro Leu Gln Pro Ser Gln Val Pro Gln Phe Ser Glu Gly Arg
                485                 490                 495

Val Lys Ile Ile Val Gly His Gln Val Pro Gln Ala Asn Thr Ile Val
            500                 505                 510

Gln Ala Ala Ala Ala Ala Val Asn Ile Val Pro Pro Ala Leu Val Ala
        515                 520                 525

Gln Asn Pro Glu Glu Leu Pro Gly Asn Ser Arg Leu Gln Ile Leu Arg
    530                 535                 540

Gln Val Ser Leu Ile Ala Pro Pro Gln Ser Ser Arg Cys Pro Ser Glu
545                 550                 555                 560

Ala Gly Ala Met Thr Gln Pro Ala Val Leu Leu Thr Thr His Glu Gln
                565                 570                 575

Thr Asp Gly Ala Thr Leu His Gln Thr Leu Ile Pro Thr Ala Ser Gly
            580                 585                 590

Gly Pro Gln Glu Gly Ser Gly Asn Gln Thr Phe Ile Thr Ser Ser Gly
        595                 600                 605

Ile Thr Cys Thr Asp Phe Glu Gly Leu Asn Ala Leu Ile Gln Glu Gly
    610                 615                 620

Thr Ala Glu Val Thr Val Val Ser Asp Gly Gly Gln Asn Ile Ala Val
625                 630                 635                 640

Ala Thr Thr Ala Pro Pro Val Phe Ser Ser Ser Ser Gln Gln Glu Leu
                645                 650                 655

Pro Lys Gln Thr Tyr Ser Ile Ile Gln Gly Ala Ala His Pro Ala Leu
            660                 665                 670

Leu Cys Pro Ala Asp Ser Ile Pro Asp
        675                 680


<210> SEQ ID NO 53
<211> LENGTH: 5457
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 53

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ccgaggagac cccgggcgag gagctgcgag ccggaggagg ccgcgcggac tccgggcttt    120

ccgccgtcgc ggggatctcg gggggcaaag ggatcgccgg ggagggggac cagagagccg    180

cgcccgccgc gcggagcgcc ccttcgcgtc ccctgcacca tgagctgggg caccgagctc    240

tgggatcagt ttgacaactt agaaaaacac acacagtggg gaattgatat tcttgagaaa    300

tatatcaagt ttgtgaaaga aaggacagag attgaactca gctatgcaaa gcaactcagg    360

aatctttcaa agaagtacca acctaaaaag aactcgaagg aggaagaaga atacaagtat    420

acgtcatgta aagctttcat ttccaacctg aacgaaatga atgattacgc agggcagcat    480

gaagttatct ccgagaacat ggcatcacag atcattgtgg acttggcacg ctatgttcag    540

gaactgaaac aggagaggaa atcaaacttt cacgatggcc gtaaagcaca gcagcacatc    600

gagacttgct ggaagcagct tgaatctagt aaaaggcgat ttgaacgcga ttgcaaagag    660

gcggacaggg cgcagcagta ctttgagaaa atggacgctg acatcaatgt cacaaaagcg    720

gatgttgaaa aggcccgaca acaagctcaa atacgtcacc aaatggcaga ggacagcaaa    780

gcagattact catccattct ccagaaattc aaccatgagc agcatgaata ttaccatact    840
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cacatcccca acatcttcca gaaaatacaa gagatggagg aaaggaggat tgtgagaatg 900

ggagagtcca tgaagacata tgcagaggtt gatcggcagg tgatcccaat cattgggaag 960

tgcctggatg gaatagtaaa agcagccgaa tcaattgatc agaaaaatga ttcacagctg 1020

gtaatagaag cttataaatc agggtttgag cctcctggag acattgaatt tgaggattac 1080

actcagccaa tgaagcgcac tgtgtcagat aacagccttt caaattccag aggagaaggc 1140

aaaccagacc tcaaatttgg tggcaaatcc aaaggaaagt tatggccgtt catcaaaaaa 1200

aataagctta tgtccctttt aacatccccc catcagcctc cccctccccc tcctgcctct 1260

gcctcaccct ctgctgttcc caacggcccc cagtctccca agcagcaaaa ggaacccctc 1320

tcccatcgct tcaacgagtt catgacctcc aaacccaaaa tccactgctt caggagccta 1380

aagcgtgggc tttctctcaa gctgggtgca acaccggagg atttcagcaa cctcccacct 1440

gaacaaagaa ggaaaaagct gcagcagaaa gtcgatgagt taaataaaga aattcagaag 1500

gagatggatc aaagagatgc cataacaaaa atgaaagatg tctacctaaa gaatcctcag 1560

atgggagacc cagccagttt ggatcacaaa ttagcagaag tcagccaaaa tatagagaaa 1620

ctgcgagtag agacccagaa atttgaggcc tggctggctg aggttgaagg ccggctccca 1680

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gacagcccac ccctccgcag ccccatccct gcggggcggt ctctctctct ctccagcatg 2220

ctccctgcgg ccctgccctc ccgcccagcc cgggccacct cgtgggggac aagtctcgcc 2280

agcgcccacc cccatggctc gggtcagtcc tcatcgctcc ccctccccac cccgcgcagg 2340

ccactgagac ggtgggacac acgcccctac ctgctccttc ctgggccctc agtccacccg 2400

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ttcctgtccc tgagaactgt agatcatgcg cttgtgagcg aggccctccc ctctgcacca 2940

gctcattgca aagcgaacat cctctccttt ccaggagccc caggattagc atctgaaaag 3000

ggtagcactt ccttttttgt tgttgttttt ttttttttgt tgagacggga gtctcgctct 3060

attgttcaga ctggagtgca gtggcatgat ctcggctcac tacaacctcc acctcctggg 3120

ttccagcgat tctcctgcct cagcctccca aatagctgtg attacaggcg tgcaccacca 3180

cgcccggcta atgtttgtat ttttagtaga gacagggttt caccgtgttg gtcaggctgg 3240

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ctcgtggtcc tttgagggat cccgccgcca ccacccttgt attttatcac gtgctcttca 3420

gggcatgtgg aattcgttga gtttgctttt agagccaagt ttctttccct gtgtgggttt 3480

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agagcagagc agcccctcct ctcatttggt gcagaaacag tcaagaggaa ccattggcct 3600

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atgaatctaa gacaaggaag tcctatagaa gccaaaggga cagggacgga aaggacaggt 3780

cccaagggat ggggctgtct ttacttgtgg aaaccaggaa attgctcctc tcagccaacc 3840

aaggttgacc acacaccacc cttccggagc agctcagtca gccctcgggg acgagaaacc 3900

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gtaggtgagc gtgagcctct ctgactgctt cttccccggg ggggactgca aaccgctcag 4020

ggttgcggca gagccatgga cttccggtcc ctgcaacggg tgacctaagc gtggtgcacc 4080

catcagtcac gcaggaggac tgacttgaca gacgaaagac aagcccggat gacacagggt 4140

gagaagagtc agggccgcac ctctgtccct gcaaaccaac aggtgcatgg tgagtgtggc 4200

agtccccaca gctccacaat gggctccccc gccaacgggg acgacaggga tcttcaggaa 4260

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gaatttcccg tgaacgtctc cttcctcccc cgtatctgcc gcctgtcact tcgccaccgt 4800

gctagaatac tgttgtgttg taagatgact aattttaaaa gaacctgccc tgaaaagttc 4860

ttagaaacgc agtgaaaggg aggaacttgt cctttaccca gtttttcctt tgtaggatgg 4920

gaaagtataa aaaggcacag aaggttgtca tgggctgttc cttgggggtt tttatcctgc 4980

tcaccgtgga gataagcctg cggcttgtct aaccagcgca gcgcaaaggt ctcgatgcct 5040

tttggtaaca tccgtcattg cagaagaaag tttacacgac gtcaaaaagt gacgttcatg 5100

ctaagtgttt ttccagaaat attggtttca tgtttcttat tggctctgcc tcctgtgctt 5160

atatcatcca aaaacttttt aaaaaggtcc agaattctat tttaacctga tgttgagcac 5220

ctttaaaatg ttcgtatgtg tgttgcacta attctaaact ttggaggcat tttgctgtgt 5280

gaggccgatc gccactgtaa aggtcctaga gttgcctgtt tgtctctgga gatggaatta 5340

aaccaaataa agagcttcca ctggaggctt gtattgacct tgtaactata tgttaatctc 5400

gtgttaaaat aaaatataac ttgtgaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaa 5457

<210> SEQ ID NO 54
<211> LENGTH: 617
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 54

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Met Ser Trp Gly Thr Glu Leu Trp Asp Gln Phe Asp Asn Leu Glu Lys
1               5                  10                  15

His Thr Gln Trp Gly Ile Asp Ile Leu Glu Lys Tyr Ile Lys Phe Val
            20                  25                  30

Lys Glu Arg Thr Glu Ile Glu Leu Ser Tyr Ala Lys Gln Leu Arg Asn
        35                  40                  45

Leu Ser Lys Lys Tyr Gln Pro Lys Lys Asn Ser Lys Glu Glu Glu Glu
    50                  55                  60

Tyr Lys Tyr Thr Ser Cys Lys Ala Phe Ile Ser Asn Leu Asn Glu Met
65                  70                  75                  80

Asn Asp Tyr Ala Gly Gln His Glu Val Ile Ser Glu Asn Met Ala Ser
                85                  90                  95

Gln Ile Ile Val Asp Leu Ala Arg Tyr Val Gln Glu Leu Lys Gln Glu
            100                 105                 110

Arg Lys Ser Asn Phe His Asp Gly Arg Lys Ala Gln Gln His Ile Glu
        115                 120                 125

Thr Cys Trp Lys Gln Leu Glu Ser Ser Lys Arg Arg Phe Glu Arg Asp
    130                 135                 140

Cys Lys Glu Ala Asp Arg Ala Gln Gln Tyr Phe Glu Lys Met Asp Ala
145                 150                 155                 160

Asp Ile Asn Val Thr Lys Ala Asp Val Glu Lys Ala Arg Gln Gln Ala
                165                 170                 175

Gln Ile Arg His Gln Met Ala Glu Asp Ser Lys Ala Asp Tyr Ser Ser
            180                 185                 190

Ile Leu Gln Lys Phe Asn His Glu Gln His Glu Tyr Tyr His Thr His
        195                 200                 205

Ile Pro Asn Ile Phe Gln Lys Ile Gln Glu Met Glu Glu Arg Arg Ile
    210                 215                 220

Val Arg Met Gly Glu Ser Met Lys Thr Tyr Ala Glu Val Asp Arg Gln
225                 230                 235                 240

Val Ile Pro Ile Ile Gly Lys Cys Leu Asp Gly Ile Val Lys Ala Ala
                245                 250                 255

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

Lys Ser Gly Phe Glu Pro Pro Gly Asp Ile Glu Phe Glu Asp Tyr Thr
        275                 280                 285

Gln Pro Met Lys Arg Thr Val Ser Asp Asn Ser Leu Ser Asn Ser Arg
    290                 295                 300

Gly Glu Gly Lys Pro Asp Leu Lys Phe Gly Gly Lys Ser Lys Gly Lys
305                 310                 315                 320

Leu Trp Pro Phe Ile Lys Lys Asn Lys Leu Met Ser Leu Leu Thr Ser
                325                 330                 335

Pro His Gln Pro Pro Pro Pro Pro Pro Ala Ser Ala Ser Pro Ser Ala
            340                 345                 350

Val Pro Asn Gly Pro Gln Ser Pro Lys Gln Gln Lys Glu Pro Leu Ser
        355                 360                 365

His Arg Phe Asn Glu Phe Met Thr Ser Lys Pro Lys Ile His Cys Phe
    370                 375                 380

Arg Ser Leu Lys Arg Gly Leu Ser Leu Lys Leu Gly Ala Thr Pro Glu
385                 390                 395                 400

Asp Phe Ser Asn Leu Pro Pro Glu Gln Arg Arg Lys Lys Leu Gln Gln
                405                 410                 415
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Lys Val Asp Glu Leu Asn Lys Glu Ile Gln Lys Glu Met Asp Gln Arg
            420                 425                 430

Asp Ala Ile Thr Lys Met Lys Asp Val Tyr Leu Lys Asn Pro Gln Met
        435                 440                 445

Gly Asp Pro Ala Ser Leu Asp His Lys Leu Ala Glu Val Ser Gln Asn
    450                 455                 460

Ile Glu Lys Leu Arg Val Glu Thr Gln Lys Phe Glu Ala Trp Leu Ala
465                 470                 475                 480

Glu Val Glu Gly Arg Leu Pro Ala Arg Ser Glu Gln Ala Arg Arg Gln
                485                 490                 495

Ser Gly Leu Tyr Asp Ser Gln Asn Pro Pro Thr Val Asn Asn Cys Ala
            500                 505                 510

Gln Asp Arg Glu Ser Pro Asp Gly Ser Tyr Thr Glu Glu Gln Ser Gln
        515                 520                 525

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

Asp Glu Glu Pro Leu Pro Ala Ile Gly Thr Cys Lys Ala Leu Tyr Thr
545                 550                 555                 560

Phe Glu Gly Gln Asn Glu Gly Thr Ile Ser Val Val Glu Gly Glu Thr
                565                 570                 575

Leu Tyr Val Ile Glu Glu Asp Lys Gly Asp Gly Trp Thr Arg Ile Arg
            580                 585                 590

Arg Asn Glu Asp Glu Glu Gly Tyr Val Pro Thr Ser Tyr Val Glu Val
        595                 600                 605

Cys Leu Asp Lys Asn Ala Lys Asp Ser
    610                 615


<210> SEQ ID NO 55
<211> LENGTH: 696
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

ttccccccccc ccccccccc ccccgcccga gcacaggaca cagctgggtt ctgaagcttc     60

tgagttctgc agcctcacct ctgagaaaac ctcttttcca ccaataccat gaagctctgc    120

gtgactgtcc tgtctctcct catgctagta gctgccttct gctctccagc gctctcagca    180

ccaatgggct cagaccctcc caccgcctgc tgcttttctt acaccgcgag gaagcttcct    240

cgcaactttg tggtagatta ctatgagacc agcagcctct gctcccagcc agctgtggta    300

ttccaaacca aaagaagcaa gcaagtctgt gctgatccca gtgaatcctg ggtccaggag    360

tacgtgtatg acctggaact gaactgagct gctcagagac aggaagtctt cagggaaggt    420

cacctgagcc cggatgcttc tccatgagac acatctcctc catactcagg actcctctcc    480

gcagttcctg tcccttctct taatttaatc ttttttatgt gccgtgttat tgtattaggt    540

gtcatttcca ttatttatat tagtttagcc aaaggataag tgtcctatgg ggatggtcca    600

ctgtcactgt ttctctgctg ttgcaaatac atggataaca catttgattc tgtgtgtttt    660

ccataataaa actttaaaat aaaatgcaga cagtta                              696


<210> SEQ ID NO 56
<211> LENGTH: 92
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 56

Met Lys Leu Cys Val Thr Val Leu Ser Leu Leu Met Leu Val Ala Ala
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-continued

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1               5                   10                  15

Phe Cys Ser Pro Ala Leu Ser Ala Pro Met Gly Ser Asp Pro Pro Thr
            20                  25                  30

Ala Cys Cys Phe Ser Tyr Thr Ala Arg Lys Leu Pro Arg Asn Phe Val
        35                  40                  45

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

Phe Gln Thr Lys Arg Ser Lys Gln Val Cys Ala Asp Pro Ser Glu Ser
65                  70                  75                  80

Trp Val Gln Glu Tyr Val Tyr Asp Leu Glu Leu Asn
                85                  90
```

<210> SEQ ID NO 57
<211> LENGTH: 5064
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57

```
gagaagggga ccttcaggtc caggcaaagg gggaacttct gtcgtgggaa cgaaaaagaa     60

agaggattta cagggtgggg ggacagaggg gcagcaggaa ccagaaggga gacagtggcg    120

gtcgcaccgg ggccgatccg agagttcccc ttagagaacg gagctcacgg gcggggaggc    180

ctcacctgct agtaggacgc agaaagacag aaggcgaagg agacccccctg ccgtagccat    240

cttgcctctc tgctgagcgg aagcccccgt tcggctcctg tctgttagcg gcctctctag    300

gctaccactg acaccgtctc tgtggcccgg agcctaagag accggaagtt cgtgtttcca    360

ggcgcttccg gaaaccgcgg gagagggtcg ctgacgtgga ggcgtccgaa gggcagcagg    420

gtgtgtcggg gctcggatta agacatcgga gtcggagacc tgagagatgt taaccaaatt    480

cgagaccaag agcgcgcggg tcaaagggct cagctttcac cccaaaagac cttggatcct    540

gactagttta cataatgggg tcatccagtt atgggactat cggatgtgca ctctcattga    600

caagtttgat gaacatgatg gtccagtgcg aggcattgac ttccataagc agcagccact    660

gttcgtctct ggaggagatg actataagat taaggtttgg aattacaagc ttcggcgctg    720

tcttttcaca ttgcttgggc acttagatta tattcgcacc acgtttttc atcatgaata    780

tccctggatt ctgagtgcct ccgatgatca gaccatccga gtgtggaatt ggcaatctag    840

aacctgtgtt tgtgtgttaa cagggcacaa ccattatgtg atgtgtgctc agttccaccc    900

cacagaagac ttggtagtat cagccagcct ggaccagact gtgcgcgttt gggatatttc    960

tggtctgagg aaaaaaaacc tgtcccctgg tgcggtggaa tcggatgtga gaggaataac   1020

tggggttgat ctatttggaa ctacagatgc agtggtgaag catgtactag agggtcacga   1080

tcgtggagta aactgggctg ccttccaccc cactatgccc cttattgtat ctggggcaga   1140

tgatcgtcaa gtgaagatct ggcgcatgaa tgaatcaaag gcatgggagg ttgatacctg   1200

ccggggccat tacaacaatg tatcttgtgc cgtcttccac cctcgccaag agttgatcct   1260

cagcaattct gaggacaaga gtattcgagt ctgggatatg tctaagcgga ctggggttca   1320

gactttccgc agagaccatg atcgtttctg ggtcctagct gctcacccta accttaacct   1380

ctttgcagca ggccatgatg gtggtatgat tgtgtttaag ctggaacggg aacggccagc   1440

ctatgctgtt catggcaata tgctacacta tgtcaaggac cgattcttac gacagctgga   1500

tttcaacagc tccaaagatg tagctgtgat gcagttgcgg agtggttcca agtttccagt   1560

attcaatatg tcatacaatc cagcagaaaa tgcagtcctg ctttgtacaa gagctagcaa   1620

tctagagaat agtacctatg acctgtacac catccctaaa gatgctgact cccagaatcc   1680
```

-continued

tgatgcgcct gaagggaaac gatcctcagg cctgacagcc gtttgggtcg ctcgaaatcg 1740

gtttgctgtc ctagatcgga tgcattcgct tctgatcaag aatctgaaga atgagatcac 1800

caaaaaggta caggtgccca actgtgatga gatcttctat gctggcacag gcaatctcct 1860

gcttcgagat gcggactcta tcacactctt tgacgtacag cagaagcgga ctctggcatc 1920

tgtgaagatt tctaaagtga aatacgttat ctggtcagca gacatgtcac atgtagcact 1980

actagccaaa cacgccattg tgatctgtaa ccgcaaactg gatgctttat gtaacattca 2040

tgagaacatt cgtgtcaaga gtggggcctg ggatgagagt ggggtattta tctataccac 2100

aagcaaccac atcaaatatg ctgtcaccac tggggaccac gggatcattc gaactctgga 2160

tttacccatc tatgtcacac gggtgaaggg caacaatgta tactgcctag acagggagtg 2220

tcgtccccgg gtactcacca ttgatcccac tgagttcaaa ttcaagctgg ccctgatcaa 2280

cagaaaatat gatgaggtac tgcacatggt gaggaatgcc aaactagttg gccagtctat 2340

tattgcttat ctccagaaga agggctatcc tgaagtggca ctgcattttg tcaaggatga 2400

gaaaactcgc tttagtctgg cactggagtg tggaaacatt gagattgctc tggaagcagc 2460

caaagcactg gatgacaaga actgctggga aaagctggga gaagtggccc tgctgcaggg 2520

gaaccaccag attgtggaaa tgtgctatca gcgtaccaaa aactttgaca aagtttcctt 2580

cctgtatctt atcactggca acttagaaaa acttcgcaag atgatgaaga ttgctgagat 2640

cagaaaggac atgagtggcc actatcagaa tgccctatac ctgggtgatg tgtcagagcg 2700

tgtgcggatc ctgaagaact gtggacagaa gtccctggcc tatctcacag ctgctaccca 2760

tggcttagat gaagaagctg agagcctaaa ggagacattt gacccagaga aggagacaat 2820

cccagacatt gaccctaatg ccaagctgct ccagccacct gcacctatca tgccattgga 2880

taccaattgg cctttattga ctgtatccaa aggatttttt gaaggcacca ttgccagcaa 2940

agggaaggga ggagcactgg ctgctgacat tgacattgac actgttggta cagagggctg 3000

gggagaggat gcagagctgc agttggatga agatgggttt gtggaggcta cagaaggttt 3060

gggggatgat gctcttggca agggacagga agaaggaggt ggctgggatg tagaagaaga 3120

tctggagctc cctcctgagc tggatatatc ccctggggca gctggtgggg ctgaagatgg 3180

tttctttgtg cccccaacca agggaacaag tccaactcag atctggtgta ataactctca 3240

gcttccagtt gatcacatcc tggcaggctc tttcgaaaca gccatgcggc tccttcatga 3300

ccaagtaggg gtaatccagt ttggccccta caagcaactg ttcctacaga catacgcccg 3360

aggccgcaca acctatcagg ctctgccctg cctaccctcc atgtatggct atcctaatcg 3420

caactggaag gatgcagggc tgaagaatgg tgtaccagct gtgggcctga agcttaatga 3480

cctcatccaa cggttgcagc tgtgctacca gctcaccaca gttggcaaat ttgaggaggc 3540

tgtggaaaaa ttccgttcca tccttctcag tgtgccactt cttgttgtgg acaataaaca 3600

agagattgca gaggcccagc agctcatcac catttgccgt gagtacattg tgggtttgtc 3660

cgtggagaca gaaaggaaga agctgcccaa agagactcta gaacagcaga agcgcatctg 3720

tgagatggca gcctatttca cccactcaaa cctgcagcct gtgcacatga tcctggtgct 3780

gcgtacagcc ctcaatctgt tcttcaagct caagaacttc aagacagctg ccacctttgc 3840

tcggcgccta ctagaactcg ggcccaagcc tgaggtggcc caacagaccc gaaaaatcct 3900

gtctgcctgt gagaagaatc ccacagatgc ctaccagctc aattatgaca tgcacaaccc 3960

ctttgacatt tgtgctgcat catatcggcc catctaccgt ggaaagccag tagaaaagtg 4020

tccactcagt ggggcctgct attcccctga gttcaaaggt caaatctgca gggtcaccac 4080

-continued

agtgacagag attggcaaag atgtgattgg tttaaggatc agtcctctgc agtttcgcta 4140

aggccccctt tgtgtgcatg ggtcagtcac catatgttcc ccccagagaa tgtgtctata 4200

tcctccttct aacagcacct tccccctgca gctactcttc agatctggct ctctgtaccc 4260

taaaacctag tatcttttttc tcttctatgg aaaatccgaa ggtctaaact tgacttttt 4320

gaggtcttct caacttgact acagttgtgc tcataattgt ccttgccttt ccagcttaat 4380

tattttaagg aacaaatgaa aactctgggc tgggtggagt ggctcatacc tgtaatccca 4440

gcactttggg aggctacggt gggcagatca tctgaggcca ggagttcgag acctgcctgg 4500

ccaacatggc aacaccccgt ctctaataaa aatataaaaa ttagcctggc atggtagcat 4560

gcgcctatag tcccagctgc tcaggaggct gaggcatgag aatcgcttga acctaggagg 4620

tggaggttgc attcaactga gatcatacca cttcattcca gcctgggtga cagagcaaga 4680

ctctgtctca aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaggaaaac tctgtgatgg 4740

acatttgttt agtaaatccc ttcagtattt atccctcctt tccccacagc agctttcttt 4800

cctgtcaact agaaaggagc aggatgtaat aaatacattt tggtgtgact aggccacacc 4860

aactcttaat catctcccat tttccttaga catttaaatt tcaaggcagg taccctctgt 4920

gtactcagaa atttgaagaa gttatttggt tttccaaaat gcacactgcg ggttattgat 4980

ttgttcttta caactattgt tctcatattt ctcacactaa ataaatctct atgagagctt 5040

cttgaaaaaa aaaaaaaaaa agcg 5064

<210> SEQ ID NO 58
<211> LENGTH: 1224
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

Met Leu Thr Lys Phe Glu Thr Lys Ser Ala Arg Val Lys Gly Leu Ser
1 5 10 15

Phe His Pro Lys Arg Pro Trp Ile Leu Thr Ser Leu His Asn Gly Val
20 25 30

Ile Gln Leu Trp Asp Tyr Arg Met Cys Thr Leu Ile Asp Lys Phe Asp
35 40 45

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

Leu Phe Val Ser Gly Gly Asp Asp Tyr Lys Ile Lys Val Trp Asn Tyr
65 70 75 80

Lys Leu Arg Arg Cys Leu Phe Thr Leu Leu Gly His Leu Asp Tyr Ile
85 90 95

Arg Thr Thr Phe Phe His His Glu Tyr Pro Trp Ile Leu Ser Ala Ser
100 105 110

Asp Asp Gln Thr Ile Arg Val Trp Asn Trp Gln Ser Arg Thr Cys Val
115 120 125

Cys Val Leu Thr Gly His Asn His Tyr Val Met Cys Ala Gln Phe His
130 135 140

Pro Thr Glu Asp Leu Val Val Ser Ala Ser Leu Asp Gln Thr Val Arg
145 150 155 160

Val Trp Asp Ile Ser Gly Leu Arg Lys Lys Asn Leu Ser Pro Gly Ala
165 170 175

Val Glu Ser Asp Val Arg Gly Ile Thr Gly Val Asp Leu Phe Gly Thr
180 185 190

Thr Asp Ala Val Val Lys His Val Leu Glu Gly His Asp Arg Gly Val

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        195                 200                 205

Asn Trp Ala Ala Phe His Pro Thr Met Pro Leu Ile Val Ser Gly Ala
    210                 215                 220

Asp Asp Arg Gln Val Lys Ile Trp Arg Met Asn Glu Ser Lys Ala Trp
225                 230                 235                 240

Glu Val Asp Thr Cys Arg Gly His Tyr Asn Asn Val Ser Cys Ala Val
                245                 250                 255

Phe His Pro Arg Gln Glu Leu Ile Leu Ser Asn Ser Glu Asp Lys Ser
            260                 265                 270

Ile Arg Val Trp Asp Met Ser Lys Arg Thr Gly Val Gln Thr Phe Arg
        275                 280                 285

Arg Asp His Asp Arg Phe Trp Val Leu Ala Ala His Pro Asn Leu Asn
    290                 295                 300

Leu Phe Ala Ala Gly His Asp Gly Gly Met Ile Val Phe Lys Leu Glu
305                 310                 315                 320

Arg Glu Arg Pro Ala Tyr Ala Val His Gly Asn Met Leu His Tyr Val
                325                 330                 335

Lys Asp Arg Phe Leu Arg Gln Leu Asp Phe Asn Ser Ser Lys Asp Val
            340                 345                 350

Ala Val Met Gln Leu Arg Ser Gly Ser Lys Phe Pro Val Phe Asn Met
        355                 360                 365

Ser Tyr Asn Pro Ala Glu Asn Ala Val Leu Leu Cys Thr Arg Ala Ser
    370                 375                 380

Asn Leu Glu Asn Ser Thr Tyr Asp Leu Tyr Thr Ile Pro Lys Asp Ala
385                 390                 395                 400

Asp Ser Gln Asn Pro Asp Ala Pro Glu Gly Lys Arg Ser Ser Gly Leu
                405                 410                 415

Thr Ala Val Trp Val Ala Arg Asn Arg Phe Ala Val Leu Asp Arg Met
            420                 425                 430

His Ser Leu Leu Ile Lys Asn Leu Lys Asn Glu Ile Thr Lys Lys Val
        435                 440                 445

Gln Val Pro Asn Cys Asp Glu Ile Phe Tyr Ala Gly Thr Gly Asn Leu
    450                 455                 460

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

Arg Thr Leu Ala Ser Val Lys Ile Ser Lys Val Lys Tyr Val Ile Trp
                485                 490                 495

Ser Ala Asp Met Ser His Val Ala Leu Leu Ala Lys His Ala Ile Val
            500                 505                 510

Ile Cys Asn Arg Lys Leu Asp Ala Leu Cys Asn Ile His Glu Asn Ile
        515                 520                 525

Arg Val Lys Ser Gly Ala Trp Asp Glu Ser Gly Val Phe Ile Tyr Thr
    530                 535                 540

Thr Ser Asn His Ile Lys Tyr Ala Val Thr Thr Gly Asp His Gly Ile
545                 550                 555                 560

Ile Arg Thr Leu Asp Leu Pro Ile Tyr Val Thr Arg Val Lys Gly Asn
                565                 570                 575

Asn Val Tyr Cys Leu Asp Arg Glu Cys Arg Pro Arg Val Leu Thr Ile
            580                 585                 590

Asp Pro Thr Glu Phe Lys Phe Lys Leu Ala Leu Ile Asn Arg Lys Tyr
        595                 600                 605

Asp Glu Val Leu His Met Val Arg Asn Ala Lys Leu Val Gly Gln Ser
    610                 615                 620
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Ile Ile Ala Tyr Leu Gln Lys Lys Gly Tyr Pro Glu Val Ala Leu His
625                 630                 635                 640

Phe Val Lys Asp Glu Lys Thr Arg Phe Ser Leu Ala Leu Glu Cys Gly
                645                 650                 655

Asn Ile Glu Ile Ala Leu Glu Ala Ala Lys Ala Leu Asp Asp Lys Asn
            660                 665                 670

Cys Trp Glu Lys Leu Gly Glu Val Ala Leu Leu Gln Gly Asn His Gln
        675                 680                 685

Ile Val Glu Met Cys Tyr Gln Arg Thr Lys Asn Phe Asp Lys Val Ser
    690                 695                 700

Phe Leu Tyr Leu Ile Thr Gly Asn Leu Glu Lys Leu Arg Lys Met Met
705                 710                 715                 720

Lys Ile Ala Glu Ile Arg Lys Asp Met Ser Gly His Tyr Gln Asn Ala
                725                 730                 735

Leu Tyr Leu Gly Asp Val Ser Glu Arg Val Arg Ile Leu Lys Asn Cys
            740                 745                 750

Gly Gln Lys Ser Leu Ala Tyr Leu Thr Ala Ala Thr His Gly Leu Asp
        755                 760                 765

Glu Glu Ala Glu Ser Leu Lys Glu Thr Phe Asp Pro Glu Lys Glu Thr
    770                 775                 780

Ile Pro Asp Ile Asp Pro Asn Ala Lys Leu Leu Gln Pro Pro Ala Pro
785                 790                 795                 800

Ile Met Pro Leu Asp Thr Asn Trp Pro Leu Leu Thr Val Ser Lys Gly
                805                 810                 815

Phe Phe Glu Gly Thr Ile Ala Ser Lys Gly Lys Gly Gly Ala Leu Ala
            820                 825                 830

Ala Asp Ile Asp Ile Asp Thr Val Gly Thr Glu Gly Trp Gly Glu Asp
        835                 840                 845

Ala Glu Leu Gln Leu Asp Glu Asp Gly Phe Val Glu Ala Thr Glu Gly
    850                 855                 860

Leu Gly Asp Asp Ala Leu Gly Lys Gly Gln Glu Glu Gly Gly Gly Trp
865                 870                 875                 880

Asp Val Glu Glu Asp Leu Glu Leu Pro Pro Glu Leu Asp Ile Ser Pro
                885                 890                 895

Gly Ala Ala Gly Gly Ala Glu Asp Gly Phe Phe Val Pro Pro Thr Lys
            900                 905                 910

Gly Thr Ser Pro Thr Gln Ile Trp Cys Asn Asn Ser Gln Leu Pro Val
        915                 920                 925

Asp His Ile Leu Ala Gly Ser Phe Glu Thr Ala Met Arg Leu Leu His
    930                 935                 940

Asp Gln Val Gly Val Ile Gln Phe Gly Pro Tyr Lys Gln Leu Phe Leu
945                 950                 955                 960

Gln Thr Tyr Ala Arg Gly Arg Thr Thr Tyr Gln Ala Leu Pro Cys Leu
                965                 970                 975

Pro Ser Met Tyr Gly Tyr Pro Asn Arg Asn Trp Lys Asp Ala Gly Leu
            980                 985                 990

Lys Asn Gly Val Pro Ala Val Gly  Leu Lys Leu Asn Asp  Leu Ile Gln
        995                 1000                1005

Arg Leu  Gln Leu Cys Tyr Gln  Leu Thr Thr Val Gly  Lys Phe Glu
    1010                1015                1020

Glu Ala  Val Glu Lys Phe Arg  Ser Ile Leu Leu Ser  Val Pro Leu
    1025                1030                1035

Leu Val  Val Asp Asn Lys Gln  Glu Ile Ala Glu Ala  Gln Gln Leu
    1040                1045                1050
```

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Ile Thr  Ile Cys Arg Glu Tyr  Ile Val Gly Leu Ser  Val Glu Thr
    1055                 1060                 1065

Glu Arg  Lys Lys Leu Pro Lys  Glu Thr Leu Glu Gln  Gln Lys Arg
    1070                 1075                 1080

Ile Cys  Glu Met Ala Ala Tyr  Phe Thr His Ser Asn  Leu Gln Pro
    1085                 1090                 1095

Val His  Met Ile Leu Val Leu  Arg Thr Ala Leu Asn  Leu Phe Phe
    1100                 1105                 1110

Lys Leu  Lys Asn Phe Lys Thr  Ala Ala Thr Phe Ala  Arg Arg Leu
    1115                 1120                 1125

Leu Glu  Leu Gly Pro Lys Pro  Glu Val Ala Gln Gln  Thr Arg Lys
    1130                 1135                 1140

Ile Leu  Ser Ala Cys Glu Lys  Asn Pro Thr Asp Ala  Tyr Gln Leu
    1145                 1150                 1155

Asn Tyr  Asp Met His Asn Pro  Phe Asp Ile Cys Ala  Ala Ser Tyr
    1160                 1165                 1170

Arg Pro  Ile Tyr Arg Gly Lys  Pro Val Glu Lys Cys  Pro Leu Ser
    1175                 1180                 1185

Gly Ala  Cys Tyr Ser Pro Glu  Phe Lys Gly Gln Ile  Cys Arg Val
    1190                 1195                 1200

Thr Thr  Val Thr Glu Ile Gly  Lys Asp Val Ile Gly  Leu Arg Ile
    1205                 1210                 1215

Ser Pro  Leu Gln Phe Arg
    1220
```

<210> SEQ ID NO 59
<211> LENGTH: 2374
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

```
gtcatgcagt gcgccggaga actgtgctct ttgaggccga cgctaggggc ccggaaggaa     60

actgcgaggc gaaggtgacc ggggaccgag catttcagat ctgctcggta gacctggtgc    120

accaccacca tgttggctgc aaggctggtg tgtctccgga cactaccttc tagggttttc    180

cacccagctt tcaccaaggc ctcccctgtt gtgaagaatt ccatcacgaa gaatcaatgg    240

ctgttaacac ctagcaggga atatgccacc aaaacaagaa ttgggatccg gcgtgggaga    300

actggccaag aactcaaaga ggcagcattg gaaccatcga tggaaaaaat atttaaaatt    360

gatcagatgg gaagatggtt tgttgctgga ggggctgctg ttggtcttgg agcattgtgc    420

tactatggct tgggactgtc taatgagatt ggagctattg aaaaggctgt aatttggcct    480

cagtatgtca aggatagaat tcattccacc tatatgtact tagcagggag tattggttta    540

acagctttgt ctgccatagc aatcagcaga acgcctgttc tcatgaactt catgatgaga    600

ggctcttggg tgacaattgg tgtgaccttt gcagccatgg ttggagctgg aatgctggta    660

cgatcaatac catatgacca gagcccaggc ccaaagcatc ttgcttggtt gctacattct    720

ggtgtgatgg gtgcagtggt ggctcctctg acaatattag ggggtcctct tctcatcaga    780

gctgcatggt acacagctgg cattgtggga ggcctctcca ctgtggccat gtgtgcgccc    840

agtgaaaagt ttctgaacat gggtgcaccc ctgggagtgg gcctgggtct cgtctttgtg    900

tcctcattgg gatctatgtt tcttccacct accaccgtgg ctggtgccac tctttactca    960

gtggcaatgt acggtggatt agttcttttc agcatgttcc ttctgtatga tacccagaaa   1020

gtatcaagcg tgcagaagta tcaccaatgt atggagttca aaaatatgat cccattaact   1080
```

cgatgctgag tatctacatg gatacattaa atatatttat gcgagttgca actatgctgg 1140

caactggagg caacagaaag aaatgaagtg actcagcttc tggcttctct gctacatcaa 1200

atatcttgtt taatggggca gatatgcatt aaatagtttg tacaagcagc tttcgttgaa 1260

gtttagaaga taagaaacat gtcatcatat ttaaatgttc cggtaatgtg atgcctcagg 1320

tctgcctttt tttctggaga ataaatgcag taatcctctc ccaaataagc acacacattt 1380

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gtcatgagaa tgtaagtctt ttttctactt taaaatttag taggttcact gagtaactaa 1500

aatttagcaa acctgtgttt gcatatttttt ttggagtgca gaatattgta attaatgtca 1560

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tttccaatat agatgtggtc atgtttgact tgtacagaat gttaatcata cagagaatcc 1860

ttgatggaat tatatatgtg tgttttactt ttgaatgtta caaaaggaaa taactttaaa 1920

actattctca agagaaaata ttcaaagcat gaaatatgtt gctttttcca gaatacaaac 1980

agtatactca tgaattgcta agtgtttttt tatttttgca tatttattga actgtctaat 2040

tgaatacagc ttgctcttgt cacctcttca agctttcaag cctttataga aaagcttctt 2100

tgtggcttac actggaaatt atgaaagcag tttttctcct aagacttttg gtttctcgca 2160

ttgcctctca gactaagcac taaaaagcaa agcaaaacag aactagttct gtcttaatga 2220

aatatatcaa cccaaaagtg taatgaggaa aatgcttcat tagtttcccc tagcagactt 2280

ttacttctct tacactgcta caccattact ttcttgagac atttgtaagt cctttgatac 2340

agaagagtta tatttaggag gctttaatga aggg 2374

<210> SEQ ID NO 60
<211> LENGTH: 319
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

Met Leu Ala Ala Arg Leu Val Cys Leu Arg Thr Leu Pro Ser Arg Val
1 5 10 15

Phe His Pro Ala Phe Thr Lys Ala Ser Pro Val Val Lys Asn Ser Ile
20 25 30

Thr Lys Asn Gln Trp Leu Leu Thr Pro Ser Arg Glu Tyr Ala Thr Lys
35 40 45

Thr Arg Ile Gly Ile Arg Arg Gly Arg Thr Gly Gln Glu Leu Lys Glu
50 55 60

Ala Ala Leu Glu Pro Ser Met Glu Lys Ile Phe Lys Ile Asp Gln Met
65 70 75 80

Gly Arg Trp Phe Val Ala Gly Gly Ala Ala Val Gly Leu Gly Ala Leu
85 90 95

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

Ala Val Ile Trp Pro Gln Tyr Val Lys Asp Arg Ile His Ser Thr Tyr
115 120 125

Met Tyr Leu Ala Gly Ser Ile Gly Leu Thr Ala Leu Ser Ala Ile Ala
130 135 140

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Ile Ser Arg Thr Pro Val Leu Met Asn Phe Met Met Arg Gly Ser Trp
145                 150                 155                 160

Val Thr Ile Gly Val Thr Phe Ala Ala Met Val Gly Ala Gly Met Leu
                165                 170                 175

Val Arg Ser Ile Pro Tyr Asp Gln Ser Pro Gly Pro Lys His Leu Ala
            180                 185                 190

Trp Leu Leu His Ser Gly Val Met Gly Ala Val Val Ala Pro Leu Thr
        195                 200                 205

Ile Leu Gly Gly Pro Leu Leu Ile Arg Ala Ala Trp Tyr Thr Ala Gly
    210                 215                 220

Ile Val Gly Gly Leu Ser Thr Val Ala Met Cys Ala Pro Ser Glu Lys
225                 230                 235                 240

Phe Leu Asn Met Gly Ala Pro Leu Gly Val Gly Leu Gly Leu Val Phe
                245                 250                 255

Val Ser Ser Leu Gly Ser Met Phe Leu Pro Pro Thr Thr Val Ala Gly
            260                 265                 270

Ala Thr Leu Tyr Ser Val Ala Met Tyr Gly Gly Leu Val Leu Phe Ser
        275                 280                 285

Met Phe Leu Leu Tyr Asp Thr Gln Lys Val Ser Ser Val Gln Lys Tyr
    290                 295                 300

His Gln Cys Met Glu Phe Lys Asn Met Ile Pro Leu Thr Arg Cys
305                 310                 315


<210> SEQ ID NO 61
<211> LENGTH: 2182
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 61

ggagagcgag gggcggcggc ggcgcccgct ggcgctcaag catggcggcg gcggcattgg     60

gcagctcctc aggctcggcg tccccggccg tggctgagct ctgccagaac accccggaga    120

ccttttgga ggcctccaag ctgctgctca cctatgctga caacatcctc agaaacccta    180

atgatgaaaa atatagatcc atccggattg gaaacacagc cttttctact agactcttgc    240

ctgtcagagg agctgttgaa tgtttatttg aaatgggctt tgaagaggga gaaacacatc    300

tcatctttcc taaaaaagct tcagtggagc agctgcaaaa aattcgtgac ctgattgcca    360

tagagagaag tagcagactg gatggctcaa ataagagcca caaagtaaag tcatctcagc    420

aacctgcagc cagtacccag cttcctacaa caccatcttc aaatcccagt gggttaaacc    480

agcacacaag gaaccgtcaa gggcagtcat cagatccacc atctgcttca acggttgctg    540

ctgactcagc cattctagaa gttcttcagt ccaacattca gcatgtgctg gtctatgaaa    600

atcctgctct tcaggagaaa gcgttggctt gtattccggt ccaagaacta aaaaggaaat    660

cacaagaaaa gttatcgaga gctagaaaat tggataaagg tatcaatata agtgatgagg    720

attttctttt gctggagctt ttgcactggt ttaaggaaga attttttcac tgggtgaata    780

acgttttgtg cagcaaatgt ggtggacaga ctaggtctag agatagatca ttactgccca    840

gtgatgatga gctgaagtgg ggtgcaaagg aagtggaaga tcattactgt gatgcctgcc    900

agttcagcaa tcgattccca agatataata accctgagaa acttttggaa acaagatgtg    960

gacggtgtgg cgagtgggcc aattgtttta cactgtgctg ccgagctgta gggtttgaag   1020

ctcgctatgt ttgggattac acagaccatg tctggacaga agtctattct ccttctcagc   1080

agcggtggct gcactgtgat gcatgtgaag atgtctgtga caagccactc ctttatgaaa   1140

taggatgggg caagaagctt tcctatgtca tagcattttc aaaagatgag gtagttgatg   1200
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tcacttggcg atattcctgc aaacatgaag aggtgattgc cagaagaact aaggttaaag 1260

aagcattact tcgagacact attaatgggc ttaataagca gaggcaactg tttttgtcag 1320

aaaacagaag gaaagaactt ctccagagga taattgtgga gcttgttgaa tttatatctc 1380

ccaaaacccc taaacctgga gaacttgggg gaagaatatc tgggtcagtg gcttggagag 1440

tagcccgagg tgaaatgggt ctacagagaa aagaaacctt gtttattccc tgtgaaaatg 1500

agaagatttc taaacagctc cacctttgtt acaatattgt gaaagatcgt tatgttcgag 1560

tttcaaataa caatcaaacc atttctggat gggagaatgg cgtgtggaaa atggaatcta 1620

tattcagaaa agttgaaaca gactggcaca tggtatattt ggcccgaaag gaaggatcat 1680

cttttgctta tatttcctgg aagtttgagt gtgggtcagt tggcctaaaa gtagatagca 1740

tttctattag aacaagtagt caaacttttc agactggaac agtagaatgg aaattgcgat 1800

ctgatacagc acaagtagaa ctgacaggcg ataacagtct tcactcctat gctgattttt 1860

ctggtgccac tgaagttatt ttggaagcag aattaagcag aggagatggt gatgtcgctt 1920

ggcaacacac ccagctgttt agacaaagct taaatgacca tgaagaaaat tgtttggaga 1980

taattataaa attcagtgac ctttgagaac ctgaacatta tagaaaagct ggcaataatc 2040

aaggacttac tgaagtagtc tgttggttca gtgcatgctt agttggcagt taccaccctg 2100

tgctagcata tttcttttgc tagctatcca tcatgtaacc ctcatgaaaa ttatctttat 2160

acgtggacta taataaaata tt 2182

<210> SEQ ID NO 62
<211> LENGTH: 654
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

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

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

Lys Leu Leu Leu Thr Tyr Ala Asp Asn Ile Leu Arg Asn Pro Asn Asp
35 40 45

Glu Lys Tyr Arg Ser Ile Arg Ile Gly Asn Thr Ala Phe Ser Thr Arg
50 55 60

Leu Leu Pro Val Arg Gly Ala Val Glu Cys Leu Phe Glu Met Gly Phe
65 70 75 80

Glu Glu Gly Glu Thr His Leu Ile Phe Pro Lys Lys Ala Ser Val Glu
85 90 95

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

Leu Asp Gly Ser Asn Lys Ser His Lys Val Lys Ser Ser Gln Gln Pro
115 120 125

Ala Ala Ser Thr Gln Leu Pro Thr Thr Pro Ser Ser Asn Pro Ser Gly
130 135 140

Leu Asn Gln His Thr Arg Asn Arg Gln Gly Gln Ser Ser Asp Pro Pro
145 150 155 160

Ser Ala Ser Thr Val Ala Ala Asp Ser Ala Ile Leu Glu Val Leu Gln
165 170 175

Ser Asn Ile Gln His Val Leu Val Tyr Glu Asn Pro Ala Leu Gln Glu
180 185 190

Lys Ala Leu Ala Cys Ile Pro Val Gln Glu Leu Lys Arg Lys Ser Gln

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        195                 200                 205

Glu Lys Leu Ser Arg Ala Arg Lys Leu Asp Lys Gly Ile Asn Ile Ser
    210                 215                 220

Asp Glu Asp Phe Leu Leu Leu Glu Leu Leu His Trp Phe Lys Glu Glu
225                 230                 235                 240

Phe Phe His Trp Val Asn Asn Val Leu Cys Ser Lys Cys Gly Gly Gln
                245                 250                 255

Thr Arg Ser Arg Asp Arg Ser Leu Leu Pro Ser Asp Asp Glu Leu Lys
            260                 265                 270

Trp Gly Ala Lys Glu Val Glu Asp His Tyr Cys Asp Ala Cys Gln Phe
        275                 280                 285

Ser Asn Arg Phe Pro Arg Tyr Asn Asn Pro Glu Lys Leu Leu Glu Thr
    290                 295                 300

Arg Cys Gly Arg Cys Gly Glu Trp Ala Asn Cys Phe Thr Leu Cys Cys
305                 310                 315                 320

Arg Ala Val Gly Phe Glu Ala Arg Tyr Val Trp Asp Tyr Thr Asp His
                325                 330                 335

Val Trp Thr Glu Val Tyr Ser Pro Ser Gln Gln Arg Trp Leu His Cys
            340                 345                 350

Asp Ala Cys Glu Asp Val Cys Asp Lys Pro Leu Leu Tyr Glu Ile Gly
        355                 360                 365

Trp Gly Lys Lys Leu Ser Tyr Val Ile Ala Phe Ser Lys Asp Glu Val
    370                 375                 380

Val Asp Val Thr Trp Arg Tyr Ser Cys Lys His Glu Glu Val Ile Ala
385                 390                 395                 400

Arg Arg Thr Lys Val Lys Glu Ala Leu Leu Arg Asp Thr Ile Asn Gly
                405                 410                 415

Leu Asn Lys Gln Arg Gln Leu Phe Leu Ser Glu Asn Arg Arg Lys Glu
            420                 425                 430

Leu Leu Gln Arg Ile Ile Val Glu Leu Val Glu Phe Ile Ser Pro Lys
        435                 440                 445

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

Trp Arg Val Ala Arg Gly Glu Met Gly Leu Gln Arg Lys Glu Thr Leu
465                 470                 475                 480

Phe Ile Pro Cys Glu Asn Glu Lys Ile Ser Lys Gln Leu His Leu Cys
                485                 490                 495

Tyr Asn Ile Val Lys Asp Arg Tyr Val Arg Val Ser Asn Asn Asn Gln
            500                 505                 510

Thr Ile Ser Gly Trp Glu Asn Gly Val Trp Lys Met Glu Ser Ile Phe
        515                 520                 525

Arg Lys Val Glu Thr Asp Trp His Met Val Tyr Leu Ala Arg Lys Glu
    530                 535                 540

Gly Ser Ser Phe Ala Tyr Ile Ser Trp Lys Phe Glu Cys Gly Ser Val
545                 550                 555                 560

Gly Leu Lys Val Asp Ser Ile Ser Ile Arg Thr Ser Ser Gln Thr Phe
                565                 570                 575

Gln Thr Gly Thr Val Glu Trp Lys Leu Arg Ser Asp Thr Ala Gln Val
            580                 585                 590

Glu Leu Thr Gly Asp Asn Ser Leu His Ser Tyr Ala Asp Phe Ser Gly
        595                 600                 605

Ala Thr Glu Val Ile Leu Glu Ala Glu Leu Ser Arg Gly Asp Gly Asp
    610                 615                 620
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Val Ala Trp Gln His Thr Gln Leu Phe Arg Gln Ser Leu Asn Asp His
625 630 635 640

Glu Glu Asn Cys Leu Glu Ile Ile Ile Lys Phe Ser Asp Leu
645 650

<210> SEQ ID NO 63
<211> LENGTH: 4816
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

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ggagtgcagt ggtgtgacct tggcttgctg caacccttg cctcctgggt tcaagtgatt 120

ctcattgcct cagcctccta agtagctggg attacaggtt ttataggatc acattgacaa 180

aagtaccatg gagttttatg agtcagcata ttttattgtt cttattcctt caatagttat 240

tacagtaatt ttcctcttct tctggctttt catgaaagaa acattatatg atgaagttct 300

tgcaaaacag aaaagagaac aaaagcttat tcctaccaaa acagataaaa agaaagcaga 360

aaagaaaaag aataaaaaga aagaaatcca gaatggaaac ctccatgaat ccgactctga 420

gagtgtacct cgagacttta aattatcaga tgctttggca gtagaagatg atcaagttgc 480

acctgttcca ttgaatgtcg ttgaaacttc aagtagtgtt agggaaagaa aaaagaagga 540

aaagaaacaa aagcctgtgc ttgaagagca ggtcatcaaa gaaagtgacg catcaaagat 600

tcctggcaaa aaagtagaac ctgtcccagt tactaaacag cccacccctc cctctgaagc 660

agctgcctcg aagaagaaac cagggcagaa gaagtctaaa aatggaagcg atgaccagga 720

taaaaaggtg gaaactctca tggtaccatc aaaaaggcaa gaagcattgc ccctccacca 780

agagactaaa caagaaagtg gatcagggaa gaagaaagct tcatcaaaga aacaaaagac 840

agaaaatgtc ttcgtagatg aaccccttat tcatgcaact acttatattc ctttgatgga 900

taatgctgac tcaagtcctg tggtagataa gagagaggtt attgatttgc ttaaacctga 960

ccaagtagaa gggatccaga aatctgggac taaaaaactg aagaccgaaa ctgacaaaga 1020

aaatgctgaa gtgaagttta aagattttct tctgtccttg aagactatga tgttttctga 1080

agatgaggct ctttgtgttg tagacttgct aaaggagaag tctggtgtaa tacaagatgc 1140

tttaaagaag tcaagtaagg gagaattgac tacgcttata catcagcttc aagaaaagga 1200

caagttactc gctgctgtga aggaagatgc tgctgctaca aaggatcggt gtaagcagtt 1260

aacccaggaa atgatgacag agaaagaaag aagcaatgtg gttataacaa ggatgaaaga 1320

tcgaattgga acattagaaa aggaacataa tgtatttcaa aacaaaatac atgtcagtta 1380

tcaagagact caacagatgc agatgaagtt tcagcaagtt cgtgagcaga tggaggcaga 1440

gatagctcac ttgaagcagg aaaatggtat actgagagat gcagtcagca acactacaaa 1500

tcaactggaa agcaagcagt ctgcagaact aaataaacta cgccaggatt atgctaggtt 1560

ggtgaatgag ctgactgaga aaacaggaaa gctacagcaa gaggaagtcc aaaagaagaa 1620

tgctgagcaa gcagctactc agttgaaggt tcaactacaa gaagctgaga gaaggtggga 1680

agaagttcag agctacatca ggaagagaac agcggaacat gaggcagcac agcaagattt 1740

acagagtaaa tttgtggcca aagaaaatga agtacagagt ctgcatagta agcttacaga 1800

taccttggta tcaaaacaac agttggagca aagactaatg cagttaatgg aatcagagca 1860

gaaaagggtg aacaaagaag agtctctaca aatgcaggtt caggatattt tggagcagaa 1920

tgaggctttg aaagctcaaa ttcagcagtt ccattcccag atagcagccc agacctccgc 1980

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ttcagttcta gcagaagaat tacataaagt gattgcagaa aaggataagc agataaaaca 2040

gactgaagat tctttagcaa gtgaacgtga tcgtttaaca agtaaagaag aggaacttaa 2100

ggatatacag aatatgaatt tcttattaaa agctgaagtg cagaaattac aggccctggc 2160

aaatgagcag gctgctgctg cacatgaatt ggagaagatg caacaaagtg tttatgttaa 2220

agatgataaa ataagattgc tggaagagca actacaacat gaaatttcaa acaaaatgga 2280

agaatttaag attctaaatg accaaaacaa agcattaaaa tcagaagttc agaagctaca 2340

gactcttgtt tctgaacagc ctaataagga tgttgtggaa caaatggaaa aatgcattca 2400

agaaaaagat gagaagttaa agactgtgga agaattactt gaaactggac ttattcaggt 2460

ggcaactaaa gaagaggagc tgaatgcaat aagaacagaa aattcatctc tgacaaaaga 2520

agttcaagac ttaaaagcta agcaaaatga tcaggtttct tttgcctctc tagttgaaga 2580

acttaagaaa gtgatccatg agaaagatgg aaagatcaag tctgtagaag agcttctgga 2640

ggcagaactt ctcaaagttg ctaacaagga gaaaactgtt caggatttga aacaggaaat 2700

aaaggctcta aaagaagaaa taggaaatgt ccagcttgaa aaggctcaac agttatctat 2760

cacttccaaa gttcaggagc ttcagaactt attaaaagga aaagaggaac agatgaatac 2820

catgaaggct gttttggaag agaaagagaa agacctagcc aatacaggga agtggttaca 2880

ggatcttcaa gaagaaaatg aatctttaaa agcacatgtt caggaagtag cacaacataa 2940

cttgaaagag gcctcttctg catcacagtt tgaagaactt gagattgtgt tgaaagaaaa 3000

ggaaaatgaa ttgaagaggt tagaagccat gctaaaagag agggagagtg atctttctag 3060

caaaacacag ctgttacagg atgtacaaga tgaaaacaaa ttgtttaagt cccaaattga 3120

gcagcttaaa caacaaaact accaacaggc atcttctttt ccccctcatg aagaattatt 3180

aaaagtaatt tcagaaagag agaaagaaat aagtggtctc tggaatgagt tagattcttt 3240

gaaggatgca gttgaacacc agaggaagaa aaacaatgac cttcgggaga aaaactggga 3300

agcaatggaa gcattggcat caactgaaaa aatgctgcag gacaaagtga acaagacttc 3360

caaggaaagg cagcaacagg tggaagctgt tgagttggag gctaaagaag ttctcaaaaa 3420

attatttcca aaggtgtctg tcccttctaa tttgagttat ggtgaatggt tgcatggatt 3480

tgaaaaaaag gcaaaagaat gtatggctgg aacttcaggg tcagaggagg ttaaggttct 3540

agagcacaag ttgaaagaag ctgatgaaat gcacacattg ttacagctag agtgtgaaaa 3600

atacaaatcc gtccttgcag aaacagaagg aattttacag aagctacaga gaagtgttga 3660

gcaagaagaa aataaatgga aagttaaggt cgatgaatca cacaagacta ttaaacagat 3720

gcagtcatca tttacatctt cagaacaaga gctagagcga ttaagaagcg aaaataagga 3780

tattgaaaat ctgagaagag aacgagaaca tttggaaatg gaactagaaa aggcagagat 3840

ggaacgatct acctatgtta cagaagtcag agagctgaaa gatctgttga ctgaattgca 3900

gaaaaaactt gatgattcat attctgaagc agtaagacag aatgaagagc taaatttgtt 3960

gaaggcacag ttaaatgaaa cactcacaaa acttagaact gaacaaaatg aaagacagaa 4020

ggtagctggt gatttgcata aggctcaaca gtcactggag cttatccagt caaaaatagt 4080

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aattgggaaa ctgttcattt gaggataaaa aaggcattgt attatatttt gccaaattaa 4380

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agccttattt atgttttcac cctttctact ttgtcagaaa cactgaacag agttttgtct   4440

tttctaatcc ttgttagact actgatttaa agaaggaaaa aaaaaagcca actctgtaga   4500

caccttcaga gtttagtttt ataataaaaa ctgtttgaat aattagacct ttacattcct   4560

gaagataaac atgtaatctt ttatcttatt ttgctcaata aaattgttca gaagatcaaa   4620

gtggtaaaga caatgtaaaa tttaacattt taatactgat gttgtacact gttttactta   4680

acattttggg aagtaactgc ctctgacttc aactcaagaa aacacttttt tgttgctaat   4740

gtaatcggtt tttgtaatgg cgtcagcaaa taaaaggatg cttattattc aaaaaaaaaa   4800

aaaaaaaaaa aaaaaa                                                   4816


<210> SEQ ID NO 64
<211> LENGTH: 1357
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

Met Glu Phe Tyr Glu Ser Ala Tyr Phe Ile Val Leu Ile Pro Ser Ile
1               5                  10                  15

Val Ile Thr Val Ile Phe Leu Phe Phe Trp Leu Phe Met Lys Glu Thr
            20                  25                  30

Leu Tyr Asp Glu Val Leu Ala Lys Gln Lys Arg Glu Gln Lys Leu Ile
        35                  40                  45

Pro Thr Lys Thr Asp Lys Lys Lys Ala Glu Lys Lys Lys Asn Lys Lys
    50                  55                  60

Lys Glu Ile Gln Asn Gly Asn Leu His Glu Ser Asp Ser Glu Ser Val
65                  70                  75                  80

Pro Arg Asp Phe Lys Leu Ser Asp Ala Leu Ala Val Glu Asp Asp Gln
                85                  90                  95

Val Ala Pro Val Pro Leu Asn Val Val Glu Thr Ser Ser Ser Val Arg
            100                 105                 110

Glu Arg Lys Lys Lys Glu Lys Lys Gln Lys Pro Val Leu Glu Glu Gln
        115                 120                 125

Val Ile Lys Glu Ser Asp Ala Ser Lys Ile Pro Gly Lys Lys Val Glu
    130                 135                 140

Pro Val Pro Val Thr Lys Gln Pro Thr Pro Pro Ser Glu Ala Ala Ala
145                 150                 155                 160

Ser Lys Lys Lys Pro Gly Gln Lys Lys Ser Lys Asn Gly Ser Asp Asp
                165                 170                 175

Gln Asp Lys Lys Val Glu Thr Leu Met Val Pro Ser Lys Arg Gln Glu
            180                 185                 190

Ala Leu Pro Leu His Gln Glu Thr Lys Gln Glu Ser Gly Ser Gly Lys
        195                 200                 205

Lys Lys Ala Ser Ser Lys Lys Gln Lys Thr Glu Asn Val Phe Val Asp
    210                 215                 220

Glu Pro Leu Ile His Ala Thr Thr Tyr Ile Pro Leu Met Asp Asn Ala
225                 230                 235                 240

Asp Ser Ser Pro Val Val Asp Lys Arg Glu Val Ile Asp Leu Leu Lys
                245                 250                 255

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

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

Leu Ser Leu Lys Thr Met Met Phe Ser Glu Asp Glu Ala Leu Cys Val
    290                 295                 300
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Val Asp Leu Leu Lys Glu Lys Ser Gly Val Ile Gln Asp Ala Leu Lys
305                 310                 315                 320

Lys Ser Ser Lys Gly Glu Leu Thr Thr Leu Ile His Gln Leu Gln Glu
                325                 330                 335

Lys Asp Lys Leu Leu Ala Ala Val Lys Glu Asp Ala Ala Ala Thr Lys
            340                 345                 350

Asp Arg Cys Lys Gln Leu Thr Gln Glu Met Met Thr Glu Lys Glu Arg
        355                 360                 365

Ser Asn Val Val Ile Thr Arg Met Lys Asp Arg Ile Gly Thr Leu Glu
    370                 375                 380

Lys Glu His Asn Val Phe Gln Asn Lys Ile His Val Ser Tyr Gln Glu
385                 390                 395                 400

Thr Gln Gln Met Gln Met Lys Phe Gln Gln Val Arg Glu Gln Met Glu
                405                 410                 415

Ala Glu Ile Ala His Leu Lys Gln Glu Asn Gly Ile Leu Arg Asp Ala
            420                 425                 430

Val Ser Asn Thr Thr Asn Gln Leu Glu Ser Lys Gln Ser Ala Glu Leu
        435                 440                 445

Asn Lys Leu Arg Gln Asp Tyr Ala Arg Leu Val Asn Glu Leu Thr Glu
    450                 455                 460

Lys Thr Gly Lys Leu Gln Gln Glu Glu Val Gln Lys Lys Asn Ala Glu
465                 470                 475                 480

Gln Ala Ala Thr Gln Leu Lys Val Gln Leu Gln Glu Ala Glu Arg Arg
                485                 490                 495

Trp Glu Glu Val Gln Ser Tyr Ile Arg Lys Arg Thr Ala Glu His Glu
            500                 505                 510

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

Val Gln Ser Leu His Ser Lys Leu Thr Asp Thr Leu Val Ser Lys Gln
    530                 535                 540

Gln Leu Glu Gln Arg Leu Met Gln Leu Met Glu Ser Glu Gln Lys Arg
545                 550                 555                 560

Val Asn Lys Glu Glu Ser Leu Gln Met Gln Val Gln Asp Ile Leu Glu
                565                 570                 575

Gln Asn Glu Ala Leu Lys Ala Gln Ile Gln Gln Phe His Ser Gln Ile
            580                 585                 590

Ala Ala Gln Thr Ser Ala Ser Val Leu Ala Glu Glu Leu His Lys Val
        595                 600                 605

Ile Ala Glu Lys Asp Lys Gln Ile Lys Gln Thr Glu Asp Ser Leu Ala
    610                 615                 620

Ser Glu Arg Asp Arg Leu Thr Ser Lys Glu Glu Glu Leu Lys Asp Ile
625                 630                 635                 640

Gln Asn Met Asn Phe Leu Leu Lys Ala Glu Val Gln Lys Leu Gln Ala
                645                 650                 655

Leu Ala Asn Glu Gln Ala Ala Ala Ala His Glu Leu Glu Lys Met Gln
            660                 665                 670

Gln Ser Val Tyr Val Lys Asp Asp Lys Ile Arg Leu Leu Glu Glu Gln
        675                 680                 685

Leu Gln His Glu Ile Ser Asn Lys Met Glu Glu Phe Lys Ile Leu Asn
    690                 695                 700

Asp Gln Asn Lys Ala Leu Lys Ser Glu Val Gln Lys Leu Gln Thr Leu
705                 710                 715                 720

Val Ser Glu Gln Pro Asn Lys Asp Val Val Glu Gln Met Glu Lys Cys
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               725                 730                 735

Ile Gln Glu Lys Asp Glu Lys Leu Lys Thr Val Glu Glu Leu Leu Glu
            740                 745                 750

Thr Gly Leu Ile Gln Val Ala Thr Lys Glu Glu Glu Leu Asn Ala Ile
        755                 760                 765

Arg Thr Glu Asn Ser Ser Leu Thr Lys Glu Val Gln Asp Leu Lys Ala
    770                 775                 780

Lys Gln Asn Asp Gln Val Ser Phe Ala Ser Leu Val Glu Glu Leu Lys
785                 790                 795                 800

Lys Val Ile His Glu Lys Asp Gly Lys Ile Lys Ser Val Glu Glu Leu
                805                 810                 815

Leu Glu Ala Glu Leu Leu Lys Val Ala Asn Lys Glu Lys Thr Val Gln
            820                 825                 830

Asp Leu Lys Gln Glu Ile Lys Ala Leu Lys Glu Glu Ile Gly Asn Val
        835                 840                 845

Gln Leu Glu Lys Ala Gln Gln Leu Ser Ile Thr Ser Lys Val Gln Glu
    850                 855                 860

Leu Gln Asn Leu Leu Lys Gly Lys Glu Glu Gln Met Asn Thr Met Lys
865                 870                 875                 880

Ala Val Leu Glu Glu Lys Glu Lys Asp Leu Ala Asn Thr Gly Lys Trp
                885                 890                 895

Leu Gln Asp Leu Gln Glu Glu Asn Glu Ser Leu Lys Ala His Val Gln
            900                 905                 910

Glu Val Ala Gln His Asn Leu Lys Glu Ala Ser Ser Ala Ser Gln Phe
        915                 920                 925

Glu Glu Leu Glu Ile Val Leu Lys Glu Lys Glu Asn Glu Leu Lys Arg
    930                 935                 940

Leu Glu Ala Met Leu Lys Glu Arg Glu Ser Asp Leu Ser Ser Lys Thr
945                 950                 955                 960

Gln Leu Leu Gln Asp Val Gln Asp Glu Asn Lys Leu Phe Lys Ser Gln
                965                 970                 975

Ile Glu Gln Leu Lys Gln Gln Asn Tyr Gln Gln Ala Ser Ser Phe Pro
            980                 985                 990

Pro His Glu Glu Leu Leu Lys Val  Ile Ser Glu Arg Glu  Lys Glu Ile
        995                 1000                1005

Ser Gly  Leu Trp Asn Glu Leu  Asp Ser Leu Lys Asp  Ala Val Glu
    1010                1015                1020

His Gln  Arg Lys Lys Asn Asn  Asp Leu Arg Glu Lys  Asn Trp Glu
    1025                1030                1035

Ala Met  Glu Ala Leu Ala Ser  Thr Glu Lys Met Leu  Gln Asp Lys
    1040                1045                1050

Val Asn  Lys Thr Ser Lys Glu  Arg Gln Gln Gln Val  Glu Ala Val
    1055                1060                1065

Glu Leu  Glu Ala Lys Glu Val  Leu Lys Lys Leu Phe  Pro Lys Val
    1070                1075                1080

Ser Val  Pro Ser Asn Leu Ser  Tyr Gly Glu Trp Leu  His Gly Phe
    1085                1090                1095

Glu Lys  Lys Ala Lys Glu Cys  Met Ala Gly Thr Ser  Gly Ser Glu
    1100                1105                1110

Glu Val  Lys Val Leu Glu His  Lys Leu Lys Glu Ala  Asp Glu Met
    1115                1120                1125

His Thr  Leu Leu Gln Leu Glu  Cys Glu Lys Tyr Lys  Ser Val Leu
    1130                1135                1140
```

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```
Ala Glu  Thr Glu Gly Ile Leu  Gln Lys Leu Gln Arg  Ser Val Glu
    1145                1150                1155

Gln Glu  Glu Asn Lys Trp Lys  Val Lys Val Asp Glu  Ser His Lys
    1160                1165                1170

Thr Ile  Lys Gln Met Gln Ser  Ser Phe Thr Ser Ser  Glu Gln Glu
    1175                1180                1185

Leu Glu  Arg Leu Arg Ser Glu  Asn Lys Asp Ile Glu  Asn Leu Arg
    1190                1195                1200

Arg Glu  Arg Glu His Leu Glu  Met Glu Leu Glu Lys  Ala Glu Met
    1205                1210                1215

Glu Arg  Ser Thr Tyr Val Thr  Glu Val Arg Glu Leu  Lys Asp Leu
    1220                1225                1230

Leu Thr  Glu Leu Gln Lys Lys  Leu Asp Asp Ser Tyr  Ser Glu Ala
    1235                1240                1245

Val Arg  Gln Asn Glu Glu Leu  Asn Leu Leu Lys Ala  Gln Leu Asn
    1250                1255                1260

Glu Thr  Leu Thr Lys Leu Arg  Thr Glu Gln Asn Glu  Arg Gln Lys
    1265                1270                1275

Val Ala  Gly Asp Leu His Lys  Ala Gln Gln Ser Leu  Glu Leu Ile
    1280                1285                1290

Gln Ser  Lys Ile Val Lys Ala  Ala Gly Asp Thr Thr  Val Ile Glu
    1295                1300                1305

Asn Ser  Asp Val Ser Pro Glu  Thr Glu Ser Ser Glu  Lys Glu Thr
    1310                1315                1320

Met Ser  Val Ser Leu Asn Gln  Thr Val Thr Gln Leu  Gln Gln Leu
    1325                1330                1335

Leu Gln  Ala Val Asn Gln Gln  Leu Thr Lys Glu Lys  Glu His Tyr
    1340                1345                1350

Gln Val  Leu Glu
    1355
```

<210> SEQ ID NO 65
<211> LENGTH: 2775
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65

```
gcagtccaga tgtcgtcagc accagcgcct gggctggagg acagagaagc cttttccgtt     60

gccggtgccg gcctagcgtc ctggaattac ttcaatcaac aggagcgaga acccgagcag    120

cgccatgagc aacactaccg tcgtccccag cactgcaggt ccgggcccca gcggcgggcc    180

cggtggcgga ggtggtggtg gcggcggagg cggcggcacc gaggtaatcc aggtgactaa    240

tgtctccccg agcgctagct ctgagcagat gcggactctc ttcggtttcc taggcaagat    300

cgacgaactg cgcctcttcc cgccggatga ttcgcctttg ccagtctcat ctcgtgtctg    360

ctttgttaag ttccatgatc cagactcagc agttgtggca cagcatctga caaacactgt    420

attcgttgac agagctttga tagtcgtacc atatgcagaa ggagttattc ctgatgaagc    480

taaagctttg tctctgttgg caccagctaa tgcagtggca ggtcttctgc ctggtggtgg    540

actcctgcct actcctaacc cacttaccca gattggcgct gttccactgg ctgctttggg    600

ggctcctact cttgatcctg cccttgctgc acttgggctt cctggagcaa acttgaactc    660

tcagtctctt gctgcagatc agttgctgaa gcttatgagt actgttgatc ccaagttgaa    720

tcatgtagct gctggtctcg tttcaccaag tctgaaatcg gatacctcta gtaaagaaat    780

agaggaagct atgaaaagag tacgagaagc acagtcccta atttctgctg ctatagaacc    840
```

-continued

agataagaaa gaagaaaaaa gaaggcattc aagatcaaga tcacgttcta ggaggaggag 900

gactccctca tcttctagac acaggcggtc aagaagcaga tcgagacggc ggtcacattc 960

taagtctagg agtcggcgac gatccaaaag cccaaggcgg agaagatctc attccagaga 1020

aagaggtaga aggtcaagga gcacatcaaa aacaagagac aaaaagaaag aagacaaaga 1080

aaagaaacgt tctaaaacac caccaaaaag ttacagcaca gccagacgtt ctagaagtgc 1140

aagcagagag agacgacgac gaagaagcag gagtggcaca agatctccta aaaagcctcg 1200

gtctcctaaa agaaaattgt cccgctcacc atcccctagg agacataaaa aggagaagaa 1260

gaaagataaa gacaaagaaa gaagtaggga tgaaagagaa cgatcaacaa gcaagaagaa 1320

gaagagtaaa gataaggaaa aggaccggga aagaaaatca gagagtgata aagatgtaaa 1380

acaggttaca cgggattatg atgaagagga acaggggtat gacagtgaga aagagaaaaa 1440

agaagagaag aaaccaatag aaacaggttc ccctaaaaca aaggaatgtt ctgtggaaaa 1500

gggaactggt gattcactaa gagaatccaa agtgaatggg gatgatcatc atgaagaaga 1560

catggatatg agtgactgaa tattgcctct gagggagtcc aactgtatac ctgcatcagt 1620

gtcattcctt tgtgtgattt cttaatgctg tatttgttca tctcaaacct agatgtatac 1680

agctctgagt tataaatggt tataaagctc ctgttactca tattagttat ttacatcaaa 1740

aagcttttag aaaatggtac gaggtaacca attcttgtca tggtgaaatc tgattgagta 1800

accaagcagt tttactattc tggtgctgct tcataacaaa aatgaaaagc tgcatgcatc 1860

tacagcaggc atggattgtt tatgtcgtat gatatccttt attaagtaag ttcacttata 1920

gtatttctat aatttgattc attgccgtaa tagagccatg taggaaatgc actgattgca 1980

tgttattgtg gcaagaatat cctaaatgtc attaaaatcc tccaacatga tggatctact 2040

tatggtcttg tttgttgaca tgacaaatta acattcttat agttacatct ggaaatgagc 2100

atttgaaata gataatcctt taagccttgt ggcaaaattt ttgtggcttt tgtttaactt 2160

tgaaaggtta ttatgcacta accttttttg gtggctaatt agggtttaaa tacagaaaca 2220

agatttcaaa taaaactgtc tttggcagtg agtaaatagc atattttgaa gtagagttgt 2280

atacttttc ataagatgtt tgggaatttt tttcctgaag taataattta ttccacatct 2340

acatcagtga aagctatcta cctatcctga gtctatctta aaggaaaaaa agaaaaaaac 2400

cttatctctt gcccttattt tgaattttcc actctttcat taatttgttt taagctccgt 2460

gttggaaaaa aggggtagtg cattttaaat tgaccttcat acgcttttaa aataagacaa 2520

atctacttga taatgtacct ttatttgatc tcaagttgta taaaaccaat aaatttgtgt 2580

tactgcagta gtaatcttat gcacacggtg atttcatgtt atatatgcaa agtaggcaac 2640

tgttttctta gttacagaag tttcaagctt cacttttgtg cagtagaaac aaaagtaggc 2700

tacagtctgt gccatgttga tgtacagttt ctgaaattgt tttacaagac tttgataata 2760

aaacccttaa actta 2775

<210> SEQ ID NO 66
<211> LENGTH: 484
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

Met Ser Asn Thr Thr Val Val Pro Ser Thr Ala Gly Pro Gly Pro Ser
1 5 10 15

Gly Gly Pro Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Thr
20 25 30

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```
Glu Val Ile Gln Val Thr Asn Val Ser Pro Ser Ala Ser Ser Glu Gln
        35                  40                  45

Met Arg Thr Leu Phe Gly Phe Leu Gly Lys Ile Asp Glu Leu Arg Leu
    50                  55                  60

Phe Pro Pro Asp Asp Ser Pro Leu Pro Val Ser Ser Arg Val Cys Phe
65                  70                  75                  80

Val Lys Phe His Asp Pro Asp Ser Ala Val Val Ala Gln His Leu Thr
                85                  90                  95

Asn Thr Val Phe Val Asp Arg Ala Leu Ile Val Val Pro Tyr Ala Glu
            100                 105                 110

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

Asn Ala Val Ala Gly Leu Leu Pro Gly Gly Gly Leu Leu Pro Thr Pro
    130                 135                 140

Asn Pro Leu Thr Gln Ile Gly Ala Val Pro Leu Ala Ala Leu Gly Ala
145                 150                 155                 160

Pro Thr Leu Asp Pro Ala Leu Ala Ala Leu Gly Leu Pro Gly Ala Asn
                165                 170                 175

Leu Asn Ser Gln Ser Leu Ala Ala Asp Gln Leu Leu Lys Leu Met Ser
            180                 185                 190

Thr Val Asp Pro Lys Leu Asn His Val Ala Ala Gly Leu Val Ser Pro
        195                 200                 205

Ser Leu Lys Ser Asp Thr Ser Ser Lys Glu Ile Glu Glu Ala Met Lys
    210                 215                 220

Arg Val Arg Glu Ala Gln Ser Leu Ile Ser Ala Ala Ile Glu Pro Asp
225                 230                 235                 240

Lys Lys Glu Glu Lys Arg Arg His Ser Arg Ser Arg Ser Arg Ser Arg
                245                 250                 255

Arg Arg Arg Thr Pro Ser Ser Ser Arg His Arg Arg Ser Arg Ser Arg
            260                 265                 270

Ser Arg Arg Arg Ser His Ser Lys Ser Arg Ser Arg Arg Arg Ser Lys
        275                 280                 285

Ser Pro Arg Arg Arg Arg Ser His Ser Arg Glu Arg Gly Arg Arg Ser
    290                 295                 300

Arg Ser Thr Ser Lys Thr Arg Asp Lys Lys Lys Glu Asp Lys Glu Lys
305                 310                 315                 320

Lys Arg Ser Lys Thr Pro Pro Lys Ser Tyr Ser Thr Ala Arg Arg Ser
                325                 330                 335

Arg Ser Ala Ser Arg Glu Arg Arg Arg Arg Arg Ser Arg Ser Gly Thr
            340                 345                 350

Arg Ser Pro Lys Lys Pro Arg Ser Pro Lys Arg Lys Leu Ser Arg Ser
        355                 360                 365

Pro Ser Pro Arg Arg His Lys Lys Glu Lys Lys Lys Asp Lys Asp Lys
    370                 375                 380

Glu Arg Ser Arg Asp Glu Arg Glu Arg Ser Thr Ser Lys Lys Lys Lys
385                 390                 395                 400

Ser Lys Asp Lys Glu Lys Asp Arg Glu Arg Lys Ser Glu Ser Asp Lys
                405                 410                 415

Asp Val Lys Gln Val Thr Arg Asp Tyr Asp Glu Glu Glu Gln Gly Tyr
            420                 425                 430

Asp Ser Glu Lys Glu Lys Lys Glu Glu Lys Lys Pro Ile Glu Thr Gly
        435                 440                 445

Ser Pro Lys Thr Lys Glu Cys Ser Val Glu Lys Gly Thr Gly Asp Ser
```

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    450                 455                 460

Leu Arg Glu Ser Lys Val Asn Gly Asp Asp His His Glu Glu Asp Met
465                 470                 475                 480

Asp Met Ser Asp
```

<210> SEQ ID NO 67
<211> LENGTH: 1107
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67

```
gcagaagcgt tccgtgcgtg caagtgctgc gaaccacgtg ggtcccgggc gcgtttcggg     60

tgctggcggc tgcagccgga gttcaaacct aagcagctgg aaggaaccat ggccaactgt    120

gagcgtacct tcattgcgat caaaccagat ggggtccagc ggggtcttgt gggagagatt    180

atcaagcgtt ttgagcagaa aggattccgc cttgttggtc tgaaattcat gcaagcttcc    240

gaagatcttc tcaaggaaca ctacgttgac ctgaaggacc gtccattctt tgccggcctg    300

gtgaaataca tgcactcagg gccggtagtt gccatggtct gggaggggct gaatgtggtg    360

aagacgggcc gagtcatgct cggggagacc aaccctgcag actccaagcc tgggaccatc    420

cgtggagact tctgcataca agttggcagg accatggcca acctggagcg caccttcatc    480

gccatcaagc cggacggcgt gcagcgcggc ctggtgggcg agatcatcaa gcgcttcgag    540

cagaagggat tccgcctcgt ggccatgaag ttcctccggg cctctgaaga acacctgaag    600

cagcactaca ttgacctgaa agaccgacca ttcttccctg ggctggtgaa gtacatgaac    660

tcagggccgg ttgtggccat ggtctgggag gggctgaacg tggtgaagac aggccgagtg    720

atgcttgggg agaccaatcc agcagattca aagccaggca ccattcgtgg ggacttctgc    780

attcaggttg gcaggaacat cattcatggc agtgattcag taaaaagtgc tgaaaaagaa    840

atcagcctat ggtttaagcc tgaagaactg gttgactaca agtcttgtgc tcatgactgg    900

gtctatgaat aagaggtgga cacaacagca gtctccttca gcacggcgtg gtgtgtccct    960

ggacacagct cttcattcca ttgacttaga ggcaacagga ttgatcattc ttttatagag   1020

catatttgcc aataaagctt ttggaagccg gaaaaaaaaa aaaaaaaaaa aaaaaaaaaa   1080

aaaaaaaaaa aaaaaaaaaa aaaaaaa                                       1107
```

<210> SEQ ID NO 68
<211> LENGTH: 267
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68

```
Met Ala Asn Cys Glu Arg Thr Phe Ile Ala Ile Lys Pro Asp Gly Val
1               5                   10                  15

Gln Arg Gly Leu Val Gly Glu Ile Ile Lys Arg Phe Glu Gln Lys Gly
            20                  25                  30

Phe Arg Leu Val Gly Leu Lys Phe Met Gln Ala Ser Glu Asp Leu Leu
        35                  40                  45

Lys Glu His Tyr Val Asp Leu Lys Asp Arg Pro Phe Phe Ala Gly Leu
    50                  55                  60

Val Lys Tyr Met His Ser Gly Pro Val Val Ala Met Val Trp Glu Gly
65                  70                  75                  80

Leu Asn Val Val Lys Thr Gly Arg Val Met Leu Gly Glu Thr Asn Pro
                85                  90                  95

Ala Asp Ser Lys Pro Gly Thr Ile Arg Gly Asp Phe Cys Ile Gln Val
```

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            100                 105                 110

Gly Arg Thr Met Ala Asn Leu Glu Arg Thr Phe Ile Ala Ile Lys Pro
        115                 120                 125

Asp Gly Val Gln Arg Gly Leu Val Gly Glu Ile Ile Lys Arg Phe Glu
    130                 135                 140

Gln Lys Gly Phe Arg Leu Val Ala Met Lys Phe Leu Arg Ala Ser Glu
145                 150                 155                 160

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

Pro Gly Leu Val Lys Tyr Met Asn Ser Gly Pro Val Val Ala Met Val
            180                 185                 190

Trp Glu Gly Leu Asn Val Val Lys Thr Gly Arg Val Met Leu Gly Glu
        195                 200                 205

Thr Asn Pro Ala Asp Ser Lys Pro Gly Thr Ile Arg Gly Asp Phe Cys
    210                 215                 220

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

Ala Glu Lys Glu Ile Ser Leu Trp Phe Lys Pro Glu Glu Leu Val Asp
                245                 250                 255

Tyr Lys Ser Cys Ala His Asp Trp Val Tyr Glu
            260                 265


<210> SEQ ID NO 69
<211> LENGTH: 531
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69

ggcagtctcg cgataactgc gcaggcgcgg accaaagcga tctcttctga ggatccggca     60

agatggcaga agtagagcag aagaagaagc ggaccttccg caagttcacc taccgcggcg    120

tggacctcga ccagctgctg gacatgtcct acgagcagct gatgcagctg tacagtgcgc    180

gccagcggcg gcggctgaac cggggcctgc ggcggaagca gcactccctg ctgaagcgcc    240

tgcgcaaggc caagaaggag gcgccgccca tggagaagcc ggaagtggtg aagacgcacc    300

tgcgggacat gatcatccta cccgagatgg tgggcagcat ggtgggcgtc tacaacggca    360

agaccttcaa ccaggtggag atcaagcccg agatgatcgg ccactacctg ggcgagttct    420

ccatcaccta caagcccgta aagcatggcc ggcccggcat cggggccacc cactcctccc    480

gcttcatccc tctcaagtaa tggctcagct aataaaggcg cacatgactc c              531


<210> SEQ ID NO 70
<211> LENGTH: 145
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 70

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

Tyr Arg Gly Val Asp Leu Asp Gln Leu Leu Asp Met Ser Tyr Glu Gln
            20                  25                  30

Leu Met Gln Leu Tyr Ser Ala Arg Gln Arg Arg Arg Leu Asn Arg Gly
        35                  40                  45

Leu Arg Arg Lys Gln His Ser Leu Leu Lys Arg Leu Arg Lys Ala Lys
    50                  55                  60

Lys Glu Ala Pro Pro Met Glu Lys Pro Glu Val Val Lys Thr His Leu
65                  70                  75                  80
```

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Arg Asp Met Ile Ile Leu Pro Glu Met Val Gly Ser Met Val Gly Val
85 90 95

Tyr Asn Gly Lys Thr Phe Asn Gln Val Glu Ile Lys Pro Glu Met Ile
100 105 110

Gly His Tyr Leu Gly Glu Phe Ser Ile Thr Tyr Lys Pro Val Lys His
115 120 125

Gly Arg Pro Gly Ile Gly Ala Thr His Ser Ser Arg Phe Ile Pro Leu
130 135 140

Lys
145

<210> SEQ ID NO 71
<211> LENGTH: 10151
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71

gcagcgccgc ctgcccaggc ccggaccggg ctttgtccgc cccggagccc ctgcccgcgc 60

cgcggagacc ccggagcccg cgcgctccga ggccaccccg ggccgggatt tccggtgggg 120

cccgcggagc cgcgcagagg gaggaggccc cagacccagg cgccccgcca gcccagctgc 180

acgtaagcgg acgctgcagg agctgaagat ggcgagctcc gtggcgccct acgagcagct 240

ggtgaggcag gtggaggcct tgaaggctga gaacagccac ctgaggcagg agctaaggga 300

caactccagc cacctgtcca agctggagac agagacgtcg ggcatgaagg aggtcctgaa 360

gcacctacag ggaaaactgg agcaggaggc ccgagtgctg gtgtcctcgg ggcagacgga 420

ggtgctggag cagctgaagg ccctacagat ggacatcacc agcctgtaca acctcaagtt 480

ccagccgccc accctgggcc cggagcctgc cgcccggacc cccgagggca gcccagtaca 540

cggctccggg ccctccaagg acagctttgg ggagctgagc cgggccacca tccggctgct 600

ggaggaactg gaccgggaac ggtgtttcct gctgaatgag attgagaagg aggagaagga 660

gaagctctgg tactactctc agctgcaggg cctgtccaag cgcctggacg agctgccgca 720

cgtggagacg cagttctcga tgcagatgga cctgatccgg cagcagcttg agttcgaggc 780

ccagcacatc cgctcgctga tggaggagcg cttcggcacc tcggacgaga tggtgcagcg 840

ggcacagatc cgcgcctcgc gcctggagca gattgacaag gagctgctgg aggcgcagga 900

ccgagtgcag cagacggagc cccaggcctt gctggcggtg aagtcggtgc cggtggacga 960

ggaccccgag acagaggtcc ccacacaccc tgaggatggc acccctcagc cgggcaacag 1020

caaggtggag gtggtcttct ggctgttgtc catgttggcg acgcgcgacc aggaggatac 1080

agcgcgcacg ctgctggcca tgtccagctc gcccgagagc tgcgtggcca tgcgccgctc 1140

gggctgtctg cctctgctgc tgcaaatcct ccacggcacc gaggccgcgg ccgggggtcg 1200

cgccggggcc ccaggggcac cgggcgccaa ggacgcacgc atgcgcgcca acgcggcgct 1260

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gaacgagcta ggtgggctgc aggccgtggc agagctgctg caggttgact atgagatgca 1560

caagatgacc cgggacccgc tgaacctggc gctgcgccgc tacgcgggca tgaccctcac 1620

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ggaggccatc gtggcccagc tggcctccga cagtgaggag ctccaccagg tggtgtccag 1740

catccttcgg aacttgtcct ggagggccga catcaacagc aagaaggtgc tgagggaggc 1800

gggcagcgtg actgccctgg tgcagtgtgt cctgcgggcc accaaggagt ccaccctgaa 1860

gagcgtgctg agcgccctgt ggaatctgtc tgcacacagc acagagaaca aggcggccat 1920

ctgccaggtg gatggcgccc tgggcttcct ggtgagcacc ctgacctaca agtgtcagag 1980

caactcgctg gccatcatcg agagcggcgg cggcatcctc cgcaatgtgt ccagcctcgt 2040

cgccacccgt gaggactaca ggcaggtgct ccgggatcac aactgtctgc agacgctgct 2100

gcagcatctg acttcgcaca gcctgaccat cgtgagcaac gcgtgcggca cgctctggaa 2160

cctgtcggcc cgcagcgccc gtgaccagga gctgctgtgg gacctgggcg ccgtgggcat 2220

gctgcgtaat ctggtgcact ccaagcacaa gatgatcgcc atgggcagcg ccgccgccct 2280

gcgcaacctg ctggcccatc ggcccgccaa gcaccaggcg gccgccaccg ccgtgtcccc 2340

aggcagctgc gtgcccagcc tgtacgtgcg caagcagcgg gcgctggagg ccgagctgga 2400

cgcacggcac ctcgcgcagg cgctggagca cctggagaag cagggcccgc cggcagccga 2460

ggccgccact aagaagccgc tgccgccccc gcgacacctg gacggcctgg cccaagacta 2520

tgcttccgat tcgggctgct ttgacgacga cgatgcaccg tcatccctgg ctgcggccgc 2580

ggccaccggg gagccagcca gccctgccgc gctgtccctc ttcctgggca gccccttcct 2640

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tgccagcgac gggtactgcc cacgcgaaca tatgctgccc tgcccgctgg ccgcactggc 3060

ttcgcgccgc gaggacccca ggtgtgggca gcctcggccc agccggcttg accttgacct 3120

gcccggctgc caggccgagc ccccggcccg cgaggccacc tccgccgacg cccgcgtgcg 3180

caccatcaag ctgtcgccta cctatcagca cgtgccactg cttgagggtg cctcaagggc 3240

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gccggcagac cacctgagca aggttcccga gaagctggcg gctgccccgc tgtctgtggc 3360

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ctcccttttcc tcgctgtcct cggccggccg cccaggcccc agcgagggtg gtgacctgga 3480

tgacagtgac tcctccctgg aggggctgga ggaggccggc cccagcgagg ctgagctgga 3540

cagcacgtgg cgggcgcccg gggccacctc gctgcccgta gccattccgg ctccccggcg 3600

taaccgaggc cggggcctgg gggtggaaga cgccacgccg tccagctcgt cggagaacta 3660

cgtgcaggag acaccgcttg tgctgagccg ctgcagctct gtgagctcgc tgggcagctt 3720

cgagagcccg tccatcgcca gctccatccc cagtgaacct tgcagcgggc agggcagcgg 3780

caccatcagc cctagcgagc tgcccgacag ccccggacag accatgcctc ccagccggag 3840

caagacgcca ccgctggcgc ccgcgccaca gggtcccccc gaggccaccc agttcagcct 3900

gcagtgggag agctacgtga agcgcttcct ggacatcgcc gactgccggg agcgctgccg 3960

gctgccatct gagctggacg caggcagcgt gcgctttacc gtggagaagc cagacgagaa 4020

cttctcgtgc gcctccagcc tcagcgcgct ggccttgcac gagcactacg tgcagcagga 4080

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cgtggagctg cggctgctgc cctcggcctg ccccgagcgc ggcgggggcg ccgggggcgc 4140

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ccctcgcggc gccgcggacc aggagctgga actgctgcgg gagtgcctgg gagccgccgt 4260

gcctgcccgg ctgcgcaagg tggcctccgc gctggtgcca ggtcgccgcg cactccccgt 4320

gcccgtctac atgttggtgc ccgccccggc cccggcccag gaggacgact cctgcactga 4380

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 72

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Ala Leu Lys Ala Glu Asn Ser His Leu Arg Gln Glu Leu Arg Asp Asn
            20                  25                  30

Ser Ser His Leu Ser Lys Leu Glu Thr Glu Thr Ser Gly Met Lys Glu
        35                  40                  45

Val Leu Lys His Leu Gln Gly Lys Leu Glu Gln Glu Ala Arg Val Leu
    50                  55                  60

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

Met Asp Ile Thr Ser Leu Tyr Asn Leu Lys Phe Gln Pro Pro Thr Leu
                85                  90                  95

Gly Pro Glu Pro Ala Ala Arg Thr Pro Glu Gly Ser Pro Val His Gly
            100                 105                 110

Ser Gly Pro Ser Lys Asp Ser Phe Gly Glu Leu Ser Arg Ala Thr Ile
        115                 120                 125

Arg Leu Leu Glu Glu Leu Asp Arg Glu Arg Cys Phe Leu Leu Asn Glu
    130                 135                 140

Ile Glu Lys Glu Glu Lys Glu Lys Leu Trp Tyr Tyr Ser Gln Leu Gln
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Gly Leu Ser Lys Arg Leu Asp Glu Leu Pro His Val Glu Thr Gln Phe
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Ser Met Gln Met Asp Leu Ile Arg Gln Gln Leu Glu Phe Glu Ala Gln
            180                 185                 190

His Ile Arg Ser Leu Met Glu Glu Arg Phe Gly Thr Ser Asp Glu Met
        195                 200                 205

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

Glu Leu Leu Glu Ala Gln Asp Arg Val Gln Gln Thr Glu Pro Gln Ala
225                 230                 235                 240

Leu Leu Ala Val Lys Ser Val Pro Val Asp Glu Asp Pro Glu Thr Glu
                245                 250                 255

Val Pro Thr His Pro Glu Asp Gly Thr Pro Gln Pro Gly Asn Ser Lys
            260                 265                 270

Val Glu Val Val Phe Trp Leu Leu Ser Met Leu Ala Thr Arg Asp Gln
        275                 280                 285

Glu Asp Thr Ala Arg Thr Leu Leu Ala Met Ser Ser Ser Pro Glu Ser
    290                 295                 300

Cys Val Ala Met Arg Arg Ser Gly Cys Leu Pro Leu Leu Leu Gln Ile
305                 310                 315                 320

Leu His Gly Thr Glu Ala Ala Ala Gly Gly Arg Ala Gly Ala Pro Gly
                325                 330                 335

Ala Pro Gly Ala Lys Asp Ala Arg Met Arg Ala Asn Ala Ala Leu His
            340                 345                 350

Asn Ile Val Phe Ser Gln Pro Asp Gln Gly Leu Ala Arg Lys Glu Met
        355                 360                 365

Arg Val Leu His Val Leu Glu Gln Ile Arg Ala Tyr Cys Glu Thr Cys
    370                 375                 380

Trp Asp Trp Leu Gln Ala Arg Asp Gly Gly Pro Glu Gly Gly Gly Ala
385                 390                 395                 400

Gly Ser Ala Pro Ile Pro Ile Glu Pro Gln Ile Cys Gln Ala Thr Cys
                405                 410                 415

Ala Val Met Lys Leu Ser Phe Asp Glu Glu Tyr Arg Arg Ala Met Asn
            420                 425                 430

Glu Leu Gly Gly Leu Gln Ala Val Ala Glu Leu Leu Gln Val Asp Tyr
        435                 440                 445

Glu Met His Lys Met Thr Arg Asp Pro Leu Asn Leu Ala Leu Arg Arg
    450                 455                 460

Tyr Ala Gly Met Thr Leu Thr Asn Leu Thr Phe Gly Asp Val Ala Asn
465                 470                 475                 480

Lys Ala Thr Leu Cys Ala Arg Arg Gly Cys Met Glu Ala Ile Val Ala
                485                 490                 495

Gln Leu Ala Ser Asp Ser Glu Glu Leu His Gln Val Val Ser Ser Ile
            500                 505                 510

Leu Arg Asn Leu Ser Trp Arg Ala Asp Ile Asn Ser Lys Lys Val Leu
        515                 520                 525

Arg Glu Ala Gly Ser Val Thr Ala Leu Val Gln Cys Val Leu Arg Ala
    530                 535                 540

Thr Lys Glu Ser Thr Leu Lys Ser Val Leu Ser Ala Leu Trp Asn Leu
545                 550                 555                 560

Ser Ala His Ser Thr Glu Asn Lys Ala Ala Ile Cys Gln Val Asp Gly
                565                 570                 575
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Ala Leu Gly Phe Leu Val Ser Thr Leu Thr Tyr Lys Cys Gln Ser Asn
            580                 585                 590

Ser Leu Ala Ile Ile Glu Ser Gly Gly Gly Ile Leu Arg Asn Val Ser
        595                 600                 605

Ser Leu Val Ala Thr Arg Glu Asp Tyr Arg Gln Val Leu Arg Asp His
    610                 615                 620

Asn Cys Leu Gln Thr Leu Leu Gln His Leu Thr Ser His Ser Leu Thr
625                 630                 635                 640

Ile Val Ser Asn Ala Cys Gly Thr Leu Trp Asn Leu Ser Ala Arg Ser
                645                 650                 655

Ala Arg Asp Gln Glu Leu Leu Trp Asp Leu Gly Ala Val Gly Met Leu
            660                 665                 670

Arg Asn Leu Val His Ser Lys His Lys Met Ile Ala Met Gly Ser Ala
        675                 680                 685

Ala Ala Leu Arg Asn Leu Leu Ala His Arg Pro Ala Lys His Gln Ala
    690                 695                 700

Ala Ala Thr Ala Val Ser Pro Gly Ser Cys Val Pro Ser Leu Tyr Val
705                 710                 715                 720

Arg Lys Gln Arg Ala Leu Glu Ala Glu Leu Asp Ala Arg His Leu Ala
                725                 730                 735

Gln Ala Leu Glu His Leu Glu Lys Gln Gly Pro Pro Ala Ala Glu Ala
            740                 745                 750

Ala Thr Lys Lys Pro Leu Pro Pro Leu Arg His Leu Asp Gly Leu Ala
        755                 760                 765

Gln Asp Tyr Ala Ser Asp Ser Gly Cys Phe Asp Asp Asp Asp Ala Pro
    770                 775                 780

Ser Ser Leu Ala Ala Ala Ala Ala Thr Gly Glu Pro Ala Ser Pro Ala
785                 790                 795                 800

Ala Leu Ser Leu Phe Leu Gly Ser Pro Phe Leu Gln Gly Gln Ala Leu
                805                 810                 815

Ala Arg Thr Pro Pro Thr Arg Arg Gly Gly Lys Glu Ala Glu Lys Asp
            820                 825                 830

Thr Ser Gly Glu Ala Ala Val Ala Ala Lys Ala Lys Ala Lys Leu Ala
        835                 840                 845

Leu Ala Val Ala Arg Ile Asp Gln Leu Val Glu Asp Ile Ser Ala Leu
    850                 855                 860

His Thr Ser Ser Asp Asp Ser Phe Ser Leu Ser Ser Gly Asp Pro Gly
865                 870                 875                 880

Gln Glu Ala Pro Arg Glu Gly Arg Ala Gln Ser Cys Ser Pro Cys Arg
                885                 890                 895

Gly Pro Glu Gly Gly Arg Arg Glu Ala Gly Ser Arg Ala His Pro Leu
            900                 905                 910

Leu Arg Leu Lys Ala Ala His Ala Ser Leu Ser Asn Asp Ser Leu Asn
        915                 920                 925

Ser Gly Ser Ala Ser Asp Gly Tyr Cys Pro Arg Glu His Met Leu Pro
    930                 935                 940

Cys Pro Leu Ala Ala Leu Ala Ser Arg Arg Glu Asp Pro Arg Cys Gly
945                 950                 955                 960

Gln Pro Arg Pro Ser Arg Leu Asp Leu Asp Leu Pro Gly Cys Gln Ala
                965                 970                 975

Glu Pro Pro Ala Arg Glu Ala Thr Ser Ala Asp Ala Arg Val Arg Thr
            980                 985                 990

Ile Lys Leu Ser Pro Thr Tyr Gln  His Val Pro Leu Leu  Glu Gly Ala
        995                 1000                1005
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Ser Arg  Ala Gly Ala Glu Pro  Leu Ala Gly Pro Gly  Ile Ser Pro
    1010                1015                1020

Gly Ala  Arg Lys Gln Ala Trp  Leu Pro Ala Asp His  Leu Ser Lys
    1025                1030                1035

Val Pro  Glu Lys Leu Ala Ala  Ala Pro Leu Ser Val  Ala Ser Lys
    1040                1045                1050

Ala Leu  Gln Lys Leu Ala Ala  Gln Glu Gly Pro Leu  Ser Leu Ser
    1055                1060                1065

Arg Cys  Ser Ser Leu Ser Ser  Leu Ser Ser Ala Gly  Arg Pro Gly
    1070                1075                1080

Pro Ser  Glu Gly Gly Asp Leu  Asp Asp Ser Asp Ser  Ser Leu Glu
    1085                1090                1095

Gly Leu  Glu Glu Ala Gly Pro  Ser Glu Ala Glu Leu  Asp Ser Thr
    1100                1105                1110

Trp Arg  Ala Pro Gly Ala Thr  Ser Leu Pro Val Ala  Ile Pro Ala
    1115                1120                1125

Pro Arg  Arg Asn Arg Gly Arg  Gly Leu Gly Val Glu  Asp Ala Thr
    1130                1135                1140

Pro Ser  Ser Ser Ser Glu Asn  Tyr Val Gln Glu Thr  Pro Leu Val
    1145                1150                1155

Leu Ser  Arg Cys Ser Ser Val  Ser Ser Leu Gly Ser  Phe Glu Ser
    1160                1165                1170

Pro Ser  Ile Ala Ser Ser Ile  Pro Ser Glu Pro Cys  Ser Gly Gln
    1175                1180                1185

Gly Ser  Gly Thr Ile Ser Pro  Ser Glu Leu Pro Asp  Ser Pro Gly
    1190                1195                1200

Gln Thr  Met Pro Pro Ser Arg  Ser Lys Thr Pro Pro  Leu Ala Pro
    1205                1210                1215

Ala Pro  Gln Gly Pro Pro Glu  Ala Thr Gln Phe Ser  Leu Gln Trp
    1220                1225                1230

Glu Ser  Tyr Val Lys Arg Phe  Leu Asp Ile Ala Asp  Cys Arg Glu
    1235                1240                1245

Arg Cys  Arg Leu Pro Ser Glu  Leu Asp Ala Gly Ser  Val Arg Phe
    1250                1255                1260

Thr Val  Glu Lys Pro Asp Glu  Asn Phe Ser Cys Ala  Ser Ser Leu
    1265                1270                1275

Ser Ala  Leu Ala Leu His Glu  His Tyr Val Gln Gln  Asp Val Glu
    1280                1285                1290

Leu Arg  Leu Leu Pro Ser Ala  Cys Pro Glu Arg Gly  Gly Gly Ala
    1295                1300                1305

Gly Gly  Ala Gly Leu His Phe  Ala Gly His Arg Arg  Arg Glu Glu
    1310                1315                1320

Gly Pro  Ala Pro Thr Gly Ser  Arg Pro Arg Gly Ala  Ala Asp Gln
    1325                1330                1335

Glu Leu  Glu Leu Leu Arg Glu  Cys Leu Gly Ala Ala  Val Pro Ala
    1340                1345                1350

Arg Leu  Arg Lys Val Ala Ser  Ala Leu Val Pro Gly  Arg Arg Ala
    1355                1360                1365

Leu Pro  Val Pro Val Tyr Met  Leu Val Pro Ala Pro  Ala Pro Ala
    1370                1375                1380

Gln Glu  Asp Asp Ser Cys Thr  Asp Ser Ala Glu Gly  Thr Pro Val
    1385                1390                1395

Asn Phe  Ser Ser Ala Ala Ser  Leu Ser Asp Glu Thr  Leu Gln Gly
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Pro Pro  Arg Asp Gln Pro Gly  Gly Pro Ala Gly Arg  Gln Arg Pro
    1415                1420                1425

Thr Gly  Arg Pro Thr Ser Ala  Arg Gln Ala Met Gly  His Arg His
    1430                1435                1440

Lys Ala  Gly Gly Ala Gly Arg  Ser Ala Glu Gln Ser  Arg Gly Ala
    1445                1450                1455

Gly Lys  Asn Arg Ala Gly Leu  Glu Leu Pro Leu Gly  Arg Pro Pro
    1460                1465                1470

Ser Ala  Pro Ala Asp Lys Asp  Gly Ser Lys Pro Gly  Arg Thr Arg
    1475                1480                1485

Gly Asp  Gly Ala Leu Gln Ser  Leu Cys Leu Thr Thr  Pro Thr Glu
    1490                1495                1500

Glu Ala  Val Tyr Cys Phe Tyr  Gly Asn Asp Ser Asp  Glu Glu Pro
    1505                1510                1515

Pro Ala  Ala Ala Pro Thr Pro  Thr His Arg Arg Thr  Ser Ala Ile
    1520                1525                1530

Pro Arg  Ala Phe Thr Arg Glu  Arg Pro Gln Gly Arg  Lys Glu Ala
    1535                1540                1545

Pro Ala  Pro Ser Lys Ala Ala  Pro Ala Ala Pro Pro  Pro Ala Arg
    1550                1555                1560

Thr Gln  Pro Ser Leu Ile Ala  Asp Glu Thr Pro Pro  Cys Tyr Ser
    1565                1570                1575

Leu Ser  Ser Ser Ala Ser Ser  Leu Ser Glu Pro Glu  Pro Ser Glu
    1580                1585                1590

Pro Pro  Ala Val His Pro Arg  Gly Arg Glu Pro Ala  Val Thr Lys
    1595                1600                1605

Asp Pro  Gly Pro Gly Gly Gly  Arg Asp Ser Ser Pro  Ser Pro Arg
    1610                1615                1620

Ala Ala  Glu Glu Leu Leu Gln  Arg Cys Ile Ser Ser  Ala Leu Pro
    1625                1630                1635

Arg Arg  Arg Pro Pro Val Ser  Gly Leu Arg Arg Arg  Lys Pro Arg
    1640                1645                1650

Ala Thr  Arg Leu Asp Glu Arg  Pro Ala Glu Gly Ser  Arg Glu Arg
    1655                1660                1665

Gly Glu  Glu Ala Ala Gly Ser  Asp Arg Ala Ser Asp  Leu Asp Ser
    1670                1675                1680

Val Glu  Trp Arg Ala Ile Gln  Glu Gly Ala Asn Ser  Ile Val Thr
    1685                1690                1695

Trp Leu  His Gln Ala Ala Ala  Ala Thr Arg Glu Ala  Ser Ser Glu
    1700                1705                1710

Ser Asp  Ser Ile Leu Ser Phe  Val Ser Gly Leu Ser  Val Gly Ser
    1715                1720                1725

Thr Leu  Gln Pro Pro Lys His  Arg Lys Gly Arg Gln  Ala Glu Gly
    1730                1735                1740

Glu Met  Gly Ser Ala Arg Arg  Pro Glu Lys Arg Gly  Ala Ala Ser
    1745                1750                1755

Val Lys  Thr Ser Gly Ser Pro  Arg Ser Pro Ala Gly  Pro Glu Lys
    1760                1765                1770

Pro Arg  Gly Thr Gln Lys Thr  Thr Pro Gly Val Pro  Ala Val Leu
    1775                1780                1785

Arg Gly  Arg Thr Val Ile Tyr  Val Pro Ser Pro Ala  Pro Arg Ala
    1790                1795                1800
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Gln Pro  Lys Gly Thr Pro Gly  Pro Arg Ala Thr Pro  Arg Lys Val
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Ala Pro  Pro Cys Leu Ala Gln  Pro Ala Ala Pro Ala  Lys Val Pro
    1820                 1825                 1830

Ser Pro  Gly Gln Gln Arg Ser  Arg Ser Leu His Arg  Pro Ala Lys
    1835                 1840                 1845

Thr Ser  Glu Leu Ala Thr Leu  Ser Gln Pro Pro Arg  Ser Ala Thr
    1850                 1855                 1860

Pro Pro  Ala Arg Leu Ala Lys  Thr Pro Ser Ser Ser  Ser Ser Gln
    1865                 1870                 1875

Thr Ser  Pro Ala Ser Gln Pro  Leu Pro Arg Lys Arg  Pro Pro Val
    1880                 1885                 1890

Thr Gln  Ala Ala Gly Ala Leu  Pro Gly Pro Gly Ala  Ser Pro Val
    1895                 1900                 1905

Pro Lys  Thr Pro Ala Arg Thr  Leu Leu Ala Lys Gln  His Lys Thr
    1910                 1915                 1920

Gln Arg  Ser Pro Val Arg Ile  Pro Phe Met Gln Arg  Pro Ala Arg
    1925                 1930                 1935

Arg Gly  Pro Pro Pro Leu Ala  Arg Ala Val Pro Glu  Pro Gly Pro
    1940                 1945                 1950

Arg Gly  Arg Ala Gly Thr Glu  Ala Gly Pro Gly Ala  Arg Gly Gly
    1955                 1960                 1965

Arg Leu  Gly Leu Val Arg Val  Ala Ser Ala Leu Ser  Ser Gly Ser
    1970                 1975                 1980

Glu Ser  Ser Asp Arg Ser Gly  Phe Arg Arg Gln Leu  Thr Phe Ile
    1985                 1990                 1995

Lys Glu  Ser Pro Gly Leu Arg  Arg Arg Arg Ser Glu  Leu Ser Ser
    2000                 2005                 2010

Ala Glu  Ser Ala Ala Ser Ala  Pro Gln Gly Ala Ser  Pro Arg Arg
    2015                 2020                 2025

Gly Arg  Pro Ala Leu Pro Ala  Val Phe Leu Cys Ser  Ser Arg Cys
    2030                 2035                 2040

Glu Glu  Leu Arg Ala Ala Pro  Arg Gln Gly Pro Ala  Pro Ala Arg
    2045                 2050                 2055

Gln Arg  Pro Pro Ala Ala Arg  Pro Ser Pro Gly Glu  Arg Pro Ala
    2060                 2065                 2070

Arg Arg  Thr Thr Ser Glu Ser  Pro Ser Arg Leu Pro  Val Arg Ala
    2075                 2080                 2085

Pro Ala  Ala Arg Pro Glu Thr  Val Lys Arg Tyr Ala  Ser Leu Pro
    2090                 2095                 2100

His Ile  Ser Val Ala Arg Arg  Pro Asp Gly Ala Val  Pro Ala Ala
    2105                 2110                 2115

Pro Ala  Ser Ala Asp Ala Ala  Arg Arg Ser Ser Asp  Gly Glu Pro
    2120                 2125                 2130

Arg Pro  Leu Pro Arg Val Ala  Ala Pro Gly Thr Thr  Trp Arg Arg
    2135                 2140                 2145

Ile Arg  Asp Glu Asp Val Pro  His Ile Leu Arg Ser  Thr Leu Pro
    2150                 2155                 2160

Ala Thr  Ala Leu Pro Leu Arg  Gly Ser Thr Pro Glu  Asp Ala Pro
    2165                 2170                 2175

Ala Gly  Pro Pro Pro Arg Lys  Thr Ser Asp Ala Val  Val Gln Thr
    2180                 2185                 2190

Glu Glu  Val Ala Ala Pro Lys  Thr Asn Ser Ser Thr  Ser Pro Ser
    2195                 2200                 2205
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Leu Glu  Thr Arg Glu Pro Pro  Gly Ala Pro Ala Gly  Gly Gln Leu
    2210                2215                2220

Ser Leu  Leu Gly Ser Asp Val  Asp Gly Pro Ser Leu  Ala Lys Ala
    2225                2230                2235

Pro Ile  Ser Ala Pro Phe Val  His Glu Gly Leu Gly  Val Ala Val
    2240                2245                2250

Gly Gly  Phe Pro Ala Ser Arg  His Gly Ser Pro Ser  Arg Ser Ala
    2255                2260                2265

Arg Val  Pro Pro Phe Asn Tyr  Val Pro Ser Pro Met  Val Val Ala
    2270                2275                2280

Ala Thr  Thr Asp Ser Ala Ala  Glu Lys Ala Pro Ala  Thr Ala Ser
    2285                2290                2295

Ala Thr  Leu Leu Glu
    2300
```

<210> SEQ ID NO 73
<211> LENGTH: 2636
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73

```
cacccactag aaagccaccc gggttctcct tcatccccaa cgctcctcac ctagcccctg     60

tcctgagggt gcccctaacc ctggagccag ctttaaaggg gcaggcccct tctcctgccc    120

cagccccagc cccacccacc gggcccacat tctccgtctt ccaggtccag cgctccctca    180

cagaactccc ccgcaccttg tctcgctcgc tccgcccctc cttcccagcc acagctagag    240

gtcccgggcg cacctgcaga gccggaggct tgctggggca tgcgctccat gaaggctctg    300

cagaaggccc tgagccgggc tggcagtcac tgcgggcgag gaggctgggg tcacccgagc    360

cggagccccc tccttggcgg gggcgtccgg caccacctca gtgaggccgc ggcgcagggc    420

agagagacgc cacacagcca ccagccgcag caccaggatc atgattcatc agaaagtggc    480

atgctgtccc gcctgggtga tttgctcttt tacactattg ctgaaggaca ggaacgaatc    540

cctatccaca agttcaccac tgcactaaag gccactggac tgcagacatc agatcctcgg    600

ctccgagact gcatgagcga gatgcaccgc gtggtccaag agtccagtag tggtggcctc    660

ttggaccgag atctcttccg aaagtgtgtg agcagcaaca ttgtgctcct gacccaggca    720

ttccgaaaga agtttgtcat tcctgatttt gaggagttca cgggccatgt ggatcgcatc    780

tttgaggatg tcaaagagct cactggaggc aaagtggcag cctacatccc tcagctggcc    840

aagtcaaacc cagacctgtg gggtgtctcc ctgtgcactg tggatggtca acggcactct    900

gtgggccaca caaagatccc cttctgcctg cagtcctgtg tgaagcccct cacctatgcc    960

atctccataa gcaccctagg cactgactac gtgcacaagt ttgtgggcaa agagccaagt   1020

ggcctgcgct acaacaagct ctccctcaat gaggaaggaa tcccccataa ccccatggtc   1080

aatgctggtg ccattgttgt cagctccctg atcaagatgg actgtaacaa agcagagaag   1140

tttgattttg tgttgcagta tctcaacaaa atggctggga atgaatacat gggtttcagc   1200

aatgccacat tccagtcaga gaaggaaaca ggggatcgga attatgccat cggctattat   1260

ctcaaggaaa agaagtgctt tcctaagggg gtggacatga tggctgccct tgatctctac   1320

ttccagctgt gttctgtgga ggtcacttgt gaatcaggca gtgtcatggc agccaccctc   1380

gccaacggtg ggatctgccc catcacaggc gagagtgtgc tgagtgctga agcagtgcgc   1440

aacaccctca gcctcatgca ttcctgcggc atgtatgact tctctggcca gtttgccttc   1500
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cacgtgggcc tgccagccaa gtcagctgta tcaggagcca tcctcctggt ggtacccaat 1560

gtcatgggaa tgatgtgcct gtcaccccca ttggacaagc tggggaacag ccataggggg 1620

accagcttct gccagaagtt ggtgtctctc ttcaatttcc acaactatga caacctgagg 1680

cactgtgctc ggaagttaga cccacggcgt gaaggggcag aaattcggaa caagactgtg 1740

gtcaacctgt tatttgctgc ctatagtggc gatgtctcag ctcttcgaag gtttgccttg 1800

tcagccatgg atatggaaca gaaagactat gactcgcgca cagctctgca tgttgctgca 1860

gctgaaggac acatcgaagt tgttaaattc ctgatcgagg cttgcaaagt gaatcctttt 1920

gccaaggaca ggtggggcaa cattcccctg gatgatgctg tgcagttcaa ccatctggag 1980

gtggtcaaac tgcttcaaga ttaccaggac tcctacacac tctctgaaac tcaggctgag 2040

gcagcagctg aggccctgtc caaagagaac ttagaaagca tggtatgagc acaggtcatg 2100

gacagcccct gctcaagaaa aagcatgagc tggccacaca tgtaatccat aaccaccaaa 2160

aatactatgg agagctacac tgcttcagtg gggaccaagc agtcatttgg tgacttaggc 2220

tagtgctttc tatgggagtc aaaatacccc attccctcag cagacagagt acagagaagg 2280

gcctcagagg acacctgcag tacagctatc cagagagact gggcttcaag gtacagccta 2340

atggcttgcc ccactcaaaa ccatcccagc tcttcaccca ggtctcctct tcctctccct 2400

gaagaaacca tcatgagaga gatactctgg tggagggact ctagctacca tgcacatgta 2460

catatccaca gaatatggga agtgggaatg gctatataca tggctttagt agtctggaga 2520

aatctactcc ccttggccag gacatgctgc tgctactgct aacagccaat tttatagaca 2580

gagaaagtat tttgtgttca aataaacttt aattaccaaa tcaaaaaaaa aaaaaa 2636

<210> SEQ ID NO 74
<211> LENGTH: 602
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 74

Met Arg Ser Met Lys Ala Leu Gln Lys Ala Leu Ser Arg Ala Gly Ser
1 5 10 15

His Cys Gly Arg Gly Gly Trp Gly His Pro Ser Arg Ser Pro Leu Leu
20 25 30

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

Glu Thr Pro His Ser His Gln Pro Gln His Gln Asp His Asp Ser Ser
50 55 60

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

Ala Glu Gly Gln Glu Arg Ile Pro Ile His Lys Phe Thr Thr Ala Leu
85 90 95

Lys Ala Thr Gly Leu Gln Thr Ser Asp Pro Arg Leu Arg Asp Cys Met
100 105 110

Ser Glu Met His Arg Val Val Gln Glu Ser Ser Ser Gly Gly Leu Leu
115 120 125

Asp Arg Asp Leu Phe Arg Lys Cys Val Ser Ser Asn Ile Val Leu Leu
130 135 140

Thr Gln Ala Phe Arg Lys Lys Phe Val Ile Pro Asp Phe Glu Glu Phe
145 150 155 160

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

Gly Lys Val Ala Ala Tyr Ile Pro Gln Leu Ala Lys Ser Asn Pro Asp

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            180                 185                 190

Leu Trp Gly Val Ser Leu Cys Thr Val Asp Gly Gln Arg His Ser Val
        195                 200                 205

Gly His Thr Lys Ile Pro Phe Cys Leu Gln Ser Cys Val Lys Pro Leu
    210                 215                 220

Thr Tyr Ala Ile Ser Ile Ser Thr Leu Gly Thr Asp Tyr Val His Lys
225                 230                 235                 240

Phe Val Gly Lys Glu Pro Ser Gly Leu Arg Tyr Asn Lys Leu Ser Leu
                245                 250                 255

Asn Glu Glu Gly Ile Pro His Asn Pro Met Val Asn Ala Gly Ala Ile
            260                 265                 270

Val Val Ser Ser Leu Ile Lys Met Asp Cys Asn Lys Ala Glu Lys Phe
        275                 280                 285

Asp Phe Val Leu Gln Tyr Leu Asn Lys Met Ala Gly Asn Glu Tyr Met
    290                 295                 300

Gly Phe Ser Asn Ala Thr Phe Gln Ser Glu Lys Glu Thr Gly Asp Arg
305                 310                 315                 320

Asn Tyr Ala Ile Gly Tyr Tyr Leu Lys Glu Lys Lys Cys Phe Pro Lys
                325                 330                 335

Gly Val Asp Met Met Ala Ala Leu Asp Leu Tyr Phe Gln Leu Cys Ser
            340                 345                 350

Val Glu Val Thr Cys Glu Ser Gly Ser Val Met Ala Ala Thr Leu Ala
        355                 360                 365

Asn Gly Gly Ile Cys Pro Ile Thr Gly Glu Ser Val Leu Ser Ala Glu
    370                 375                 380

Ala Val Arg Asn Thr Leu Ser Leu Met His Ser Cys Gly Met Tyr Asp
385                 390                 395                 400

Phe Ser Gly Gln Phe Ala Phe His Val Gly Leu Pro Ala Lys Ser Ala
                405                 410                 415

Val Ser Gly Ala Ile Leu Leu Val Val Pro Asn Val Met Gly Met Met
            420                 425                 430

Cys Leu Ser Pro Pro Leu Asp Lys Leu Gly Asn Ser His Arg Gly Thr
        435                 440                 445

Ser Phe Cys Gln Lys Leu Val Ser Leu Phe Asn Phe His Asn Tyr Asp
    450                 455                 460

Asn Leu Arg His Cys Ala Arg Lys Leu Asp Pro Arg Arg Glu Gly Ala
465                 470                 475                 480

Glu Ile Arg Asn Lys Thr Val Val Asn Leu Leu Phe Ala Ala Tyr Ser
                485                 490                 495

Gly Asp Val Ser Ala Leu Arg Arg Phe Ala Leu Ser Ala Met Asp Met
            500                 505                 510

Glu Gln Lys Asp Tyr Asp Ser Arg Thr Ala Leu His Val Ala Ala Ala
        515                 520                 525

Glu Gly His Ile Glu Val Val Lys Phe Leu Ile Glu Ala Cys Lys Val
    530                 535                 540

Asn Pro Phe Ala Lys Asp Arg Trp Gly Asn Ile Pro Leu Asp Asp Ala
545                 550                 555                 560

Val Gln Phe Asn His Leu Glu Val Val Lys Leu Leu Gln Asp Tyr Gln
                565                 570                 575

Asp Ser Tyr Thr Leu Ser Glu Thr Gln Ala Glu Ala Ala Ala Glu Ala
            580                 585                 590

Leu Ser Lys Glu Asn Leu Glu Ser Met Val
        595                 600
```

<210> SEQ ID NO 75
<211> LENGTH: 1231
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 75

cgactctcac gtgaccagga gtcgacgtgt gcagaagtcc ttatagtcca gggcctgttt 60

ccctgtagca gctccttatt gctggagaag gagaaaagtg cccaagatcc tttcaggata 120

tttggttttt tgggcgcgac acaaatcgag gtgagggaag agagaggaaa atcccctgaa 180

tccctgcagg attaatttat tcaaaaagga aataaaaaat actcaatatg caaaagtctt 240

gtgaagaaaa tgagggaaaa ccacagaaca tgccaaaggc cgaggaagat cgccctttgg 300

aggatgtacc acaggaggca gaaggaaatc ctcaaccttc cgaagaaggc gtaagccagg 360

aagcagaagg aaaccccaga ggagggccga atcagcctgg ccagggattt aaagaggaca 420

cacccgttag gcatttggac cctgaagaaa tgataagagg agtagatgag cttgaaaggc 480

ttagggaaga gataagaaga gtaagaaaca agtttgtgat gatgcattgg aagcaaagac 540

attcacgcag ccgtccttat cctgtgtgct ttaggccttg aattcatttt tgcctaatat 600

taaaatctgg ccccagcttt ctttctgtta gcattttctg atgtatcttt gacctccatt 660

ttacttttaa tcatctgatg aaattttgtt ttaggtaatt tccttggtac cagcatctca 720

ttggattttg gattttgacc cattttccag gtctattttt caattggaaa ctttcacaca 780

tttgcatggg aatatgttca ttccatgttg taaagtaaaa cataacaggt tatggcaaag 840

cagcatattt aatatcagct cacatatgta ggataaaatt ccaaactttg tgtgtgtgcg 900

tgtgtgtata catacatcca tataacatat atcacaaact taaccaagct tatttctgtg 960

tggtgtgaaa ttttatttgt tttcttcttt ttgttctttt tgcttatatg tacttttttaa 1020

tgaacacgtg tctcacacac aaaaagaatt aaggattttt tttacaagta agagtcaaat 1080

aatttgcaac cagcttatga gggcaatggg ggcacctaaa ctcttgatga aagaacttta 1140

aaaagaaatg taaacctcaa attacctctg gatctcttag ccagaggaat aaactggcaa 1200

ttattacaga taaaaaaaaa aaaaaaaaaa a 1231

<210> SEQ ID NO 76
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 76

Met Gln Lys Ser Cys Glu Glu Asn Glu Gly Lys Pro Gln Asn Met Pro
1 5 10 15

Lys Ala Glu Glu Asp Arg Pro Leu Glu Asp Val Pro Gln Glu Ala Glu
20 25 30

Gly Asn Pro Gln Pro Ser Glu Glu Gly Val Ser Gln Glu Ala Glu Gly
35 40 45

Asn Pro Arg Gly Gly Pro Asn Gln Pro Gly Gln Gly Phe Lys Glu Asp
50 55 60

Thr Pro Val Arg His Leu Asp Pro Glu Glu Met Ile Arg Gly Val Asp
65 70 75 80

Glu Leu Glu Arg Leu Arg Glu Glu Ile Arg Arg Val Arg Asn Lys Phe
85 90 95

Val Met Met His Trp Lys Gln Arg His Ser Arg Ser Arg Pro Tyr Pro
100 105 110

Val Cys Phe Arg Pro

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115

<210> SEQ ID NO 77
<211> LENGTH: 2213
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 77

gcgggactcg gccttctggg cgcgcgcgac gtcagtttga gttctgtgtt ctccccgccc 60

gtgtcccgcc cgacccgcgc ccgcgatgct ggcgctgcgc tgcggctccc gctggctcgg 120

cctgctctcc gtcccgcgct ccgtgccgct gcgcctcccc gcggcccgcg cctgcagcaa 180

gggctccggc gacccgtcct cttcctcctc ctccgggaac ccgctcgtgt acctggacgt 240

ggacgccaac gggaagccgc tcggccgcgt ggtgctggag ctgaaggcag atgtcgtccc 300

aaagacagct gagaacttca gagccctgtg cactggtgag aagggcttcg gctacaaagg 360

ctccaccttc cacagggtga tcccttcctt catgtgccag gcgggcgact tcaccaacca 420

caatggcaca ggcgggaagt ccatctacgg aagccgcttt cctgacgaga actttacact 480

gaagcacgtg gggccaggtg tcctgtccat ggctaatgct ggtcctaaca ccaacggctc 540

ccagttcttc atctgcacca taaagacaga ctggttggat ggcaagcatg ttgtgttcgg 600

tcacgtcaaa gagggcatgg acgtcgtgaa gaaaatagaa tctttcggct ctaagagtgg 660

gaggacatcc aagaagattg tcatcacaga ctgtggccag ttgagctaat ctgtggccag 720

ggtgctggca tggtggcagc tgcaaatgtc catgcaccca ggtggccgcg ttgggctgtc 780

agccaaggtg cctgaaacga tacgtgtgcc cactccactg tcacagtgtg cctgaggaag 840

gctgctaggg atgttagacc tcggccagga cccaccacat tgcttcctaa tacccaccct 900

tcctcacgac ctcatttctg ggcatctttg tggacatgat gtcacccacc ccttgtcaag 960

cattgcctgt gattgcccag cccagattca tctgtgcctt ggacatggtg atggtgatgg 1020

gttgccatcc aagtgaaagt cttttccttg accaaggggg acagtcagtt ttgcaaaagg 1080

actctaatac ctgtttaata ttgtcttcct aattgggata atttaattaa caagattgac 1140

tagaagtgaa actgcaacac taacttcccc gtgctgtggt gtgacctgag ttggtgacac 1200

aggccacaga ccccagagct tggcttttga aacacaactc agggcttttg tgaaggttcc 1260

cccgctgaga tctttcctcc tggttactgt gaagcctgtt ggtttgctgc tgtcgttttt 1320

gaggagggcc catgggggta ggagcagttg aacctgggaa caaacctcac ttgagctgtg 1380

cctagacaat gtgaattcct gtgttgctaa cagaagtggc ctgtaagctc ctgtgctccg 1440

gagggaagca tttcctggta ggctttgatt tttctgtgtg ttaaagaaat tcaatctact 1500

catgatgtgt tatgcataaa acatttctgg aacatggatt tgtgttcacc ttaaatgtga 1560

aaataaatcc tattttctat ggaagactgg tacctggttt ctggaagagg ggtctgtgac 1620

ttggagctga tctttactga gctcgccgtg gcagatgcca tgctcaggac gttcatgtgg 1680

atggtttcat gtcatcgtgc tggcaacttg tcctccctgc cttagagatg aggctcagac 1740

aaacgacctt agcacccata gcctatgcca tgagcactgg ctccaccctg aatcccagct 1800

cctcccctta gtgaccccaa gtctgtttcc ctcagctgca taaggaggcg atatagtttg 1860

aatatttgtc cccagccaaa tctcatgttg aactgtaatc cccagtgctg gaggtggggc 1920

ctgctacgag gtgtttggat catggggacg ggtatttcat ggcttggtgc tgttttcttg 1980

atggtgaatt attgcaagat acggtcattt aaaattgtgt ggcacctccc cctgcccccc 2040

tcttgctcct gctttcacca tgtgacatgc ctgatccccc ttcacctttt gccatggtca 2100

taagcttcct gaggcctccc tggaagctga gcagatgcca gcaccatgct tcctgtacat 2160

cctgcagaac cataagccaa ttaaaccttt ttaataataa aaaaaaaaaa aaa 2213

<210> SEQ ID NO 78
<211> LENGTH: 207
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 78

Met Leu Ala Leu Arg Cys Gly Ser Arg Trp Leu Gly Leu Leu Ser Val
1 5 10 15

Pro Arg Ser Val Pro Leu Arg Leu Pro Ala Ala Arg Ala Cys Ser Lys
20 25 30

Gly Ser Gly Asp Pro Ser Ser Ser Ser Ser Ser Gly Asn Pro Leu Val
35 40 45

Tyr Leu Asp Val Asp Ala Asn Gly Lys Pro Leu Gly Arg Val Val Leu
50 55 60

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

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

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

Asn Gly Thr Gly Gly Lys Ser Ile Tyr Gly Ser Arg Phe Pro Asp Glu
115 120 125

Asn Phe Thr Leu Lys His Val Gly Pro Gly Val Leu Ser Met Ala Asn
130 135 140

Ala Gly Pro Asn Thr Asn Gly Ser Gln Phe Phe Ile Cys Thr Ile Lys
145 150 155 160

Thr Asp Trp Leu Asp Gly Lys His Val Val Phe Gly His Val Lys Glu
165 170 175

Gly Met Asp Val Val Lys Lys Ile Glu Ser Phe Gly Ser Lys Ser Gly
180 185 190

Arg Thr Ser Lys Lys Ile Val Ile Thr Asp Cys Gly Gln Leu Ser
195 200 205

<210> SEQ ID NO 79
<211> LENGTH: 1668
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 79

atgcccctca tttacataaa tattatacta gcatttacca tctcacttct aggaatacta 60

gtatatcgct cacacctcat atcctcccta ctatgcctag aaggaataat actatcgctg 120

ttcattatag ctactctcat aaccctcaac acccactccc tcttagccaa tattgtgcct 180

attgccatac tagtctttgc cgcctgcgaa gcagcggtgg gcctagccct actagtctca 240

atctccaaca catatggcct agactacgta cataacctaa acctactcca atgctaaaac 300

taatcgtccc aacaattata ttactaccac tgacatgact ttccaaaaaa cacataattt 360

gaatcaacac aaccacccac agcctaatta ttagcatcat ccctctacta ttttttaacc 420

aaatcaacaa caacctattt agctgttccc caacctttc ctccgacccc ctaacaaccc 480

ccctcctaat actaactacc tgactcctac ccctcacaat catggcaagc caacgccact 540

tatccagtga accactatca cgaaaaaaac tctacctctc tatactaatc tccctacaaa 600

tctccttaat tataacattc acagccacag aactaatcat attttatatc ttcttcgaaa 660

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ccacacttat ccccaccttg gctatcatca cccgatgagg caaccagcca gaacgcctga 720

acgcaggcac atacttccta ttctacaccc tagtaggctc ccttccccta ctcatcgcac 780

taatttacac tcacaacacc ctaggctcac taaacattct actactcact ctcactgccc 840

aagaactatc aaactcctga gccaataact taatatgact agcttacaca atagctttta 900

tagtaaagat acctctttac ggactccact tatgactccc taaagcccat gtcgaagccc 960

ccatcgctgg gtcaatagta cttgccgcag tactcttaaa actaggcggc tatggtataa 1020

tacgcctcac actcattctc aacccccctga caaaacacat agcctacccc ttccttgtac 1080

tatccctatg aggcataatt ataacaagct ccatctgcct acgacaaaca gacctaaaat 1140

cgctcattgc atactcttca atcagccaca tagccctcgt agtaacagcc attctcatcc 1200

aaaccccctg aagcttcacc ggcgcagtca ttctcataat cgcccacggg cttacatcct 1260

cattactatt ctgcctagca aactcaaact acgaacgcac tcacagtcgc atcataatcc 1320

tctctcaagg acttcaaact ctactcccac taatagcttt ttgatgactt ctagcaagcc 1380

tcgctaacct cgccttaccc cccactatta acctactggg agaactctct gtgctagtaa 1440

ccacgttctc ctgatcaaat atcactctcc tacttacagg actcaacata ctagtcacag 1500

ccctatactc cctctacata tttaccacaa cacaatgggg ctcactcacc caccacatta 1560

acaacataaa accctcattc acacgagaaa acaccctcat gttcatacac ctatccccca 1620

ttctcctcct atccctcaac cccgacatca ttaccgggtt ttcctctt 1668

<210> SEQ ID NO 80
<211> LENGTH: 459
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 80

Met Leu Lys Leu Ile Val Pro Thr Ile Met Leu Leu Pro Leu Thr Trp
1 5 10 15

Leu Ser Lys Lys His Met Ile Trp Ile Asn Thr Thr Thr His Ser Leu
20 25 30

Ile Ile Ser Ile Ile Pro Leu Leu Phe Phe Asn Gln Ile Asn Asn Asn
35 40 45

Leu Phe Ser Cys Ser Pro Thr Phe Ser Ser Asp Pro Leu Thr Thr Pro
50 55 60

Leu Leu Met Leu Thr Thr Trp Leu Leu Pro Leu Thr Ile Met Ala Ser
65 70 75 80

Gln Arg His Leu Ser Ser Glu Pro Leu Ser Arg Lys Lys Leu Tyr Leu
85 90 95

Ser Met Leu Ile Ser Leu Gln Ile Ser Leu Ile Met Thr Phe Thr Ala
100 105 110

Thr Glu Leu Ile Met Phe Tyr Ile Phe Phe Glu Thr Thr Leu Ile Pro
115 120 125

Thr Leu Ala Ile Ile Thr Arg Trp Gly Asn Gln Pro Glu Arg Leu Asn
130 135 140

Ala Gly Thr Tyr Phe Leu Phe Tyr Thr Leu Val Gly Ser Leu Pro Leu
145 150 155 160

Leu Ile Ala Leu Ile Tyr Thr His Asn Thr Leu Gly Ser Leu Asn Ile
165 170 175

Leu Leu Leu Thr Leu Thr Ala Gln Glu Leu Ser Asn Ser Trp Ala Asn
180 185 190

Asn Leu Met Trp Leu Ala Tyr Thr Met Ala Phe Met Val Lys Met Pro

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        195                 200                 205

Leu Tyr Gly Leu His Leu Trp Leu Pro Lys Ala His Val Glu Ala Pro
    210                 215                 220

Ile Ala Gly Ser Met Val Leu Ala Ala Val Leu Leu Lys Leu Gly Gly
225                 230                 235                 240

Tyr Gly Met Met Arg Leu Thr Leu Ile Leu Asn Pro Leu Thr Lys His
                245                 250                 255

Met Ala Tyr Pro Phe Leu Val Leu Ser Leu Trp Gly Met Ile Met Thr
            260                 265                 270

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

Ser Ser Ile Ser His Met Ala Leu Val Val Thr Ala Ile Leu Ile Gln
    290                 295                 300

Thr Pro Trp Ser Phe Thr Gly Ala Val Ile Leu Met Ile Ala His Gly
305                 310                 315                 320

Leu Thr Ser Ser Leu Leu Phe Cys Leu Ala Asn Ser Asn Tyr Glu Arg
                325                 330                 335

Thr His Ser Arg Ile Met Ile Leu Ser Gln Gly Leu Gln Thr Leu Leu
            340                 345                 350

Pro Leu Met Ala Phe Trp Trp Leu Leu Ala Ser Leu Ala Asn Leu Ala
        355                 360                 365

Leu Pro Pro Thr Ile Asn Leu Leu Gly Glu Leu Ser Val Leu Val Thr
    370                 375                 380

Thr Phe Ser Trp Ser Asn Ile Thr Leu Leu Leu Thr Gly Leu Asn Met
385                 390                 395                 400

Leu Val Thr Ala Leu Tyr Ser Leu Tyr Met Phe Thr Thr Thr Gln Trp
                405                 410                 415

Gly Ser Leu Thr His His Ile Asn Asn Met Lys Pro Ser Phe Thr Arg
            420                 425                 430

Glu Asn Thr Leu Met Phe Met His Leu Ser Pro Ile Leu Leu Leu Ser
        435                 440                 445

Leu Asn Pro Asp Ile Ile Thr Gly Phe Ser Ser
    450                 455


<210> SEQ ID NO 81
<211> LENGTH: 628
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 81

tgacccactt ccgttacttg ctgcggagga ccgtgggcag ccagggtcgg tgaaggatcc     60

caaaatggct gggcgaaaac ttgctctaaa aaccattgac tgggtagctt ttgcagagat    120

catacccag aaccaaaagg ccattgctag ttccctgaaa tcctggaatg agaccctcac    180

ctccaggttg gctgctttac ctgagaatcc accagctatc gactgggctt actacaaggc    240

caatgtggcc aaggctggct tggtggatga ctttgagaag aagtttaatg cgctgaaggt    300

tcccgtgcca gaggataaat atactgccca ggtggatgcc gaagaaaaag aagatgtgaa    360

atcttgtgct gagtgggtgt ctctctcaaa ggccaggatt gtagaatatg agaaagagat    420

ggagaagatg aagaacttaa ttccatttga tcagatgacc attgaggact tgaatgaagc    480

tttcccagaa accaaattag acaagaaaaa gtatccctat tggcctcacc aaccaattga    540

gaatttataa aattgagtcc aggaggaagc tctggccctt gtattacaca ttctggacat    600

taaaaataat aattatacag ttaaaaaa                                       628
```

<210> SEQ ID NO 82
<211> LENGTH: 161
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 82

Met Ala Gly Arg Lys Leu Ala Leu Lys Thr Ile Asp Trp Val Ala Phe
1 5 10 15

Ala Glu Ile Ile Pro Gln Asn Gln Lys Ala Ile Ala Ser Ser Leu Lys
20 25 30

Ser Trp Asn Glu Thr Leu Thr Ser Arg Leu Ala Ala Leu Pro Glu Asn
35 40 45

Pro Pro Ala Ile Asp Trp Ala Tyr Tyr Lys Ala Asn Val Ala Lys Ala
50 55 60

Gly Leu Val Asp Asp Phe Glu Lys Lys Phe Asn Ala Leu Lys Val Pro
65 70 75 80

Val Pro Glu Asp Lys Tyr Thr Ala Gln Val Asp Ala Glu Glu Lys Glu
85 90 95

Asp Val Lys Ser Cys Ala Glu Trp Val Ser Leu Ser Lys Ala Arg Ile
100 105 110

Val Glu Tyr Glu Lys Glu Met Glu Lys Met Lys Asn Leu Ile Pro Phe
115 120 125

Asp Gln Met Thr Ile Glu Asp Leu Asn Glu Ala Phe Pro Glu Thr Lys
130 135 140

Leu Asp Lys Lys Lys Tyr Pro Tyr Trp Pro His Gln Pro Ile Glu Asn
145 150 155 160

Leu

<210> SEQ ID NO 83
<211> LENGTH: 1617
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 83

ctgatgttcg ccgaccgttg actattctct acaaaccaca aagacattgg aacactatac 60

ctattattcg gcgcatgagc tggagtccta ggcacagctc taagcctcct tattcgagcc 120

gagctgggcc agccaggcaa ccttctaggt aacgaccaca tctacaacgt tatcgtcaca 180

gcccatgcat ttgtaataat cttcttcata gtaataccca tcataatcgg aggctttggc 240

aactgactag ttcccctaat aatcggtgcc cccgatatgg cgtttccccg cataaacaac 300

ataagcttct gactcttacc tccctctctc ctactcctgc tcgcatctgc tatagtggag 360

gccggagcag gaacaggttg aacagtctac cctcccttag cagggaacta ctcccaccct 420

ggagcctccg tagacctaac catcttctcc ttacacctag caggtgtctc ctctatctta 480

ggggccatca atttcatcac aacaattatc aatataaaac cccctgccat aacccaatac 540

caaacgcccc tcttcgtctg atccgtccta atcacagcag tcctacttct cctatctctc 600

ccagtcctag ctgctggcat cactatacta ctaacagacc gcaacctcaa caccaccttc 660

ttcgaccccg ccggaggagg agaccccatt ctataccaac acctattctg atttttcggt 720

caccctgaag tttatattct tatcctacca ggcttcggaa taatctccca tattgtaact 780

tactactccg gaaaaaaaga accatttgga tacataggta tggtctgagc tatgatatca 840

attggcttcc tagggtttat cgtgtgagca caccatatat ttacagtagg aatagacgta 900

gacacacgag catatttcac ctccgctacc ataatcatcg ctatccccac cggcgtcaaa 960

-continued

gtatttagct gactcgccac actccacgga agcaatatga aatgatctgc tgcagtgctc 1020

tgagccctag gattcatctt tcttttcacc gtaggtggcc tgactggcat tgtattagca 1080

aactcatcac tagacatcgt actacacgac acgtactacg ttgtagccca cttccactat 1140

gtcctatcaa taggagctgt atttgccatc ataggaggct tcattcactg atttccccta 1200

ttctcaggct acaccctaga ccaaacctac gccaaaatcc atttcactat catattcatc 1260

ggcgtaaatc taactttctt cccacaacac tttctcggcc tatccggaat gccccgacgt 1320

tactcggact accccgatgc atacaccaca tgaaacatcc tatcatctgt aggctcattc 1380

atttctctaa cagcagtaat attaataatt ttcatgattt gagaagcctt cgcttcgaag 1440

cgaaaagtcc taatagtaga agaaccctcc ataaacctgg agtgactata tggatgcccc 1500

ccaccctacc acacattcga agaacccgta tacataaaat ctagacaaaa aaggaaggaa 1560

tcgaaccccc caaagctggt ttcaagccaa ccccatggcc tccatgactt tttcaaa 1617

<210> SEQ ID NO 84
<211> LENGTH: 513
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 84

Met Phe Ala Asp Arg Trp Leu Phe Ser Thr Asn His Lys Asp Ile Gly
1 5 10 15

Thr Leu Tyr Leu Leu Phe Gly Ala Trp Ala Gly Val Leu Gly Thr Ala
20 25 30

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

Gly Asn Asp His Ile Tyr Asn Val Ile Val Thr Ala His Ala Phe Val
50 55 60

Met Ile Phe Phe Met Val Met Pro Ile Met Ile Gly Gly Phe Gly Asn
65 70 75 80

Trp Leu Val Pro Leu Met Ile Gly Ala Pro Asp Met Ala Phe Pro Arg
85 90 95

Met Asn Asn Met Ser Phe Trp Leu Leu Pro Pro Ser Leu Leu Leu Leu
100 105 110

Leu Ala Ser Ala Met Val Glu Ala Gly Ala Gly Thr Gly Trp Thr Val
115 120 125

Tyr Pro Pro Leu Ala Gly Asn Tyr Ser His Pro Gly Ala Ser Val Asp
130 135 140

Leu Thr Ile Phe Ser Leu His Leu Ala Gly Val Ser Ser Ile Leu Gly
145 150 155 160

Ala Ile Asn Phe Ile Thr Thr Ile Ile Asn Met Lys Pro Pro Ala Met
165 170 175

Thr Gln Tyr Gln Thr Pro Leu Phe Val Trp Ser Val Leu Ile Thr Ala
180 185 190

Val Leu Leu Leu Leu Ser Leu Pro Val Leu Ala Ala Gly Ile Thr Met
195 200 205

Leu Leu Thr Asp Arg Asn Leu Asn Thr Thr Phe Phe Asp Pro Ala Gly
210 215 220

Gly Gly Asp Pro Ile Leu Tyr Gln His Leu Phe Trp Phe Phe Gly His
225 230 235 240

Pro Glu Val Tyr Ile Leu Ile Leu Pro Gly Phe Gly Met Ile Ser His
245 250 255

Ile Val Thr Tyr Tyr Ser Gly Lys Lys Glu Pro Phe Gly Tyr Met Gly
260 265 270

-continued

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Met Val Trp Ala Met Met Ser Ile Gly Phe Leu Gly Phe Ile Val Trp
        275                 280                 285

Ala His His Met Phe Thr Val Gly Met Asp Val Asp Thr Arg Ala Tyr
    290                 295                 300

Phe Thr Ser Ala Thr Met Ile Ile Ala Ile Pro Thr Gly Val Lys Val
305                 310                 315                 320

Phe Ser Trp Leu Ala Thr Leu His Gly Ser Asn Met Lys Trp Ser Ala
                325                 330                 335

Ala Val Leu Trp Ala Leu Gly Phe Ile Phe Leu Phe Thr Val Gly Gly
            340                 345                 350

Leu Thr Gly Ile Val Leu Ala Asn Ser Ser Leu Asp Ile Val Leu His
        355                 360                 365

Asp Thr Tyr Tyr Val Val Ala His Phe His Tyr Val Leu Ser Met Gly
    370                 375                 380

Ala Val Phe Ala Ile Met Gly Gly Phe Ile His Trp Phe Pro Leu Phe
385                 390                 395                 400

Ser Gly Tyr Thr Leu Asp Gln Thr Tyr Ala Lys Ile His Phe Thr Ile
                405                 410                 415

Met Phe Ile Gly Val Asn Leu Thr Phe Phe Pro Gln His Phe Leu Gly
            420                 425                 430

Leu Ser Gly Met Pro Arg Arg Tyr Ser Asp Tyr Pro Asp Ala Tyr Thr
        435                 440                 445

Thr Trp Asn Ile Leu Ser Ser Val Gly Ser Phe Ile Ser Leu Thr Ala
    450                 455                 460

Val Met Leu Met Ile Phe Met Ile Trp Glu Ala Phe Ala Ser Lys Arg
465                 470                 475                 480

Lys Val Leu Met Val Glu Glu Pro Ser Met Asn Leu Glu Trp Leu Tyr
                485                 490                 495

Gly Cys Pro Pro Pro Tyr His Thr Phe Glu Glu Pro Val Tyr Met Lys
            500                 505                 510

Ser
```

<210> SEQ ID NO 85
<211> LENGTH: 709
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 85

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atggcacatg cagcgcaagt aggtctacaa gacgctactt cccctatcat agaagagctt     60

atcacctttc atgatcacgc cctcataatc attttcctta tctgcttcct agtcctgtat    120

gccctttttcc taacactcac aacaaaacta actaatacta acatctcaga cgctcaggaa    180

atagaaaccg tctgaactat cctgcccgcc atcatcctag tcctcatcgc cctcccatcc    240

ctacgcatcc tttacataac agacgaggtc aacgatccct cccttaccat caaatcaatt    300

ggccaccaat ggtactgaac ctacgagtac accgactacg gcggactaat cttcaactcc    360

tacatacttc ccccattatt cctagaacca ggcgacctgc gactccttga cgttgacaat    420

cgagtagtac tcccgattga agcccccatt cgtataataa ttacatcaca agacgtcttg    480

cactcatgag ctgtccccac attaggctta aaaacagatg caattcccgg acgtctaaac    540

caaaccactt tcaccgctac acgaccgggg gtatactacg gtcaatgctc tgaaatctgt    600

ggagcaaacc acagtttcat gcccatcgtc ctagaattaa ttcccctaaa aatctttgaa    660

atagggcccg tatttaccct atagcacccc ctctaccccc tctagagcc                709
```

<210> SEQ ID NO 86
<211> LENGTH: 227
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 86

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

Met Glu Glu Leu Ile Thr Phe His Asp His Ala Leu Met Ile Ile Phe
20 25 30

Leu Ile Cys Phe Leu Val Leu Tyr Ala Leu Phe Leu Thr Leu Thr Thr
35 40 45

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

Trp Thr Ile Leu Pro Ala Ile Ile Leu Val Leu Ile Ala Leu Pro Ser
65 70 75 80

Leu Arg Ile Leu Tyr Met Thr Asp Glu Val Asn Asp Pro Ser Leu Thr
85 90 95

Ile Lys Ser Ile Gly His Gln Trp Tyr Trp Thr Tyr Glu Tyr Thr Asp
100 105 110

Tyr Gly Gly Leu Ile Phe Asn Ser Tyr Met Leu Pro Pro Leu Phe Leu
115 120 125

Glu Pro Gly Asp Leu Arg Leu Leu Asp Val Asp Asn Arg Val Val Leu
130 135 140

Pro Ile Glu Ala Pro Ile Arg Met Met Ile Thr Ser Gln Asp Val Leu
145 150 155 160

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

Gly Arg Leu Asn Gln Thr Thr Phe Thr Ala Thr Arg Pro Gly Val Tyr
180 185 190

Tyr Gly Gln Cys Ser Glu Ile Cys Gly Ala Asn His Ser Phe Met Pro
195 200 205

Ile Val Leu Glu Leu Ile Pro Leu Lys Ile Phe Glu Met Gly Pro Val
210 215 220

Phe Thr Leu
225

<210> SEQ ID NO 87
<211> LENGTH: 781
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 87

atgacccacc aatcacatgc ctatcatata gtaaaaccca gcccatgacc cctaacaggg 60

gccctctcag ccctcctaat gacctccggc ctagccatgt gatttcactt ccactccata 120

acgctcctca tactaggcct actaaccaac acactaacca tataccaatg gtggcgcgat 180

gtaacacgag aaagcacata ccaaggccac cacacaccac ctgtccaaaa aggccttcga 240

tacgggataa tcctatttat tacctcagaa gtttttttct tcgcaggatt tttctgagcc 300

ttttaccact ccagcctagc ccctaccccc caactaggag ggcactggcc cccaacaggc 360

atcaccccgc taaatccccc agaagtccca ctcctaaaca catccgtatt actcgcatca 420

ggagtatcaa tcacctgagc tcaccatagt ctaatagaaa acaaccgaaa ccaaataatt 480

caagcactgc ttattacaat tttactgggt ctctatttta ccctcctaca agcctcagag 540

tacttcgagt ctcccttcac catttccgac ggcatctacg gctcaacatt ttttgtagcc 600

acaggcttcc acggacttca cgtcattatt ggctcaactt tcctcactat ctgcttcatc 660

cgccaactaa tatttcactt tacatccaaa catcactttg gcttcgaagc cgccgcctga 720

tactggcatt ttgtagatgt ggtttgacta tttctgtatg tctccatcta ttgatgaggg 780

t 781

<210> SEQ ID NO 88
<211> LENGTH: 260
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 88

Met Thr His Gln Ser His Ala Tyr His Met Val Lys Pro Ser Pro Trp
1 5 10 15

Pro Leu Thr Gly Ala Leu Ser Ala Leu Leu Met Thr Ser Gly Leu Ala
20 25 30

Met Trp Phe His Phe His Ser Met Thr Leu Leu Met Leu Gly Leu Leu
35 40 45

Thr Asn Thr Leu Thr Met Tyr Gln Trp Trp Arg Asp Val Thr Arg Glu
50 55 60

Ser Thr Tyr Gln Gly His His Thr Pro Pro Val Gln Lys Gly Leu Arg
65 70 75 80

Tyr Gly Met Ile Leu Phe Ile Thr Ser Glu Val Phe Phe Phe Ala Gly
85 90 95

Phe Phe Trp Ala Phe Tyr His Ser Ser Leu Ala Pro Thr Pro Gln Leu
100 105 110

Gly Gly His Trp Pro Pro Thr Gly Ile Thr Pro Leu Asn Pro Leu Glu
115 120 125

Val Pro Leu Leu Asn Thr Ser Val Leu Leu Ala Ser Gly Val Ser Ile
130 135 140

Thr Trp Ala His His Ser Leu Met Glu Asn Asn Arg Asn Gln Met Ile
145 150 155 160

Gln Ala Leu Leu Ile Thr Ile Leu Leu Gly Leu Tyr Phe Thr Leu Leu
165 170 175

Gln Ala Ser Glu Tyr Phe Glu Ser Pro Phe Thr Ile Ser Asp Gly Ile
180 185 190

Tyr Gly Ser Thr Phe Phe Val Ala Thr Gly Phe His Gly Leu His Val
195 200 205

Ile Ile Gly Ser Thr Phe Leu Thr Ile Cys Phe Ile Arg Gln Leu Met
210 215 220

Phe His Phe Thr Ser Lys His His Phe Gly Phe Glu Ala Ala Ala Trp
225 230 235 240

Tyr Trp His Phe Val Asp Val Val Trp Leu Phe Leu Tyr Val Ser Ile
245 250 255

Tyr Trp Trp Gly
260

<210> SEQ ID NO 89
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of the artificial sequence:
oligonucleotide

<400> SEQUENCE: 89

cacccgttcg cagtcgtccc 20

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<210> SEQ ID NO 90
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of the artificial sequence: oligonucleotide

<400> SEQUENCE: 90

tcgccgtcct cgctttcc 18

<210> SEQ ID NO 91
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of the artificial sequence: oligonucleotide

<400> SEQUENCE: 91

gaaatggaag ataaagtgac 20

<210> SEQ ID NO 92
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of the artificial sequence: oligonucleotide

<400> SEQUENCE: 92

gttcttcatt tttgctttag 20

<210> SEQ ID NO 93
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of the artificial sequence: oligonucleotide

<400> SEQUENCE: 93

aagattcgga gtttgggctg c 21

<210> SEQ ID NO 94
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of the artificial sequence: oligonucleotide

<400> SEQUENCE: 94

ccagccgcac caataagg 18

<210> SEQ ID NO 95
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of the artificial sequence: oligonucleotide

<400> SEQUENCE: 95

atgagcctgg tgagcctg 18

<210> SEQ ID NO 96
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of the artificial sequence:
oligonucleotide

<400> SEQUENCE: 96

gagacgctgc cttctcaa 18

<210> SEQ ID NO 97
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of the artificial sequence:
oligonucleotide

<400> SEQUENCE: 97

actacggggc ttgtgacgg 19

<210> SEQ ID NO 98
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of the artificial sequence:
oligonucleotide

<400> SEQUENCE: 98

cccgcaggac agccaggt 18

<210> SEQ ID NO 99
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of the artificial sequence:
oligonucleotide

<400> SEQUENCE: 99

ctgaatgaca ggtatcctaa g 21

<210> SEQ ID NO 100
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of the artificial sequence:
oligonucleotide

<400> SEQUENCE: 100

aggatgggtt ctggatgt 18

<210> SEQ ID NO 101
<211> LENGTH: 7
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: polyA tail

<400> SEQUENCE: 101

aaaaaaa 7

<210> SEQ ID NO 102
<211> LENGTH: 13
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: OligodT with XhoI cleavage site

<400> SEQUENCE: 102

ctcgagtttt ttt 13

<210> SEQ ID NO 103
<211> LENGTH: 13
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: polyA tail with XhoI cleavage site

<400> SEQUENCE: 103

aaaaaaactc gag 13

<210> SEQ ID NO 104
<211> LENGTH: 5
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: EcoR1 linker

<400> SEQUENCE: 104

aattc 5

<210> SEQ ID NO 105
<211> LENGTH: 8
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: oligonucleotide

<400> SEQUENCE: 105

aaaaaaac 8

<210> SEQ ID NO 106
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: XhoI linker

<400> SEQUENCE: 106

tcgagttttt tt 12

The invention claimed is:

1. A method for the diagnosis of multiple sclerosis in a patient, comprising detection of moderately to strongly positive presence of autoantibodies, wherein the autoantibody is specific for a protein or peptide which is encoded by the nucleic acid sequence of SEQ ID NO: 1 in blood, serum or plasma isolated from a patient.

2. The method as claimed in claim **1**, where the protein or peptide for which the autoantibody is specific comprises the sequence of SEQ ID NO: 2.

3. The method as claimed in claim **1** or **2**, which further comprises detection of the autoantibody in blood, serum or plasma isolated from a patient without multiple sclerosis.

4. The method as claimed in claim **1** or **2**, where the detection of the autoantibody takes place with an immunoassay.

5. The method as claimed in claim **1** or **2**, where the detection of the autoantibody comprises

(i) contacting the blood, serum or plasma with an agent which specifically binds to the autoantibody, and

(ii) detecting the formation of a complex between the agent and the autoantibody.

6. The method as claimed in claim **5**, where the agent which specifically binds to the autoantibody is immobilized on a support material.

7. The method as claimed in claim **5**, where the agent which specifically binds to the autoantibody is a protein or peptide which specifically binds to the autoantibody.

8. The method as claimed in claim **7**, where the protein or peptide which specifically binds to the autoantibody comprises an amino acid sequence which is encoded by the nucleic acid of SEQ ID NO: 1.

9. The method as claimed in claim **7**, where the protein or peptide which specifically binds to the autoantibody comprises the sequence of SEQ ID NO: 2.

* * * * *

专利名称(译)	自身抗原用于改善炎症性神经疾病的诊断，预后和治疗		
公开(公告)号	US8399210	公开(公告)日	2013-03-19
申请号	US12/420627	申请日	2009-04-08
[标]申请(专利权)人(译)	SAHIN UGUR TURECI OZLEM ZAIGLER ALEXANDER		
申请(专利权)人(译)	SAHIN UGUR TURECI OZLEM ZAIGLER ALEXANDER		
当前申请(专利权)人(译)	GANYMED制药公司 古腾堡安大学		
[标]发明人	SAHIN UGUR TURECI OZLEM ZAIGLER ALEXANDER		
发明人	SAHIN, UGUR TURECI, OZLEM ZAIGLER, ALEXANDER		
IPC分类号	G01N33/53 G01N33/537 G01N33/567		
CPC分类号	G01N33/564 G01N33/56972 G01N2800/285 A61P25/00 A61P25/28		
优先权	102006048201 2006-10-11 DE		
其他公开文献	US20090252714A1		
外部链接	Espacenet USPTO		

摘要(译)

根据本发明，检测其外观是神经性自身免疫疾病，特别是多发性硬化的特征的自身抗体，并鉴定各自的自身抗原。可以进一步显示许多这些自身抗原在脑中特异性表达。自身抗原和自身抗体的鉴定可用于诊断和治疗。自身抗原的脑特异性表达进一步强调了抗原和抗体在神经性自身免疫疾病的起源和发展中的重要作用。

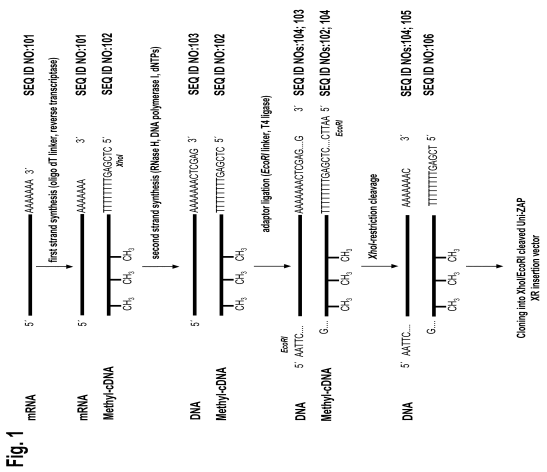

Fig. 1