DESCRIPTION

METHODS AND SYSTEMS FOR ANALYZING A NETWORK OF BIOLOGICAL FUNCTIONS

FIELD OF THE INVENTION

The present invention relates to the field of analysis of biology. More specifically, the present invention relates to the logical analysis of a biological entity such as a cell.

BACKGRAOUND ART

The survival of organisms depends on their ability to perceive and respond to perturbation factors such as extracellular signals. At the molecular level, perturbation factors such as signals are perceived and transmitted through networks of interacting agents present in a biological entity such as proteins, metabolites or the like, that act cooperatively to maintain biological homeostasis and regulate activities like growth, division, differentiation, drug response, and the like. Information transmission through networks of a biological entity is mediated largely by interactions between agents having a variety of functions that may assemble and disassemble dynamically in response to signals, creating transient circuits that link external events to specific internal outputs, such as changes in gene expression, cell shapes, organelle shapes, cell mobility, enzyme activities, metabolite concentrations, and localization of cellular components. Numerous strategies have been developed to map the interactions that underlie these networks. These

studies have collectively provided a wealth of data delineating genome-wide protein-protein interactions for *Escherichia coli*, *Saccharomyces cervisiae* and other organisms. While powerful, these approaches have provided only partial pictures and are likely to overlook many interactions that are context dependent, forming only in the presence of their appropriate signals.

The change in interactions by perturbation factors such as siRNA, antibodies, ligands, hormones, drugs, proteins, mutation or small-molecules can create biological fulcrums that enable small perturbations of a network of biological functions, such as those presented in transcriptional factors, structural genes, cellular markers, cell surface markers, cell shapes, organelle shapes, cell mobility, enzyme activities, metabolite concentrations, and localization of cellular components to elicit large changes in biological phenotype, such as cellular phenotype. However not all interactions in a given signaling pathway are likely to possess this power. As such, complementary strategies which aim to identify global interactions by artificially introducing foreign factors or peptides into cells which compete with and titrate-out the endogenous regulatory interactions, thereby disrupting the normal circuits that connect external signals to cellular responses, are of interest. By combining this strategy with functional assays, such as the activation of a gene in response to a signal, screens for functional interference can be used to identify peptides that perturb regulatory protein-protein interactions. This strategy, often referred to as dominant-interfering or dominant-negative genetics, has been successfully employed in several model organisms where high-throughput screening

methods are easily applied but to a lesser extent in mammals, which traditionally have been less amenable to these types of screens. One advantage of dominant-negative strategies is that such strategies can pinpoint the functionally relevant protein-protein interactions "fulcrum points" and thereby expose the small number of nodes within the larger web of a protein network that are susceptible to functional modulation by external agents. As such, their results can provide vital information about the regulatory components that define a particular pathway and can allow the elucidation of key interactions suitable for targeting by drug screening programs.

Rosetta Inpharmatics has proposed cellular information as a profile in some patent applications (WO01/006013, WO01/005935, WO00/39339, WO00/39338, WO00/39337, WO00/24936, WO00/17402, WO99/66067, WO99/66024, WO99/58720, and WO99/59037). In such a profile, information from separate cells is processed as a group of separate pieces of information but not continuous information. Therefore, this technique is limited in that information analysis is not conducted on a single (the same) cell. Particularly, in this technique, analysis is conducted only at one specific time point before and after a certain change, and a series of temporal changes in a point (gene) are not analyzed.

Recent advances in the profiling technique have led to accurate measurement of cellular components, and thus, profiling of cellular information (e.g., Schena et al., 1995, "Quantitative monitoring of gene expression patterns with a complementary DNA microarray", Science 270:467-470; Lockhart et al., 1996, "Expression monitoring by

hybridization to high-density oligonucleotide arrays", Nature Biotechnology 14:1675-1680; Blanchard et al., 1996, "Sequence to array: Probing the genome's secrets", Nature Biotechnology 14:1649; and WO01/006013). For organisms whose genome has been entirely elucidated, it is possible to analyze the transcripts of all genes in a cell. In the case of other organisms where knowledge of genomic information is increasing, a number of genes in a cell can be simultaneously monitored.

As array technology advances, arrays also have been utilized in the field of drug search (e.g., Marton et al., "Drug target validation and identification of secondary drug target effects using Microarrays", Nat. Med., 1998 Nov, 4(11):1293-301; and Gray et al., 1998, "Exploiting chemical libraries, structure, and genomics in the search for kinase inhibitors", Science, 281:533-538). Analysis using a profile (e.g., US Patent No. 5,777,888) and clustering of profiles provides information about conditions of cells, transplantation, target molecules and candidates for drugs, and/or the relevant functions, efficacy and toxicity of drugs. These techniques can be used to induce a common profile which represents ideal drug activity and disease conditions. Comparing profiles assists in detecting diseases in patients at early stages and provides prediction of improved clinical results for patients who have been diagnosed as having a disease.

However, there has been no technique which can provide actual information about networks of biological functions present in a biological entity such as a cell in a simple, efficient, and correct manner. In the above-described techniques, data is only analyzed in a

binary-wise manner, in other words, only relationships between two particular networks are analyzed, and therefore are not analyzed in a global manner. Analysis and evaluations based on such data lack accuracy and sometimes allow misleading interpretations. Therefore, there is an increasing demand for a method for providing analyzing methods for networks of biological functions in a biological entity.

An object of the present invention is to provide a method and system for analyzing a network of biological functions such as transcriptional factors, structural genes, cellular markers, cell surface markers, cell shapes, organelle shapes, cell mobility, enzyme activities, metabolite concentrations, and localization of cellular components, in a biological entity such as a cell. Particularly, an object of the present invention is to provide a system and method for presenting biological information in a global manner without modification where the cell is considered a complex system.

SUMMARY OF THE INVENTION

The above-described objects of the present invention were achieved by providing a method comprising the steps of: A) subjecting a biological entity to at least one perturbation agent; B) obtaining information on at least two functional reporters in said biological entity wherein the functional reporters reflect a biological function; and C) subjecting the obtained information to set theory processing to calculate a relationship between the functional reporters in order to generate a network relationship of the biological functions and to develop a

system for analyzing a network of biological functions in a biological entity, comprising the steps of: A) at least one perturbation agent for a biological entity; B) means for obtaining information on at least two functional reporters in said biological entity, wherein the functional reporters reflect a biological function; and C) means for subjecting the obtained information to set theory processing to calculate a relationship between the functional reporters to generate a network relationship of the biological functions.

The present invention achieved a simple, efficient and correct method and system for analyzing a network of a biological entity such as a cell. Using the present invention, global networks can be easily and completely analyzed. Such complete and global analysis of the network of biological functions have not been provided in the prior art. Therefore, the present invention provides significant effects not expected by the conventional art.

Accordingly, the present invention is useful for a variety of uses including identification of a biomarker, analysis of a drug target, analysis of a side effect, diagnosis of a cellular function, analysis of a cellular pathway, evaluation of a biological effect of a compound, and diagnosis of an infectious disease and the like.

Therefore the present invention provides the following:

1. A method for analyzing a network of biological functions in a biological entity, comprising the steps of:

A) subjecting a biological entity to at least one

perturbation agent;

B) obtaining information on at least two functional reporters in said biological entity, wherein the functional reporters reflect a biological function; and

C) subjecting the obtained information to set theory processing to calculate a relationship between the functional reporters to generate a network relationship of the biological functions.

2. The method according to Item 1, wherein the biological entity is a cell.

3. The method according to Item 1, wherein the perturbation agent is selected from the group consisting of RNA including siRNA, shRNA, miRNA, and ribozyme, chemical compound, cDNA, antibody, polypeptides, light, sound, pressure change, radiation, heat, and gas.

4. The method according to Item 1, wherein said perturbation agent comprises a siRNA capable of specifically regulating a function of said functional reporter.

5. The method according to Item 1, wherein said functional reporter is capable of transmitting a measurable signal.

6. The method according to Item 1, wherein said functional reporter is selected from the group consisting of transcriptional factors, regulatory genes, structural genes, cellular markers, cell surface markers, cell shapes, organelle shapes, cell mobility, enzyme activities, metabolite concentrations, and localization of cellular

components.

7. The method according to Item 1, wherein said set theory processing comprises:

classifying two specific functional reporters of at least two said functional reporters into a relationship selected from the group consisting of

a) independent;

b) inclusion; and

c) intersection,

wherein when it is determined to be independent, the two specific functional reporters are determined to have no relationship in the network;

when it is determined to be inclusion, one of the two specific functional reporters is determined to be included in the other of the two specific functional reporters, and is located downstream of the other;

when it is determined to be intersection, the two specific functional reporters are determined to be located downstream, branched from another by a common function.

8. The method according to Item 1, wherein the set theory processing comprises the step of mapping the absence or presence of a response by said perturbation agent per said functional reporter.

9. The method according to Item 1, wherein said calculation of relationship between said reporters comprises correlation between each functional reporter as classified into independent, inclusion and intersection to generate a summary of the correlation.

10. The method according to Item 1, wherein said

perturbation factors are prepared with the number sufficient for equally targeting an intracellular pathway.

11. The method according to Item 1, wherein the information on at least two functional reporters is based on an effect of said perturbation agent after a desired time.

12. The method according to Item 1, wherein said effect is classified into the following three groups in terms of a threshold value: positive effect = +; no effect= 0; and negative effect = -.

13. The method according to Item 1, wherein the information on at least two functional reporters is based on an effect of said perturbation agent after a desired time; wherein the set theory processing comprises:

a) classifying the information into three categories by comparing the effect with a threshold value for the functional reporter and classifying into the following three groups: positive effect = +; no effect= 0; and negative effect = -;

b) determining if two of the functional reporters have a common perturbation agent, wherein the common perturbation agent has the same type of effect, and if there is no such common perturbation agent, then the two functions corresponding to the two functional reporters are located under different perturbation agents and if there is such a common perturbation agent, then the following step c) is conducted:

c) determining if the perturbation agent set for one function of the two functions is completely included into the perturbation agent set for the other function of the two functions, and if this is the case, then the one

function having the bigger set is located downstream of the other function having the smaller set, and if this is not the case, then the two functions are located in parallel under the same perturbation agents;

d) determining if all combinations of the functional reporters are investigated, if this is the case, then integrate all the relationships of functions to a present global perturbation effects network, and if this is not the case then repeat the steps a) to c).

14. The method according to Item 13, wherein said three groups are classified into +1, 0 and -1.

15. The method according to Item 13, wherein said steps of a) to c) are calculated by producing M x N matrix, wherein M refers to the number of functional reporters and N refers to the number of perturbation agents.

16. The method according to Item 1, further comprising analyzing the generated network by conducting an actual biological experiment.

17. The method according to Item 16, wherein said step of analyzing comprises the use of a regulation agent specific to the function.

18. The method according to Item 17, wherein the regulation agent is an siRNA.

19. The method according to Item 1, wherein said network comprises a signal transduction pathway and a cellular pathway.

20. The method according to Item 1, wherein said network is used for a use selected from the group consisting of identification of a biomarker, analysis of a drug target, analysis of a side effect, diagnosis of a cellular function, analysis of a cellular pathway, evaluation of a biological effect of a compound, and diagnosis of an infectious disease.

21. A system for analyzing a network of biological functions in a biological entity, comprising:

A) at least one perturbation agent for a biological entity;

B) means for obtaining information on at least two functional reporters in said biological entity, wherein the functional reporters reflect a biological function; and

C) means for subjecting the obtained information to set theory processing to calculate a relationship between the functional reporters to generate a network relationship of the biological functions.

22. The system according to Item 21, wherein the biological entity is a cell.

23. The system according to Item 21, wherein the perturbation agent is selected from the group consisting of siRNA, chemical compound, cDNA, antibody, polypeptides, light, sound, pressure change, radiation, heat and gas.

24. The system according to Item 21, wherein said perturbation agent comprises a siRNA capable of specifically regulating a function of said functional reporter.

25. The system according to Item 21, wherein said

functional reporter is capable of transmitting a measurable signal.

26. The system according to Item 21, wherein said functional reporter is selected from the group consisting of transcriptional factors, structural genes, cellular markers, cell surface markers cell shapes, organelle shapes, cell mobility, enzyme activities, metabolite concentrations, and localization of cellular components.

27. The system according to Item 21, wherein said set theory processing comprises:

classifying two specific functional reporters of at least two said functional reporters into a relationship selected from the group consisting of

a) independent;

b) inclusion; and

c) intersection,

wherein when it is determined to be independent, the two specific functional reporters are determined to have no relationships in the network;

when it is determined to be inclusion, one of the two specific functional reporters is determined to be included in the other of the two specific functional reporters and is located downstream of the other;

when it is determined to be intersection, the two specific functional reporters are determined to be located downstream, branched from another common function.

28. The system according to Item 21, wherein the set theory processing comprises the step of mapping the absence or presence of a response by said perturbation agent per said functional reporter.

29. The system according to Item 21, wherein said calculation of relationship between said reporters comprises a correlation between each functional reporter as classified into independent, inclusion and intersection to generate a summary of the correlation.

30. The system according to Item 1, wherein said perturbation factors are prepared with the number sufficient for equally targeting an intracellular pathway.

31. The system according to Item 21, wherein said means for obtaining information comprises means for obtaining the information on at least two functional reporters is based on an effect of said perturbation agent after a desired time.

32. The system according to Item 21, wherein said effect is classified into the following three groups in terms of a threshold value: positive effect = +; no effect= 0; and negative effect = -.

33. The method according to Item 1, wherein the information on at least two functional reporters is based on an effect of said perturbation agent after a desired time;

wherein the means for subjecting the obtained information to set theory processing comprises:

a) means for classifying the information into three categories by comparing the effect with a threshold value for the functional reporter and classifying into the following three groups: positive effect = +; no effect= 0; and negative effect = -;

b) means for determining if two out of the functional reporters have a common perturbation agent, wherein the

common perturbation agent has the same type of effect, and if there is no such common perturbation agent, then the two functions corresponding to the two functional reporters are located under different perturbation agents and if there is such a common perturbation agent, then the following step c) is conducted:

c) means for determining if the perturbation agent set for one function of the two functions is completely included into the perturbation agent set for the other function of the two functions, and if this is the case, then one function having the bigger set is located downstream of the other function having the smaller set, and if this is not the case, then the two functions are located in parallel under the same perturbation agents;

d) means for determining if all combinations of the functional reporters are investigated, if this is the case, then integrate all the relationships of functions to a present global perturbation effects network, and if this is not the case then repeat the steps conducted by the means a) to c).

34. The system according to Item 33, wherein said three groups are classified into +1, 0 and -1.

35. The system according to Item 33, wherein said means of a) to c) are conducted by producing M x N matrix, wherein M refers to the number of functional reporters and N refers to the number of perturbation agents.

36. The system according to Item 21, further comprising means for analyzing the generated network by conducting an actual biological experiment.

37. The system according to Item 36, wherein said means for analyzing comprises a regulation agent specific to the function.

38. The system according to Item 37, wherein the regulation agent is an siRNA.

39. The system according to Item 21, wherein said network comprises a signal transduction pathway.

40. The system according to Item 21, wherein said network is used for a use selected from the group consisting of identification of a biomarker, analysis of a drug target, analysis of a side effect, diagnosis of a cellular function, analysis of a cellular pathway, evaluation of a biological effect of a compound, and diagnosis of an infectious disease.

41. A computer program for implementing in a computer, a method for analyzing a network of biological functions in a biological entity, comprising the steps of:

A) subjecting a biological entity to at least one perturbation agent;

B) obtaining information on at least two functional reporters in said biological entity wherein the functional reporters reflect a biological function; and

C) subjecting the obtained information to set theory processing to calculate a relationship between the functional reporters to generate a network relationship of the biological functions.

42. A storage medium comprising a computer program for implementing in a computer, a method for analyzing a network of biological functions in a biological entity, comprising

the steps of:

A) subjecting a biological entity to at least one perturbation agent;

B) obtaining information on at least two functional reporters in said biological entity, wherein the functional reporters reflect a biological function; and

C) subjecting the obtained information to set theory processing to calculate a relationship between the functional reporters to generate a network relationship of the biological functions.

43. A transmission medium comprising a computer program for implementing in a computer, a method for analyzing a network of biological functions in a biological entity, comprising the steps of:

A) subjecting a biological entity to at least one perturbation agent;

B) obtaining information on at least two functional reporters in said biological entity, wherein the functional reporters reflect a biological function; and

C) subjecting the obtained information to set theory processing to calculate a relationship between the functional reporters to generate a network relationship of the biological functions.

Hereinafter, the present invention will be described by way of preferred embodiments. It will be understood by those skilled in the art that the embodiments of the present invention can be appropriately made or carried out based on the description of the present specification and the accompanying drawings, and commonly used techniques well known in the art. The function and effect of the present invention can be easily recognized by those skilled in the

art.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure **1** shows a schematic diagram of analysis according to one embodiment of the present invention. A and B refer to functional reporters (sets), which reflect functions of a biological entity such as a cell. Perturbation agents used are located within set A, within set B, within the intersection of set A and set B, outside of set A or set B. i) shows a case where there are no perturbation agents for function A (set A) and function B (set B). In i), function A and B are located under different perturbation agents. ii) shows a case where there are perturbation agents for functions A and B, and all the perturbation agents to be included into function B are also included in function A. In ii), function B is located downstream of function A. iii) shows a case where there are common perturbation agents, but some are included only in function A and some are included only in function B. In iii), functions A and B are located under a common perturbation agent in parallel. iv) and v) show cases where three functions are involved. These can be explained in a similar manner as when two functions are used. In principle, integration of all combinations of two functions will produce the global network of all functions.

Figure **2** shows an exemplary scheme of the present invention, in which a pathway analysis is presented using RNAi and functional reporters. An RNAi library (siRNA library) is used for measuring inhibitory effects on cellular functions such as change in metabolites, gene expression levels, etc. Functions A, B and C will encompass

perturbation agents (siRNAs) having effects on the particular functions.

Figure **3** shows an analyzed scheme presented in Figure **2**. By identifying common genes inhibited by an RNAi and those not being in common, genes specific to a specific function can be identified (e.g. "A" specific genes, etc.). Intracellular pathway structure is calculated from such RNAi inhibitory experimental results.

Figure **4** shows a scheme showing an embodiment of the present invention using a transfection device for analysis of cellular pathways. Upper left panel shows an overview of a chip type device typically used in the present invention. Lower left shows how RNAi and functional reporters are used and analyzed for analyzing a network such as a pathway of a biological entity.

Figure **5** shows a graph showing the results of perturbation agents used in an example using HeLa cell as a biological entity. The y-axis shows the expression level, and the threshold value is set to 80 % in this example. Arrows on the x-axis show the functions reflected on the functional reporters used such as CRE, AP1, GRE, ISRE, Myc, RARE, and actin.

Figure **6** shows a result of HeLa cell transcriptional network analysis and confirmation thereof. The global network is shown with the transcriptional factors (genes) used for the analysis. Arrows from upwards show the genes down-regulated when CRE is inhibited by siRNA specific thereto.

Figure **7** shows a graph showing the results of perturbation agents used in an example using HepG2 cell as a biological entity. Y-axis shows the expression level. The threshold value is set to 80 % in this example. Arrows on the x-axis show the functions reflected on the functional reporters used such as CRE, ISRE, Myc, SRE and RARE.

Figure **8** shows a result of HepG2 cell transcriptional network analysis and confirmation thereof. The global network is shown with the transcriptional factors (genes) used for the analysis. Arrows from upwards show the genes down-regulated when CRE is inhibited by siRNA specific thereto.

Figure **9** shows a schematic flow chart for an exemplary embodiment of the present invention. This flow chart can be conducted in a computer.

Figure **10** shows an exemplary computer system of the present invention.

Figure **11** shows an exemplary combination matrix of functional reporters and siRNA.

Figure **12** shows HeLa array scanned images (16-bit tiff image). Each mixture solution was printed as in the lower panel. After seeding cells, an array scanner was used for obtaining images (see upper panel).

Figure **13** shows neuritegenesis of human neuroblastoma SHSY5Y. SH-SY5Y cell were cultured and when RA is added, they differentiacted into cholinergic neuron-line cells, and when NGF is added, they

differentiated into doperminergic neuron-like cells. In this experiments, 1512 spots/chip of siRNA were studied.

Figure **14** shows graphs of total neurite length/no. nucleus vs. tyrosine kinase targeted siRNA (85 types were used).

Figure **15** shows an overview of the rational approach to analyze functional roles of tyrosine kinases in neuritegenesis.

Figure **15A** (upper left) shows the case in which siRNAs inhibited neurite extension in the presence of retinoic acid (RA; hereinafter the RA set), and the set in which siRNAs inhibited neurite extension in the presence of NGF (hereinafter the NGF set) are separately (independently) present.

Figure **15B** (upper right) shows the case in which the RA set and the NGF set have overlapping members.

Figure **15C** (lower left) shows the case in which the NGF set is encompassed by the RA set.

Figure **15D** (lower right) the case in which the RA set is encompassed by the NGF set.

Figure **16** depicts elucidation of a number of kinases by rational relation from the comprehensive data of the cell-based siRNA assay.

Figure **17** shows the results of EGFR-siRNA,

EPHA2-siRNA, EPHA3-siRNA, #075-siRNA, KIT-siRNA, #054-siRNA, RET-siRNA and #006-siRNA

Figure **18** shows neurite bearing cell percentages are shown for each agent.

Figure **19** shows the marker enzyme expression in the presence of each ligand of the receptor tyrosine kinase.

Figure **20** shows the comparison between the rational relation and biological results.

DESCRIPTION OF SEQUENCE LISTING

SEQ ID NO: 1 refers to a nucleotide sequence of c-Myc (Gene accession No: V00568).
SEQ ID NO: 2 refers to an amino acid sequence of c-Myc (Gene accession No: V00568).
SEQ ID NO: 3 refers to a nucleotide sequence of c-Fos (Gene accession No: K00650).
SEQ ID NO: 4 refers to an amino acid sequence of c-Fos (Gene accession No: K00650).
SEQ ID NO: 5 refers to a nucleotide sequence of c-Jun (Gene accession No: J04111).
SEQ ID NO: 6 refers to an amino acid sequence of c-Jun (Gene accession No: J04111).
SEQ ID NO: 7 refers to a nucleotide sequence of CREB (Gene accession No: M27691).
SEQ ID NO: 8 refers to an amino acid sequence of CREB (Gene accession No: M27691).
SEQ ID NO: 9 refers to a nucleotide sequence of E2F (Gene accession No: M96577).

SEQ ID NO: 10 refers to an amino acid sequence of E2F (Gene accession No: M96577).

SEQ ID NO: 11 refers to a nucleotide sequence of ER (Gene accession No: M12674).

SEQ ID NO: 12 refers to an amino acid sequence of ER (Gene accession No: M12674).

SEQ ID NO: 13 refers to a nucleotide sequence of GR (Gene accession No: M10901).

SEQ ID NO: 14 refers to an amino acid sequence of GR (Gene accession No: M10901).

SEQ ID NO: 15 refers to a nucleotide sequence of HSF-1 (Gene accession No: NM_005526).

SEQ ID NO: 16 refers to an amino acid sequence of HSF-1 (Gene accession No: NM_005526).

SEQ ID NO: 17 refers to a nucleotide sequence of HSF-2 (Gene accession No: M65217).

SEQ ID NO: 18 refers to an amino acid sequence of HSF-2 (Gene accession No: M65217).

SEQ ID NO: 19 refers to a nucleotide sequence of HSF-4 (Gene accession No: D87673).

SEQ ID NO: 20 refers to an amino acid sequence of HSF-4 (Gene accession No: D87673).

SEQ ID NO: 21 refers to a nucleotide sequence of IkBa (Gene accession No: M69043).

SEQ ID NO: 22 refers to an amino acid sequence of IkBa (Gene accession No: M69043).

SEQ ID NO: 23 refers to a nucleotide sequence of NFAT3 (Gene accession No: L41066).

SEQ ID NO: 24 refers to an amino acid sequence of NFAT3 (Gene accession No: L41066).

SEQ ID NO: 25 refers to a nucleotide sequence of NFkB (Gene accession No: S76638).

SEQ ID NO: 26 refers to an amino acid sequence of NFkB (Gene

accession No: S76638).

SEQ ID NO: 27 refers to a nucleotide sequence of RARA (Gene accession No: NM_000964).

SEQ ID NO: 28 refers to an amino acid sequence of RARA (Gene accession No: NM_000964).

SEQ ID NO: 29 refers to a nucleotide sequence of RARA (Gene accession No: NM_000965).

SEQ ID NO: 30 refers to an amino acid sequence of RARA (Gene accession No: NM_000965).

SEQ ID NO: 31 refers to a nucleotide sequence of RARB1 (Gene accession No: NM_016152).

SEQ ID NO: 32 refers to an amino acid sequence of RARB1 (Gene accession No: NM_016152).

SEQ ID NO: 33 refers to a nucleotide sequence of RARB2 (Gene accession No: M57707).

SEQ ID NO: 34 refers to an amino acid sequence of RARB2 (Gene accession No: M57707).

SEQ ID NO: 35 refers to a nucleotide sequence of RARG (Gene accession No: M15400).

SEQ ID NO: 36 refers to an amino acid sequence of RARG (Gene accession No: M15400).

SEQ ID NO: 37 refers to a nucleotide sequence of Rb (Gene accession No: J03161).

SEQ ID NO: 38 refers to an amino acid sequence of Rb (Gene accession No: J03161).

SEQ ID NO: 39 refers to a nucleotide sequence of SRF (Gene accession No: M97935).

SEQ ID NO: 40 refers to an amino acid sequence of SRF (Gene accession No: M97935).

SEQ ID NO: 41 refers to a nucleotide sequence of STAT1a (Gene accession No: M97936).

SEQ ID NO: 42 refers to an amino acid sequence of STAT1a (Gene accession No: M97936).

SEQ ID NO: 43 refers to a nucleotide sequence of STAT1b (Gene accession No: M97934).

SEQ ID NO: 44 refers to an amino acid sequence of STAT1b (Gene accession No: M97934).

SEQ ID NO: 45 refers to a nucleotide sequence of STAT2 (Gene accession No: L29277).

SEQ ID NO: 46 refers to an amino acid sequence of STAT2 (Gene accession No: L29277).

SEQ ID NO: 47 refers to a nucleotide sequence of STAT3 (Gene accession No: Y00479).

SEQ ID NO: 48 refers to an amino acid sequence of STAT3 (Gene accession No: Y00479).

SEQ ID NO: 49 refers to a nucleotide sequence of P53 (Gene accession No: AF307851).

SEQ ID NO: 50 refers to an amino acid sequence of Scramble (Gene accession No: AF307851).

SEQ ID NO: 51 refers to a nucleotide sequence to fibronectin.

SEQ ID NO:52 shows an amino acid sequence to fibronectin.

SEQ ID NO: 53 refers to a nucleotide sequence of c-Fos siRNA.

SEQ ID NO: 54 refers to a nucleotide sequence of c-Jun siRNA.

SEQ ID NO: 55 refers to a nucleotide sequence of CREB siRNA.

SEQ ID NO: 56 refers to a nucleotide sequence of E2F siRNA.

SEQ ID NO: 57 refers to a nucleotide sequence of ER siRNA.

SEQ ID NO: 58 refers to a nucleotide sequence of GR siRNA.

SEQ ID NO: 59 refers to a nucleotide sequence of HSF-1 siRNA.

SEQ ID NO: 60 refers to a nucleotide sequence of HSF-2 siRNA.

SEQ ID NO: 61 refers to a nucleotide sequence of HSF-4 siRNA.

SEQ ID NO: 62 refers to a nucleotide sequence of IkBa siRNA.

SEQ ID NO: 63 refers to a nucleotide sequence of NFAT3 siRNA.

SEQ ID NO: 64 refers to a nucleotide sequence of NFkB siRNA.

SEQ ID NO: 65 refers to a nucleotide sequence of RARA siRNA.

SEQ ID NO: 66 refers to a nucleotide sequence of RARB1 siRNA.

SEQ ID NO: 67 refers to a nucleotide sequence of RARB2 siRNA.

SEQ ID NO: 68 refers to a nucleotide sequence of RARG siRNA.
SEQ ID NO: 69 refers to a nucleotide sequence of Rb siRNA.
SEQ ID NO: 70 refers to a nucleotide sequence of SRF siRNA.
SEQ ID NO: 71 refers to a nucleotide sequence of STAT1a siRNA.
SEQ ID NO: 72 refers to a nucleotide sequence of STAT1b siRNA.
SEQ ID NO: 73 refers to a nucleotide sequence of STAT2 siRNA.
SEQ ID NO: 74 refers to a nucleotide sequence of STAT3 siRNA.
SEQ ID NO: 75 refers to a nucleotide sequence of TR siRNA.
SEQ ID NO: 76 refers to a nucleotide sequence of p53 siRNA.
SEQ ID NO: 77 refers to a nucleotide sequence of scramble II Duplex (Gene accession No: AF307851).
SEQ ID NO: 78 refers to a nucleotide sequence of the kinase EGFR.
SEQ ID NO: 79 refers to an amino acid sequence of the kinase EGFR.
SEQ ID NO: 80 refers to a nucleotide sequence of the kinase EPHA2.
SEQ ID NO: 81 refers to an amino acid sequence of the kinase EPHA2.
SEQ ID NO: 82 refers to a nucleotide sequence of the kinase EPHA3.
SEQ ID NO: 83 refers to an amino acid sequence of the kinase EPHA3.
SEQ ID NO: 84 refers to a nucleotide sequence of the kinase #075.
SEQ ID NO: 85 refers to an amino acid sequence of the kinase #075.
SEQ ID NO: 86 refers to a nucleotide sequence of the kinase KIT.
SEQ ID NO: 87 refers to an amino acid sequence of the kinase KIT.
SEQ ID NO: 88 refers to a nucleotide sequence of the kinase #054.

SEQ ID NO: 89 refers to an amino acid sequence of the kinase #054.

SEQ ID NO: 90 refers to a nucleotide sequence of the kinase RET.

SEQ ID NO: 91 refers to an amino acid sequence of the kinase RET.

SEQ ID NO: 92 refers to a nucleotide sequence of the kinase #006.

SEQ ID NO: 93 refers to an amino acid sequence of the kinase #006.

EGFR-siRNA, EPHA2-siRNA, EPHA3-siRNA, #075-siRNA, KIT-siRNA, #054-siRNA, RET-siRNA and #006-siRNA used herein are available from Amersham Biosciences Japan, as the following catalog numbers: EGFR siRNA: M-003114-01; KIT siRNA: M-003150-01; RET siRNA: M-003170-01; EPHA2 siRNA: M-003116-01; EPHA3 siRNA: M-003117-01; #006 siRNA: M-003171-01; #075 siRNA: M-003149-01; and #054 siRNA: M-003152-01. The sequences thereof are unpublished but equivalents thereof can be prepared using well known technology in the art.

A nucleotide sequence of c-Myc siRNA used herein can be obtained from Ambion, Inc. as Silencer™ c-myc siRNA.

BEST MODE FOR CARRYING OUT THE INVENTION

It should be understood throughout the present specification that articles for singular forms include the concept of their plurality unless otherwise mentioned. Therefore, articles or adjectives for singular forms (e.g., "a", "an", "the", etc. in English, and articles, adjectives, etc. in other languages) include the concept of their

plurality unless otherwise specified. As such, the terms "a" or "an", "one or more" and "at least one" can be used interchangeably herein. It is also to be noted that the terms "comprising," "including," and "having" can be used interchangeably. Furthermore, a compound "selected from the group consisting of refers to one or more of the compounds in the list that follows, including mixtures (i.e. combinations) of two or more of the compounds. It should be also understood that terms as used herein have definitions ordinarily used in the art unless otherwise mentioned. Therefore, all technical and scientific terms used herein have the same meanings as commonly understood by those skilled in the art. Otherwise, the present application (including definitions) takes precedence.

Before the present compounds, compositions, system, device and/or methods are disclosed and described, it is to be understood that this invention is not limited to specific synthetic methods, specific reagents or to laboratory or manufacturing techniques, as such may, of course, vary unless it is otherwise indicated. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

(Definition of terms)

Hereinafter, terms specifically used herein will be defined.

(Biological Functions)

As used herein the term "network of biological functions" refers to any network of parameters of a biological entity, such as genes, transcriptional factors,

structural genes, cellular markers, cell surface markers, cell shapes, organelle shapes, cell mobility, enzyme activities, metabolite concentrations, and localization of cellular components and the like. Such networks may be but are not limited to a pathway of parameters such as genes, signal transduction pathway, and the like.

As used herein a "pathway" refers to any pathway of parameters of a biological entity. Such pathways may be but are not limited to a pathway of a drug stimulation and the like.

As used herein the term "biological function" refers to any parameter which is related to and/or reflects the living state of a biological entity such as a cell. Such biological functions include but are not limited to transcriptional factors, regulatory genes, structural genes, cellular markers, cell surface markers, cell shapes, organelle shapes, cell mobility, enzyme activities, metabolite concentrations, and localization of cellular components. Such biological function may be measured by using a functional reporter which is specific to the function. As used herein the term "specific" in terms of the biological function refers to the relationship between a biological function and a functional reporter, wherein a change in the functional reporter is related to the change in the state of the biological function.

As used herein the term "perturbation agent" refers to any agent that causes perturbation in a biological entity. Such perturbation agents include but are not limited to, for example, RNA (e.g. siRNA, shRNA, miRNA, ribozyme), chemical compound, cDNA, antibody, polypeptides,

light, sound, pressure change, radiation, heat, gas, and the like, particularly siRNA capable of specifically regulating a function of said functional reporter is preferred, since such siRNA specifically targets the function in a biological entity such as a cell.

As used herein the term "functional reporter" refers to an agent which changes the signal of a biological function to a measurable signal, such as light, expression of protein, production of metabolite, change in color, fluorescence, chemilunescence, and the like.

As used herein the term "set theory" refers to a theory as used and understood in the art, and the branch of pure mathematics that deals with the nature and relationships of sets. A mathematical formalization of the theory of "sets" (aggregates or collections) of objects ("elements" or "members"). Many mathematicians use set theory as the basis for all other mathematics. Such set theory includes the analysis of members into sets and classification of sets into inclusion, independent and intersection, and the like.

As used herein the term "set" is used as in the set theory in the art, and refers to a group of members or elements.

As used herein the term "member", "cardinality" or "element" is interchangeably used to refer to a basic unit of a set. In the present invention, a functional reporter can be regarded as a set, and a perturbation agent or information/data/result derived therefrom can be regarded as a member.

As used herein the term "inclusion" refers to a relationship of two sets where all members of one set there of is included in the other set.

As used herein the term "independent" refers to a relationship of two groups where all members of one set are not included in the other set and *vice versa*.

As used herein the term "intersection" refers to a relationship of two sets where some members of one set are included and some are not, and *vice versa*, and therefore there is an overlap set between the two sets.

As used herein the term "network relationship" refers to a relationship of members of a network. Such relationship may be presented in a map of members with arrows, which shows the direction of influence of one member on the other.

As used herein the term "parallel" when used for relationship of two parameters refers to the state where the two parameters are located in different pathways in a network.

As used herein the term "downstream" when used for relationship of two parameters refers to the state where one of the two parameters is located downstream of the other in a pathway or a network.

As used herein the term "upstream" when used for relationship of two parameters refers to the state where one of the two parameters is located upstream of the other

in a pathway or a network.

As used herein the term "common" refers to a state where two parameters are in the same relationship for a function or any other parameter of a biological entity.

As used herein the phrase "equally targeting" refers to a condition of distributing perturbation agents, where the perturbation agents to be introduced have substantially the same effects on the targets of interest. In the present invention, two or more perturbation agents are usually used to change the network structure of a biological entity such as a cell, it is preferable to use such equally targeting perturbation agents.

As used herein the term "threshold" refers to a specific value for evaluating whether a function is activated or suppressed. Such a threshold may be determined experimentally, empirically, or theoretically. Threshold may be arbitrarily selected for certain cases.

(Biology)

As used herein the term "biological entity" refers to any entity which is biologically living. Examples of such biological entities include living organism, organ, tissue, cell, microorganisms such as bacteria, virus, and the like.

The term "cell" is herein used in its broadest sense in the art, referring to a structural unit of tissue of a multicellular organism, which is capable of self replicating, has genetic information and a mechanism for expressing it, and is surrounded by a membrane structure

which isolates the cell from the outside. Cells used herein may be either naturally-occurring cells or artificially modified cells (e.g., fusion cells, genetically modified cells, etc.). Examples of cell sources include, but are not limited to, a single-cell culture; the embryo, blood, or body tissue of normally-grown transgenic animal; a mixture of cells derived from normally-grown cell lines; and the like.

Cells used herein may be derived from any organism (e.g., any unicellular organisms (e.g., bacteria and yeast) or any multicellular organisms (e.g., animals (e.g., vertebrates and invertebrates), plants (e.g., monocotyledons and dicotyledons, etc.)). For example, cells used herein are derived from a vertebrate (e.g., Myxiniformes, Petronyzoniformes, Chondrichthyes, Osteichthyes, amphibian, reptilian, avian, mammalian, etc.), more preferably mammalian (e.g., monotremata, marsupialia, edentate, dermoptera, chiroptera, carnivore, insectivore, proboscidea, perissodactyla, artiodactyla, tubulidentata, pholidota, sirenia, cetacean, primates, rodentia, lagomorpha, etc.). In one embodiment, cells derived from Primates (e.g., chimpanzee, Japanese monkey, human) are used. The above-described cells may be either stem cells or somatic cells. Also, the cells may be adherent cells, suspended cells, tissue forming cells, and mixtures thereof. The cells may be used for transplantation.

Any organ may be targeted by the present invention. A biological entity such as a tissue or cell targeted by the present invention may be derived from any organ. As used herein, the term "organ" refers to a morphologically independent structure localized at a

particular portion of an individual organism in which a certain function is performed. In multicellular organisms (e.g., animals, plants), an organ consists of several tissues spatially arranged in a particular manner, each tissue being composed of a number of cells. An example of such an organ includes an organ relating to the vascular system. In one embodiment, organs targeted by the present invention include, but are not limited to, skin, blood vessel, cornea, kidney, heart, liver, umbilical cord, intestine, nerve, lung, placenta, pancreas, brain, peripheral limbs, retina, and the like. Examples of cells differentiated from pluripotent cells include epidermic cells, pancreatic parenchymal cells, pancreatic duct cells, hepatic cells, blood cells, cardiac muscle cells, skeletal muscle cells, osteoblasts, skeletal myoblasts, neurons, vascular endothelial cells, pigment cells, smooth muscle cells, fat cells, bone cells, cartilage cells, and the like.

As used herein, the term "tissue" refers to an aggregate of cells having substantially the same function and/or form in a multicellular organism. "Tissue" is typically an aggregate of cells of the same origin, but may be an aggregate of cells of different origins as long as the cells have the same function and/or form. Therefore, tissues used herein may be composed of an aggregate of cells of two or more different origins. Typically, a tissue constitutes a part of an organ. Animal tissues are separated into epithelial tissue, connective tissue, muscular tissue, nervous tissue, and the like, on a morphological, functional, or developmental basis. Plant tissues are roughly separated into meristematic tissue and permanent tissue according to the developmental stage of the cells constituting the tissue. Alternatively, tissues

may be separated into single tissues and composite tissues according to the type of cells constituting the tissue. Thus, tissues are separated into various categories.

As used herein, the term "isolated" means that naturally accompanying material is at least reduced, or preferably substantially completely eliminated, in normal circumstances. As used herein, an isolated biological entity can be targeted by the present invention. Therefore, the term "isolated cell" refers to a cell substantially free from other accompanying substances (e.g., other cells, proteins, nucleic acids, etc.) in natural circumstances. The term "isolated" in relation to nucleic acids or polypeptides means that, for example, the nucleic acids or the polypeptides are substantially free from cellular substances or culture media when they are produced by recombinant DNA techniques; or precursory chemical substances or other chemical substances when they are chemically synthesized. Isolated nucleic acids are preferably free from sequences naturally flanking the nucleic acid within an organism from which the nucleic acid is derived (i.e., sequences positioned at the 5' terminus and the 3' terminus of the nucleic acid). Preferably, an isolated cell is used for analysis of the present invention.

As used herein, the term "established" in relation to cells refers to a state of a cell in which a particular property (such as pluripotency) of the cell is maintained and the cell undergoes stable proliferation under culture conditions. In the present invention, such an established cell may be used.

As used herein, the term "state" refers to a

condition concerning various parameters of a biological entity such as a cell (e.g., cell cycle, response to an external factor, signal transduction, gene expression, gene transcription, etc.). Examples of such a state include, but are not limited to, differentiated states, undifferentiated states, responses to external factors, cell cycles, growth states, and the like. As used herein, the term "gene state" refers to any state associated with a gene (e.g., an expression state, a transcription state, etc.).

As used herein, the terms "differentiation" or "cell differentiation" refers to a phenomenon where two or more types of cells having qualitative differences in form and/or function occur in a daughter cell population derived from the division of a single cell. Therefore, "differentiation" includes a process during which a population (family tree) of cells, which do not originally have a specific detectable feature, acquire a feature, such as production of a specific protein, or the like. At present, cell differentiation is generally considered to be a state of a cell in which a specific group of genes in the genome are expressed. Cell differentiation can be identified by searching for intracellular or extracellular agents or conditions which elicit the above-described state of gene expression. Differentiated cells are stable in principle. Particularly, animal cells which have been once differentiated are rarely differentiated into other types of cells.

As used herein, the term "pluripotency" refers to a nature of a cell, i.e., an ability to differentiate into one or more, preferably two or more, tissues or organs. Therefore, the terms "pluripotent" and "undifferentiated"

are herein used interchangeably unless otherwise mentioned. Typically, the pluripotency of a cell is limited during development, and in an adult, cells constituting a tissue or organ rarely alter to different cells, that is, the pluripotency is usually lost. Particularly, epithelial cells resist altering to other types of epithelial cells. Such alteration typically occurs in pathological conditions, and is called metaplasia. However, mesenchymal cells tend to easily undergo metaplasia, i.e., alter to other mesenchymal cells, with relatively simple stimuli. Therefore, mesenchymal cells have a high level of pluripotency. Embryonic stem cells have pluripotency. Tissue stem cells have pluripotency. Thus, the term "pluripotency" may include the concept of totipotency. An example of an *in vitro* assay for determining whether or not a cell has pluripotency, includes, but is not limited to, culturing under conditions for inducing the formation and differentiation of embryoid bodies. Examples of an *in vivo* assay for determining the presence or absence of pluripotency, include, but are not limited to, implantation of a cell into an immunodeficient mouse so as to form teratoma, injection of a cell into a blastocyst so as to form a chimeric embryo, implantation of a cell into a tissue of an organism (e.g., injection of a cell into ascites) so as to undergo proliferation, and the like. As used herein, one type of pluripotency is "totipotency", which refers to an ability to be differentiated into all kinds of cells which constitute an organism. The idea of pluripotency encompasses totipotency. An example of a totipotent cell is a fertilized ovum. An ability to be differentiated into only one type of cell is called "unipotency".

As used herein, the term "gene" refers to an

element defining a genetic trait, which is a biological function of a biological entity. A gene is typically arranged in a given sequence on a chromosome or other extrachromosomal factor. A gene which defines the primary structure of a protein is called a structural gene. A gene which regulates the expression of a structural gene is called a regulatory gene (e.g., promoter). Genes herein include structural genes and regulatory genes unless otherwise specified. Therefore, for example, the term "cyclin gene" typically includes the structural gene of cyclin and the promoter of cyclin. As used herein, "gene" may refer to "polynucleotide", "oligonucleotide", "nucleic acid", and "nucleic acid molecule" and/or "protein", "polypeptide", "oligopeptide" and "peptide". As used herein, "gene product" includes "polynucleotide", "oligonucleotide", "nucleic acid" and "nucleic acid molecule" and/or "protein", "polypeptide", "oligopeptide" and "peptide", which are expressed by a gene. Those skilled in the art understand what a gene product is, according to the context.

As used herein, the term "homology" in relation to a sequence (e.g., a nucleic acid sequence, an amino acid sequence, etc.) refers to the proportion of identity between two or more gene sequences. Therefore, the greater the homology between two given genes, the greater the identity or similarity between their sequences. Whether or not two genes have homology is determined by comparing their sequences directly or by a hybridization method under stringent conditions. When two gene sequences are directly compared with each other, these genes have homology if the DNA sequences of the genes have representatively at least 50% identity, preferably at least 70% identity, more preferably at least 80%, 90%, 95%, 96%, 97%, 98%, or 99%

identity with each other. As used herein, the term "similarity" in relation to a sequence (e.g., a nucleic acid sequence, an amino acid sequence, or the like) refers to the proportion of identity between two or more sequences when conservative substitution is regarded as positive (identical) in the above-described homology. Therefore, homology and similarity differ from each other in the presence of conservative substitutions. If no conservative substitutions are present, homology and similarity have the same value. Such homologous genes and the like may be used as the same function in a network, if applicable, and may be used as different perturbation agents and the like, if applicable.

The terms "protein", "polypeptide", "oligopeptide" and "peptide" as used herein have the same meaning and refer to an amino acid polymer of any length. This polymer may be a straight, branched or cyclic chain polymer. An amino acid may be a naturally-occurring or nonnaturally-occurring amino acid, or a variant amino acid. The term may include those assembled into a composite of a plurality of polypeptide chains. The term also includes a naturally-occurring or artificially modified amino acid polymer. Such modification includes, for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification (e.g., conjugation with a labeling moiety). This definition encompasses a polypeptide containing at least one amino acid analog (e.g., nonnaturally-occurring amino acid, etc.), a peptide-like compound (e.g., peptoid), and other variants known in the art, for example. Gene products, such as extracellular matrix proteins (e.g., fibronectin, etc.), are usually in the form of a polypeptide.

Polypeptides used in the present invention may be produced by, for example, cultivating primary culture cells producing the peptides or cell lines thereof, followed by separation or purification of the peptides from the culture supernatant. Alternatively, genetic manipulation techniques can be used to incorporate a gene encoding a polypeptide of interest into an appropriate expression vector, transform an expression host with the vector, and collect recombinant polypeptides from the culture supernatant of the transformed cells. The above-described host cell may be any host cells conventionally used in genetic manipulation techniques as long as they can express a polypeptide of interest while maintaining the physiological activity of the peptide (e.g., *E. coli*, yeast, an animal cell, etc.). Polypeptides derived from the thus-obtained cells may have at least one amino acid substitution, addition, and/or deletion or at least one sugar chain substitution, addition, and/or deletion as long as they have substantially the same function as that of naturally-occurring polypeptides.

The terms "polynucleotide", "oligonucleotide", "nucleic acid molecule" and "nucleic acid" as used herein have the same meaning and refer to a nucleotide polymer having any length. This term also includes an "oligonucleotide derivative" or a "polynucleotide derivative". An "oligonucleotide derivative" or a "polynucleotide derivative" includes a nucleotide derivative, or refers to an oligonucleotide or a polynucleotide having different linkages between nucleotides from typical linkages, which are interchangeably used. Examples of such an oligonucleotide specifically include 2'-O-methyl-ribonucleotide, an

oligonucleotide derivative in which a phosphodiester bond in an oligonucleotide is converted to a phosphorothioate bond, an oligonucleotide derivative in which a phosphodiester bond in an oligonucleotide is converted to a N3'-P5' phosphoroamidate bond, an oligonucleotide derivative in which a ribose and a phosphodiester bond in an oligonucleotide are converted to a peptide-nucleic acid bond, an oligonucleotide derivative in which uracil in an oligonucleotide is substituted with C-5 propynyl uracil, an oligonucleotide derivative in which uracil in an oligonucleotide is substituted with C-5 thiazole uracil, an oligonucleotide derivative in which cytosine in an oligonucleotide is substituted with C-5 propynyl cytosine, an oligonucleotide derivative in which cytosine in an oligonucleotide is substituted with phenoxazine-modified cytosine, an oligonucleotide derivative in which ribose in DNA is substituted with 2'-O-propyl ribose, and an oligonucleotide derivative in which ribose in an oligonucleotide is substituted with 2'-methoxyethoxy ribose. Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively-modified variants thereof (e.g. degenerate codon substitutions) and complementary sequences as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions may be produced by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer et al., Nucleic Acid Res. 19:5081(1991); Ohtsuka et al., J. Biol. Chem. 260:2605-2608 (1985); Rossolini et al., Mol. Cell. Probes 8:91-98(1994)). A gene encoding an extracellular matrix protein (e.g., fibronectin, etc.) or the like is usually in the form of a polynucleotide. A molecule to be

transfected is in the form of a polynucleotide.

As used herein, the term "corresponding", when used for the relationship between a functional reporter and function, refers to a state where the signal derived from a functional reporter of interest reflects the state of a function. Therefore one can determine the state of such a function based on the signal of the functional reporter corresponding to the function. For example, a gene expressing a fluorescent protein operably linked under a transcriptional factor is said to be a functional reporter corresponding to the transcriptional factor, and the like.

As used herein, the term "corresponding" amino acid or nucleic acid refers to an amino acid or nucleotide in a given polypeptide or polynucleotide molecule, which has, or is anticipated to have, a function similar to that of a predetermined amino acid or nucleotide in a polypeptide or polynucleotide as a reference for comparison. Particularly, in the case of enzyme molecules, the term refers to an amino acid which is present at a similar position in an active site and similarly contributes to catalytic activity. For example, in the case of antisense molecules for a certain polynucleotide, the term refers to a similar portion in an ortholog corresponding to a particular portion of the antisense molecule.

As used herein, the term "corresponding" gene (e.g., a polypeptide or polynucleotide molecule) refers to a gene in a given species, which has, or is anticipated to have, a function similar to that of a predetermined gene in a species as a reference for comparison. When there are a plurality of genes having such a function, the term refers

to a gene having the same evolutionary origin. Therefore, a gene corresponding to a given gene may be an ortholog of the given gene. Therefore, genes corresponding to mouse cyclin genes can be found in other animals. Such a corresponding gene can be identified by techniques well known in the art. Therefore, for example, a corresponding gene in a given animal can be found by searching a sequence database of the animal (e.g., human, rat) using the sequence of a reference gene (e.g., mouse cyclin gene, etc.) as a query sequence.

As used herein, the term "fragment" with respect to a polypeptide or polynucleotide refer to a polypeptide or polynucleotide having a sequence length ranging from 1 to n-1 with respect to the full length of the reference polypeptide or polynucleotide (of length n). The length of the fragment can be appropriately changed depending on the purpose. For example, in the case of polypeptides, the lower limit of the length of the fragment includes 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50 or more nucleotides. Lengths represented by integers which are not herein specified (e.g., 11 and the like) may be appropriate as a lower limit. For example, in the case of polynucleotides, the lower limit of the length of the fragment includes 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 75, 100 or more nucleotides. Lengths represented by integers which are not herein specified (e.g., 11 and the like) may be appropriate as a lower limit. As used herein, the length of polypeptides or polynucleotides can be represented by the number of amino acids or nucleic acids, respectively. However, the above-described numbers are not absolute. The above-described numbers as the upper or lower limit are intended to include some greater or smaller numbers (e.g.,

±10%), as long as the same function is maintained. For this purpose, "about" may be herein put ahead of the numbers. However, it should be understood that the interpretation of numbers is not affected by the presence or absence of "about" in the present specification.

As used herein, the term "biological activity" refers to activity possessed by an agent (e.g., a polynucleotide, a protein, etc.) within an organism, including activities exhibiting various functions (e.g., transcription promoting activity, etc.). For example, when a certain factor is an enzyme, the biological activity thereof includes its enzyme activity. In another example, when a certain factor is a ligand, the biological activity thereof includes the binding of the ligand to a receptor corresponding thereto. The above-described biological activity can be measured by techniques well-known in the art.

As used herein, the term "search" indicates that a given nucleic acid sequence is utilized to find other nucleic acid base sequences having a specific function and/or property either electronically or biologically, or using other methods. Examples of an electronic search include, but are not limited to, BLAST (Altschul et al., J. Mol. Biol. 215:403-410 (1990)), FASTA (Pearson & Lipman, Proc. Natl. Acad. Sci., USA 85:2444-2448 (1988)), Smith and Waterman method (Smith and Waterman, J. Mol. Biol. 147:195-197 (1981)), and Needleman and Wunsch method (Needleman and Wunsch, J. Mol. Biol. 48:443-453 (1970)), and the like. Examples of a biological search include, but are not limited to, a macroarray in which genomic DNA is attached to a nylon membrane or the like or a microarray

(microassay) in which genomic DNA is attached to a glass plate under stringent hybridization conditions, PCR and *in situ* hybridization, and the like. Such a search may be conducted by using a method or system of the present invention.

As used herein, the term "probe" refers to a substance for use in searching, which is used in a biological experiment, such as *in vitro* and/or *in vivo* screening or the like, including, but not being limited to, for example, a nucleic acid molecule having a specific base sequence or a peptide containing a specific amino acid sequence.

Examples of a nucleic acid molecule as a common probe include one having a nucleic acid sequence having a length of at least 8 contiguous nucleotides, which is homologous or complementary to the nucleic acid sequence of a gene of interest. Such a nucleic acid sequence may be preferably a nucleic acid sequence having a length of at least 9 contiguous nucleotides, more preferably a length of at least 10 contiguous nucleotides, and even more preferably a length of at least 11 contiguous nucleotides, a length of at least 12 contiguous nucleotides, a length of at least 13 contiguous nucleotides, a length of at least 14 contiguous nucleotides, a length of at least 15 contiguous nucleotides, a length of at least 20 contiguous nucleotides, a length of at least 25 contiguous nucleotides, a length of at least 30 contiguous nucleotides, a length of at least 40 contiguous nucleotides, or a length of at least 50 contiguous nucleotides. A nucleic acid sequence used as a probe includes a nucleic acid sequence having at least 70% homology to the above-described sequence, more preferably at least 80%, and even more preferably at least 90% or at

least 95%.

As used herein, the term "primer" refers to a substance required for initiation of a reaction of a macromolecule compound to be synthesized, in a macromolecule synthesis enzymatic reaction. In a reaction for synthesizing a nucleic acid molecule, a nucleic acid molecule (e.g., DNA, RNA, or the like) which is complementary to part of a macromolecule compound to be synthesized may be used.

A nucleic acid molecule which is ordinarily used as a primer includes one that has a nucleic acid sequence having a length of at least 8 contiguous nucleotides, which is complementary to the nucleic acid sequence of a gene of interest. Such a nucleic acid sequence preferably has a length of at least 9 contiguous nucleotides, more preferably a length of at least 10 contiguous nucleotides, even more preferably a length of at least 11 contiguous nucleotides, a length of at least 12 contiguous nucleotides, a length of at least 13 contiguous nucleotides, a length of at least 14 contiguous nucleotides, a length of at least 15 contiguous nucleotides, a length of at least 16 contiguous nucleotides, a length of at least 17 contiguous nucleotides, a length of at least 18 contiguous nucleotides, a length of at least 19 contiguous nucleotides, a length of at least 20 contiguous nucleotides, a length of at least 25 contiguous nucleotides, a length of at least 30 contiguous nucleotides, a length of at least 40 contiguous nucleotides, and a length of at least 50 contiguous nucleotides. A nucleic acid sequence used as a primer includes a nucleic acid sequence having at least 70% homology to the above-described sequence, more preferably at least 80%, even more preferably at least 90%,

and most preferably at least 95%. An appropriate sequence as a primer may vary depending on the property of the sequence to be synthesized (amplified). Those skilled in the art can design an appropriate primer depending on the sequence of interest. Such primer design is well known in the art and may be performed manually or using a computer program (e.g., LASERGENE, Primer Select, DNAStar).

As used herein, the term "epitope" refers to an antigenic determinant. Therefore, the term "epitope" includes a set of amino acid residues which is involved in recognition by a particular immunoglobulin, or in the context of T cells, those residues necessary for recognition by the T cell receptor proteins and/or Major Histocompatibility Complex (MHC) receptors. This term is also used interchangeably with "antigenic determinant" or "antigenic determinant site". In the field of immunology, *in vivo* or *in vitro*, an epitope is a feature of a molecule (e.g., primary, secondary and tertiary peptide structure, and charge) that forms a site recognized by an immunoglobulin, T cell receptor or HLA molecule. An epitope including a peptide comprises 3 or more amino acids in a spatial conformation which is unique to the epitope. Generally, an epitope consists of at least 5 such amino acids, and more ordinarily, consists of at least 6, 7, 8, 9 or 10 such amino acids. The greater the length of an epitope, the more the similarity of the epitope to the original peptide, i.e., longer epitopes are generally preferable. This is not necessarily the case when the conformation is taken into account. Methods of determining the spatial conformation of amino acids are known in the art, and include, for example, X-ray crystallography and 2-dimensional nuclear magnetic resonance spectroscopy. Furthermore, the identification

of epitopes in a given protein is readily accomplished using techniques well known in the art. See, also, Geysen et al., Proc. Natl. Acad. Sci. USA (1984) 81: 3998 (general method of rapidly synthesizing peptides to determine the location of immunogenic epitopes in a given antigen); U. S. Patent No. 4,708,871 (procedures for identifying and chemically synthesizing epitopes of antigens); and Geysen et al., Molecular immunology (1986) 23: 709 (technique for identifying peptides with high affinity for a given antibody). Antibodies that recognize the same epitope can be identified in a simple immunoassay. Thus, methods for determining epitopes including a peptide are well known in the art. Such an epitope can be determined using a well-known, common technique by those skilled in the art if the primary nucleic acid or amino acid sequence of the epitope is provided.

Therefore, an epitope including a peptide requires a sequence having a length of at least 3 amino acids, preferably at least 4 amino acids, more preferably at least 5 amino acids, at least 6 amino acids, at least 7 amino acids, at least 8 amino acids, at least 9 amino acids, at least 10 amino acids, at least 15 amino acids, at least 20 amino acids, and 25 amino acids. Epitopes may be linear or conformational.

As used herein, the term "biological molecule" refers to molecules or aggregates of molecules relating to an organism and aggregates of organisms. As used herein, the term "biological" or "organism" refers to a biological organism, including, but being not limited to, an animal, a plant, a fungus, a virus, and the like. Biological molecules include molecules extracted from an organism and

aggregations thereof, though the present invention is not limited to this. Any molecules or aggregates of molecules relating to an organism and aggregates of organisms fall within the definition of a biological molecule. Therefore, low molecular weight molecules (e.g., low molecular weight molecule ligands, etc.) capable of being used as medicaments fall within the definition of a biological molecule as long as an effect on an organism is intended. Examples of such a biological molecule include, but are not limited to, proteins, polypeptides, oligopeptides, peptides, polynucleotides, oligonucleotides, nucleotides, nucleic acids (e.g., DNA such as cDNA and genomic DNA; RNA such as mRNA), polysaccharides, oligosaccharides, lipids, low molecular weight molecules (e.g., hormones, ligands, information transmitting substances, low molecular weight organic molecules, etc.), and composite molecules thereof and aggregations thereof (e.g., glycolipids, glycoproteins, lipoproteins, etc.), and the like. A biological molecule may include a cell itself or a portion of tissue as long as it is intended to be introduced into a cell. Typically, a biological molecule may be a nucleic acid, a protein, a lipid, a sugar, a proteolipid, a lipoprotein, a glycoprotein, a proteoglycan, or the like. Preferably, a biological molecule may include a nucleic acid (DNA or RNA) or a protein. In an embodiment, a biological molecule is a nucleic acid (e.g., genomic DNA or cDNA, or DNA synthesized by PCR or the like). In another embodiment, a biological molecule may be a protein. Such a biological molecule may be a hormone or a cytokine.

The term "cytokine" is used herein in the broadest sense in the art and refers to a physiologically active substance which is produced by a cell and acts on

the same or a different cell. Cytokines are generally proteins or polypeptides having a function of controlling an immune response, regulating the endocrine system, regulating the nervous system, acting against a tumor, acting against a virus, regulating cell growth, regulating cell differentiation, or the like. Cytokines are used herein in the form of a protein or a nucleic acid or in other forms. In actual practice, cytokines are typically proteins. The term "growth factor" refers to a substance which promotes or controls cell growth. Growth factors are also called "proliferation factors" or "development factors". Growth factors may be added to cell or tissue culture medium, substituting for serum macromolecules. It has been revealed that a number of growth factors have a function of controlling differentiation in addition to a function of promoting cell growth. Examples of cytokines representatively include, but are not limited to, interleukins, chemokines, hematopoietic factors (e.g., colony stimulating factors), tumor necrosis factor, and interferons. Representative examples of growth factors include, but are not limited to, platelet-derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), endothelial cell growth factor (VEGF), cardiotrophin, and the like, which have proliferative activity.

The term "hormone" is herein used in its broadest sense in the art, referring to a physiological organic compound which is produced in a particular organ or cell of an animal or plant, and has a physiological effect on an organ apart from the site producing the compound. Examples of such a hormone include, but are not limited to, growth hormones, sex hormones, thyroid hormones, and the

like. The scope of hormones may intersect partially with that of cytokines.

As used herein, the terms "cell adhesion agent", "cell adhesion molecule", "adhesion agent" and "adhesion molecule" are used interchangeably to refer to a molecule capable of mediating the joining of two or more cells (cell adhesion) or adhesion between a substrate and a cell. Cell adhesion molecules such as fibronectin may be used for transfection array used in the present invention. In general, cell adhesion molecules are divided into two groups: molecules involved in cell-cell adhesion (intercellular adhesion) (cell-cell adhesion molecules) and molecules involved in cell-extracellular matrix adhesion (cell-substrate adhesion) (cell-substrate adhesion molecules). For a method of the present invention, either type of molecule is useful and can be effectively used. Therefore, cell adhesion molecules herein include a substrate protein and a cellular protein (e.g., integrin, etc.) involved in cell-substrate adhesion. A molecule other than a protein can fall within the concept of cell adhesion molecule as long as it can mediate cell adhesion.

For cell-cell adhesion, cadherin, a number of molecules belonging in an immunoglobulin superfamily (NCAM, L1, ICAM, fasciclin II, III, etc.), selectin, and the like are known, each of which is known to connect to cell membranes via a specific molecular reaction.

On the other hand, major cell adhesion molecules functioning for cell-substrate adhesion are integrins, which recognize and bind to various proteins contained in extracellular matrices. These cell adhesion molecules are

all located on cell membranes and can be regarded as a type of receptor (cell adhesion receptor). Therefore, receptors present on cell membranes can also be used in a method of the present invention. Examples of such a receptor include, but are not limited to, α-integrin, β-integrin, CD44, syndecan, aggrecan, and the like. Techniques for cell adhesion are well known as described above and as described in, for example, "Saibogaimatorikkusu -Rinsho heno Oyo- [Extracellular matrix -Clinical Applications-], Medical Review.

It can be determined whether or not a certain molecule is a cell adhesion molecule, by an assay, such as biochemical quantification (an SDS-PAGE method, a labeled-collagen method, etc.), immunological quantification (an enzyme antibody method, a fluorescent antibody method, an immunohistological study, etc.), a PDR method, a hybridization method, or the like, in which a positive reaction is detected. Examples of such a cell adhesion molecule include, but are not limited to, collagen, integrin, fibronectin, laminin, vitronectin, fibrinogen, immunoglobulin superfamily members (e.g., CD2, CD4, CD8, ICAM1, ICAM2, VCAM1), selectin, cadherin, and the like. Most of these cell adhesion molecules transmit an auxiliary signal for cell activation into a cell due to intercellular interaction as well as cell adhesion. It can be determined whether or not such an auxiliary signal can be transmitted into a cell, by an assay, such as biochemical quantification (an SDS-PAGE method, a labeled-collagen method, etc.), immunological quantification (an enzyme antibody method, a fluorescent antibody method, an immunohistological study, etc.), a PCR method, a hybridization method, or the like, in which a positive reaction is detected.

Examples of cell adhesion molecules include, but are not limited to, immunoglobulin superfamily molecules (LFA-3, ICAM-1, CD2, CD4, CD8, ICAM1, ICAM2, VCAM1, etc.); integrin family molecules (LFA-1, Mac-1, gpIIbIIIa, p150, p95, VLA1, VLA2, VLA3, VLA4, VLA5, VLA6, etc.); selectin family molecules (L-selectin, E-selectin, P-selectin, etc.), and the like.

As used herein, the term "extracellular matrix protein" refers to a protein constituting an "extracellular matrix". As used herein, the term "extracellular matrix" (ECM) is also called "extracellular substrate" and has the same meaning as commonly used in the art, and refers to a substance existing between somatic cells no matter whether the cells are epithelial cells or non-epithelial cells. Extracellular matrices are involved in supporting tissue as well as in internal environmental structures essential for survival of all somatic cells. Extracellular matrices are generally produced from connective tissue cells. Some extracellular matrices are secreted from cells possessing basal membrane, such as epithelial cells or endothelial cells. Extracellular matrices are roughly divided into fibrous components and matrices filling therebetween. Fibrous components include collagen fibers and elastic fibers. A basic component of matrices is glycosaminoglycan (acidic mucopolysaccharide), most of which is bound to non-collagenous protein to form a polymer of a proteoglycan (acidic mucopolysaccharide-protein complex). In addition, matrices include glycoproteins, such as laminin of basal membrane, microfibrils around elastic fibers, fibers, fibronectins on cell surfaces, and the like. Particularly differentiated tissue has the same basic structure. For

example, in hyaline cartilage, chondroblasts characteristically produce a large amount of cartilage matrices including proteoglycans. In bones, osteoblasts produce bone matrices which cause calcification. Examples of extracellular matrices for use in the present invention include, but are not limited to, collagen, elastin, proteoglycan, glycosaminoglycan, fibronectin, laminin, elastic fiber, collagen fiber, and the like.

As used herein, the term "receptor" refers to a molecule which is present on cells, within nuclei, or the like, and is capable of binding to an extracellular or intracellular agent where the binding mediates signal transduction. Receptors are typically in the form of proteins. The binding partner of a receptor is usually referred to as a ligand.

As used herein, the term "agonist" refers to an agent which binds to the receptor of a certain biologically acting substance (e.g., ligand, etc.), and has the same or similar function as the function of the substance.

As used herein, the term "antagonist" refers to a factor which competitively binds to the receptor of a certain biologically acting substance (ligand), and does not produce physiological action via the receptor. Antagonists include antagonist drugs, blockers, inhibitors, and the like.

As used herein, the term "agent" may be any substance or other entity (e.g., energy, such as light, radiation, heat, electricity, or the like) as long as the intended purpose can be achieved. Examples of such a

substance include, but are not limited to, proteins, polypeptides, oligopeptides, peptides, polynucleotides, oligonucleotides, nucleotides, nucleic acids (e.g., DNA such as cDNA , genomic DNA , or the like, and RNA such as mRNA), polysaccharides, oligosaccharides, lipids, low molecular weight organic molecules (e.g., hormones, ligands, information transfer substances, molecules synthesized by combinatorial chemistry, low molecular weight molecules (e.g., pharmaceutically acceptable low molecular weight ligands and the like), and the like), and combinations of these molecules. Examples of an agent specific to a polynucleotide include, but are not limited to, representatively, a polynucleotide having complementarity to the sequence of the polynucleotide with a predetermined sequence homology (e.g., 70% or more sequence identity), a polypeptide such as a transcriptional agent binding to a promoter region, and the like. Examples of an agent specific to a polypeptide include, but are not limited to, representatively, an antibody specifically directed to the polypeptide or derivatives or analogs thereof (e.g., single chain antibody), a specific ligand or receptor when the polypeptide is a receptor or ligand, a substrate when the polypeptide is an enzyme, and the like.

As used herein, the term "agent binding specifically to" a certain agent such as a nucleic acid molecule or polypeptide refers to an agent which has a level of binding to the nucleic acid molecule or polypeptide equal to or higher than a level of binding to other nucleic acid molecules or polypeptides. Examples of such an agent include, but are not limited to, when a target is a nucleic acid molecule, a nucleic acid molecule having a complementary sequence of a nucleic acid molecule of

interest, a polypeptide capable of binding to a nucleic acid sequence of interest (e.g., a transcription agent, etc.), and the like, and when a target is a polypeptide, an antibody, a single chain antibody, either of a pair of a receptor and a ligand, either of a pair of an enzyme and a substrate, and the like.

As used herein, the term "compound" refers to any identifiable chemical substance or molecule, including, but not limited to, a low molecular weight molecule, a peptide, a protein, a sugar, a nucleotide, or a nucleic acid. Such a compound may be a naturally-occurring product or a synthetic product.

As used herein, the term "low molecular weight organic molecule" refers to an organic molecule having a relatively small molecular weight. Usually, the low molecular weight organic molecule refers to a molecular weight of about 1,000 or less, or may refer to a molecular weight of more than 1,000. Low molecular weight organic molecules can be ordinarily synthesized by methods known in the art or combinations thereof. These low molecular weight organic molecules may be produced by organisms. Examples of the low molecular weight organic molecules include, but are not limited to, hormones, ligands, information transfer substances, synthesized by combinatorial chemistry, pharmaceutically acceptable low molecular weight molecules (e.g., low molecular weight ligands and the like), and the like.

As used herein, the term "contact" refers to direct or indirect placement of a compound physically close to the polypeptide or polynucleotide of the present

invention. Polypeptides or polynucleotides may be present in a number of buffers, salts, solutions, and the like. The term "contact" includes placement of a compound in a beaker, a microtiter plate, a cell culture flask, a microarray (e.g., a gene chip) or the like containing a polypeptide encoded by a nucleic acid or a fragment thereof.

As used herein, the term "antibody" encompasses polyclonal antibodies, monoclonal antibodies, human antibodies, humanized antibodies, polyfunctional antibodies, chimeric antibodies, and anti-idiotype antibodies, and fragments thereof (e.g., F(ab')2 and Fab fragments), and other recombinant conjugates. These antibodies may be fused with an enzyme (e.g., alkaline phosphatase, horseradish peroxidase, α-galactosidase, and the like) via a covalent bond or by recombination. Antibodies can be used as a perturbation agent in the present invention.

As used herein, the term "antigen" refers to any substrate to which an antibody molecule may specifically bind. As used herein, the term "immunogen" refers to an antigen capable of initiating activation of the antigen-specific immune response of a lymphocyte. Antigens can be used as a perturbation agent in the present invention.

In a given protein molecule, a given amino acid may be substituted with another amino acid in a structurally important region, such as a cationic region or a substrate molecule binding site, without a clear reduction or loss of interactive binding ability. A given biological function of a protein is defined by the interactive ability or other property of the protein. Therefore, a particular

amino acid substitution may be performed in an amino acid sequence, or at the DNA sequence level, to produce a protein which maintains the original property after the substitution. Therefore, various modifications of peptides as disclosed herein and DNA encoding such peptides may be performed without clear losses of biological activity.

When the above-described modifications are designed, the hydrophobicity indices of amino acids may be taken into consideration. The hydrophobic amino acid indices play an important role in providing a protein with an interactive biological function, which is generally recognized in the art (Kyte, J. and Doolittle, R.F., J. Mol. Biol. 157(1):105-132, 1982). The hydrophobic property of an amino acid contributes to the secondary structure of a protein and then regulates interactions between the protein and other molecules (e.g., enzymes, substrates, receptors, DNA, antibodies, antigens, etc.). Each amino acid is given a hydrophobicity index based on the hydrophobicity and charge properties thereof as follows: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamic acid (-3.5); glutamine (-3.5); aspartic acid (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

It is well known that if a given amino acid is substituted with another amino acid having a similar hydrophobicity index, the resultant protein may still have a biological function similar to that of the original protein

(e.g., a protein having an equivalent enzymatic activity). For such an amino acid substitution, the hydrophobicity index is preferably within ±2, more preferably within ±1, and even more preferably within ±0.5. It is understood in the art that such an amino acid substitution based on hydrophobicity is efficient. As described in US Patent No. 4,554,101, amino acid residues are given the following hydrophilicity indices: arginine (+3.0); lysine (+3.0); aspartic acid (+3.0±1); glutamic acid (+3.0±1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5±1); alanine (-0.5); histidine (-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5); and tryptophan (-3.4). It is understood that an amino acid may be substituted with another amino acid which has a similar hydrophilicity index and can still provide a biological equivalent. For such an amino acid substitution, the hydrophilicity index is preferably within ±2, more preferably ± 1, and even more preferably ±0.5.

(Devices and solid phase supports)

As used herein, the term "device" refers to a part which can constitute the whole or a portion of an apparatus, and comprises a support (preferably, a solid phase support) and a target substance carried thereon. Examples of such a device include, but are not limited to, chips, arrays, microtiter plates, cell culture plates, Petri dishes, films, beads, and the like. Such a device may constitute a system of the present invention. In particular, such a device may be used as means for obtaining information on at least two functional reporters in said biological entity, wherein the functional reporters reflect a

biological function

As used herein, the term "support" refers to a material which can fix a substance, such as a biological molecule. Such a support may be made from any fixing material which has a capability of binding to a biological molecule as used herein via covalent or noncovalent bonds, or which may be induced to have such a capability.

Examples of materials used for supports include any material capable of forming a solid surface, such as, without limitation, glass, silica, silicon, ceramics, silicon dioxide, plastics, metals (including alloys), naturally-occurring and synthetic polymers (e.g., polystyrene, cellulose, chitosan, dextran, and nylon), and the like. A support may be formed of layers made of a plurality of materials. For example, a support may be made of an inorganic insulating material, such as glass, quartz glass, alumina, sapphire, forsterite, silicon oxide, silicon carbide, silicon nitride, or the like. A support may be made of an organic material, such as polyethylene, ethylene, polypropylene, polyisobutylene, polyethylene terephthalate, unsaturated polyester, fluorine-containing resin, polyvinyl chloride, polyvinylidene chloride, polyvinyl acetate, polyvinyl alcohol, polyvinyl acetal, acrylic resin, polyacrylonitrile, polystyrene, acetal resin, polycarbonate, polyamide, phenol resin, urea resin, epoxy resin, melamine resin, styrene-acrylonitrile copolymer, acrylonitrile-butadiene-styrene copolymer, silicone resin, polyphenylene oxide, polysulfone, and the like. Also in the present invention, nitrocellulose film, nylon film, PVDF film, or the like, which are used in blotting, may be used as a material for a support. When a material

constituting a support is in the solid phase, such as a support is herein particularly referred to as a "solid phase support". A solid phase support may be herein in the form of a plate, a microwell plate, a chip, a glass slide, a film, beads, a metal (surface), or the like. A support may not be coated or may be coated.

As used herein, the term "liquid phase" has the same meaning as commonly understood by those skilled in the art, typically referring a state in solution.

As used herein, the term "solid phase" has the same meaning as commonly understood by those skilled in the art, typically referring to a solid state. As used herein, liquid and solid may be collectively referred to as a "fluid".

As used herein, the term "substrate" refers to a material (preferably, solid) which is used to construct a chip or array according to the present invention. Therefore, substrates are included in the concept of plates. Such a substrate may be made from any solid material which has a capability of binding to a biological molecule as used herein via covalent or noncovalent bonds, or which may be induced to have such a capability.

Examples of materials used for plates and substrates include any material capable of forming a solid surface, such as, without limitation, glass, silica, silicon, ceramics, silicon dioxide, plastics, metals (including alloys), naturally-occurring and synthetic polymers (e.g., polystyrene, cellulose, chitosan, dextran, and nylon), and the like. A support may be formed of layers

made of a plurality of materials. For example, a support may be made of an inorganic insulating material, such as glass, quartz glass, alumina, sapphire, forsterite, silicon oxide, silicon carbide, silicon nitride, or the like. A support may be made of an organic material, such as polyethylene, ethylene, polypropylene, polyisobutylene, polyethylene terephthalate, unsaturated polyester, fluorine-containing resin, polyvinyl chloride, polyvinylidene chloride, polyvinyl acetate, polyvinyl alcohol, polyvinyl acetal, acrylic resin, polyacrylonitrile, polystyrene, acetal resin, polycarbonate, polyamide, phenol resin, urea resin, epoxy resin, melamine resin, styrene-acrylonitrile copolymer, acrylonitrile-butadiene-styrene copolymer, silicone resin, polyphenylene oxide, polysulfone, and the like. A material preferable as a substrate varies depending on various parameters such as a measuring device, and can be selected from the above-described various materials as appropriate by those skilled in the art. For transfection arrays, glass slides are preferable. Preferably, such a substrate may have a coating.

As used herein, the term "coating" in relation to a solid phase support or substrate refers to an act of forming a film of a material on a surface of the solid phase support or substrate, and also refers to a film itself. Coating is performed for various purposes, such as, for example, improvement in the quality of a solid phase support and substrate (e.g., elongation of life span, improvement in resistance to hostile environment, such as resistance to acids, etc.), an improvement in affinity to a substance integrated with a solid phase support or substrate, and the like. Various materials may be used for such coating,

including, without limitation, biological substances (e.g., DNA, RNA, protein, lipid, etc.), polymers (e.g., poly-L-lysine, MAS (available from Matsunami Glass, Kishiwada, Japan), and hydrophobic fluorine resin), silane (APS (e.g., γ-aminopropyl silane, etc.)), metals (e.g., gold, etc.), in addition to the above-described solid phase support and substrate. The selection of such materials is within the technical scope of those skilled in the art and thus can be performed using techniques well known in the art. In one preferred embodiment, such a coating may be advantageously made of poly-L-lysine, silane (e.g., epoxy silane or mercaptosilane, APS (γ-aminopropyl silane), etc.), MAS, hydrophobic fluorine resin, a metal (e.g., gold, etc.). Such a material may be preferably a substance suitable for cells or objects containing cells (e.g., organisms, organs, etc.).

As used herein, the terms "chip" or "microchip" are used interchangeably to refer to a micro integrated circuit which has versatile functions and constitutes a portion of a system. Examples of a chip include, but are not limited to, DNA chips, protein chips, and the like.

As used herein, the term "array" refers to a substrate (e.g., a chip, etc.) which has a pattern of a composition containing at least one (e.g., 1000 or more, etc.) target substances (e.g., DNA, proteins, transfection mixtures, etc.), which are arrayed. Among arrays, patterned substrates having a small size (e.g., 10×10 mm, etc.) are particularly referred to as microarrays. The terms "microarray" and "array" are used interchangeably. Therefore, a patterned substrate having a larger size than that which is described above may be referred to as a

microarray. For example, an array comprises a set of desired transfection mixtures fixed to a solid phase surface or a film thereof. An array preferably comprises at least 10^2 antibodies of the same or different types, more preferably at least 10^3, even more preferablyat least 10^4, and still even more preferably at least 10^5. These antibodies are placed on a surface of up to 125x80 mm, more preferably 10x10 mm. An array includes, but is not limited to, a 96-well microtiter plate, a 384-well microtiter plate, a microtiter plate the size of a glass slide, and the like. A composition to be fixed may contain one or a plurality of types of target substances. Such a number of target substance types may be in the range of from one to the number of spots, including, without limitation, about 10, about 100, about 500, and about 1,000.

As used herein, the term "transfection array" refers to an array which embodies transfection on each of the spots or addresses on the array. Such transfection may be conducted using the technology described herein and exemplified in the Examples.

As described above, any number of target substances (e.g., proteins, such as antibodies) may be provided on a solid phase surface or film, typically including no more than 10^8 biological molecules per substrate, in another embodiment no more than 10^7 biological molecules, no more than 10^6 biological molecules, no more than 10^5 biological molecules, no more than 10^4 biological molecules, no more than 10^3 biological molecules, or no more than 10^2 biological molecules. A composition containing more than 10^8 biological molecule target substances may be provided on a substrate. In these cases, the size of a

substrate is preferably small. Particularly, the size of a spot of a composition containing target substances (e.g., proteins such as antibodies) may be as small as the size of a single biological molecule (e.g., 1 to 2 nm order). In some cases, the minimum area of a substrate may be determined based on the number of biological molecules on a substrate. A composition containing target substances, which are intended to be introduced into cells, are herein typically arrayed on and fixed via covalent bonds or physical interaction to a substrate in the form of spots having a size of 0.01 mm to 10 mm.

"Spots" of biological molecules may be provided on an array. As used herein, the term "spot" refers to a certain set of compositions containing target substances. As used herein, the term "spotting" refers to an act of preparing a spot of a composition containing a certain target substance on a substrate or plate. Spotting may be performed by any method, for example, pipetting or the like, or alternatively, using an automatic device. These methods are well known in the art.

As used herein, the term "address" refers to a unique position on a substrate, which may be distinguished from other unique positions. Addresses are appropriately associated with spots. Addresses can have any distinguishable shape such that substances at each address may be distinguished from substances at other addresses (e.g., optically). A shape defining an address may be, for example, without limitation, a circle, an ellipse, a square, a rectangle, or an irregular shape. Therefore, the term "address" is used to indicate an abstract concept, while the term "spot" is used to indicate a specific concept.

Unless it is necessary to distinguish them from each other, the terms "address" and "spot" may be herein used interchangeably.

The size of each address particularly depends on the size of the substrate, the number of addresses on the substrate, the amount of a composition containing target substances and/or available reagents, the size of microparticles, and the level of resolution required for any method used for the array. The size of each address may be, for example, in the range of from 1-2 nm to several centimeters, though the address may have any size suited to an array.

The spatial arrangement and shape which define an address are designed so that the microarray is suited to a particular application. Addresses may be densely arranged or sparsely distributed, or subgrouped into a desired pattern appropriate for a particular type of material to be analyzed.

Microarrays are widely reviewed in, for example, "Genomu Kino Kenkyu Purotokoru [Genomic Function Research Protocol] (Jikken Igaku Bessatsu [Special Issue of Experimental Medicine], Posuto Genomu Jidai no Jikken Koza 1 [Lecture 1 on Experimentation in Post-genome Era), "Genomu Ikagaku to korekarano Genomu Iryo [Genome Medical Science and Future Genome Therapy (Jikken Igaku Zokan [Special Issue of Experimental Medicine]), and the like.

A vast amount of data can be obtained from a microarray. Therefore, data analyzsis software is important for administration of correspondence between

clones and spots, data analysis, and the like. Such software may be attached to various detection systems (e.g., Ermolaeva O. et al., (1998) Nat. Genet., 20: 19-23). The format of database includes, for example, GATC (genetic analysis technology consortium) proposed by Affymetrix.

Micromachining for arrays is described in, for example, Campbell, S.A. (1996), "The Science and Engineering of Microelectronic Fabrication", Oxford University Press; Zaut, P.V. (1996), "Microarray Fabrication: a Practical Guide to Semiconductor Processing", Semiconductor Services; Madou, M.J. (1997), "Fundamentals of Microfabrication", CRC1 5 Press; Rai-Choudhury, P. (1997), "Handbook of Microlithography, Micromachining, & Microfabrication: Microlithography"; and the like, portions related thereto of which are herein incorporated by reference.

(Detection)

In cell analysis or determination in the present invention, various detection methods and means can be used as long as they can be used to detect information attributed to a cell or a substance interacting therewith. Examples of such detection methods and means include, but are not limited to, visual inspection, optical microscopes, confocal microscopes, reading devices using a laser light source, surface plasmon resonance (SPR) imaging, electric signals, chemical or biochemical markers, which may be used singly or in combination. Examples of such a detecting device include, but are not limited to, fluorescence analyzing devices, spectrophotometers, scintillation counters, CCD, luminometers, and the like. Any means capable of detecting a biological molecule may be used.

As used herein, the term "marker" or "biomarker" is interchangeably used to refer to a biological agent for indicating a level or frequency of a substance or state of interest. Examples of such markers include, but are not limited to, nucleic acids encoding a gene, gene products, metabolic products, receptors, ligands, antibodies, and the like.

Therefore, as used herein, the term "marker" in relation to a state of a cell refers to an agent (e.g., ligands, antibodies, complementary nucleic acids, etc.) interacting with intracellular factors indicating the state of the cell (e.g., nucleic acids encoding a gene, gene products (e.g., mRNA, proteins, posttranscriptionally modified proteins, etc.), metabolic products, receptors, etc.) in addition to transcription control factors. In the present invention, such a marker may be used to produce information which is in turn analyzed. Such a marker may preferably interact with a factor of interest. As used herein, the term "specificity" in relation to a marker refers to a property of the marker which interacts with a molecule of interest to a significantly higher extent than it does with other similar molecules. Such a marker is herein preferably present within cells or may be present outside cells.

As used herein, the term "label" refers to a factor which distinguishes a molecule or substance of interest from others (e.g., substances, energy, electromagnetic waves, etc.). Examples of labeling methods include, but are not limited to, RI (radioisotope) methods, fluorescence methods, biotinylation methods,

chemoluminance methods, and the like. When the above-described nucleic acid fragments and complementary oligonucleotides are labeled by fluorescence methods, fluorescent substances having different fluorescence emission maximum wavelengths are used for labeling. The difference between each fluorescence emission maximum wavelength may be preferably 10 nm or more. Any fluorescent substance which can bind to a base portion of a nucleic acid may be used, preferably including a cyanine dye (e.g., Cy3 and Cy5 in the Cy Dye™ series, etc.), a rhodamine 6G reagent, N-acetoxy-N2-acetyl amino fluorene (AAF), AAIF (iodine derivative of AAF), and the like. Examples of fluorescent substances having a difference in fluorescence emission maximum wavelength of 10 nm or more include a combination of Cy5 and a rhodamine 6G reagent, a combination of Cy3 and fluorescein, a combination of a rhodamine 6G reagent and fluorescein, and the like. In the present invention, such a label can be used to alter a sample of interest so that the sample can be detected by detecting means. Such alteration is known in the art. Those skilled in the art can perform such alteration using a method appropriate for a label and a sample of interest.

As used herein, the term "interaction" refers to, without limitation, hydrophobic interactions, hydrophilic interactions, hydrogen bonds, Van der Waals forces, ionic interactions, nonionic interactions, electrostatic interactions, and the like.

As used herein, the term "interaction level" in relation to the interaction between two substances (e.g., cells, etc.) refers to the extent or frequency of interaction between the two substances. Such an interaction level can

be measured by methods well known in the art. For example, the number of cells which are fixed and actually perform an interaction is counted directly or indirectly (e.g., the intensity of reflected light) for example, without limitation, by using an optical microscope, a fluorescence microscope, a phase-contrast microscope, or the like, or alternatively by staining cells with a marker, an antibody, a fluorescent label or the like, specific thereto and measuring the intensity thereof. Such a level can be displayed directly from a marker or indirectly via a label. Based on the measured value of such a level, the number or frequency of genes, which are actually transcribed or expressed in a certain spot, can be calculated.

(Presentation and display)

As used herein, the terms "display" and "presentation" are used interchangeably to refer to an act of providing information obtained by a method of the present invention or information derived therefrom directly or indirectly, or in an information-processed form. Examples of such displayed forms include, but are not limited to, various methods, such as graphs, photographs, tables, animations, and the like. Such techniques are described in, for example, METHODS IN CELL BIOLOGY, VOL. 56, ed. 1998, pp:185-215, A High-Resolution Multimode Digital Microscope System (Sluder & Wolf, Salmon), which discusses application software for automating a microscope and controlling a camera and the design of a hardware device comprising an automated optical microscope, a camera, and a Z-axis focusing device, which can be used herein. Image acquisition by a camera is described in detail in, for example, Inoue and Spring, Video Miroscopy, 2d. Edition, 1997, which is herein incorporated by reference. Real time

display can also be performed using techniques well known in the art. For example, after all images are obtained and stored in a semi-permanent memory, or substantially at the same time as when an image is obtained, the image can be processed with appropriate application software to obtain processed data. For example, data may be processed by a method for playing back a sequence of images without interruption, a method for displaying images in real time, or a method for displaying images as a "movie" showing irradiating light as changes or continuation on a focal plane.

In another embodiment, application software for measurement and presentation typically includes software for setting conditions for applying stimuli or conditions for recording detected signals. With such a measurement and presentation application, a computer can have a means for applying a stimulus to cells and a means for processing signals detected from cells, and in addition, can control an optical observing means (a SIT camera and an image filing device) and/or a cell culturing means.

By inputting conditions for stimulation on a parameter setting screen using a keyboard, a touch panel, a mouse, or the like, it is possible to set desired complicated conditions for stimulation. In addition, various conditions, such as a temperature for cell culture, pH, and the like, can be set using a keyboard, a mouse, or the like. A display screen displays information on a network detected from a cell or information derived therefrom in real time or after recording. In addition, another recorded information or information derived therefrom of a cell can be displayed while being superimposed

with a microscopic image of the cell. In addition to recorded information, measurement parameters in recording (stimulation conditions, recording conditions, display conditions, process conditions, various conditions for cells, temperature, pH, etc.) can be displayed in real time. The present invention may be equipped with a function of issuing an alarm when a temperature or pH departs from the tolerable range.

On a data analysis screen, in addition to the set theory as used in the present invention, it is possible to set conditions for various mathematical analyses, such as Fourier transformation, cluster analysis, FFT analysis, coherence analysis, correlation analysis, and the like. The present invention may be equipped with a function of temporarily displaying information on a network, a function of displaying topography, or the like. The results of these analyses can be displayed while being superimposed with microscopic images stored in a recording medium.

(Gene introduction)

Any technique may be used herein for introduction of a nucleic acid molecule into cells, including, for example, transformation, transduction, transfection, and the like. In the present invention, transfection is preferable.

As used herein, the term "transfection" refers to an act of performing gene introduction or transfection by culturing cells with gene DNA, plasmid DNA, viral DNA, viral RNA or the like in a substantially naked form (excluding viral particles), or adding such a genetic material into cell suspension to allow the cells to take

in the genetic material. A gene introduced by transfection is typically expressed within cells in a temporary manner or may be incorporated into cells in a permanent manner.

Such a nucleic acid molecule introduction technique is well known in the art and commonly used, and is described in, for example, Ausubel F.A. et al., editors, (1988), Current Protocols in Molecular Biology, Wiley, New York, NY; Sambrook J. et al. (1987) Molecular Cloning: A Laboratory Manual, 2nd Ed. and its 3rd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Special issue, Jikken Igaku [Experimental Medicine] "Experimental Methods for Gene introduction & Expression Analysis", Yodo-sha, 1997; and the like. Gene introduction can be confirmed by methods as described herein, such as Northern blotting analysis and Western blotting analysis, or other well-known, common techniques.

When a gene is mentioned herein, the term "vector" or "recombinant vector" refers to a vector transferring a polynucleotide sequence of interest to a target cell. Such a vector is capable of self-replication or incorporation into a chromosome in a host cell (e.g., a prokaryotic cell, yeast, an animal cell, a plant cell, an insect cell, an individual animal, and an individual plant, etc.), and contains a promoter at a site suitable for transcription of a polynucleotide of the present invention. A vector suitable for performing cloning is referred to as a "cloning vector". Such a cloning vector ordinarily contains a multiple cloning site containing a plurality of restriction sites. Restriction enzyme sites and multiple cloning sites as described above are well known in the art and can be used as appropriate by those skilled in the art

depending on the purpose in accordance with publications described herein (e.g., Sambrook et al., *supra*).

As used herein, the term "expression vector" refers to a nucleic acid sequence comprising a structural gene and a promoter for regulating expression thereof, and in addition, various regulatory elements in a state that allows them to operate within host cells. The regulatory element may include, preferably, terminators, selectable markers such as drug-resistance genes, and enhancers.

Examples of "recombinant vectors" for prokaryotic cells include, but are not limited to, pcDNA3(+), pBluescript-SK(+/-), pGEM-T, pEF-BOS, pEGFP , pHAT, pUC18, pFT-DEST™42GATEWAY (Invitrogen), and the like.

Examples of "recombinant vectors" for animal cells include, but are not limited to, pcDNAI/Amp, pcDNAI, pCDM8 (all commercially available from Funakoshi), pAGE107 [Japanese Laid-Open Publication No. 3-229 (Invitrogen), pAGE103 [J. Biochem., 101, 1307(1987)], pAMo, pAMoA [J. Biol. Chem., 268, 22782-22787(1993)], a retrovirus expression vector based on a murine stem cell virus (MSCV), pEF-BOS, pEGFP, and the like.

Examples of recombinant vectors for plant cells include, but are not limited to, pPCVICEn4HPT, pCGN1548, pCGN1549, pBI221, pBI121, and the like.

Any of the above-described methods for introducing DNA into cells can be used as a vector introduction method, including, for example, transfection, transduction, transformation, and the like (e.g., a calcium

phosphate method, a liposome method, a DEAE dextran method, an electroporation method, a particle gun (gene gun) method, and the like), a lipofection method, a spheroplast method (Proc. Natl. Acad. Sci. USA, 84, 1929(1978)), a lithium acetate method (J. Bacteriol., 153, 163(1983); and Proc. Natl. Acad. Sci. USA, 75, 1929(1978)), and the like.

As used herein, the term "gene introduction reagent" refers to a reagent which is used in a gene introduction method so as to enhance introduction efficiency. Examples of such a gene introduction reagent include, but are not limited to, cationic polymers, cationic lipids, polyamine-based reagents, polyimine-based reagents, calcium phosphate, and the like. Specific examples of a reagent used in transfection include reagents available from various sources, such as, without limitation, Effectene Transfection Reagent (cat. no. 301425, Qiagen, CA), TransFast™ Transfection Reagent (E2431, Promega, WI), Tfx™-20 Reagent (E2391, Promega, WI), SuperFect Transfection Reagent (301305, Qiagen, CA), PolyFect Transfection Reagent (301105, Qiagen, CA), LipofectAMINE 2000 Reagent (11668-019, Invitrogen corporation, CA), JetPEI (×4) conc. (101-30, Polyplus-transfection, France) and ExGen 500 (R0511, Fermentas Inc., MD), and the like.

Gene expression (e.g., mRNA expression, polypeptide expression) may be "detected" or "quantified" by an appropriate method, including mRNA measurement and immunological measurement methods. Examples of molecular biological measurement methods include Northern blotting methods, dot blotting methods, PCR methods, and the like. Examples of immunological measurement methods include ELISA methods, RIA methods, fluorescent antibody methods, Western

blotting methods, immunohistological staining methods, and the like, where a microtiter plate may be used. Examples of quantification methods include ELISA methods, RIA methods, and the like. A gene analysis method using an array (e.g., a DNA array, a protein array, etc.) may be used. The DNA array is widely reviewed in Saibo-Kogaku [Cell Engineering], special issue, "DNA Microarray and Up-to-date PCR Method", edited by Shujun-sha. The protein array is described in detail in Nat Genet. 2002 Dec; 32 Suppl:526-32. Examples of methods for analyzing gene expression include, but are not limited to, RT-PCR methods, RACE methods, SSCP methods, immunoprecipitation methods, two-hybrid systems, *in vitro* translation methods, and the like in addition to the above-described techniques. Other analysis methods are described in, for example, "Genome Analysis Experimental Method, Yusuke Nakamura's Lab-Manual, edited by Yusuke Nakamura, Yodo-sha (2002), and the like. All of the above-described publications are herein incorporated by reference.

As used herein, the term "expression level" refers to the amount of a polypeptide or mRNA expressed in a subject cell. The term "expression level" includes the level of protein expression of a polypeptide evaluated by any appropriate method using an antibody, including immunological measurement methods (e.g., an ELISA method, an RIA method, a fluorescent antibody method, a Western blotting method, an immunohistological staining method, and the like, or the mRNA level of expression of a polypeptide evaluated by any appropriate method, including molecular biological measurement methods (e.g., a Northern blotting method, a dot blotting method, a PCR method, and the like). The term "change in expression level" indicates that an

increase or decrease in the protein or mRNA level of expression of a polypeptide evaluated by an appropriate method including the above-described immunological measurement method or molecular biological measurement method.

(Screening)

As used herein, the term "screening" refers to selection of a target, such as an organism, a substance, or the like, a given specific property of interest from a population containing a number of elements using a specific operation/evaluation method. For screening, an agent (e.g., an antibody), a polypeptide or a nucleic acid molecule of the present invention can be used.

As used herein, screening by utilizing an immunological reaction is also referred to as "immunophenotyping". In this case, an antibody or a single chain antibody may be used for immunophenotyping a cell line and a biological sample. A transcription or translation product of a gene may be useful as a cell specific marker, or more particularly, a cell marker which is distinctively expressed in various stages in differentiation and/or maturation of a specific cell type. A monoclonal antibody directed to a specific epitope, or a combination of epitopes allows for screening of a cell population expressing a marker. Various techniques employ monoclonal antibodies to screen for a cell population expressing a marker. Examples of such techniques include, but are not limited to, magnetic separation using magnetic beads coated with antibodies, "panning" using antibodies attached to a solid matrix (i.e., a plate), flow cytometry, and the like (e.g., US Patent No. 5,985,660; and Morrison et al., Cell, 96:737-49(1999)).

These techniques may be used to screen cell populations containing undifferentiated cells, which can grow and/or differentiate as seen in human umbilical cord blood or which are treated and modified into an undifferentiated state (e.g., embryonic stem cells, tissue stem cells, etc.).

(Diagnosis)

As used herein, the term "diagnosis" refers to an act of identifying various parameters associated with a disease, a disorder, a condition, or the like of a subject and determining a current state of the disease, the disorder, the condition, or the like. A method, device, or system of the present invention can be used to analyze cellular networks, a drug resistance level, identification of a biomarker, analysis of a drug target, analysis of a side effect, diagnosis of a cellular function, analysis of a cellular pathway, evaluation of a biological effect of a compound, and diagnosis of an infectious disease and the like. Such information can be used to select parameters, such as a disease, a disorder, a condition, and a prescription or method for treatment or prevention of a subject.

A diagnosis method of the present invention can use, in principle, a sample which is derived from the body of a subject. Therefore, it is possible for someone which is not a medical practitioner, such as a medical doctor, to deal with such a sample. The present invention is industrially useful.

(Therapy)

As used herein, the term "therapy" refers to an act of preventing progression of a disease or a disorder, preferably maintaining the current state of a disease or a disorder, more preferably alleviating a disease or a disorder, and more preferably extinguishing a disease or a disorder.

As used herein, the term "subject" refers to an organism which is subjected to the treatment of the present invention. A subject is also referred to as a "patient". A patient or subject may preferably be a human.

As used herein, the term "cause" or "pathogen" in relation to a disease, a disorder or a condition of a subject refers to an agent associated with the disease, the disorder or the condition (also collectively referred to as a "lesion", or "disease damage" in plants), including, without limitation, a causative or pathogenic substance (pathogenic agent), a disease agent, a diseased cell, a pathogenic virus, and the like.

A disease targeted by the present invention may be any disease associated with a pathogenic gene. Examples of such a disease include, but are not limited to, cancer, infectious diseases due to viruses or bacteria, allergy, hypertension, hyperlipemia, diabetes, cardiac diseases, cerebral infarction, dementia, obesity, arteriosclerosis, infertility, mental and nervous diseases, cataract, progeria, hypersensitivity to ultraviolet radiation, and the like.

A disorder targeted by the present invention may be any disorder associated with a pathogenic gene.

Examples of such a disease, disorder or condition include, but are not limited to, circulatory diseases (anemia (e.g., aplastic anemia (particularly, severe aplastic anemia), renal anemia, cancerous anemia, secondary anemia, refractory anemia, etc.), cancer or tumors (e.g., leukemia, multiple myeloma), etc.); neurological diseases (dementia, cerebral stroke and sequela thereof, cerebral tumor, spinal injury, etc.); immunological diseases (T-cell deficiency syndrome, leukemia, etc.); motor organ and the skeletal system diseases (fracture, osteoporosis, luxation of joints, subluxation, sprain, ligament injury, osteoarthritis, osteosarcoma, Ewing's sarcoma, osteogenesis imperfecta, osteochondrodysplasia, etc.); dermatologic diseases (atrichia, melanoma, cutis malignant lympoma, hemangiosarcoma, histiocytosis, hydroa, pustulosis, dermatitis, eczema, etc.); endocrinologic diseases (hypothalamus/hypophysis diseases, thyroid gland diseases, accessory thyroid gland (parathyroid) diseases, adrenal cortex/medulla diseases, saccharometabolism abnormality, lipid metabolism abnormality, protein metabolism abnormality, nucleic acid metabolism abnormality, inborn error of metabolism (phenylketonuria, galactosemia, homocystinuria, maple syrup urine disease), analbuminemia, lack of ascorbic acid synthetic ability, hyperbilirubinemia, hyperbilirubinuria, kallikrein deficiency, mast cell deficiency, diabetes insipidus, vasopressin secretion abnormality, dwarfism, Wolman's disease (acid lipase deficiency)), mucopolysaccharidosis VI, etc.); respiratory diseases (pulmonary diseases (e.g., pneumonia, lung cancer, etc.), bronchial diseases, lung cancer, bronchial cancer, etc.); alimentary diseases (esophagial diseases (e.g.,

esophagial cancer, etc.), stomach/duodenum diseases (e.g., stomach cancer, duodenum cancer, etc.), small intestine diseases/large intestine diseases (e.g., polyps of the colon, colon cancer, rectal cancer, etc.), bile duct diseases, liver diseases (e.g., liver cirrhosis, hepatitis (A, B, C, D, E, etc.), fulminant hepatitis, chronic hepatitis, primary liver cancer, alcoholic liver disorders, drug induced liver disorders, etc.), pancreatic diseases (acute pancreatitis, chronic pancreatitis, pancreas cancer, cystic pancreas diseases, etc.), peritoneum/abdominal wall/diaphragm diseases (hernia, etc.), Hirschsprung's disease, etc.); urinary diseases (kidney diseases (e.g., renal failure, primary glomerulus diseases, renovascular disorders, tubular function abnormality, interstitial kidney diseases, kidney disorders due to systemic diseases, kidney cancer, etc.), bladder diseases (e.g., cystitis, bladder cancer, etc.); genital diseases (male genital organ diseases (e.g., male sterility, prostatomegaly, prostate cancer, testicular cancer, etc.), female genital organ diseases (e.g., female sterility, ovary function disorders, hysteromyoma, adenomyosis uteri, uterine cancer, endometriosis, ovarian cancer, villosity diseases, etc.), etc); circulatory diseases (heart failure, angina pectoris, myocardial infarct, arrhythmia, valvulitis, cardiac muscle/pericardium diseases, congenital heart diseases (e.g., atrial septal defect, arterial canal patency, tetralogy of Fallot, etc.), artery diseases (e.g., arteriosclerosis, aneurysm), vein diseases (e.g., phlebeurysm, etc.), lymphoduct diseases (e.g., lymphedema, etc.), etc.); and the like.

As used herein, the term "pharmaceutically acceptable carrier" refers to a material for use in

production of a medicament, an animal drug or an agricultural chemical, which does not have an adverse effect on an effective component. Examples of such a pharmaceutically acceptable carrier include, but are not limited to, antioxidants, preservatives, colorants, flavoring agents, diluents, emulsifiers, suspending agents, solvents, fillers, bulking agents, buffers, delivery vehicles, excipients, agricultural or pharmaceutical adjuvants, and the like.

The type and amount of a pharmaceutical agent used in a treatment method of the present invention can be easily determined by those skilled in the art based on information obtained by a method of the present invention (e.g., information about the level of drug resistance, etc.) and with reference to the purpose of use, a target disease (type, severity, and the like), the patient's age, weight, sex, and case history, the form or type of the cell, and the like. The frequency of the treatment method of the present invention applied to a subject (or patient) is also determined by those skilled in the art with respect to the purpose of use, target disease (type, severity, and the like), the patient's age, weight, sex, and case history, the progression of the therapy, and the like. Examples of the frequency include once per day to several months (e.g., once per week to once per month). Preferably, administration is performed once per week to month with reference to the progression.

As used herein, the term "instructions" refers to a description of a tailor made therapy of the present invention for a person who performs administration, such as a medical doctor, a patient, or the like. Instructions

state when to administer a medicament of the present invention, such as immediately after or before radiation therapy (e.g., within 24 hours, etc.). The instructions are prepared in accordance with a format defined by an authority of a country in which the present invention is practiced (e.g., Health, Labor and Welfare Ministry in Japan, Food and Drug Administration (FDA) in the U.S., and the like), explicitly describing that the instructions are approved by the authority. The instructions are so-called a package insert and are typically provided as paper media. The instructions are not so limited and may be provided in the form of electronic media (e.g., web sites, electronic mails, and the like provided on the internet).

In a therapy of the present invention, two or more pharmaceutical agents may be used as required. When two or more pharmaceutical agents are used, these agents may have similar properties or may be derived from similar origins, or alternatively, may have different properties or may be derived from different origins. A method of the present invention can be used to obtain information about the drug resistance level of a method of administering two or more pharmaceutical agents.

Also, in the present invention, a gene therapy can be performed based on the resultant information about drug resistance. As used herein, the term "gene therapy" refers to a therapy in which a nucleic acid, which has been expressed or can be expressed, is administered into a subject. In such an embodiment of the present invention, a protein encoded by a nucleic acid is produced to mediate a therapeutic effect.

In the present invention, it will be understood by those skilled in the art that if the result of analysis of a certain specific information is once correlated with a state of a biological entity such as a cell in a similar organism (e.g., mouse with respect to human, etc.), the result of analysis of the corresponding information can be correlated with a state of a biological entity such as a cell. This feature is supported by, for example, Dobutsu Baiyo Saibo Manuaru [Animal Culture Cell Manual], Seno, ed., Kyoritsu Shuppan, 1993, which is herein incorporated by reference.

The present invention may be applied to gene therapies based on such a certain specific information of the result of network analysis.

Any methods for gene therapy available in the art may be used in accordance with the present invention. Illustrative methods will be described below.

Methods for gene therapy are generally reviewed in, for example, Goldspiel et al., Clinical Pharmacy 12: 488-505(1993); Wu and Wu, Biotherapy 3: 87-95(1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol., 32: 573-596(1993); Mulligan, Science 260: 926-932(1993); Morgan and Anderson, Ann. Rev. Biochem., 62: 191-217(1993); and May, TIBTECH 11(5): 155-215(1993). Commonly known recombinant DNA techniques used in gene therapy are described in, for example, Ausubel et al. (ed.), Current Protocols in Molecular Biology, John Wiley & Sons, NY(1993); and Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990).

(Basic techniques)

Techniques used herein are within the technical scope of the present invention unless otherwise specified. These techniques are commonly used in the fields of fluidics, micromachining, organic chemistry, biochemistry, genetic engineering, molecular biology, microbiology, genetics, and their relevant fields. The techniques are well described in documents described below and the documents mentioned herein elsewhere.

Micromachining is described in, for example, Campbell, S.A. (1996), "The Science and Engineering of Microelectronic Fabrication", Oxford University Press; Zaut, P.V. (1996), "Microarray Fabrication: a Practical Guide to Semiconductor Processing", Semiconductor Services; Madou, M.J. (1997), "Fundamentals of Microfabrication", CRC1 5 Press; Rai-Choudhury, P. (1997), "Handbook of Microlithography, Micromachining, & Microfabrication: Microlithography". Relevant portions (or possibly the entirety) of each of these publications are herein incorporated by reference.

Molecular biology techniques, biochemistry techniques, and microbiology techniques used herein are well known and commonly used in the art, and are described in, for example, Sambrook J. et al. (1989), "Molecular Cloning: A Laboratory Manual", Cold Spring Harbor and its 3rd Ed. (2001); Ausubel, F.M. (1987), "Current Protocols in Molecular Biology", Greene Pub. Associates and Wiley-Interscience; Ausubel, F.M. (1989), "Short Protocols in Molecular Biology: A Compendium of Methods from Current Protocols in Molecular Biology", Greene Pub. Associates and Wiley-Interscience; Innis, M.A. (1990), "PCR Protocols:

A Guide to Methods and Applications", Academic Press; Ausubel, F.M. (1992), "Short Protocols in Molecular Biology: A Compendium of Methods from Current Protocols in Molecular Biology", Greene Pub. Associates; Ausubel, F.M. (1995), "Short Protocols in Molecular Biology: A Compendium of Methods from Current Protocols in Molecular Biology", Greene Pub. Associates; Innis, M.A. et al. (1995), "PCR Strategies", Academic Press; Ausubel, F.M. (1999), "Short Protocols in Molecular Biology: A Compendium of Methods from Current Protocols in Molecular Biology", Wiley, and annual updates; Sninsky, J.J. et al. (1999), "PCR Applications: Protocols for Functional Genomics", Academic Press; Special issue, Jikken Igaku [Experimental Medicine] "Idenshi Donyu & Hatsugenkaiseki Jikkenho [Experimental Method for Gene introduction & Expression Analysis]", Yodo-sha, 1997; and the like. Relevant portions (or possibly the entirety) of each of these publications are herein incorporated by reference.

DNA synthesis techniques and nucleic acid chemistry for producing artificially synthesized genes are described in, for example, Gait, M.J. (1985), "Oligonucleotide Synthesis: A Practical Approach", IRL Press; Gait, M.J. (1990), "Oligonucleotide Synthesis: A Practical Approach", IRL Press; Eckstein, F. (1991), "Oligonucleotides and Analogues: A Practical Approach", IRL Press; Adams, R.L. et al. (1992), "The Biochemistry of the Nucleic Acids", Chapman & Hall; Shabarova, Z. et al. (1994), "Advanced Organic Chemistry of Nucleic Acids", Weinheim; Blackburn, G.M. et al. (1996), "Nucleic Acids in Chemistry and Biology", Oxford University Press; Hermanson, G.T. (I996), "Bioconjugate Techniques", Academic Press; and the like. Relevant portions (or possibly the entirety) of each

of these publications are herein incorporated by reference.

(RNAi)

As used herein, the term "RNAi" is an abbreviation of RNA interference and refers to a phenomenon where an agent for causing RNAi, such as double-stranded RNA (also called dsRNA), is introduced into cells and mRNA homologous thereto is specifically degraded, so that synthesis of gene products are suppressed, and a technique using the phenomenon. As used herein, RNAi may have the same meaning as that of an agent which causes RNAi.

As used herein, the term "an agent causing RNAi" refers to any agent capable of causing RNAi. As used herein, "an agent causing RNAi of a gene" indicates that the agent causes RNAi relating to the gene and the effect of RNAi is achieved (e.g., suppression of expression of the gene, and the like). Examples of such an agent causing RNAi include, but are not limited to, a sequence having at least about 70% homology to the nucleic acid sequence of a target gene or a sequence hybridizable under stringent conditions, RNA containing a double-stranded portion having a length of at least 10 nucleotides or variants thereof. Here, this agent may be preferably DNA containing a 3' protruding end, and more preferably the 3' protruding end has a length of 2 or more nucleotides (e.g., 2-4 nucleotides in length).

Though not wishing to be bound by any theory, a mechanism which causes RNAi is considered to be as follows. When a molecule which causes RNAi, such as dsRNA, is introduced into a cell, an RNaseIII-like nuclease having a helicase domain (called dicer) cleaves the molecule on about a 20 base pair basis from the 3' terminus in the

presence of ATP in the case where the RNA is relatively long (e.g., 40 or more base pairs). As used herein, the term "siRNA" is an abbreviation of short interfering RNA and refers to short double-stranded RNA of 10 or more base pairs which are artificially chemically synthesized or biochemically synthesized, synthesized in the organism body, or produced by double-stranded RNA of about 40 or more base pairs being degraded within the organism. siRNA typically has a structure having 5'-phosphate and 3'-OH, where the 3' terminus projects by about 2 bases. A specific protein is bound to siRNA to form RISC (RNA-induced-silencing-complex). This complex recognizes and binds to mRNA having the same sequence as that of siRNA and cleaves mRNA at the middle of siRNA due to RNaseIII-like enzymatic activity. It is preferable that the relationship between the sequence of siRNA and the sequence of mRNA to be cleaved as a target is a 100% match. However, base mutations at a site away from the middle of siRNA do not completely remove the cleavage activity by RNAi, leaving partial activity, while base mutations in the middle of siRNA have a large influence and the mRNA cleavage activity by RNAi is considerably lowered. By utilizing such a nature, only mRNA having a mutation can be specifically degraded. Specifically, siRNA in which the mutation is provided in the middle thereof is synthesized and is introduced into a cell. Therefore, in the present invention, siRNA per se as well as an agent capable of producing siRNA (e.g., representatively dsRNA of about 40 or more base pairs) can be used as an agent capable of eliciting RNAi.

Also, though not wishing to be bound by any theory, apart from the above-described pathway, the antisense strand of siRNA binds to mRNA such that the siRNA

functions as a primer for RNA-dependent RNA polymerase (RdRP), so that dsRNA is synthesized. This dsRNA is a substrate for a dicer, leading to production of new siRNA. It is intended that such an action is amplified. Therefore, in the present invention, siRNA per se and an agent capable of producing siRNA are useful. In fact, in insects and the like, for example, 35 dsRNA molecules can completely degrade 1,000 or more copies of intracellular mRNA, and therefore, it will be understood that siRNA per se as well as an agent capable of producing siRNA are useful.

In the present invention, double-stranded RNA having a length of about 20 bases (e.g., representatively about 21 to 23 bases) or less than about 20 bases, which is called siRNA, can be used. Expression of siRNA in cells can suppress expression of a pathogenic gene targeted by the siRNA. Therefore, siRNA can be used for treatment, prophylaxis, prognosis, and the like of diseases.

The siRNA of the present invention may be in any form as long as it can elicit RNAi.

In another embodiment, an agent capable of causing RNAi may have a short hairpin structure having a sticky portion at the 3' terminus (shRNA; short hairpin RNA). As used herein, the term "shRNA" refers to a molecule of about 20 or more base pairs in which a single-stranded RNA partially contains a palindromic base sequence and forms a double-strand structure therein (i.e., a hairpin structure). shRNA can be artificially chemically synthesized. Alternatively, shRNA can be produced by linking sense and antisense strands of a DNA sequence in reverse directions and synthesizing RNA *in vitro* with T7

RNA polymerase using the DNA as a template. Though not wishing to be bound by any theory, it should be understood that after shRNA is introduced into a cell, the shRNA is degraded in the cell into a length of about 20 bases (e.g., representatively 21, 22, 23 bases) and causes RNAi in the same manner as siRNA, leading to the treatment effect of the present invention. It should be understood that such an effect is exhibited in a wide range of organisms, such as insects, plants, animals (including mammals), and the like. Thus, shRNA elicits RNAi in the same manner as siRNA and therefore can be used as an effective component of the present invention. shRNA may preferably have a 3′ protruding end. The length of the double-stranded portion is not particularly limited, but is preferably about 10 or more nucleotides, and more preferably about 20 or more nucleotides. Here, the 3′ protruding end may be preferably DNA, more preferably DNA of at least 2 nucleotides in length, and even more preferably DNA of 2-4 nucleotides in length.

An agent capable of causing RNAi used in the present invention may be artificially synthesized (chemically or biochemically) or naturally occurring. There is substantially no difference therebetween in terms of the effect of the present invention. A chemically synthesized agent is preferably purified by liquid chromatography or the like.

An agent capable of causing RNAi used in the present invention can be produced *in vitro*. In this synthesis system, T7 RNA polymerase and T7 promoter are used to synthesize antisense and sense RNAs from template DNA. These RNAs are annealed and thereafter are introduced into a cell. In this case, RNAi is caused via the above-described

mechanism, thereby achieving the effect of the present invention. Here, for example, the introduction of RNA into cell can be carried out by a calcium phosphate method.

Another example of an agent capable of causing RNAi according to the present invention is a single-stranded nucleic acid hybridizable to mRNA or all nucleic acid analogs thereof. Such agents are useful for the method and composition of the present invention.

(Set theory)

As mentioned above, the term "set theory" refers to a theory as used and understood in the art and the branch of pure mathematics, that deals with the nature and relationships of sets. Many mathematicians use set theory as the basis for all other mathematics. Such set theory includes the analysis of objects ("elements or "members") into sets (aggregates or collections) and classifying these sets into inclusion, independent and intersection, and the like. Set theory is well known in the art and one skilled in the art can refer to Cantor, G., 1932, Gesammelte Abhandlungen, Berlin: Springer-Verlag; Ulam, S., 1930, 'Zur Masstheorie in der allgemeinen Mengenlehre', Fund. Math., 16, 140-150; Gödel, K., 1940, 'The consistency of the axiom of choice and the generalized continuum hypothesis', Ann. Math. Studies, 3; Scott, D., 1961, 'Measurable cardinals and constructible sets', Bull. Acad. Pol. Sci., 9, 521-524; Cohen, P., 1966, Set theory and the continuum hypothesis, New York: Benjamin; Jensen, R., 1972, 'The fine structure of the constructible hierarchy', Ann. Math. Logic, 4, 229-308; Martin, D. and Steel, J., 1989, 'A proof of projective determinacy', J. Amer. Math. Soc., 2, 71-125; Hrbacek, K. and Jech, T., 1999, Introduction to Set Theory,

New York: Marcel Dekker, Inc, http://plato.stanford.edu/entries/set-theory/primer.html and the like.

The language of set theory is based on a single fundamental relation, called membership. We say that A is a member of B (in symbols A ∈ B), or that the set B contains A as its element. The understanding is that a set is determined by its elements. In other words, two sets are deemed equal if they have exactly the same elements. In practice, one considers sets of numbers, sets of points, sets of functions, sets of other sets and so on. In theory, it is not necessary to distinguish between objects. One only need to consider sets.

Using the membership relation, one can derive other concepts usually associated with sets, such as unions and intersections of sets. For example, a set C is the union of two sets A and B if its members are exactly those objects that are either members of A or members of B. The set C is uniquely determined, because we have specified what its elements are. There are more complicated operations on sets that can be defined in the language of set theory (i.e. using only the relation ∈), and we shall not concern ourselves with those. Let us mention another operation: the (unordered) pair {A, B} has as its elements exactly the sets A and B. (If it happens that A=B, then the "pair" has exactly one member, and is called a singleton {A}.) By combining the operations of union and pairing, one can produce from any finite list of sets the set that contains these sets as members: {A,B,C,D,...,K,L,M}. It should also be mentioned that the empty set, the set that has no elements. (The empty set is uniquely determined by this property, as

it is the only set that has no elements - this is a consequence of the understanding that sets are determined by their elements.). When dealing with sets informally, such operations on sets are self-evident; with the axiomatic approach, it is postulated that such operations can be applied: for instance, one postulates that for any sets A and B, the set {A,B} exists. In order to endow set theory with sufficient expressive power one needs to postulate more general construction principles than those alluded to above. The guiding principle is that any objects that can be singled out can be collected into a set.

If a and b are sets, then the unordered pair {a, b} is a set whose elements are exactly a and b. The "order" in which a and b are put together plays no role; {a, b} = {b, a}. For many applications, it is necessary to pair a and b in such a way that one can "read off" which set comes "first" and which comes "second." It is denoted that this ordered pair of a and b by (a, b); a is the first coordinate of the pair (a, b), b is the second coordinate.

As any object of our study, the ordered pair has to be a set. It should be defined in such a way that two ordered pairs are equal if and only if their first coordinates are equal and their second coordinates are equal. This guarantees in particular that (a, b) $\neq$ (b,a) if a $\neq$ b.

Definition. (a, b) = {{a}, {a, b}}.

If a $\neq$ b, (a, b) has two elements, a singleton {a} and an unordered pair {a, b}. The first coordinate can be found by looking at the element of {a}. The second

coordinate is then the other element of {a, b}. If a = b, then (a, a) = {{a}, {a,a}} = {{a}} has only one element. In any case, it seems obvious that both coordinates can be uniquely "read off" from the set (a, b). This statement is made precise in the following theorem.

Theorem. (a, b) = (a′ , b′) if and only if a = a′ and b = b′ .

Proof. If a = a′ and b = b′ , then, of course, (a, b) = {{a}, {a, b}} = {{a′ }, {a′ , b′ }} = (a′ ,b′). The other implication is more intricate. Let us assume that {{a}, {a, b}} = {{a ′ }, {a′ , b ′ }}. If a ≠ b, {a} = {a′ } and {a, b} = {a ′ , b′ }. So, first, a = a′ and then {a, b} = {a, b′ } implies b = b′ . If a = b, {{a}, {a, a}} = {{a}}. So {a} = {a′ }, {a} = {a′ ,b ′ }, and we get a = a′ = b′ , so a = a ′ and b = b′ holds in this case, too.

With ordered pairs at our disposal, ordered triples can be defined:

(a, b, c) = ((a, b), c),

ordered quadruples

(a, b, c, d) = ((a, b, c), d),

and so on. Also, ordered "one-tuples" can be defined.

(a) = a.

A binary relation is determined by specifying

all ordered pairs of objects in that relation; it does not matter by what property the set of these ordered pairs is described. We are led to the following definition.

Definition. A set R is a binary relation if all elements of R are ordered pairs, i.e., if for any $z \in R$ there exist x and y such that $z = (x, y)$.

It is customary to write xRy instead of $(x, y) \in R$. We say that x is in relation R with y if xRy holds.

The set of all x which are in relation R with some y is called the domain of R and denoted by "dom R." So dom R = {x | there exists y such that xRy}. dom R is the set of all first coordinates of ordered pairs in R.

The set of all y such that, for some x, x is in relation R with y is called the range of R, denoted by "ran R." So ran R = {y | there exists x such that xRy}.

Function, as understood in mathematics, is a procedure or a rule, assigning to any object a from the domain of the function a unique object, b, the value of the function at a. A function, therefore, represents a special type of relation, a relation where every object, a, from the domain is related to precisely one object in the range, namely, to the value of the function at a.

Definition. A binary relation F is called a function (or mapping, correspondence) if aFb1 and aFb2 imply b1 = b2 for any a, b1, and b2. In other words, a binary relation F is a function if and only if for every a from dom F there is exactly one b such that aFb. This unique b is called the

value of F at a and is denoted F(a) or Fa. [F(a) is not defined if a dom F.] If F is a function with dom F = A and ran F $\subseteq$ B, it is customary to use the notations F : A B, <F(a) | a $\in$A>, <Fa | a $\in$ A>, <Fa >a $\in$ A for the function F. The range of the function F can then be denoted {F(a) | a $\in$ A} or {Fa}a $\in$A.

The Axiom of Extensionality can be applied to functions as follows.

Lemma. Let F and G be functions. F = G if and only if dom F = dom G and F(x) = G(x) for all x $\in$ dom F.

A function f is called one-to-one or injective if a1 $\in$ dom f, a2 $\in$ dom f, and a1 $\neq$ a2 implies f(a1) $\neq$ f(a2). In other words if a1 $\in$ dom f, a 2$\in$ dom f, and f(a1) = f(a2), then a1 = a2.

In order to develop mathematics within the framework of the axiomatic set theory, it is necessary to define natural numbers. Natural numbers are known intuitively: 0, 1, 2, 3, ..., 15, …, 515, etc., and examples of sets having zero, one, two, or three elements can be easily given.

To define number 0, a representative of all sets having no elements is chosen. However, this is easy, since there is only one such set. 0 = $\emptyset$ is defined. Let us proceed to sets having one element (singletons): {$\emptyset$}, {{$\emptyset$}}, {{$\emptyset$, {$\emptyset$}}}; in general, {x}. A representative can be chosen as follows: Since we already defined one particular object, namely 0, a natural choice is {0}. So it is defined:

$1 = \{0\} = \{\emptyset\}$.

Next sets with two elements are considered: $\{\emptyset, \{\emptyset\}\}$, $\{\{\emptyset\}, \{\emptyset, \{\emptyset\}\}\}$, $\{\{\emptyset\}, \{\{\emptyset\}\}\}$, etc. By now, defined 0 and 1 have been defined, and $0 \neq 1$. A particular two-element set is singled out, the set whose elements are the previously defined numbers 0 and 1:

$2 = \{0,1\} = \{\emptyset, \{\emptyset\}\}$.

It should begin to be obvious how the process continues:

$3 = \{0, 1, 2\} = \{\emptyset, \{\emptyset\}, \{\emptyset,\{\emptyset\}\}\}$
$4 = \{0, 1, 2, 3\} = \{\emptyset,\{\emptyset\}, \{\emptyset,\{\emptyset\}\}, \{\emptyset, \{\emptyset\}, \{\emptyset, \{\emptyset\}\}\}\}$
$5 = \{0, 1, 2, 3, 4\}$etc.

The idea is simply to define a natural number n as the set of all smaller natural numbers: {0, 1, …, n - 1}. In this way, n is a particular set of n elements.

This idea still has a fundamental deficiency. 0, 1, 2, 3, 4, and 5 have been defined and could easily define 15 and not so easily 515. But no list of such definitions tells us what a natural number is in general. A statement of the form is necessary: A set n is a natural number if …. We cannot just say that a set n is a natural number if its elements are all the smaller natural numbers, because such a "definition" would involve the very concept being defined.

The construction of the first few numbers is observed again. We defined 2 = {0, 1}. To get 3, we had to

adjoin a third element to 2, namely, 2 itself:

$$3 = 2 \cup \{2\} = \{0, 1\} \cup \{2\}.$$

Similarly,

$$4 = 3 \cup \{3\} = \{0, 1, 2\} \cup \{3\},$$
$$5 = 4 \cup \{4\}, \text{etc.}$$

Given a natural number n, we get the "next" number by adjoining one more element to n, namely, n itself. The procedure works even for 1 and 2: $1 = 0 \cup \{0\}$, $2 = 1 \cup \{1\}$, but, of course, not for 0, the least natural number.

These considerations suggest the following.

Definition. The successor of a set x is the set $S(x) = x \cup \{x\}$.

Intuitively, the successor S(n) of a natural number n is the "one bigger" number n + 1. We use the more suggestive notation n+1 for S(n) in what follows. We later define addition of natural numbers (using the notion of successor) in such a way that n + 1 indeed equals the sum of n and 1. Until then, it is just a notation, and no properties of addition are assumed or implied by it.

It can now be summarized the intuitive understanding of natural numbers as follows:

1. 0 is a natural number.
2. If n is a natural number, then its successor n + 1 is also a natural number.

3. All natural numbers are obtained by application of (a) and (b), i.e., by starting with 0 and repeatedly applying the successor operation: 0, 0 + 1 = 1, 1 + 1 = 2, 2 + 1 = 3, 3 + 1 = 4, 4 + 1 = 5, ...etc.

Definition. A set I is called inductive if

1. $0 \in I$.
2. If $n \in I$, then $(n + 1) \in I$.

An inductive set contains 0 and, with each element, also its successor. According to (c), an inductive set should contain all natural numbers. The precise meaning of (c) is that the set of natural numbers is an inductive set which contains no other elements but natural numbers, i.e., it is the smallest inductive set. This leads to the following definition.

Definition. The set of all natural numbers is the set

$$= \{x \mid x \in I \text{ for every inductive set } I\}.$$

The elements of the set are called natural numbers. Thus a set x is a natural number if and only if it belongs to every inductive set.

From the point of view of pure set theory, the most basic question about a set is: How many elements does it have? It is a fundamental observation that we can define the statement "sets A and B have the same number of elements" without knowing anything about numbers.

Definition. Sets A and B have the same cardinality if there is a one-to-one function f with domain A and range B. We denote this by $|A| = |B|$.

Definition. The cardinality of A is less than or equal to the cardinality of B (notation: $|A| \leq |B|$) if there is a one-to-one mapping of A onto B.

Notice that $|A| \leq |B|$ means that $|A| = |C|$ for some subset C of B. We also write $|A| < |B|$ to mean that $|A| \leq |B|$ and not $|A| = |B|$, i.e., that there is a one-to-one mapping of A onto a subset of B, but there is no one-to-one mapping of A onto B.

Lemma.

1. If $|A| \leq |B|$ and $|A| = |C|$, then $|C| \leq |B|$.
2. If $|A| \leq |B|$ and $|B| = |C|$, then $|A| \leq |C|$.
3. $|A| \leq |A|$.
4. If $|A| \leq |B|$ and $|B| \leq |C|$, then $|A| \leq |C|$.

Cantor-Bernstein Theorem. If $|X| \leq |Y|$ and $|Y| \leq |X|$, then $|X| = |Y|$.

Finite sets can be defined as those sets whose size is a natural number.

Definition. A set, S, is finite if it has the same cardinality as some natural number, n . We then define $|S| = n$ and say that S has n elements. A set is infinite if it is not finite.

As described above, set theory can be applied

to an analysis of the present invention.

For example, a test result can be summarized in an Excel(trademark)-format file, in which functional reporters such as transcriptional factor reporters, and perturbation agents such as siRNA's are plotted in an x-y format, and the value corresponding to each combination thereof is filled therein. The actual value may be compared to a standard value, or a threshold of interest such as a result obtained by using a scrambled siRNA. The values may be normalized into three values such as +, 0 and -. The values are evaluated, for example, when 80 % or less of the threshold, it is normalized to "-1", and when between 80 % and 120 % of the threshold, it is normalized to "0", and when 120 % or more of the threshold, it is normalized to "+1". The normalized or degenerated matrix may be used to analyze the effects of perturbation agents (such as siRNA's) on reporters in a simpler manner, and to obtain a set of perturbation agents giving effects on each of the reporters. An exemplary table is shown below.

before normalization

	Function 1	Function 2	Function 3	Function 4
siRNA 1	70%	120%	80%	75%
siRNA 2	115%	100%	65%	130%
siRNA 3	150%	90%	105%	115%

after normalization

	Function 1	Function 2	Function 3	Function 4
siRNA 1	-1	+1	-1	-1
siRNA 2	0	0	-1	+1
siRNA 3	+1	0	0	0

(Description of preferred embodiments)

Hereinafter, the present invention will be described by way of embodiments. Embodiments described below are provided only for illustrative purposes. Accordingly, the scope of the present invention is not limited by the embodiments except as by the appended claims.

In one aspect, the present invention provides a method for analyzing a network of biological functions in a biological entity. The present method comprises the steps of: A) subjecting a biological entity to at least one perturbation agent; B) obtaining information on at least two functional reporters in said biological entity, wherein the functional reporters reflect a biological function; and C) subjecting the obtained information to set theory processing to calculate a relationship between the functional reporters to generate a network relationship of the biological functions.

The step of subjecting a biological entity to at least one perturbation agent, may be conducted in any manner as long as the perturbation agent is conducted to the entity and attains the effects of interest, and is dependent on the type of perturbation used.

The step of obtaining information on at least two functional reporters may be conducted in any manner as long as signals of such reporters can be measured. Preferably, reporters emit measurable signals such as light, fluorescence, protein expression and the like, when a perturbation agent has an effect. Therefore, preferably, the functional reporter is capable of transmitting a measurable signal.

So long set theory can be conducted, the step of subjecting the data to set theory can be conducdted.

Preferably, a biological entity used in the present invention is a cell.

Perturbation agents used in the present invention may be any agents which give a perturbation or a change to a biological entity or a system such as RNA including siRNA, shRNA, miRNA, and ribozyme, chemical compound, cDNA, antibody, polypeptides, light, sound, pressure change, radiation, heat, gas, and the like. preferably a siRNA capable of specifically regulating a function of said functional reporter.

Functional reporters used in the present invention include but are not limited to transcriptional factors, regulatory genes, structural genes, cellular markers, cell surface markers, cell shapes, organelle shapes, cell mobility, enzyme activities, metabolite concentrations, and localization of cellular components.

In a specific embodiment, the set theory processing used in the present invention may be conducted by classifying two specific functional reporters of at least two said functional reporters into a relationship selected from the group consisting of a) independent, b) inclusion, and c) intersection, wherein when it is determined to be independent, the two specific functional reporters are determined to have no relationships in the network; when it is determined to be inclusion, one of the two specific functional reporters is determined to be included in the other of the two specific functional reporters and located

downstream of the other; when it is determined to be intersection, the two specific functional reporters are determined to be located downstream branched from another common function.

In the present invention, any mathematical process of set theory can be used as long as sets can be analyzed according to set theory. In a specific embodiment of the present invention, the set theory processing comprises the step of mapping the absence or presence of a response by said perturbation agent per said functional reporter.

In a specific embodiment of the present invention, the set theory processing can comprise a calculation of a relationship between the reporters comprising correlation between each functional reporter as classified into independent, inclusion and intersection to generate a summary of the correlation. This calculation can be conducted by using a matrix.

In a preferable embodiment of the present invention, the perturbation factors used in the present invention are advantageously prepared such that the number of perturbation factors sufficient for equally targeting an intracellular pathway. In the present invention, two or more perturbation agents are usually used to change the network structure of a biological entity such as a cell. It is preferable to use equally targeting perturbation agents. Basic elements constituting biological functions are changes in networks such as a molecular network in response to the circumstantial stimulation. In other words, although not wishing bound to any particular theory, it is

considered that the existence of diversity in biological functions show that such networks in a biological entity such as a cell have also diversity. Therefore, in order to investigate M changes in a state of a biological entity such as a cell, N perturbation agents can be given to the biological entity to allow network analysis such as molecular network analysis, or an analysis of the number of the states, which have diversity. Furthermore, when analysis is conducted with respect to a fixed M, sufficient number of perturbation agents, N, is used so that the number of cases (or the number of combinations) is preferably sufficient analysis for network analysis, such as an intracellular network analysis. Moreover, equally targeting perturbation agents are considered to cause changes in network structure without causing biased effects on the network. Therefore, such equally targeting perturbation agents are preferably used, and more preferably the number of such perturbation agents is used. Such a number will be readily understood by those skilled in the art from the disclosure of the present specification.

The information on at least two functional reporters as analyzed in the present invention may be based on an effect of said perturbation agent after a desired time. As used herein such a desired time may be selected depending on the circumstances, purposes and the like of the analysis to be conducted. For example, when effects of agents on a cell are observed, tens of minutes to a couple of hours, or up to several days may usually be used.

In a specific embodiment, the effect obtained by the perturbation agents used can be classified into the following three groups in terms of a threshold value:

positive effect = + (preferably +1); no effect= 0; and negative effect = - (preferably -1).

In a preferable embodiment of the present invention, the information on at least two functional reporters is based on an effect of the perturbation agent after a desired time; wherein the set theory processing comprises: a) classifying the information into three categories by comparing the effect with a threshold value for the functional reporter and classifying them into the following three groups: positive effect = + (preferably +1); no effect= 0; and negative effect = - (preferably -1); b) determining if two out of the functional reporters have a common perturbation agent, wherein the common perturbation agent has the same type of effect, and if there is no such common perturbation agent, then the two functions corresponding to the two functional reporters are located under different perturbation agents and if there is such a common perturbation agent, then the following step c) is conducted: c) determining if the perturbation agent set for one function of the two functions is completely included into the perturbation agent set for the other function of the two functions, and if this is the case, then one function having the bigger set is located downstream of the other function having the smaller set, and if this is not the case, then the two functions are located in parallel under the same perturbation agents; d) determining if all combinations of the functional reporters are investigated, if this is the case, then integrate all the relationships of functions to present a global perturbation effects network, and if this is not the case then repeat the steps a) to c). These steps can be conducted on a computer equipped with a computer program implementing the process and steps

of interest.

In a preferable embodiment of the present invention, said steps of a) to c) are calculated by producing M x N matrix, wherein M refers to the number of functional reporters and N refers to the number of perturbation agents. By using such a matrix, the set theory can be easily processed by a normal matrix calculation process.

In a further embodiment of the present invention, the present invention may further comprise analyzing the generated network by conducting an actual biological experiment. Preferably, such an analysis comprises the use of a regulation agent such as siRNA, antibody, antisense oligonucleotide, inhibitor, activator, ligand, receptors and the like, specific to the function. Preferably, siRNA is used.

The present invention can be used for analyzing networks such as a signal transduction pathway, a cellular pathway and the like.

The present invention is useful for identification of a biomarker, analysis of a drug target, analysis of a side effect, diagnosis of a cellular function, analysis of a cellular pathway, evaluation of a biological effect of a compound, and diagnosis of an infectious disease and the like.

In another aspect of the present invention, the present invention provides a system for analyzing a network of biological functions in a biological entity, comprising:
A) at least one perturbation agent for a biological entity;

B) means for obtaining information on at least two functional reporters in said biological entity, wherein the functional reporters reflect a biological function; and C) means for subjecting the obtained information to set theory processing to calculate a relationship between the functional reporters to generate a network relationship of the biological functions. In a system of the present invention, perturbation agents may be supplied separately. Therefore, in an embodiment, the present invention merely comprises B) means for obtaining information on at least two functional reporters in said biological entity, wherein the functional reporters reflect a biological function; and C) means for subjecting the obtained information to set theory processing to calculate a relationship between the functional reporters to generate a network relationship of the biological functions.

Means for obtaining information on at least two functional reporters in said biological entity, wherein the functional reporters reflect a biological function, may be provided as a transfection array, but the present invention is not limited to this. Such a transfection array is extensively described elsewhere herein and exemplified in the following Examples.

Means for subjecting the obtained information to set theory processing to calculate a relationship between the functional reporters to generate a network relationship of the biological functions, may be provided as a computer program but the present invention is not limited to this. As set theory is known in the art, it is understood that any computer program implementing such a calculation based on set theory can be used in the present invention.

It should be noted that those skilled in the art will understand that any other specific embodiments of the method as described hereinabove may be employed and are applicable to a system of the present invention if necessary.

In a further aspect of the present invention, the present invention provides a computer program for implementing in a computer, a method for analyzing a network of biological functions in a biological entity, comprising the steps of: A) subjecting a biological entity to at least one perturbation agent; B) obtaining information on at least two functional reporters in said biological entity, wherein the functional reporters reflect a biological function; and C) subjecting the obtained information to set theory processing to calculate a relationship between the functional reporters to generate a network relationship of the biological functions.

It should be noted that those skilled in the art will understand that any other specific embodiments of the method and system as described hereinabove may be employed and are applicable to a computer program of the present invention if necessary.

A configuration of a computer or system for implementing a method of the present invention for analyzing a network of biological functions in a biological entity is shown in Figure **10.** Figure **10** shows an exemplary configuration of a computer 500 for executing the cellular state presenting method of the present invention.

The computer 500 comprises an input section 501,

a CPU 502, an output section 503, a memory 504, and a bus 505. The input section 501, the CPU 502, the output section 503, and the memory 504 are connected via a bus 505. The input section 501 and the output section 503 are connected to an I/O device 506.

An outline of a process for presenting a state of a cell, which is executed by the computer 500, will be described below.

A program for executing a method for analyzing a network of biological functions in a biological entity is stored in, for example, the memory 502. Alternatively, information necessary for the method may be stored in any type of recording medium, such as a floppy disk, MO, CD-ROM, CD-R, DVD-ROM, or the like separately or together. Alternatively, the program may be stored in an application server. The information or data stored in such a recording medium is loaded via the I/O device 506 (e.g., a disk drive, a network (e.g., the Internet)) to the memory 504 of the computer 500. The CPU 502 executes the cellular state presenting program, so that the computer 500 functions as a device for performing a method of the present invention for analyzing a network of biological functions in a biological entity.

Information about a cell or the like is input via the input section 501 as well as data obtained. Known information may be input as appropriate.

The CPU 502 generates display data based on the information about data and cells through the input section 501, and stored the display data into the memory 504.

Thereafter, the CPU 502 may store the information in the memory 504. Thereafter, the output section 503 outputs a network analyzed by the CPU 502 as display data. The output data is output through the I/O device 506.

In still different aspect of the present invention, the present invention provides that a storage medium comprising a computer program for implementing in a computer, a method for analyzing a network of biological functions in a biological entity, comprising the steps of: A) subjecting a biological entity to at least one perturbation agent; B) obtaining information on at least two functional reporters in said biological entity, wherein the functional reporters reflect a biological function; and C) subjecting the obtained information to set theory processing to calculate a relationship between the functional reporters to generate a network relationship of the biological functions.

It should be noted that those skilled in the art will understand that any other specific embodiments of the method, system and computer program as described hereinabove may be employed and are applicable to a storage medium of the present invention if necessary. Such a storage medium may be any type of recording medium, such as CD-ROMs, flexible disks, CD-Rs, CD-RWs, MOs, mini disks, DVD-ROMs, DVD-Rs, memory sticks, hard disks, and the like.

In yet still further aspect of the present invention, the present invention provides a transmission medium comprising a computer program for implementing in a computer, a method for analyzing a network of biological functions in a biological entity, comprising the steps of:

A) subjecting a biological entity to at least one perturbation agent; B) obtaining information on at least two functional reporters in said biological entity, wherein the functional reporters reflect a biological function; and C) subjecting the obtained information to set theory processing to calculate a relationship between the functional reporters to generate a network relationship of the biological functions.

It should be noted that those skilled in the art will understand that any other specific embodiments of the method, system, computer program and storage medium as described hereinabove may be employed and are applicable to a transmission medium of the present invention if necessary. Examples of such a transmission medium include, but are not limited to, networks, such as intranets, the Internet, and the like.

The preferred embodiments of the present invention have been heretofore described for a better understanding of the present invention. Hereinafter, the present invention will be described by way of examples. Examples described below are provided only for illustrative purposes. Accordingly, the scope of the present invention is not limited except as by the appended claims. According to the examples below, it will be understood that those skilled in the art can select cells, supports, biological factors, salts, positively charged substances, negatively charged substances, actin acting substances, and the like, as appropriate, and can make or carry out the present invention.

EXAMPLES

Hereinafter, the present invention will be described in greater detail by way of examples, though the present invention is not limited to the examples below. Reagents, supports, and the like were commercially available from Sigma (St. Louis, USA), Wako Pure Chemical Industries (Osaka, Japan), Matsunami Glass (Kishiwada, Japan) unless otherwise specified.

(Example 1: Reagents)

Formulations below were prepared in Example 1. Fibronectin and the like were commercially available. Fragments and variants were obtained by genetic engineering techniques:

1) fibronectin (SEQ ID NO: 52);
2) ProNectin F (Sanyo Chemical Industries, Kyoto, Japan);
3) ProNectin L (Sanyo Chemical Industries);
4) ProNectin Plus (Sanyo Chemical Industries);
5) gelatin.

Plasmids were prepared as DNA for transfection. Plasmids, pEGFP-N1, pDsRed2-N1 and other transcriptional factors and kinase encoding gene-containing plasmids (available from BD Biosciences, Clontech, CA, USA) were used. In these plasmids, gene expression was under the control of cytomegalovirus (CMV). The plasmid DNA was amplified in E. coli (XL1 blue, Stratagene, TX, USA) and the amplified plasmid DNA was used as a complex partner. The DNA was dissolved in distilled water free from DNase and RNase.

shRNA and/or siRNA were also prepared according

to the known technology.

The following transfection reagents were used: Effectene Transfection Reagent (cat. no. 301425, Qiagen, CA), TransFast™ Transfection Reagent (E2431, Promega, WI), Tfx™-20 Reagent (E2391, Promega, WI), SuperFect Transfection Reagent (301305, Qiagen, CA), PolyFect Transfection Reagent (301105, Qiagen, CA), LipofectAMINE 2000 Reagent (11668-019, Invitrogen corporation, CA), JetPEI (×4) conc. (101-30, Polyplus-transfection, France), and ExGen 500 (R0511, Fermentas Inc., MD). These transfection reagents were added to the above-described DNA and actin acting substance in advance or complexes thereof with the DNA were produced in advance.

The thus-obtained solution was used in assays using transfection arrays described below.

(Example 2: Transfection array - Demonstration using mesenchymal stem cells)

In Example 2, the transfection efficiency of the solid phase was observed. The protocol used in Example 2 will be described below.

(Protocol)

The final concentration of DNA was adjusted to 1 μg/μL. An actin acting substance was preserved as a stock having a concentration of 10 μg/μL in ddH_2O. All dilutions were made using PBS, ddH_2O, or Dulbecco's MEM. A series of dilutions, for example, 0.2 μg/μL, 0.27 μg/μL, 0.4 μg/μL, 0.53 μg/μL, 0.6 μg/μL, 0.8 μg/μL, 1.0 μg/μL, 1.07 μg/μL, 1.33 μg/μL, and the like, were formulated.

Transfection reagents were used in accordance with instructions provided by each manufacturer.

Plasmid DNA was removed from a glycerol stock and amplified in 100 mL L-amp overnight. Qiaprep Miniprep or Qiagen Plasmid Purification Maxi was used to purify DNA in accordance with a standard protocol provided by the manufacturer.

In Example 2, the following 5 cells were used to confirm an effect: human mesenchymal stem cell (hMSCs, PT-2501, Cambrex BioScience Walkersville, Inc., MD); human embryonic renal cell (HEK293, RCB1637, RIKEN Cell Bank, JPN); NIH3T3-3 cell (RCB0150, RIKEN Cell Bank, JPN); HeLa cell (RCB0007, RIKEN Cell Bank,JPN); and HepG2(RCB1648, RIKEN Cell Bank,JPN). These cells were cultured in DMEM/10% IFS containing L-glut and pen/strep.

(Dilution and DNA spots)

Transfection reagents and DNA were mixed to form a DNA-transfection reagent complex. The complex formation requires a certain period of time. Therefore, the mixture was spotted onto a solid phase support (e.g., a poly-L-lysine slide) using an arrayer. In Example 2, as a solid phase support, an APS slide, a MAS slide, and an uncoated slide were used as well as a poly-L-lysine slide. These slides are available from Matsunami Glass (Kishiwada, Japan) or the like.

For complex formation and spot fixation, the slides were dried overnight in a vacuum dryer. Drying was performed in the range of 2 hours to 1 week.

Although the fibronectin and the like might be used during the complex formation, it was also used immediately before spotting in Example 2.

(Formulation of mixed solution and application to solid phase supports)

300 μL of DNA concentrated buffer (EC buffer) + 16 μL of an enhancer were mixed in an Eppendorf tube. The mixture was mixed with a Vortex, followed by incubation for 5 minutes. 50 μL of a transfection reagent (Effectene, etc.) was added to the mixture, followed by mixing by pipetting. To apply a transfection reagent, an annular wax barrier was formed around the spots on the slide. 366 μL of the mixture was added to the spot region surrounded by the wax, followed by incubation at room temperature for 10 to 20 minutes. Thereby, the fixation to the support was manually achieved.

(Distribution of cells)

Next, a protocol for adding cells will be described. Cells were distributed for transfection. The distribution was typically performed by reduced-pressure suction in a hood. A slide was placed on a dish, and a solution containing cells was added to the dish for transfection. The cells were distributed as follows.

The growing cells were distributed to a concentration of 10^7 cells/25 mL. The cells were plated on the slide in a 100×100×15 mm squared Petri dish or a 100 mm (radius) × 15 mm circular dish. Transfection was conducted for about 40 hours. This period of time corresponded to about 2 cell cycles. The slide was treated for immunofluorescence. See Figure **4**, upper left panel for an

example of an array.

(Evaluation of gene introduction)

Gene introduction was evaluated by detection using, for example, immunofluorescence, fluorescence microscope examination, laser scanning, radioactive labels, and sensitive films, or emulsion.

When an expressed protein to be visualized is a fluorescent protein, such a protein can be observed with a fluorescence microscope and a photograph thereof can be taken. For large-sized expression arrays, slides may be scanned using a laser scanner for storage of data. If an expressed protein can be detected using fluorescence antibodies, an immunofluorescence protocol can be successively performed. If detection is based on radioactivity, the slide may be adhered as described above, and autoradiography using film or emulsion can be performed to detect radioactivity.

(Laser scanning and Quantification of fluorescence intensity)

To quantify transfection efficiency, the present inventors use a DNA microarray scanner (GeneTAC UC4×4, Genomic Solutions Inc., MI). Total fluorescence intensity (arbitrary unit) was measured, and thereafter, fluorescence intensity per unit surface area was calculated.

(Cross-sectional observation by confocal scanning microscope)

Cells were seeded on tissue culture dishes at a final concentration of 1×10^5 cells/well and cultured in

appropriate medium (Human Mesenchymal Cell Basal Medium (MSCGM BulletKit PT-3001, Cambrex BioScience Walkersville, Inc., MD). After fixation of the cell layer with 4% paraformaldehyde solution, SYTO and Texas Red-X phalloidin (Molecular Probes Inc., OR, USA) was added to the cell layer for observation of nuclei and F-actin. The samples emitting light due to gene products and the stained samples were observed with a confocal laser microscope (LSM510: Carl Zeiss Co., Ltd., pin hole size=Ch1=123 μm, Ch2=108 μm, image interval = 0.4) to obtain cross sectional views.

(Experimental protocols)

(Cell sources, culture media, and culture conditions)

In this example, five different cell lines were used: human mesenchymal stem cells (hMSCs, PT-2501, Cambrex BioScience Walkersville, Inc., MD), human embryonic kidney cell HEK293 (RCB1637, RIKEN Cell Bank, JPN), NIH3T3-3 (RCB0150, RIKEN Cell Bank, JPN), HeLa (RCB0007, RIKEN Cell Bank, JPN), and HepG2 (RCB1648, RIKEN Cell Bank, JPN). In the case of human MSCs, cells were maintained in commercially available Human Mesenchymal Cell Basal Medium (MSCGM BulletKit PT-3001, Cambrex BioScience Walkersville, Inc., MD). In case of HEK293, NIH3T3-3, HeLa and HepG2, cells were maintained in Dulbecco's Modified Eagle's Medium (DMEM, high glucose 4.5 g/L with L-Glutamine and sodium pyruvate; 14246-25, Nakalai Tesque, JPN) with 10% fetal bovine serum (FBS, 29-167-54, Lot No. 2025F, Dainippon Pharmaceutical CO., LTD., JPN). All cells were cultivated in a controlled incubator at 37°C in 5% CO_2. In experiments involving hMSCs, we used hMSCs of less than five passages, in order to avoid phenotypic changes.

(Plasmids and Transfection reagents)

To evaluate the efficiency of transfection, the pEGFP-N1 and pDsRed2-N1 vectors (cat. no. 6085-1, 6973-1, BD Biosciences Clontech, CA) were used. Both genes' expressions were under the control of cytomegalovirus (CMV) promoter. Transfected cells continuously expressed EGFP or DsRed2, respectively. Plasmid DNAs were amplified using Escherichia coli, XL1-blue strain (200249, Stratagene, TX), and purified by EndoFree Plasmid Kit (EndoFree Plasmid Maxi Kit 12362, QIAGEN, CA). In all cases, plasmid DNA was dissolved in DNase and RNase free water. Transfection reagents were obtained as below: Effectene Transfection Reagent (cat. no.301425, Qiagen, CA), TransFast™ Transfection Reagent (E2431, Promega, WI), Tfx™-20 Reagent (E2391, Promega, WI), SuperFect Transfection Reagent (301305, Qiagen, CA), PolyFect Transfection Reagent (301105, Qiagen, CA), LipofectAMINE 2000 Reagent (11668-019, Invitrogen corporation, CA), JetPEI (×4) conc. (101-30, Polyplus-transfection, France), and ExGen 500 (R0511, Fermentas Inc., MD).

(Solid-Phase Transfection Array (SPTA) production)

The detail of protocols for 'reverse transfection' was described in the web site, 'Reverse Transfection Homepage' (http://staffa.wi.mit.edu/sabatini_public/reverse_transfection.htm) or J. Ziauddin, D. M. Sabatini, Nature, 411, 2001, 107; and R.W. Zu, S.N. Bailey, D.M. Sabatini, Trends in Cell Biology, Vol. 12, No. 10, 485. In our solid phase transfection (SPTA method), three types of glass slides were studied (silanized glass slides; APS slides, and poly-L-lysine coated glass slides; PLL slides, and MAS

coated slides; Matsunami Glass, JPN) with a 48 square pattern (3 mm × 3 mm) separated by a hydrophobic fluoride resin coating.

(Plasmid DNA printing solution preparation)

Two different ways to produce a SPTA were developed. The main differences reside in the preparation of the plasmid DNA printing solution.

(Method A)

In the case of using Effectene Transfection Reagent, the printing solution contained plasmid DNA and cell adhesion molecules (bovine plasma fibronectin (cat. no. 16042-41, Nakalai Tesque, JPN), dissolved in ultra-pure water at a concentration of 4 mg/mL). The above solution was applied on the surface of the slide using an inkjet printer (synQUAD™, Cartesian Technologies, Inc., CA) or manually, using a 0.5 to 10 μL tip. This printed slide was dried up over 15 minutes at room temperature in a safety-cabinet. Before transfection, total Effectene reagent was gently poured on the DNA-printed glass slide and incubated for 15 minutes at room temperature. The excess Effectene solution was removed from the glass slide using a vacuum aspirator and dried at room temperature for 15 minutes in a safety-cabinet. The DNA-printed glass slide obtained was set in the bottom of a 100-mm culture dish and approximately 25 mL of cell suspension (2 to 4×10^4 cells/mL) was gently poured into the dish. Then, the dish was transferred to the incubator at 37°C in 5% CO_2 and incubated for 2 or 3 days.

(Method B)

In case of other transfection reagents

(TransFast™, Tfx™-20, SuperFect, PolyFect, LipofectAMINE 2000, JetPEI (×4) conc., or ExGen), plasmid DNA, fibronectin, and the transfection reagent, were mixed homogeneously in a 1.5-mL micro-tube according to the ratios indicated in the manufacturer's instructions and incubated at room temperature for 15 minutes before printing on a chip. The printing solution was applied to the surface of the glass-slide using an inkjet printer or a 0.5- to 10-μL tip. The printed glass-slide was completely dried at room temperature over 10 minutes in a safety-cabinet. The printed glass-slide was placed in the bottom of a 100-mm culture dish and approximately 3 mL of cell suspension (2 to 4×10^4 cells/mL) was added and incubated at room temperature over 15 minutes in a safety-cabinet. After incubation, fresh medium was poured gently into the dish. Then, the dish was transferred to an incubator at 37°C in 5% CO_2 and incubated for 2 to 3 days. After incubation, using fluorescence microscopy (IX-71, Olympus PROMARKETING, INC., JPN), we observed the transfectants, based on their expression of enhanced fluorescent proteins (EFP, EGFP and DsRed2). Phase contrast images were taken with the same microscope. In both protocols, cells were fixed by using a paraformaldehyde (PFA) fixation method (4% PFA in PBS, treatment time was 10 minutes at room temperature).

(Laser scanning and fluorescence intensity quantification)

In order to quantify the transfection efficiency, we used a DNA micro-array scanner (GeneTAC UC4×4, Genomic Solutions Inc., MI). The total fluorescence intensity (arbitrary units) was measured, and thereafter, the fluorescence intensity per surface area was calculated.

(Solid-phase transfection array of human mesenchymal stem cells)

The capacity of human Mesenchymal Stem Cells (hMSC) to differentiate into various kinds of cells is particularly intriguing in studies which target tissue regeneration and renewal. In particular, the genetic analysis of transformation of these cells has attracted attention with the expectation of understanding of a factor that controls the pluripotency of hMSC. In conventional hMSC studies, it is not possible to perform transfection with desired genetic materials.

It was demonstrated that solid phase transfection can be used to achieve a "transfection patch" capable of being used for *in vivo* gene delivery and a solid phase transfection array (SPTA) for high-throughput genetic function research on hMSC.

Although a number of standard techniques are available for transfecting mammalian cells, it is known that it is inconvenient and difficult to introduce genetic material into hMSC as compared with cell lines, such as HEK293, HeLa, and the like. Conventional viral vector delivery and electroporation techniques are each important. However, these techniques have the following inconveniences: potential toxicity (for the virus technique); difficulty in high-throughput analysis at the genomic scale; and limited applications in *in vivo* studies (for electroporation).

The present inventors developed solid phase support fixed system which can be easily fixed to a solid phase support and has sustained-release capability and cell

affinity, whereby most of the above-described drawbacks could be overcome and attained analysis a network of a biological entity such as a cell with set theory.

As a result of this example, several important effects were achieved: high transfection efficiency (thereby making it possible to study a group of cells having a statistically significant scale); low cross contamination between regions having different DNA molecules (thereby making it possible to study the effects of different genes separately); the extended survival of transfected cells; high-throughput, compatible and simple detecting procedure. SPTA having these features serve as an appropriate basis for further studies.

A coating agent used is crucial for the achievement of high transfection efficiency on chips. It was found that when a glass chip is used, PLL provided the best results both for transfection efficiency and cross contamination (described below). When fibronectin coating was not used, few transfectants were observed (all the other experimental conditions were retained unchanged). Although not completely established, fibronectin probably plays a role in accelerating the cell adhesion process (data not shown), and thus, limiting the time which permits the diffusion of DNA released from the surface.

(Example 3: RNAi transfection microarray)

Arrays were produced as described in Example 2. As genetic material, mixtures of plasmid DNA (pDNA) and shRNA were used. The compositions of the mixtures are shown in Table 2.

Table 2

	pDNA vs. shRNA ratio [μL/μL]				
	9:1	7:3	1:1	3:7	1:9
plasmid DNA (1 mg/mL)	1.8	1.4	1.0	0.6	0.2
shRNA (1 mg/mL)	0.2	0.6	1.0	1.4	1.8
Lipofectamine2000	4.0	4.0	4.0	4.0	4.0
Fibronectin (4 mg/mL)	5.0	5.0	5.0	5.0	5.0

Thus, it was revealed that the method of the present invention is applicable to any cells for analysis using shRNA.

(Example 4: Use of RNAi microarray using siRNA)

Next, siRNA was used instead of shRNA to construct RNAi transfection microarrays in accordance with the protocol as described in Example 2.

Functional reporters for transcriptional factors and fibronectin described in Table 2 were used to synthesize siRNAs for the transcriptional factors including SRE, TRE, E2F, p53, Rb, Actin, NFAT, NFkB, STAT3, RARE, PMA, ISRA, HSE, Myc, AP1, GAS, ERE, GRE and CRE. siRNA for EGFP was used as a control. Each siRNA was evaluated as to whether or not it knocks out a target transcription factor. Scrambled RNAs were used as negative controls, and their ratios were evaluated.

The following table shows the transcriptional factors to be targeted by the siRNA used in the present Example.

TABLE 3

Symbol (SEQ ID NO: of siRNA)	MANUFACTURER	SEQUENCE ANALYSIS	Target Gene ID (SEQ ID NOs)	Annotation
Scramble (SEQ ID NO: 77) available as Scramble II Duplex	Dharmacon	Dharmacon		Non-targeting (scramble II Duplex)
c-Myc available as Silencer™ c-myc siRNA	Ambion	Ambion	V00568 (SEQ ID NOs: 1-2)	Human mRNA encoding the c-myc oncogene
c-Fos(SEQ ID NO: 53)	Dharmacon	B-Bridge	K00650 (SEQ ID NOs: 3-4)	Human fos proto-oncogene (c-fos), complete cds
c-Jun(SEQ ID NO: 54)	Dharmacon	B-Bridge	J04111 (SEQ ID NOs 5-6)	Human c-jun proto oncogene (JUN), complete cds, clone hCJ-1
CREB(SEQ ID NO: 55)	Dharmacon	B-Bridge	M27691 (SEQ ID NOs 7-8)	Human transactivator protein (CREB) mRNA, complete cds
E2F(SEQ ID NO: 56)	Dharmacon	B-Bridge	M96577 (SEQ ID NOs 9-10)	Homo sapiens (E2F-1) pRB-binding

				protein mRNA, complete cds
ER (SEQ ID NO: 57)	Dharmacon	B-Bridge	M12674 (SEQ ID NOs 11-12)	Human estrogen receptor mRNA, complete cds
GR (SEQ ID NO: 58)	Dharmacon	B-Bridge	M10901 (SEQ ID NOs 13-14)	Human glucocorticoid receptor alpha mRNA, complete cds
HSF-1 (SEQ ID NO: 59)	Dharmacon	B-Bridge	NM_005526 (SEQ ID NOs 15-16)	Homo sapiens heat shock-transcription factor 1 (HSF1), mRNA
HSF-2 (SEQ ID NO: 60)	Dharmacon	B-Bridge	M65217 (SEQ ID NOs 17-18)	Human heat shock factor 2 (HSF2) mRNA, complete cds
HSF-4 (SEQ ID NO: 61)	Dharmacon	B-Bridge	D87673 (SEQ ID NOs 19-20)	Homo sapiens mRNA for heat shock-transcription factor 4, complete cds
IkBa (SEQ ID NO: 62)	Dharmacon	B-Bridge	M69043 (SEQ ID NOs 21-22)	Homo sapiens MAD-3 mRNA encoding IkB-like activity, complete cds
NFAT3 (SEQ ID NO: 63)	Dharmacon	B-Bridge	L41066 (SEQ ID NOs 23-24)	Homo sapiens NF-AT3 mRNA, complete cds

NFkB (SEQ ID NO: 64)	Dharmacon	B-Bridge	S76638 (SEQ ID NOs 25-26)	p50-NF-kappa B homolog [human, peripheral blood T cells, mRNA, 3113 nt]
RARA (SEQ ID NO: 65)	Dharmacon	B-Bridge	NM_000964 (SEQ ID NOs 27-28)	Homo sapiens retinoic acid receptor, alpha (RARA), mRNA
RARB1 (SEQ ID NO: 66)	Dharmacon	B-Bridge	NM_000965 (SEQ ID NOs 29-30)	Homo sapiens retinoic acid receptor, beta (RARB), transcript variant 1, mRNA
RARB2 (SEQ ID NO: 67)	Dharmacon	B-Bridge	NM_016152 (SEQ ID NOs 31-32)	Homo sapiens retinoic acid receptor, beta (RARB), transcript variant 2, mRNA
RARG (SEQ ID NO: 68)	Dharmacon	B-Bridge	M57707 (SEQ ID NOs 33-34)	Human retinoic acid receptor gamma mRNA, complete cds
Rb (SEQ ID NO: 69)	Dharmacon	B-Bridge	M15400 (SEQ ID NOs: 35-36)	Human retinoblastoma susceptibility mRNA, complete cds
SRF (SEQ ID NO: 70)	Dharmacon	B-Bridge	J03161 (SEQ ID NOs 37-38)	Human serum response factor (SRF) mRNA, complete cds

STAT1a (SEQ ID NO: 71)	Dharmacon	B-Bridge	M97935 (SEQ ID NOs 39-40)	Homo sapiens transcription factor ISGF-3 mRNA, complete cds
STAT1b (SEQ ID NO: 72)	Dharmacon	B-Bridge	M97936 (SEQ ID NOs 41-42)	Human transcription factor ISGF-3 mRNA sequence
STAT2 (SEQ ID NO: 73)	Dharmacon	B-Bridge	M97934 (SEQ ID NOs 43-44)	Homo sapiens interferon alpha induced transcriptional activator (ISGF-3) mRNA sequence
STAT3 (SEQ ID NO: 74)	Dharmacon	B-Bridge	L29277 (SEQ ID NOs 45-46)	Homo sapiens DNA-binding protein (APRF) mRNA, complete cds
TR (SEQ ID NO: 75)	Dharmacon	B-Bridge	Y00479 (SEQ ID NOs 47-48)	H.sapiens mRNA for thyroid hormone receptor
p53 (SEQ ID NO: 76)	Dharmacon	B-Bridge	AF307851 (SEQ ID NOs 49-50)	Homo sapiens p53 protein mRNA, complete cds

The functional reporters used in the present Example are as follows:

TABLE 4: FUNTIONAL REPORTER LISTS

Mercury signaling pathway	Detection Targets	Induction elements	Binding TFs	Not active	Active	Localization	Re-location
pAP1(PMA)-EGFP	PKC and Related Pathways such as MAPK/JNK	Phorbol esters (PMA)	c-jun, c-fos	low intensity	increase intensity	cytosol	No
pAP1-EGFP	AP1 induction and SAPK/JNK pathway	serum, growth factors	c-jun, c-fos	low intensity	increase intensity	cytosol	No
pCRE-EGFP	CREB activation and JNK, p38 MAPK, PKA	cAPM, forskolin	CREB, ATF	low intensity	increase intensity	cytosol	No
pERE-EGFP	activation of Estrogen response element	estrogen	ER homodimer	low intensity	increase intensity	cytosol	No
pE2F-EGFP	E2F-mediated pathwats	Rb degradation	E2F	low intensity	increase intensit	cytosol	No

	(early S-phase)				y		
pGAS-EGFP	induction of STAT1(JAK/STAT path)	Cytokines(STAT1/STAT1)	STAT1/STAT1	low intensity	increase intensity	cytosol	No
pGRE-EGFP	activation of Glucocorticoid response element	glucocorticoids	GR	low intensity	increase intensity	cytosol	No
pHSE-EGFP	activation of HSF and heat shock-mediated Path	Heat shock	HSFs	low intensity	increase intensity	cytosol	No
pISRE-EGFP	IFN-triggered path, antiviral, growth inhibitory, immunoregulatory activities, JAK/STAT	INF α, β (Type I) γ (Type II)	IRFs, STAT2/STAT1	low intensity	increase intensity	cytosol	No

pMyc-EGFP	activation cMyc and cMyc-mediated path lead to cell growth	serum, growth factors	Myc/Max heterodimer	low intensity	increase intensity	cytosol	No
pNFAT-EGFP	activation NFAT and NFAT-mediated path, carcineurin, PKC	PMA	NFAT	low intensity	increase intensity	cytosol	No
pNFkB-EGFP	activation of NFkB signal transduction	TNF, IL-1, lymphokine receptors	NFkB	low intensity	increase intensity	cytosol	No
p53-EGFP	p53-mediated path		p53	low intensity	increase intensity	cytosol	No
pRARE-EGFP	induction of retinoic acid (RA)	RA	RAR, RXR	low intensity	increase intensity	cytosol	No

pRb-EGFP	activity of Rb-mediated path, repression cell cycle progression		Rb	increase intensity	decrease intensity	cytosol	No
pSRE-EGFP	induction of SRE, MAPK/JNK	serum, growth factors	SRF, Elk-1/STAT	low intensity	increase intensity	cytosol	No
pSTAT3-EGFP	JAK/STAT-mediated path	Cytokines,	STAT3/STAT3	low intensity	increase intensity	cytosol	No
pTRE-EGFP	induction of thyroid response element			low intensity	increase intensity	cytosol	No

Each cell was subjected to solid phase transfection, followed by culture for two days. Images were taken using a fluorescence image scanner, and the fluorescence level was quantified. In detail, the assay was conducted as follows:

The following reagents were mixed for "printing" DNA onto a transfection array as follows.

TMA printing Mix	
Plasmid DNA [1ug/uL]	2.0uL
siRNA [20pmol]	7.0uL
DMEM	7.0uL
Fibronectin [4mg/mL]	5.0uL
LipofectAMINE2000	4.0uL
Final Vol. [uL]	25.0uL

Bubble Jet (trademark) DNA printer (manufactured by Cartesian Dispensing Systems, Ann Arbor, MI , USA) was used for printing the DNA mixtures as prepared above onto glass slides. All combinations of nineteen reporters, and twenty six siRNA's were prepared for the present assay, and four spots per each combination were spotted onto the transfection array to make the transfection array for the present Example.

HeLa cells (human cervical cancer cell line) and HepG2 (human hepatoma cell line) were each seeded at 2 x 10^6 cells/mL and cultured in CO_2 incubators for forty-eight hours.

After culturing the cells, a scanner for DNA microarrays (ArrayWoRx (trade name), Applied Precision, LLC, Issaquah, Washington, USA) was used for obtaining fluorescent images of EGFP expression. These images were analyzed with image analyzing software (ImaGene; BioDiscovery; El Segundo, CA USA) to obtain intensity integral value of the EGFP fluorescence.

Relative intensity ratio against the intensity in the case where Scramble II Duplex, which is a negative control, was used was calculated. Results with 120 % or more in terms of the negative control were deemed as up-regulation, results with 80% or less in terms of the negative control was deemed as down-regulation. Results therebetween (i.e., 80%<results<120%) were considered to be no change.

The results for HeLa cells and HepG2 cells are shown below.

TABLE 5-1 (HeLa cells)

Hela-K	AP1	PMA	CRE	E2F	ERE	GAS
Scramble	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
c-Myc	63.1%	63.4%	67.7%	136.7%	103.5%	89.0%
c-Fos	72.9%	89.6%	67.0%	112.5%	116.6%	86.4%
c-Jun	63.1%	78.4%	60.9%	93.4%	119.4%	84.1%
CREB	71.9%	102.1%	56.7%	128.3%	98.1%	90.7%
E2F	57.9%	104.5%	58.0%	99.2%	103.6%	81.8%
ER	44.2%	85.4%	44.3%	110.9%	97.3%	89.8%
GR	70.5%	119.9%	33.9%	124.6%	100.9%	88.9%
HSF-1	84.5%	123.2%	37.4%	109.2%	98.1%	91.3%
HSF-2	72.6%	124.5%	25.7%	144.2%	95.0%	81.6%
HSF-4	55.3%	112.9%	28.2%	104.2%	94.4%	100.0%
IkBa	68.4%	109.3%	27.6%	123.8%	97.5%	94.0%
NFAT3	79.7%	104.2%	22.7%	140.4%	95.6%	84.5%
NFkB	93.2%	89.8%	21.3%	125.2%	92.9%	100.1%
RARA	81.1%	95.4%	24.6%	183.9%	94.9%	86.1%
RARB1	87.1%	67.0%	24.8%	139.2%	95.2%	81.5%
RARB2	89.1%	65.0%	79.7%	129.6%	96.1%	86.3%
RARG	70.2%	60.3%	63.7%	110.5%	97.3%	93.8%
Rb	41.7%	59.4%	45.0%	142.8%	107.3%	83.7%
SRF	35.7%	56.2%	55.6%	140.0%	112.8%	81.9%
STAT1a	32.7%	56.3%	88.4%	93.6%	109.1%	84.9%
STAT1b	34.9%	48.8%	52.8%	140.2%	109.6%	85.2%
STAT2	32.3%	49.5%	44.2%	141.1%	105.9%	84.8%
STAT3	30.0%	59.1%	40.1%	133.3%	106.8%	81.8%
TR	29.4%	55.2%	39.2%	131.1%	101.0%	80.2%
p53	36.7%	149.7%	26.9%	174.8%	98.0%	79.9%
Anti-GFP						

TABLE 5-2 HeLa cells (continued)

Hela-K	GRE	HSE	ISRE	Myc	NFAT	NFKB
Scramble	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
c-Myc	69.7%	89.5%	126.7%	79.2%	99.7%	61.6%
c-Fos	70.1%	98.1%	68.8%	63.8%	98.3%	87.6%
c-Jun	55.5%	77.4%	108.0%	57.9%	104.4%	80.9%
CREB	66.2%	82.1%	74.7%	47.7%	109.7%	138.3%
E2F	76.5%	84.5%	67.7%	46.9%	139.3%	99.7%
ER	79.6%	87.4%	70.3%	48.9%	158.7%	60.0%
GR	115.2%	92.9%	76.1%	56.8%	215.8%	144.2%
HSF-1	51.0%	117.3%	84.0%	69.5%	253.2%	143.2%
HSF-2	51.6%	122.0%	65.2%	99.7%	177.4%	172.8%
HSF-4	77.1%	111.4%	79.5%	99.4%	141.7%	111.0%
IkBa	81.0%	89.5%	110.9%	91.6%	195.7%	62.2%
NFAT3	71.0%	80.2%	88.4%	59.7%	162.1%	109.4%
NFkB	69.1%	103.6%	86.0%	72.9%	113.9%	96.4%
RARA	58.7%	122.9%	119.1%	122.4%	119.3%	98.9%
RARB1	60.6%	102.0%	96.9%	79.4%	106.6%	93.4%
RARB2	114.5%	73.3%	77.9%	70.9%	133.6%	132.6%
RARG	73.8%	88.1%	77.1%	74.4%	124.9%	79.5%
Rb	70.3%	84.6%	107.0%	81.2%	124.3%	146.0%
SRF	63.3%	97.3%	79.3%	75.3%	101.9%	74.3%
STAT1a	82.2%	94.8%	67.5%	58.7%	89.2%	197.0%
STAT1b	85.8%	74.9%	65.9%	63.3%	86.8%	168.7%
STAT2	58.5%	84.1%	83.3%	68.7%	83.4%	77.2%
STAT3	97.8%	104.3%	89.7%	85.6%	99.0%	68.7%
TR	54.3%	80.6%	137.7%	87.6%	95.3%	177.5%
p53	60.6%	82.1%	72.8%	103.5%	177.8%	125.8%
Anti-GFP						

TABLE 5-3 HeLa cells (continued)

Hela-K	RARE	Rb	STAT3	SRE	TRE	P53	Actin
Scramble	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
c-Myc	68.6%	97.2%	85.4%	108.2%	75.4%	61.8%	64.3%
c-Fos	62.9%	99.7%	85.3%	148.1%	108.5%	148.1%	67.7%
c-Jun	76.0%	148.9%	75.8%	128.1%	127.7%	100.2%	106.0%
CREB	39.3%	259.6%	116.5%	8030.8%	134.2%	87.5%	73.8%
E2F	51.1%	151.7%	180.1%	15876.5%	125.0%	109.3%	69.3%
ER	100.5%	102.2%	114.4%	63797.3%	118.0%	82.5%	123.6%
GR	64.8%	133.4%	139.7%	44143.6%	150.1%	63.0%	134.6%
HSF-1	136.9%	252.8%	162.5%	11434.8%	223.5%	75.2%	75.1%
HSF-2	127.3%	227.3%	237.7%	32416.7%	764.1%	41.2%	41.6%
HSF-4	87.4%	128.3%	127.5%	17739.5%	179.4%	103.3%	252.6%
IkBa	130.4%	142.0%	177.4%	16354.2%	149.7%	136.5%	181.9%
NFAT3	88.7%	118.6%	129.4%	18955.4%	87.9%	135.4%	164.5%
NFkB	68.6%	106.5%	299.0%	17733.0%	170.2%	111.2%	242.1%
RARA	70.4%	147.4%	149.7%	42654.8%	94.5%	56.7%	72.9%
RARB1	69.0%	113.7%	84.0%	12200.8%	69.2%	104.5%	190.6%
RARB2	100.9%	126.6%	87.7%	30989.4%	101.4%	195.0%	195.2%
RARG	45.1%	125.5%	65.9%	107.6%	110.2%	172.5%	95.1%
Rb	43.6%	159.6%	86.6%	104.0%	112.3%	410.8%	62.1%
SRF	133.6%	116.0%	65.3%	14027.5%	234.7%	181.5%	33.2%
STAT1a	50.5%	85.2%	52.8%	15856.3%	148.3%	58.2%	121.2%
STAT1b	59.0%	126.3%	82.3%	11458.8%	119.5%	132.0%	217.9%
STAT2	52.0%	110.7%	93.0%	12913.7%	98.6%	278.9%	28.0%
STAT3	74.2%	94.9%	79.5%	13046.1%	154.1%	110.2%	129.5%
TR	108.0%	206.0%	56.7%	13107.4%	157.1%	105.4%	122.7%
p53	98.9%	84.2%	51.6%	12588.8%	152.5%	26.4%	167.7%
Anti-GFP							53.9%

Normalized matrix of the network of HeLa cells are provided as follows:

TABLE 5-4

Hela-K	AP1	PMA	CRE	E2F	ERE	GAS	GRE	HSE	ISRE	Myc	NFAT	NFKB	RARE	Rb	STAT3	SRE	TRE	P53	Actin
Scramble																			
c-Myc	-1	-1	-1	1	0	0	-1	0	1	-1	0	-1	-1	0	0	0	-1	-1	-1
c-Fos	-1	0	-1	0	0	0	-1	0	-1	-1	0	0	-1	0	0	1	0	1	-1
c-Jun	-1	-1	-1	0	0	0	-1	-1	0	-1	0	0	-1	1	-1	1	1	0	0
CREB	-1	0	-1	1	0	0	-1	0	-1	-1	0	1	-1	1	0	1	1	0	-1
E2F	-1	0	-1	0	0	0	-1	0	-1	-1	1	0	-1	1	1	1	1	0	-1
ER	-1	0	-1	0	0	0	-1	0	-1	-1	1	-1	0	0	0	1	0	0	1
GR	-1	0	-1	1	0	0	0	0	-1	-1	1	1	-1	1	1	1	1	-1	1
HSF-1	0	1	-1	0	0	0	-1	0	0	-1	1	1	1	1	1	1	1	-1	-1
HSF-2	-1	1	-1	1	0	0	-1	1	-1	0	1	1	1	1	1	1	1	-1	-1
HSF-4	-1	0	-1	0	0	0	-1	0	-1	0	1	0	0	1	1	1	1	0	1
IkBa	-1	0	-1	1	0	0	0	0	0	0	1	-1	1	1	1	1	1	1	1
NFAT3	-1	0	-1	1	0	0	-1	0	0	-1	1	0	0	0	1	1	0	1	1
NFkB	0	0	-1	1	0	0	-1	0	0	-1	0	0	-1	0	1	1	1	0	1
RARA	0	0	-1	1	0	0	-1	1	0	1	0	0	-1	1	1	1	0	-1	-1
RARB1	0	-1	-1	1	0	0	-1	0	0	-1	0	0	-1	0	0	1	-1	0	1
RARB2	0	-1	-1	1	0	0	0	-1	-1	-1	1	1	0	1	0	1	0	1	1
RARG	-1	-1	-1	0	0	0	-1	0	-1	-1	1	-1	-1	1	-1	0	0	1	0
Rb	-1	-1	-1	1	0	0	-1	0	0	0	1	1	-1	1	0	0	0	1	-1
SRF	-1	-1	-1	1	0	0	-1	0	-1	-1	0	-1	1	0	-1	1	1	1	-1
STAT1a	-1	-1	0	0	0	0	0	0	-1	-1	0	1	-1	0	-1	1	1	-1	1
STAT1b	-1	-1	-1	1	0	0	0	-1	-1	-1	0	1	-1	1	0	1	0	1	1
STAT2	-1	-1	-1	1	0	0	-1	0	0	-1	0	-1	-1	0	0	1	0	1	-1
STAT3	-1	-1	-1	1	0	0	0	0	0	0	0	-1	-1	0	-1	1	1	0	1
TR	-1	-1	-1	1	0	0	-1	0	1	0	0	1	0	1	-1	1	1	1	1
P53	-1	1	-1	1	0	-1	-1	0	-1	0	1	1	0	0	-1	1	1	-1	1
Anti-GFP																			-1

TABLE 6-1 HepG2 cells

HepG2	AP1	PMA	CRE	E2F	ERE	GAS
Scramble	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
c-Myc	72.4%	74.8%	53.6%	113.9%	97.8%	87.4%
c-Fos	89.0%	113.3%	67.5%	114.3%	95.8%	91.1%
c-Jun	97.2%	92.6%	65.1%	117.1%	106.8%	88.4%
CREB	125.7%	128.3%	48.5%	163.4%	93.4%	94.3%
E2F	107.6%	96.9%	56.7%	122.4%	92.3%	98.4%
ER	115.7%	78.6%	54.5%	136.9%	97.0%	98.9%
GR	108.1%	103.2%	48.6%	148.7%	93.7%	103.0%
HSF-1	115.7%	82.6%	54.7%	114.0%	93.2%	114.6%
HSF-2	101.9%	86.8%	64.3%	123.2%	96.5%	93.6%
HSF-4	98.5%	81.3%	66.7%	141.7%	103.6%	108.0%
IkBa	96.6%	61.1%	56.0%	154.0%	101.0%	101.8%
NFAT3	97.6%	143.1%	54.3%	160.8%	101.0%	93.7%
NFkB	85.1%	82.8%	38.2%	129.2%	113.9%	102.2%
RARA	114.0%	104.8%	35.0%	194.0%	104.7%	91.4%
RARB1	90.7%	70.1%	32.6%	142.4%	109.9%	87.4%
RARB2	101.3%	61.5%	72.0%	129.3%	111.0%	89.3%
RARG	90.9%	76.4%	69.2%	127.9%	107.2%	94.7%
Rb	108.6%	71.9%	45.4%	145.7%	101.0%	85.0%
SRF	77.1%	77.1%	53.8%	127.7%	106.3%	86.6%
STAT1a	65.5%	56.7%	86.4%	134.6%	110.1%	89.6%
STAT1b	100.9%	64.6%	70.2%	166.6%	100.2%	86.8%
STAT2	79.1%	40.6%	42.8%	163.0%	97.8%	89.9%
STAT3	167.3%	51.3%	54.4%	132.0%	96.6%	94.0%
TR	67.6%	61.1%	51.8%	134.0%	94.6%	90.9%
p53	94.0%	85.7%	53.1%	170.0%	91.8%	89.3%
Anti-GFP						

TABLE 6-2 HepG2 cells (continuted)

HepG2	GRE	HSE	ISRE	Myc	NFAT	NFKB
Scramble	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
c-Myc	75.7%	98.4%	109.0%	102.1%	82.3%	55.6%
c-Fos	83.0%	108.7%	72.3%	95.9%	86.0%	94.8%
c-Jun	70.5%	107.1%	111.4%	94.7%	81.2%	71.3%
CREB	91.4%	125.9%	73.4%	76.4%	81.8%	100.8%
E2F	78.1%	128.2%	77.0%	69.2%	111.8%	91.9%
ER	76.8%	106.7%	97.4%	66.2%	96.1%	62.3%
GR	111.5%	110.1%	75.0%	60.3%	89.8%	86.6%
HSF-1	71.0%	118.5%	94.8%	57.0%	89.4%	95.0%
HSF-2	73.3%	108.9%	68.3%	62.0%	120.0%	77.2%
HSF-4	77.4%	104.3%	82.1%	57.3%	119.6%	67.4%
IkBa	106.2%	102.3%	76.0%	61.9%	102.1%	64.5%
NFAT3	84.7%	94.2%	97.0%	55.4%	100.0%	109.9%
NFkB	89.1%	95.0%	99.7%	57.6%	94.9%	54.6%
RARA	77.3%	108.5%	104.2%	56.9%	100.8%	62.5%
RARB1	68.6%	96.4%	75.6%	45.3%	91.3%	60.8%
RARB2	112.6%	89.3%	70.7%	48.0%	99.0%	87.9%
RARG	76.8%	94.3%	91.9%	96.2%	104.2%	84.4%
Rb	84.7%	100.5%	91.6%	102.3%	149.8%	131.6%
SRF	63.1%	102.6%	89.4%	119.5%	174.7%	63.2%
STAT1a	79.9%	97.8%	77.7%	122.0%	162.6%	93.7%
STAT1b	72.1%	93.9%	66.9%	116.4%	187.8%	47.3%
STAT2	77.6%	89.5%	69.2%	140.5%	161.2%	83.7%
STAT3	89.2%	119.3%	82.9%	105.1%	118.2%	50.2%
TR	62.8%	92.3%	90.4%	87.2%	89.0%	87.9%
p53	66.1%	95.2%	63.6%	69.1%	92.8%	86.1%
Anti-GFP						

TABLE 6-3 HepG2 cells (continued)

HepG2	RARE	Rb	STAT3	SRE	TRE	P53	Actin
Scramble	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
c-Myc	96.9%	110.4%	83.8%	96.3%	103.5%	81.7%	87.4%
c-Fos	66.8%	525.5%	80.2%	88.4%	127.0%	503.7%	81.3%
c-Jun	59.1%	516.4%	81.6%	74.4%	98.6%	228.0%	108.1%
CREB	46.1%	686.6%	105.6%	63.3%	82.1%	107.9%	132.2%
E2F	59.7%	296.1%	187.0%	54.0%	89.3%	317.2%	75.4%
ER	67.4%	87.7%	105.1%	57.9%	86.7%	192.2%	60.8%
GR	51.4%	169.1%	133.8%	55.7%	85.4%	142.9%	93.9%
HSF-1	59.5%	376.9%	136.0%	47.9%	1198.2%	68.8%	50.0%
HSF-2	77.6%	320.1%	174.8%	48.6%	183.5%	54.9%	33.2%
HSF-4	47.7%	195.9%	120.3%	41.0%	233.3%	95.2%	54.1%
IkBa	65.2%	139.7%	116.1%	39.7%	139.8%	301.1%	48.6%
NFAT3	57.6%	195.5%	136.6%	53.1%	120.8%	310.6%	51.1%
NFkB	53.5%	138.8%	119.9%	44.4%	143.3%	129.4%	53.5%
RARA	60.9%	246.0%	105.4%	61.5%	112.5%	89.1%	73.1%
RARB1	71.6%	273.6%	57.7%	38.4%	120.2%	135.3%	202.0%
RARB2	50.0%	137.0%	69.0%	55.8%	142.7%	74.2%	149.0%
RARG	107.9%	258.3%	53.0%	83.2%	103.5%	132.3%	94.5%
Rb	80.3%	395.2%	92.4%	70.0%	98.8%	649.6%	127.7%
SRF	79.4%	220.9%	63.2%	55.1%	128.0%	126.2%	66.3%
STAT1a	72.3%	136.5%	39.0%	45.8%	108.7%	173.3%	100.2%
STAT1b	71.6%	150.9%	40.8%	38.1%	111.2%	156.6%	363.0%
STAT2	59.6%	104.2%	68.3%	39.8%	90.6%	116.5%	82.3%
STAT3	120.4%	144.1%	63.6%	32.6%	106.9%	86.6%	143.9%
TR	81.7%	113.6%	53.6%	26.5%	86.8%	94.3%	199.6%
p53	99.2%	181.7%	52.2%	33.2%	294.4%	26.5%	191.9%
Anti-GFP							45.7%

Normalized matrix of the network of HepG2 cells are provided as follows:

TABLE 6-4

HepG2	AP1	PMA	CRE	E2F	ERE	GAS	GRE	HSE	ISRE	Myc	NFAT	NFKB	RARE	Rb	STAT3	SRE	TRE	P53	Action
Scramble																			
c-Myc	-1	-1	-1	0	0	0	-1	0	0	0	0	-1	0	0	0	0	0	0	0
c-Fos	0	0	-1	0	0	0	0	0	-1	0	0	0	-1	1	0	0	1	1	0
c-Jun	0	0	-1	0	0	0	-1	0	0	0	0	-1	-1	1	0	-1	0	1	0
CREB	1	1	-1	1	0	0	0	1	-1	-1	0	0	-1	1	0	-1	0	0	1
E2F	0	0	-1	1	0	0	-1	1	-1	-1	0	0	-1	1	1	-1	0	1	-1
ER	0	-1	-1	1	0	0	-1	0	0	-1	0	-1	-1	0	0	-1	0	1	-1
GR	0	0	-1	1	0	0	0	0	-1	-1	0	0	-1	1	1	-1	0	1	0
HSF-1	0	0	-1	0	0	0	-1	0	0	-1	0	0	-1	1	1	-1	1	-1	-1
HSF-2	0	0	-1	1	0	0	-1	0	-1	-1	1	-1	-1	1	1	-1	1	-1	-1
HSF-4	0	0	-1	1	0	0	-1	0	0	-1	0	-1	-1	1	1	-1	1	0	-1
IkBa	0	-1	-1	1	0	0	0	0	-1	-1	0	-1	-1	1	0	-1	1	1	-1
NFAT3	0	1	-1	1	0	0	0	0	0	-1	0	0	-1	1	1	-1	1	1	-1
NFkB	0	0	-1	1	0	0	0	0	0	-1	0	-1	-1	1	0	-1	1	1	-1
RARA	0	0	-1	1	0	0	-1	0	0	-1	0	-1	-1	1	0	-1	0	0	-1
RARB1	0	-1	-1	1	0	0	-1	0	-1	-1	0	-1	-1	1	-1	-1	1	1	1
RARB2	0	-1	-1	1	0	0	0	0	-1	-1	0	0	-1	1	-1	-1	1	-1	1
RARG	0	-1	-1	1	0	0	-1	0	0	0	0	0	0	1	-1	0	0	1	0
Rb	0	-1	-1	1	0	0	0	0	0	0	1	1	0	1	0	-1	0	1	1
SRF	-1	-1	-1	1	0	0	-1	0	0	0	1	-1	-1	1	-1	-1	1	1	-1
STAT1a	-1	-1	0	1	0	0	-1	0	-1	1	1	0	-1	1	-1	-1	0	1	0
STAT1b	0	-1	-1	1	0	0	-1	0	-1	0	1	-1	-1	1	-1	-1	0	1	1
STAT2	-1	-1	-1	1	0	0	-1	0	-1	1	1	0	-1	0	-1	-1	0	0	0
STAT3	1	-1	-1	1	0	0	0	0	0	0	0	-1	1	1	-1	-1	0	0	1
TR	-1	-1	-1	1	0	0	-1	0	0	0	0	0	0	0	-1	-1	0	0	1
P53	0	0	-1	1	0	0	-1	0	-1	-1	0	0	0	1	-1	-1	1	-1	1
Anti-GFP																			-1

Exemplary results were summarized in Figures **5** and **7**.

As shown in Figures **5** and **7**, when RNAi was used, the expression of each gene was specifically suppressed in a variety of manners. Thus, it was demonstrated that an array having a plurality of genetic material, which are applicable to RNAi, can be realized and analysis using set theory can be performed for the effect of RNAi on cells.

(Example 5: Mathematical analysis using set theory)

Next, analysis using set theory was produced based on data obtained using the techniques described in Examples 2-4. Here, HeLa cells and HepG2 cell were used for analysis. For HeLa and HepG2 cells, transcriptional factors SRE, TRE, E2F, p53, Rb, Actin, NFAT, NFkB, STAT3, RARE, PMA, ISRA, HSE, Myc, AP1, GAS, ERE, GRE and CRE were used.

(Mathematical analysis technique)

A mathematical analysis technique used herein is shown in Figures **1** and **9**. Figure **1** shows a schematic diagram of analysis according to one embodiment of the present invention. A and B refer to functional reporters, which can be regarded as sets, reflecting functions of a biological entity such as a cell. Perturbation agents used are located within set A, within set B, within the intersection of set A and set B, outside of set A or set B. i) shows a case where there are no perturbation agents for function A (set A) and function B (set B). In i), function A and B are located under different perturbation agents. ii) shows a case where there are perturbation

agents for functions A and B, and all the perturbation agents to be included into function B are also included in function A. In ii), function B is located downstream of function A. iii) shows a case where there are common perturbation agents, but some are included only in function A and some are included only in function B. In iii), functions A and B are located under a common perturbation agent in parallel. iv) and v) show cases where three functions are involved. These can be explained in a similar manner as when two functions are used. In principle, integration of all combination of two functions will produce the global network of all functions. Figure **9** shows a schematic flow chart for an exemplary embodiment of the present invention. This flow chart can be conducted in a computer.

An assay was conducted using the reporters for the siRNA under control conditions (cells, supplement factors, culture conditions, etc.). For the following analysis, conditions as described in Example 4 were used.

The matrix used for calculation of a combination matrix of functional reporters and siRNA shown in Figure **11**. Each column represents a column and row corresponding to an Excel(trademark) sheet.

The actually used transfection array is shown in Figure **12**. Figure **12** shows HeLa array scanned images (16-bit tiff image). Each mixture solution was printed as in the lower panel. After seeding cells, an array scanner was used for obtaining images (see upper panel).

Exemplary results are summarized in Figure **5** and **7**. It was demonstrated that when compared only to DNA

in this manner, most of the transcription factors were induced when inducing agents were added.

Next, the activity of the siRNAs was classified into three groups including +, 0 and -. The results can be expressed using a matrix. The effects were analyzed in accordance with the set theory using scheme as shown in Figure **1**. In this case, effect of siRNA on parameters such as cellular formation, neurite growth, gene expression, and the like were compared. The measurement can be conducted at any time after a certain period of time sufficient for observing the effect of interest. For example, in this example, 1 hour and 6 hours were selected.

The results are shown in Figures **6** and **8**. As shown in Figure **6**, in HeLa cells, SRE is located most downstream of the network. Above SRE, p53, E2F, Rb and TRE are located. Actin is located above E2F and Rb, and Rb has actin, NFAT and STAT3 thereabove. NFkB is upstream of NFAT, and has RARE thereabove. STAT3 has AP1 and HSE thereabove. AP1 is located upstream of PMA and ISRE. CRE is located most upstream of the network of the parameters used, and has GRE, RARE, AP1 and Myc thereunder. GAS and ERE have no related parameter and therefore are independent in the network analyzed.

As shown in Figure **8**, in HepG2 cells, CRE is located most upstream of the network analyzed, and has GRE, ISIR and SRE thereunder. SRE has PMA, STAT3 and RARE thereunder. Rb and E2F are located downstream of HSE, actin, TRE, p53, NFAT and STAT3. STAT3 is located downstream of SRE. PMA is located upstream of AP1, which is located upstream of HSE. NFkB and Myc are located downstream of RARE.

ERE and GAS have no related parameter and therefore independent in the network analyzed.

For confirmatory experiments, effects of siRNA for CRE for HeLa and HepG2 cells were analyzed. The results are shown by arrows. Arrows show the transcriptional factors which had inhibitory effects by the addition of siRNA for CRE, therefore suggest that these factors are located very close to the CRE in the network.

In conclusion, the present invention in which a network of a biological entity such as a cell, can be correctly analyzed by applying set theory. Set theory has never been used to analyze biological functions, in particular, a network thereof. Therefore, it is a significant result to find that set theory can be used for correctly construct network relationships of parameters of a biological entity.

(Example 6 : MicroRNA)

Next, nucleic acid molecules encoding microRNA (miRNA) were used to produce cellular networks. As miRNA, miRNA-23 was used. A protocol as used in the above-described examples was used.

MicroRNA is a non-coding RNA of 18 to 25 bases (not translated into protein), which was first found in nematodes and then revealed to be preserved widely in animals and plants. It has been reported that miRNA is involved in the development and differentiation of nematodes and plants. It has been suggested that animals have a similar process. To date 200 or more miRNAs have been reported.

H. Kawasaki, K. Taira, Nature 423, 838-842(2003) reported that the target of miRNA-23 is the Hes1 gene (Hes1 is a repressor transcription factor which suppress the differentiation of stem cells into neurons). miRNA-23 is present in the vicinity of the translation terminating codon for this gene, and forms incomplete complementary base pairing (77%). Such incomplete complementary base pairing is important for the function of miRNA. Indeed, it has already been found that synthetic miRNA-23, which is introduced into NT2 human embryonic tumor cells, can suppress the expression of Hes1. This activity can be knocked out by using siRNA or the like.

According to the above-described principle, miRNA is produced.

It can be demonstrated that such a system can be used to analyze by set theory in a similar manner as described above for miRNA.

(Example 7: Biological system-ribozyme)

Next, a ribozyme was used to produce cellular networks. A ribozyme as described in 305 YAKUGAKU ZASSHI [Journal of Phamacology] 123(5) 305-313 (2003) was herein used. A protocol as described in the above mentioned Examples was used.

Ribozymes were discovered by observing that the group I intron of tetrahymena catalyzes site specific cleavage and binding reactions of RNA chains. A ribozyme refers to RNA having such an enzymatic activity. Examples of ribozymes include hammerhead ribozymes, hairpin ribozymes, and the like.

It can be demonstrated that such a system can be used to analyze by set theory in a similar manner as described above for ribozymes.

(Example 8: Drug screening)

Next, a compound library is used for screening a drug. A cell, which is a model of a disease such as a cancer cell, normal cell, and stem cell, is used for screening. A compound library containing 1,000 compounds is used as perturbation agents. Parameters such as transcriptional factors, regulatory genes, structural genes, cellular markers, cell surface markers, cell shapes, organelle shapes, cell mobility, enzyme activities, metabolite concentrations, and localization of cellular components are selected. Exemplary parameters are: cancer drugs, drugs for diabetes, and the like.

These parameters are measured in an appropriate manner for each parameter, and information collected thereon. Collected information is analyzed based on set theory as described above.

Analyzing the results to allow elucidating which compounds are likely to be a leading candidate for the drug, thereby used for drug screening.

Accordingly, the present invention is useful for identifying a novel drug.

(Example 9: Identification of biomarkers)

The present invention can be used for identification of biomarkers. Biomarkers are generally

indicators for quantifying or digitizing biological information. Such biomarkers include blood glucose level as a biomarker for diabetes, adiponectin, TNF-alpha, PAI-1 and the like, which are gradually used in clinic. Digitization of biological information can be interpreted to specification of effects of perturbation agents on a cell, and characteristic network structure in a variety of cells (cancers, normal cells, stem cells and the like).

In this regard, siRNA can be used as a target for drug discovery, and the identified siRNA may used for developing drugs.

Therefore, the present Example uses a variety of biomarkers as functional reporters of perturbation agents such as siRNA and the like. Specific functional reporters identified in the present Example may be used as biomarkers for the specific cell of interest.

(Example 10: Analysis of adverse effect and diagnosis of cellular functions)

The present invention may also be used for analyzing an adverse effect of a drug, and/or diagnosing a cell or other biological entity including diagnosis of infectious diseases. The present invention can also be used for analyzing cellular pathways.

In this example, changes in network structures by perturbation agents are sorted in a catalog format to provide an evaluation standard for distinguishing normal and abnormal cells. Further, by obtaining network structures characterizing a cellular function, a method of evaluating a cellular function can be conducted.

For example, when administering a drug to a variety of normal cells from a variety of organs, comparing with a normal network structure (without administering the drug) allows evaluation of effects including adverse effects of the drug on a biological entity such as a cell. Further, network database including catalogs of network structures, information of known databases such as KEGG signaling gateways and the like, can be used for characterizing cellular functions. Mapping of perturbation agents having effects on cellular functions on a map created by the database allow analysis of pathway characterizing cellular functions.

(Example 11: Biological evaluation of compounds)

Perturbation agents are not only those having a single target, but also those having a number of targets, and therefore compounds used in drug screening and/or siRNAs can be combined for evaluating biological effects. When using these compounds and/or siRNAs, it should be considered that these agents have a plurality of targets and therefor have effects on a plurality of functions constituting a network. Effects on such a network structure obtained by the present example, are also useful for analyzing effects of compounds on a biological entity.

(Example 12: Rational Approach to analyze functional roles of tyrosine kinases in neuritegenesis)

In the present example, human neuroblastoma, SHSY5Y was used for observing the differentiation to neuron like cells based on the information obtained from the method of the present invention.

In the presence of retinoic acid, SHSY5Y cells express choline acetyltransferase and extend the neurites thereof. In the presence of NGF, the cells express tyeorin hydroxylase and extend the neurite thereof.

Therefore, tyrosine kinases play an important role as a valve in the signaling pathway for cellular events.

In the present Example, it is studies which tyrosine kinase amongst a huge number of tyrosine kinases is responsible for choline acetyltransferase induction, tyrosine hydroxylase expression and neurite extention events.

(Experimental)

(Materials and Methods)

Cell used: SH-SY5Y (available from ATCC No: CRL-2266)

Reagents used:

Retinoic acid (all-trans available from Sigma-Aldrich, Prod. No. R 2625)

NGF (available from Sigma 2.5S #N-6009)

Eagle's minimum essential medium, foetal bovine serum, glutamine, and penicillin/streptomycin were purchased from BioWhittaker, Walkersville, MD.

(Cell culture)

Cell culture

Human neuroblastoma (SHSY5Y) cells were maintained in Eagle's minimum essential medium (EMEM) supplemented with 10% (v/v) foetal bovine serum (FBS), 2% (v/v) glutamine and 1% (v/v) penicillin/streptomycin (10% medium), hereafter referred to as growth medium. Cells were incubated at 37°C

in a humidified atmosphere of 5% carbon dioxide.

(Differentiation)

Differentiation has been performed according to Yamada Y. et al., Neurosci Lett. 2004 Jun 24; 364(1):11-15. Briefly, 100 ng/ml of NGF or 10 ug of retinoic acid was added to the culture medium differentiate the SHSY5Y cells. Usually, when retinoic acid is added, the cell differentiates into cholinergic neuron-like cell as exemplified in Figure **13**. When NGF is added, the cell differentiates into dopaminergic neuron-like cells as exemplified in Figure **13**.

(Transfection microarray)

Transfection microarray experiments were performed according to the Examples described hereinabove.

(On-chip image-based quantification of neurite outgrowth inhibition by the siRNAs targeted tyrosine kinases)

In order to analyze various types of kinases, siRNA specific to the tyrosine kinases have been used. siRNA were prepared according to the Examples described hereinabove.

Neurite growth was measured by means of image-based quantification frequency of neurite outgrowth according to Neurosci Lett. 2005 Apr 11;378(1):40-3. Epub 2005 Jan 7. In Brief, the protocols are as follows.

Rat pheochromocytoma (PC12) cells (Tischler, A. S., and L. A. Greene. 1975. Nerve growth factor-induced process formation by cultured rat pheochromocytoma cells.

Nature (Lond.). 258: 341-342.) were grown in monolayer culture in DME with 4.5 g/l glucose supplemented with 10% heat-inactivated horse serum, 5% newborn calf serum, glutamine (2 mM), and penicillin/streptomycin (100 U/ml) and were carrried for no more than 10 passages. PC12 cells were "primed" with NGF as described (Greene, L. A. 1977. A quantitative bioassay for nerve growth factor (NGF) activity employing a clonal pheochromocytoma cell line. Brain Res. 133: 350-353; Greene, L. A., D. E. Burstein, and M. M. Black. 1982. The role of transcription-dependent priming in nerve growth factor promoted neurite outgrowth. Dev. Biol. 91:305-316). For studies on process outgrowth, NGF-primed PC12 cells were passaged and mechanically divested of their neurites by trituration through a narrow bore 9-inch pasteur pipet. After washing three times in growth medium, cells were resuspended at a concentration of 10^5 cells/ml in growth medium with or without 50 ng/ml NGF, and 100 ul of this cell suspension were added per welt (0.28 cm^2 surface area).

Fixation and staining with fluorescein labeled antibody to neurofilament 100 protein or DM1A antibody to tubulin (4 hr) have been conducted. Image acquisition using IN Cell Analyzer 1000 (Amersham Bioscicences); 3 min / plate was conducted.

(Acquisition)

Images were acquired at 1392 x 1040 pixels, 12 bit precision, 400 msec exposure. Total acquisition time (move/focus/acquire) was about 3 min for an entire 96 well plate. Both epifluorescence (4X and 10X objectives) and DIC (10X) optics were used.

(Manual scoring)

Two skilled technicians traced neurites and cell bodies using MCID™ Elite image analysis software. A minimum length parameter was combined with visual evaluation to distinguish neurites from other structures.

(Automated Scoring)

The machine was given a set of scoring parameters (minimum and maximum neurite width, minimum neurite length, mean cell size per condition), defined prior to the analysis. The measurements required for the predefinition process took about an hour to obtain.

(Results)

The results are shown in Figure **14**. Figure **14** shows graphs of total neurite length/no. nucleus vs. tyrosine kinase targeted siRNA (85 types were used).

(Rational approach to analyze the functional roles of tyrosine kinases in neuritegenesis)

Overview of the rational approach to analyze the functional roles of tyrosine kinases in neuritegenesis is shown in Figure **15**. As in Figure **15A** (upper left), the set in which siRNAs inhibited neurite extension in the presence of retinoic acid (RA; hereinafter the RA set), and the set in which siRNAs inhibited neurite extension in the presence of NGF (hereinafter the NGF set) are separately (independently) present, then the two pathways triggered by choline acetyltransferase (differentiation into cholinergic neuron-like cell) and by tyrosine hydroxylase (differentiation into dopaminergic neuron-like cell) are independent. Cholinergic neuron-like cells were identified by using anti-choline acetyltransferase

antibody, and dopaminergic neuron-like cells were identified by using anti-tyrosine hydroxylase antibody, both of which are available from Clontech.

If the RA set and the NGF set have overlapping members, then the pathway is interpreted to be as shown in Figure **15B**. As shown, RA signal and NGF signal are integrated into the same pathway into the neurite direction.

If the NGF set is encompassed by the RA set as shown in Figure **15C**, then the pathway is interpreted such that the NGF signaling (tyrosine hydrophosphate) is located upstream of the RA signaling (choline acetyltransferase) and eventually results in neurite growth.

If the RA set is encompassed by the NGF set as shown in Figure **15D**, then the pathway is interpreted such that the RA signaling (choline acetyltransferase) is located upstream of the NGF signaling (tyrosine hydrophosphate) and eventually results in neurite growth.

By conducting above-mentioned analysis, we have elucidated a number of kinases by rational relation from the comprehensive data of the cell-based siRNA assay (Figure **16**). Figure **16** shows that siRNAs against FGFR1, FGFR2 and KDR inhibited neurite extension in the presence of RA, but not in the presence of NGF. EPHB1, EPHB2, EPHB3, NTRK2, PDGFRA, and INSR inhibited neurite extension in the presence of NGF but not in the presence of RA. Furthermore, siRNAs against EGFR, EPHA2, EPHA2, KIT and RET inhibited neurite extension in the present of both RA and NGF.

(Knockdown of RTK proteins)

In order to further analyze the functions of tyrosine kinases, we further conducted knockdown experiments using a variety of siRNA against tyrosine kinases. siRNA's were designed according to the protocols as described hereinabove or according to the common general knowledge of the art. Figure **17** shows the results of EGFR-siRNA, EPHA2-siRNA, EPHA3-siRNA, #075-siRNA, KIT-siRNA, #054-siRNA, RET-siRNA and #006-siRNA. The entire nucleotide sequences of EGFR, EPHA2, EPHA3, #075, KIT, #054, RET and #006 are shown in the Sequence Listings (SEQ ID NOs: 78, 80, 82, 84, 86, 88, 90 and 92, respectively). The entire amino acid sequences of EGFR, EPHA2, EPHA3, #075, KIT, #054, RET and #006 are shown in the Sequence Listings (SEQ ID NOs: 79, 81, 83, 85, 87, 89, 91 and 93, respectively)

Neurite extension in the presence of the specific ligands of the receptor tyrosine kinases was also examined. FBS without specific agents was used as a control. RA-FBS, NGF, Ephrin B2, BDNF, PDGF, insulin, VEGF, FGF1, FGF2, EGF, SCF, EphrinA3, GDNF and Neurturin were examined. Figure **18** shows neurite bearing cell percentages are shown for each agent. RA subset include KDR, FGFR1 and FGFR2, which receptors correspond to ligands VEGF, FGF1 and FGF2, respectively. NGF subset include EPHB1, EPHB2, EPHB3, NTRK2, PDFGRA and INSR, which receptors correspond to ligands EphrinB2, EphrinB2, EphrinB2, BDNF, PDGF and insulin. The intersection subset of RA and NGF subsets encompasses EGFR, KIT, EPHA2, EPHA3 and RET, which receptors correspond to ligands EGF, SCF, EpherinA3, EPhrinA3 and GFNF/Neurturin.

Next, the marker enzyme expression in the presence of each ligand of the receptor tyrosine kinase has

been studied. First, expression of each ligand enhanced by ChAT, TH and beta-actin (control) was analyzed for the ligands described above. The intensity of expression of each ligand is shown above (wet data; Figure **19**, upper panels), and in relative expression level (Figure **19**, lower panels). As shown, RA is strongly correlated with VEGF, FGF1 and FGF2, which indicates that these ligands are cholinergic, whereas NGF is strongly correlated with NGF, Ephrin B2, BDNF, PDGF, insulin and Pehrin A3, which indicates that these ligands are dopaminergic.

In summary, as shown in Figure **20**, which shows comparison of the rational relation and biological results, a variety of kinases are classified into subsets of biological significance based on the set theory analysis of the present invention. Specifically, FGFR1 and FGFR2 are classified into ones located upstream of RA signaling pathway before integration. EPHB1, EPHB2, EPHB3, NTRK2, PDGFRA, and INSR are classified into ones located upstream of NGF signaling pathway. EGFR, KIT and RET are classified into ones located downstream of the pathways after integration before proceeding to the neurite extension.

Although certain preferred embodiments have been described herein, it is not intended that such embodiments be construed as limitations on the scope of the invention except as set forth in the appended claims. Various other modifications and equivalents will be apparent to and can be readily made by those skilled in the art, after reading the description herein, without departing from the scope and spirit of this invention. All patents, published patent applications and publications cited herein are incorporated by reference as if set forth

fully herein.

INDUSTRIAL APPLICABILITY

According to the present invention, it is possible to determine the state of cells by observing a surprisingly small number of factors. Therefore, the present invention is applicable to diagnosis, prevention, and treatment. The present invention is also applicable to the fields of food, cosmetics, agriculture, environmental engineering, and the like.

Claims

1. A method for analyzing a network of biological functions in a cell, comprising the steps of:

A) subjecting a cell to at least one RNAi agent;

B) obtaining information on at least two functional reporters in said cell, wherein the functional reporters reflect a biological function and are selected from the group consisting of transcriptional factors, regulatory genes, structural genes, cellular markers, cell surface markers, cell shapes, organelle shapes, cell mobility, enzyme activities, metabolite concentrations, and localization of cellular components; and

C) subjecting the obtained information to set theory processing to calculate a relationship between the functional reporters to generate a network relationship of the biological functions;

wherein said set theory processing comprises:

classifying two specific functional reporters of said at least two functional reporters into a relationship selected from the group consisting of

a) independent;

b) inclusion; and

c) intersection,

wherein when it is determined to be independent, the two specific functional reporters are determined to have no relationship in the network; when it is determined to be inclusion, one of the two specific functional reporters is determined to be included in the other of the two specific functional reporters and is located downstream of the other;

when it is determined to be intersection,

the two specific functional reporters are determined to be located downstream, branched from another common function.

2. The method according to Claim 1, wherein said RNAi agent comprises an siRNA capable of specifically regulating a function of said functional reporter.

3. The method according to Claim 1, wherein said functional reporter is capable of transmitting a measurable signal.

4. The method according to Claim 1, wherein the set theory processing further comprises the step of mapping the absence or presence of a response by said RNAi agent per said functional reporter.

5. The method according to Claim 1, wherein said RNAi agents are prepared with the number sufficient for equally targeting an intracellular pathway.

6. The method according to Claim 1, wherein the information on at least two functional reporters is based on an effect of said RNAi agent after a desired time.

7. The method according to Claim 1, wherein said effect is classified into the following three groups in terms of a threshold value: positive effect = +; no effect= 0; and negative effect = -.

8. A method for analyzing a network of biological functions in a cell, comprising the steps of:

A) subjecting a cell to at least one RNAi agent;

B) obtaining information on at least two functional reporters in said cell, wherein the functional reporters reflect a biological function and are selected from the group consisting of transcriptional factors, regulatory genes, structural genes, cellular markers, cell surface markers, cell shapes, organelle shapes, cell mobility, enzyme activities, metabolite concentrations, and localization of cellular components; and

C) subjecting the obtained information to set theory processing to calculate a relationship between the functional reporters to generate a network relationship of biological functions;

wherein the information on at least two functional reporters is based on an effect of said RNAi agent after a desired time;

wherein the set theory processing comprises:

a) classifying the information into three categories by comparing the effect with a threshold value for the functional reporter and classifying into the following three groups: positive effect = +; no effect= 0; and negative effect = -;

b) determining if two out of the functional reporters have a common RNAi agent, wherein the common agent has the same type of effect, and if there is no such a common RNAi agent, then the two functions corresponding to the two functional reporters are located under different RNAi agents and if there is such a common RNAi agent, then the following step c) is conducted:

c) determining if the RNAi agent set for one function of the two functions is completely included into the RNAi agent set for the other function of the two functions, and if this is the case, then one function having the bigger set is located downstream of the other function having the smaller set, and if this is not the case, then the two functions are located in parallel under the same RNAi agents;

d) determining if all combinations of the functional reporters are investigated, if this is the case, then integrate all the relationships of functions to a present global RNAi effects network, and if this is not the case then repeat the steps a) to c).

9. The method according to Claim 8, wherein said three groups are classified into +1, 0 and -1.

10. The method according to Claim 9, wherein said steps of a) to c) are calculated by producing M x N matrix, wherein M refers to the number of functional reporters and N refers to the number of RNAi agents.

11. The method according to Claim 1 or 8, further comprising analyzing the generated network by conducting an actual biological experiment.

12. The method according to Claim 11, wherein said step of analyzing comprises the use of a regulation agent specific to the function.

13. The method according to Claim 12, wherein the agent is an siRNA.

14. The method according to Claim 1 or 8, wherein said network comprises a signal transduction pathway and a cellular pathway.

15. The method according to Claim 1 or 8, wherein said network is used for a use selected from the group consisting of identification of a biomarker, analysis of a drug target, analysis of a side effect, diagnosis of a cellular function, analysis of a cellular pathway, evaluation of a biological effect of a compound, and diagnosis of an infectious disease.

16. A system for analyzing a network of biological functions in a cell, comprising:

A) at least one RNAi agent for a cell;

B) means for obtaining information on at least two functional reporters in said cell, wherein the functional reporters reflect a biological function and are selected from the group consisting of transcriptional factors, regulatory genes, structural genes, cellular markers, cell surface markers, cell shapes, organelle shapes, cell mobility, enzyme activities, metabolite concentrations, and localization of cellular components; and

C) means for subjecting the obtained information to set theory processing to calculate a relationship between the functional reporters to generate a network relationship of the biological functions.

wherein said theory processing comprises:

classifying two specific functional reporters of said at least two functional reporters into a relationship selected from the group consisting of

a) independent;

b) inclusion; and

c) intersection;

wherein when it is determined to be independent, the two specific functional reporters are determined to have no relationships in the network;

when it is determined to be inclusion, one of the two specific functional reporters is determined to be included in the other of the two specific functional reporters and is located downstream of the other;

when it is determined to be intersection, the two specific functional reporters are determined that to be located downstream, branched from another common function.

17. The system according to Claim 16, wherein said RNAi agent comprises an siRNA capable of specifically regulating a function of said functional reporter.

18. The system according to Claim 16, wherein said functional reporter is capable of transmitting a measurable signal.

19. The system according to Claim 16, wherein said functional reporter is selected from the group consisting of transcriptional factors, structural genes, cellular markers, cell surface markers cell shapes, organelle shapes, cell mobility, enzyme activities, metabolite concentrations, and localization of cellular components.

20. The system according to Claim 16, wherein the set theory processing comprises the step of mapping the absence or presence of a response by said RNAi agent per said functional reporter.

21. The system according to Claim 16, wherein said RNAi are prepared with the number sufficient for equally targeting an intracellular pathway.

22. The system according to Claim 18, wherein said means for obtaining information comprises means for obtaining the information on at least two functional reporters is based on an effect of said RNAi agent after a desired time.

23. The system according to Claim 16, wherein said effect is classified into the following three groups in terms of a threshold value: positive effect = +; no effect= 0; and negative effect = -.

24. A system for analyzing a network of biological functions in a cell, comprising:

A) at least one RNAi agent for a cell;

B) means for obtaining information on at least two

functional reporters in said cell, wherein the functional reporters reflect a biological function and are selected from the group consisting of transcriptional factors, regulatory genes, cellular markers, cell surface markers, cell shapes, organelle shapes, cell mobility, enzyme activities, metabolite concentrations, and localization of cellular components; and

C) means for subjecting the obtained information to set theory processing to calculate a relationship between the functional reporters to generate a network relationship of the biological functions;

wherein the information on at least two functional reporters is based on an effect of said RNAi agent after a desired time;

wherein the means for subjecting the obtained information to set theory processing comprises:

a) means for classifying the information into three categories by comparing the effect with a threshold value for the functional reporter and classifying into the following three groups: positive effect = +; no effect= 0; and negative effect = -;

b) means for determining if two out of the functional reporters have common RNAi agent, wherein the common RNAi agent has the same type of effect, and if there is no such common RNAi agent, then the two functions corresponding to the two functional reporters are located under different RNAi agents and if there is such a common RNAi agent, then the following step c) is conducted:

c) means for determining if the RNAi agent set for one function of the two functions is completely included into the RNAi agent set for the other function of the two functions, and if this is the case, then one function

having the bigger set is located downstream of the other function having the smaller set, and if this is not the case, then the two functions are located in parallel under the same RNAi agents;

d) means for determining if all combinations of the functional reporters are investigated, if this is the case, then integrate all the relationships of functions to a present global RNAi effects network, and if this is not the case then repeat the steps conducted by the means a) to c).

25. The system according to Claim 24, wherein said three groups are classified into +1, 0 and -1.

26. The system according to Claim 24, wherein said means of a) to c) are conducted by producing M x N matrix, wherein M refers to the number of functional reporters and N refers to the number of RNAi agents.

27. The system according to Claim 16 or 24, further comprising means for analyzing the generated network by conducting an actual biological experiment.

28. The system according to Claim 27, wherein said means for analyzing comprises a regulation agent specific to the function.

29. The system according to Claim 28, wherein the agent is an siRNA.

30. The system according to Claim 16 or 24, wherein said network comprises a signal transduction pathway.

31. The system according to Claim 16 or 24, wherein said network is used for a use selected from the group consisting of identification of a biomarker, analysis of a drug target, analysis of a side effect, diagnosis of a cellular function, analysis of a cellular pathway, evaluation of a biological effect of a compound, and diagnosis of an infectious disease.

32. A computer program for implementing in a computer, a method for analyzing a network of biological functions in a cell according to claim 1 or 8.

33. A storage medium comprising a computer program for implementing in a computer, a method for analyzing a network of biological functions in a cell according to claim 1 or 8.

34. A transmission medium comprising a computer program for implementing in a computer, a method for analyzing a network of biological functions in a cell according to claim 1 or 8.

SEQUENCE LISTING

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<212> PRT
<213> Homo sapiens

<400> 6

Met Thr Ala Lys Met Glu Thr Thr Phe Tyr Asp Asp Ala Leu Asn Ala
1 5 10 15

Ser Phe Leu Pro Ser Glu Ser Gly Pro Tyr Gly Tyr Ser Asn Pro Lys
20 25 30

Ile Leu Lys Gln Ser Met Thr Leu Asn Leu Ala Asp Pro Val Gly Ser
35 40 45

Leu Lys Pro His Leu Arg Ala Lys Asn Ser Asp Leu Leu Thr Ser Pro
50 55 60

Asp Val Gly Leu Leu Lys Leu Ala Ser Pro Glu Leu Glu Arg Leu Ile
65 70 75 80

Ile Gln Ser Ser Asn Gly His Ile Thr Thr Thr Pro Thr Pro Thr Gln
85 90 95

Phe Leu Cys Pro Lys Asn Val Thr Asp Glu Gln Glu Gly Phe Ala Glu

100 105 110

Gly Phe Val Arg Ala Leu Ala Glu Leu His Ser Gln Asn Thr Leu Pro
115 120 125

Ser Val Thr Ser Ala Ala Gln Pro Val Asn Gly Ala Gly Met Val Ala
130 135 140

Pro Ala Val Ala Ser Val Ala Gly Gly Ser Gly Ser Gly Gly Phe Ser
145 150 155 160

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

Asn Pro Gly Ala Leu Ser Ser Gly Gly Gly Ala Pro Ser Tyr Gly Ala
180 185 190

Ala Gly Leu Ala Phe Pro Ala Gln Pro Gln Gln Gln Gln Gln Pro Pro
195 200 205

His His Leu Pro Gln Gln Met Pro Val Gln His Pro Arg Leu Gln Ala
210 215 220

Leu Lys Glu Glu Pro Gln Thr Val Pro Glu Met Pro Gly Glu Thr Pro
225 230 235 240

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

Arg Lys Arg Met Arg Asn Arg Ile Ala Ala Ser Lys Cys Arg Lys Arg
260 265 270

Lys Leu Glu Arg Ile Ala Arg Leu Glu Glu Lys Val Lys Thr Leu Lys
275 280 285

Ala Gln Asn Ser Glu Leu Ala Ser Thr Ala Asn Met Leu Arg Glu Gln
290 295 300

Val Ala Gln Leu Lys Gln Lys Val Met Asn His Val Asn Ser Gly Cys
305 310 315 320

Gln Leu Met Leu Thr Gln Gln Leu Gln Thr Phe
325 330

<210> 7
<211> 2454
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (117)..(1100)

<400> 7
cgcggcggag gtgtagtttg acgcggtgtg ttacgtgggg gagagaataa aactccagcg 60

agatccgggc cgtgaacgaa agcagtgacg gaggagcttg taccaccggt aactaa atg 119
Met
1

acc atg gaa tct gga gcc gag aac cag cag agt gga gat gca gct gta 167
Thr Met Glu Ser Gly Ala Glu Asn Gln Gln Ser Gly Asp Ala Ala Val
5 10 15

aca gaa gct gaa aac caa caa atg aca gtt caa gcc cag cca cag att 215
Thr Glu Ala Glu Asn Gln Gln Met Thr Val Gln Ala Gln Pro Gln Ile
20 25 30

gcc aca tta gcc cag gta tct atg cca gca gct cat gca aca tca tct 263
Ala Thr Leu Ala Gln Val Ser Met Pro Ala Ala His Ala Thr Ser Ser
35 40 45

gct ccc acc gta act cta gta cag ctg ccc aat ggg cag aca gtt caa 311
Ala Pro Thr Val Thr Leu Val Gln Leu Pro Asn Gly Gln Thr Val Gln
50 55 60 65

gtc cat gga gtc att cag gcg gcc cag cca tca gtt att cag tct cca 359
Val His Gly Val Ile Gln Ala Ala Gln Pro Ser Val Ile Gln Ser Pro
70 75 80

caa gtc caa aca gtt cag att tca act att gca gaa agt gaa gat tca 407
Gln Val Gln Thr Val Gln Ile Ser Thr Ile Ala Glu Ser Glu Asp Ser
85 90 95

cag gag tca gtg gat agt gta act gat tcc caa aag cga agg gaa att 455
Gln Glu Ser Val Asp Ser Val Thr Asp Ser Gln Lys Arg Arg Glu Ile
100 105 110

ctt tca agg agg cct tcc tac agg aaa att ttg aat gac tta tct tct 503
Leu Ser Arg Arg Pro Ser Tyr Arg Lys Ile Leu Asn Asp Leu Ser Ser
115 120 125

gat gca cca gga gtg cca agg att gaa gaa gag aag tct gaa gag gag 551
Asp Ala Pro Gly Val Pro Arg Ile Glu Glu Glu Lys Ser Glu Glu Glu
130 135 140 145

act tca gca cct gcc atc acc act gta acg gtg cca act cca att tac 599
Thr Ser Ala Pro Ala Ile Thr Thr Val Thr Val Pro Thr Pro Ile Tyr
150 155 160

caa act agc agt gga cag tat att gcc att acc cag gga gga gca ata 647
Gln Thr Ser Ser Gly Gln Tyr Ile Ala Ile Thr Gln Gly Gly Ala Ile
165 170 175

cag ctg gct aac aat ggt acc gat ggg gta cag ggc ctg caa aca tta 695
Gln Leu Ala Asn Asn Gly Thr Asp Gly Val Gln Gly Leu Gln Thr Leu
180 185 190

acc atg acc aat gca gca gcc act cag ccg ggt act acc att cta cag 743
Thr Met Thr Asn Ala Ala Ala Thr Gln Pro Gly Thr Thr Ile Leu Gln
195 200 205

tat gca cag acc act gat gga cag cag atc tta gtg ccc agc aac caa 791
Tyr Ala Gln Thr Thr Asp Gly Gln Gln Ile Leu Val Pro Ser Asn Gln
210 215 220 225

gtt gtt gtt caa gct gcc tct gga gac gta caa aca tac cag att cgc 839
Val Val Val Gln Ala Ala Ser Gly Asp Val Gln Thr Tyr Gln Ile Arg
230 235 240

aca gca ccc act agc act att gcc cct gga gtt gtt atg gca tcc tcc 887
Thr Ala Pro Thr Ser Thr Ile Ala Pro Gly Val Val Met Ala Ser Ser
245 250 255

cca gca ctt cct aca cag cct gct gaa gaa gca gca cga aag aga gag 935
Pro Ala Leu Pro Thr Gln Pro Ala Glu Glu Ala Ala Arg Lys Arg Glu
260 265 270

gtc cgt cta atg aag aac agg gaa gca gct cga gag tgt cgt aga aag 983
Val Arg Leu Met Lys Asn Arg Glu Ala Ala Arg Glu Cys Arg Arg Lys
275 280 285

aag aaa gaa tat gtg aaa tgt tta gaa aac aga gtg gca gtg ctt gaa 1031
Lys Lys Glu Tyr Val Lys Cys Leu Glu Asn Arg Val Ala Val Leu Glu

290 295 300 305

aat caa aac aag aca ttg att gag gag cta aaa gca ctt aag gac ctt 1079
Asn Gln Asn Lys Thr Leu Ile Glu Glu Leu Lys Ala Leu Lys Asp Leu
310 315 320

tac tgc cac aaa tca gat taa tttgggattt aaattttcac ctgttaaggt 1130
Tyr Cys His Lys Ser Asp
325

ggaaaatgga ctggcttggc cacaacctga aagacaaaat aaacatttta ttttctaaac 1190

atttcttttt ttctatgcgc aaaactgcct gaaagcaact acagaatttc attcatttgt 1250

gcttttgcat taaactgtga atgttccaac acctgcctcc acttctcccc tcaagaaatt 1310

ttcaacgcca ggaatcatga agagacttct gcttttcaac ccccaccctc ctcaagaagt 1370

aataatttgt ttacttgtaa attgatggga gaaatgagga aaagaaaatc tttttaaaaa 1430

tgatttcaag gtttgtgctg agctccttga ttgccttagg gacagaatta ccccagcctc 1490

ttgagctgaa gtaatgtgtg ggccgcatgc ataaagtaag taaggtgcaa tgaagaagtg 1550

ttgattgcca aattgacatg ttgtcacatt ctcattgtga attatgtaaa gttgttaaga 1610

gacataccct ctaaaaaaga actttagcat ggtattgaag gaattagaaa tgaatttgga 1670

gtgctttta tgtatgttgt cttcttcaat actgaaaatt tgtccttggt tcttaaaagc 1730

attctgtact aatacagctc ttccataggg cagttgttgc ttcttaattc agttctgtat 1790

gtgttcaaca tttttgaata cattaaaaga agtaaccaac tgaacgacaa agcatggtat 1850

ttgaatttta aattaaagca aagtaaataa aagtacaaag catattttag ttagtactaa 1910

attcttagta aaatgctgat cagtaaacca atcccttgag ttatataaca agatttttaa 1970

ataaatgtta ttgtcctcac cttcaaaaat atttatattg tcactcattt acgtaaaaag 2030

atatttctaa tttactgttg cccattgcac ttacatacca ccaccaagaa agccttcaag 2090

atgtcaaata aagcaaagtg atatatattt gtttatgaaa tgttacatgt agaaaaatac 2150

tgattttaaa tattttccat attaacaatt taacagagaa tctctagtga attttttaaa 2210

tgaaagaagt tgtaaggata taaaaagtac agtgttagat gtgcacaagg aaagttattt 2270

tcagacatat ttgaatgact gctgtactgc aatatttgga ttgtcattct tacaaaacat 2330

tttttgttc tcttgtaaaa agagtagtta ttagttctgc tttagctttc caatatgctg 2390

tatagccttt gtcattttat aattttaatt cctgattaaa acagtctgta tttgtgtata 2450

tcat 2454

<210> 8
<211> 327
<212> PRT
<213> Homo sapiens

<400> 8

Met Thr Met Glu Ser Gly Ala Glu Asn Gln Gln Ser Gly Asp Ala Ala
1 5 10 15

Val Thr Glu Ala Glu Asn Gln Gln Met Thr Val Gln Ala Gln Pro Gln
20 25 30

Ile Ala Thr Leu Ala Gln Val Ser Met Pro Ala Ala His Ala Thr Ser
35 40 45

Ser Ala Pro Thr Val Thr Leu Val Gln Leu Pro Asn Gly Gln Thr Val
50 55 60

Gln Val His Gly Val Ile Gln Ala Ala Gln Pro Ser Val Ile Gln Ser
65 70 75 80

Pro Gln Val Gln Thr Val Gln Ile Ser Thr Ile Ala Glu Ser Glu Asp
85 90 95

Ser Gln Glu Ser Val Asp Ser Val Thr Asp Ser Gln Lys Arg Arg Glu
100 105 110

Ile Leu Ser Arg Arg Pro Ser Tyr Arg Lys Ile Leu Asn Asp Leu Ser
115 120 125

Ser Asp Ala Pro Gly Val Pro Arg Ile Glu Glu Glu Lys Ser Glu Glu
130 135 140

Glu Thr Ser Ala Pro Ala Ile Thr Thr Val Thr Val Pro Thr Pro Ile
145 150 155 160

Tyr Gln Thr Ser Ser Gly Gln Tyr Ile Ala Ile Thr Gln Gly Gly Ala
165 170 175

Ile Gln Leu Ala Asn Asn Gly Thr Asp Gly Val Gln Gly Leu Gln Thr
180 185 190

Leu Thr Met Thr Asn Ala Ala Ala Thr Gln Pro Gly Thr Thr Ile Leu
195 200 205

Gln Tyr Ala Gln Thr Thr Asp Gly Gln Gln Ile Leu Val Pro Ser Asn
210 215 220

Gln Val Val Val Gln Ala Ala Ser Gly Asp Val Gln Thr Tyr Gln Ile
225 230 235 240

Arg Thr Ala Pro Thr Ser Thr Ile Ala Pro Gly Val Val Met Ala Ser
245 250 255

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

Glu Val Arg Leu Met Lys Asn Arg Glu Ala Ala Arg Glu Cys Arg Arg
275 280 285

Lys Lys Lys Glu Tyr Val Lys Cys Leu Glu Asn Arg Val Ala Val Leu
290 295 300

Glu Asn Gln Asn Lys Thr Leu Ile Glu Glu Leu Lys Ala Leu Lys Asp
305 310 315 320

Leu Tyr Cys His Lys Ser Asp
325

<210> 9
<211> 2517

<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (136)..(1449)

<400> 9
ggaattccgt ggccgggact ttgcaggcag cggcggccgg gggcggagcg ggatcgagcc 60

ctcgccgagg cctgccgcca tgggcccgcg ccgccgccgc cgcctgtcac ccgggccgcg 120

cgggccgtga gcgtc atg gcc ttg gcc ggg gcc cct gcg ggc ggc cca tgc 171
Met Ala Leu Ala Gly Ala Pro Ala Gly Gly Pro Cys
1 5 10

gcg ccg gcg ctg gag gcc ctg ctc ggg gcc ggc gcg ctg cgg ctg ctc 219
Ala Pro Ala Leu Glu Ala Leu Leu Gly Ala Gly Ala Leu Arg Leu Leu
15 20 25

gac tcc tcg cag atc gtc atc atc tcc gcc gcg cag gac gcc agc gcc 267
Asp Ser Ser Gln Ile Val Ile Ile Ser Ala Ala Gln Asp Ala Ser Ala
30 35 40

ccg ccg gct ccc acc ggc ccc gcg gcg ccc gcc gcc ggc ccc tgc gac 315
Pro Pro Ala Pro Thr Gly Pro Ala Ala Pro Ala Ala Gly Pro Cys Asp
45 50 55 60

cct gac ctg ctg ctc ttc gcc aca ccg cag gcg ccc cgg ccc aca ccc 363
Pro Asp Leu Leu Leu Phe Ala Thr Pro Gln Ala Pro Arg Pro Thr Pro
65 70 75

agt gcg ccg cgg ccc gcg ctc ggc cgc ccg ccg gtg aag cgg agg ctg 411
Ser Ala Pro Arg Pro Ala Leu Gly Arg Pro Pro Val Lys Arg Arg Leu
80 85 90

gac ctg gaa act gac cat cag tac ctg gcc gag agc agt ggg cca gct 459
Asp Leu Glu Thr Asp His Gln Tyr Leu Ala Glu Ser Ser Gly Pro Ala
95 100 105

cgg ggc aga ggc cgc cat cca gga aaa ggt gtg aaa tcc ccg ggg gag 507
Arg Gly Arg Gly Arg His Pro Gly Lys Gly Val Lys Ser Pro Gly Glu
110 115 120

aag tca cgc tat gag acc tca ctg aat ctg acc acc aag cgc ttc ctg 555
Lys Ser Arg Tyr Glu Thr Ser Leu Asn Leu Thr Thr Lys Arg Phe Leu
125 130 135 140

gag ctg ctg agc cac tcg gct gac ggt gtc gtc gac ctg aac tgg gct 603

Glu Leu Leu Ser His Ser Ala Asp Gly Val Val Asp Leu Asn Trp Ala
145 150 155

gcc gag gtg ctg aag gtg cag aag cgg cgc atc tat gac atc acc aac 651
Ala Glu Val Leu Lys Val Gln Lys Arg Arg Ile Tyr Asp Ile Thr Asn
160 165 170

gtc ctt gag ggc atc cag ctc att gcc aag aag tcc aag aac cac atc 699
Val Leu Glu Gly Ile Gln Leu Ile Ala Lys Lys Ser Lys Asn His Ile
175 180 185

cag tgg ctg ggc agc cac acc aca gtg ggc gtc ggc gga cgg ctt gag 747
Gln Trp Leu Gly Ser His Thr Thr Val Gly Val Gly Gly Arg Leu Glu
190 195 200

ggg ttg acc cag gac ctc cga cag ctg cag gag agc gag cag cag ctg 795
Gly Leu Thr Gln Asp Leu Arg Gln Leu Gln Glu Ser Glu Gln Gln Leu
205 210 215 220

gac cac ctg atg aat atc tgt act acg cag ctg cgc ctg ctc tcc gag 843
Asp His Leu Met Asn Ile Cys Thr Thr Gln Leu Arg Leu Leu Ser Glu
225 230 235

gac act gac agc cag cgc ctg gcc tac gtg acg tgt cag gac ctt cgt 891
Asp Thr Asp Ser Gln Arg Leu Ala Tyr Val Thr Cys Gln Asp Leu Arg
240 245 250

agc att gca gac cct gca gag cag atg gtt atg gtg atc aaa gcc cct 939
Ser Ile Ala Asp Pro Ala Glu Gln Met Val Met Val Ile Lys Ala Pro
255 260 265

cct gag acc cag ctc caa gcc gtg gac tct tcg gag aac ttt cag atc 987
Pro Glu Thr Gln Leu Gln Ala Val Asp Ser Ser Glu Asn Phe Gln Ile
270 275 280

tcc ctt aag agc aaa caa ggc ccg atc gat gtt ttc ctg tgc cct gag 1035
Ser Leu Lys Ser Lys Gln Gly Pro Ile Asp Val Phe Leu Cys Pro Glu
285 290 295 300

gag acc gta ggt ggg atc agc cct ggg aag acc cca tcc cag gag gtc 1083
Glu Thr Val Gly Gly Ile Ser Pro Gly Lys Thr Pro Ser Gln Glu Val
305 310 315

act tct gag gag gag aac agg gcc act gac tct gcc acc ata gtg tca 1131
Thr Ser Glu Glu Glu Asn Arg Ala Thr Asp Ser Ala Thr Ile Val Ser
320 325 330

cca cca cca tca tct ccc ccc tca tcc ctc acc aca gat ccc agc cag 1179
Pro Pro Pro Ser Ser Pro Pro Ser Ser Leu Thr Thr Asp Pro Ser Gln
335 340 345

tct cta ctc agc ctg gag caa gaa ccg ctg ttg tcc cgg atg ggc agc 1227
Ser Leu Leu Ser Leu Glu Gln Glu Pro Leu Leu Ser Arg Met Gly Ser
350 355 360

ctg cgg gct ccc gtg gac gag gac cgc ctg tcc ccg ctg gtg gcg gcc 1275
Leu Arg Ala Pro Val Asp Glu Asp Arg Leu Ser Pro Leu Val Ala Ala
365 370 375 380

gac tcg ctc ctg gag cat gtg cgg gag gac ttc tcc ggc ctc ctc cct 1323
Asp Ser Leu Leu Glu His Val Arg Glu Asp Phe Ser Gly Leu Leu Pro
385 390 395

gag gag ttc atc agc ctt tcc cca ccc cac gag gcc ctc gac tac cac 1371
Glu Glu Phe Ile Ser Leu Ser Pro Pro His Glu Ala Leu Asp Tyr His
400 405 410

ttc ggc ctc gag gag ggc gag ggc atc aga gac ctc ttc gac tgt gac 1419
Phe Gly Leu Glu Glu Gly Glu Gly Ile Arg Asp Leu Phe Asp Cys Asp
415 420 425

ttt ggg gac ctc acc ccc ctg gat ttc tga cagggcttgg agggaccagg 1469
Phe Gly Asp Leu Thr Pro Leu Asp Phe
430 435

gtttccagag tagctcacct tgtctctgca gccctggagc cccctgtccc tggccgtcct 1529

cccagcctgt ttggaaacat ttaatttata cccctctcct ctgtctccag aagcttctag 1589

ctctggggtc tggctaccgc taggaggctg agcaagccag gaagggaagg agtctgtgtg 1649

gtgtgtatgt gcatgcagcc tacacccaca cgtgtgtacc gggggtgaat gtgtgtgagc 1709

atgtgtgtgt gcatgtaccg gggaatgaag gtgaacatac acctctgtgt gtgcactgca 1769

gacacgcccc agtgtgtcca catgtgtgtg catgagtcca tctctgcgcg tgggggggct 1829

ctaactgcac tttcggccct tttgctcgtg gggtcccaca aggcccaggg cagtgcctgc 1889

tcccagaatc tggtgctctg accaggccag gtggggaggc tttggctggc tgggcgtgta 1949

ggacggtgag agcacttctg tcttaaaggt tttttctgat tgaagcttta atggagcgtt 2009

atttatttat cgaggcctct ttggtgagcc tggggaatca gcaaaagggg aggaggggtg 2069

tggggttgat accccaactc cctctaccct tgagcaaggg caggggtccc tgagctgttc 2129

ttctgcccca tactgaagga actgaggcct gggtgattta tttattggga aagtgaggga 2189

gggagacaga ctgactgaca gccatgggtg gtcagatggt ggggtgggcc ctctccaggg 2249

ggccagttca gggcccagct gccccccagg atggatatga gatgggagag gtgagtgggg 2309

gaccttcact gatgtgggca ggaggggtgg tgaaggcctc ccccagccca gaccctgtgg 2369

tccctcctgc agtgtctgaa gcgcctgcct ccccactgct ctgccccacc ctccaatctg 2429

cactttgatt tgcttcctaa cagctctgtt ccctcctgct ttggttttaa taaatatttt 2489

gatgacgtta aaaaaaggaa ttcgatat 2517

<210> 10
<211> 437
<212> PRT
<213> Homo sapiens

<400> 10

Met Ala Leu Ala Gly Ala Pro Ala Gly Gly Pro Cys Ala Pro Ala Leu
1 5 10 15

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

Ile Val Ile Ile Ser Ala Ala Gln Asp Ala Ser Ala Pro Pro Ala Pro
35 40 45

Thr Gly Pro Ala Ala Pro Ala Ala Gly Pro Cys Asp Pro Asp Leu Leu
50 55 60

Leu Phe Ala Thr Pro Gln Ala Pro Arg Pro Thr Pro Ser Ala Pro Arg
65 70 75 80

Pro Ala Leu Gly Arg Pro Pro Val Lys Arg Arg Leu Asp Leu Glu Thr
85 90 95

Asp His Gln Tyr Leu Ala Glu Ser Ser Gly Pro Ala Arg Gly Arg Gly
100 105 110

Arg His Pro Gly Lys Gly Val Lys Ser Pro Gly Glu Lys Ser Arg Tyr
115 120 125

Glu Thr Ser Leu Asn Leu Thr Thr Lys Arg Phe Leu Glu Leu Leu Ser
130 135 140

His Ser Ala Asp Gly Val Val Asp Leu Asn Trp Ala Ala Glu Val Leu
145 150 155 160

Lys Val Gln Lys Arg Arg Ile Tyr Asp Ile Thr Asn Val Leu Glu Gly
165 170 175

Ile Gln Leu Ile Ala Lys Lys Ser Lys Asn His Ile Gln Trp Leu Gly
180 185 190

Ser His Thr Thr Val Gly Val Gly Gly Arg Leu Glu Gly Leu Thr Gln
195 200 205

Asp Leu Arg Gln Leu Gln Glu Ser Glu Gln Gln Leu Asp His Leu Met
210 215 220

Asn Ile Cys Thr Thr Gln Leu Arg Leu Leu Ser Glu Asp Thr Asp Ser
225 230 235 240

Gln Arg Leu Ala Tyr Val Thr Cys Gln Asp Leu Arg Ser Ile Ala Asp
245 250 255

Pro Ala Glu Gln Met Val Met Val Ile Lys Ala Pro Pro Glu Thr Gln
260 265 270

Leu Gln Ala Val Asp Ser Ser Glu Asn Phe Gln Ile Ser Leu Lys Ser
275 280 285

Lys Gln Gly Pro Ile Asp Val Phe Leu Cys Pro Glu Glu Thr Val Gly
290 295 300

Gly Ile Ser Pro Gly Lys Thr Pro Ser Gln Glu Val Thr Ser Glu Glu
305 310 315 320

Glu Asn Arg Ala Thr Asp Ser Ala Thr Ile Val Ser Pro Pro Pro Ser

325 330 335

Ser Pro Pro Ser Ser Leu Thr Thr Asp Pro Ser Gln Ser Leu Leu Ser
340 345 350

Leu Glu Gln Glu Pro Leu Leu Ser Arg Met Gly Ser Leu Arg Ala Pro
355 360 365

Val Asp Glu Asp Arg Leu Ser Pro Leu Val Ala Ala Asp Ser Leu Leu
370 375 380

Glu His Val Arg Glu Asp Phe Ser Gly Leu Leu Pro Glu Glu Phe Ile
385 390 395 400

Ser Leu Ser Pro Pro His Glu Ala Leu Asp Tyr His Phe Gly Leu Glu
405 410 415

Glu Gly Glu Gly Ile Arg Asp Leu Phe Asp Cys Asp Phe Gly Asp Leu
420 425 430

Thr Pro Leu Asp Phe
435

<210> 11
<211> 2092
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (293)..(2080)

<400> 11
gaattccaaa attgtgatgt ttcttgtatt tttgatgaag gagaaatact gtaatgatca 60

ctgtttacac tatgtacact ttaggccagc cctttgtagc gttatacaaa ctgaaagcac 120

accggacccg caggctcccg gggcagggcc ggggccagag ctcgcgtgtc ggcgggacat 180

gcgctgcgtc gcctctaacc tcgggctgtg ctctttttcc aggtggcccg ccggtttctg 240

agccttctgc cctgcgggga cacggtctgc accctgcccg cggccacgga cc atg acc 298
Met Thr
1

atg acc ctc cac acc aaa gca tct ggg atg gcc cta ctg cat cag atc 346
Met Thr Leu His Thr Lys Ala Ser Gly Met Ala Leu Leu His Gln Ile
5 10 15

caa ggg aac gag ctg gag ccc ctg aac cgt ccg cag ctc aag atc ccc 394
Gln Gly Asn Glu Leu Glu Pro Leu Asn Arg Pro Gln Leu Lys Ile Pro
20 25 30

ctg gag cgg ccc ctg ggc gag gtg tac ctg gac agc agc aag ccc gcc 442
Leu Glu Arg Pro Leu Gly Glu Val Tyr Leu Asp Ser Ser Lys Pro Ala
35 40 45 50

gtg tac aac tac ccc gag ggc gcc gcc tac gag ttc aac gcc gcg gcc 490
Val Tyr Asn Tyr Pro Glu Gly Ala Ala Tyr Glu Phe Asn Ala Ala Ala
55 60 65

gcc gcc aac gcg cag gtc tac ggt cag acc ggc ctc ccc tac ggc ccc 538
Ala Ala Asn Ala Gln Val Tyr Gly Gln Thr Gly Leu Pro Tyr Gly Pro
70 75 80

ggg tct gag gct gcg gcg ttc ggc tcc aac ggc ctg ggg ggt ttc ccc 586
Gly Ser Glu Ala Ala Ala Phe Gly Ser Asn Gly Leu Gly Gly Phe Pro
85 90 95

cca ctc aac agc gtg tct ccg agc ccg ctg atg cta ctg cac ccg ccg 634
Pro Leu Asn Ser Val Ser Pro Ser Pro Leu Met Leu Leu His Pro Pro
100 105 110

ccg cag ctg tcg cct ttc ctg cag ccc cac ggc cag cag gtg ccc tac 682
Pro Gln Leu Ser Pro Phe Leu Gln Pro His Gly Gln Gln Val Pro Tyr
115 120 125 130

tac ctg gag aac gag ccc agc ggc tac acg gtg cgc gag gcc ggc ccg 730
Tyr Leu Glu Asn Glu Pro Ser Gly Tyr Thr Val Arg Glu Ala Gly Pro
135 140 145

ccg gca ttc tac agg cca aat tca gat aat cga cgc cag ggt ggc aga 778
Pro Ala Phe Tyr Arg Pro Asn Ser Asp Asn Arg Arg Gln Gly Gly Arg
150 155 160

gaa aga ttg gcc agt acc aat gac aag gga agt atg gct atg gaa tct 826
Glu Arg Leu Ala Ser Thr Asn Asp Lys Gly Ser Met Ala Met Glu Ser
165 170 175

gcc aag gag act cgc tac tgt gca gtg tgc aat gac tat gct tca ggc 874
Ala Lys Glu Thr Arg Tyr Cys Ala Val Cys Asn Asp Tyr Ala Ser Gly

180 185 190

tac cat tat gga gtc tgg tcc tgt gag ggc tgc aag gcc ttc ttc aag 922
Tyr His Tyr Gly Val Trp Ser Cys Glu Gly Cys Lys Ala Phe Phe Lys
195 200 205 210

aga agt att caa gga cat aac gac tat atg tgt cca gcc acc aac cag 970
Arg Ser Ile Gln Gly His Asn Asp Tyr Met Cys Pro Ala Thr Asn Gln
215 220 225

tgc acc att gat aaa aac agg agg aag agc tgc cag gcc tgc cgg ctc 1018
Cys Thr Ile Asp Lys Asn Arg Arg Lys Ser Cys Gln Ala Cys Arg Leu
230 235 240

cgc aaa tgc tac gaa gtg gga atg atg aaa ggt ggg ata cga aaa gac 1066
Arg Lys Cys Tyr Glu Val Gly Met Met Lys Gly Gly Ile Arg Lys Asp
245 250 255

cga aga gga ggg aga atg ttg aaa cac aag cgc cag aga gat gat ggg 1114
Arg Arg Gly Gly Arg Met Leu Lys His Lys Arg Gln Arg Asp Asp Gly
260 265 270

gag ggc agg ggt gaa gtg ggg tct gct gga gac atg aga gct gcc aac 1162
Glu Gly Arg Gly Glu Val Gly Ser Ala Gly Asp Met Arg Ala Ala Asn
275 280 285 290

ctt tgg cca agc ccg ctc atg atc aaa cgc tct aag aag aac agc ctg 1210
Leu Trp Pro Ser Pro Leu Met Ile Lys Arg Ser Lys Lys Asn Ser Leu
295 300 305

gcc ttg tcc ctg acg gcc gac cag atg gtc agt gcc ttg ttg gat gct 1258
Ala Leu Ser Leu Thr Ala Asp Gln Met Val Ser Ala Leu Leu Asp Ala
310 315 320

gag ccc ccc ata ctc tat tcc gag tat gat cct acc aga ccc ttc agt 1306
Glu Pro Pro Ile Leu Tyr Ser Glu Tyr Asp Pro Thr Arg Pro Phe Ser
325 330 335

gaa gct tcg atg atg ggc tta ctg acc aac ctg gca gac agg gag ctg 1354
Glu Ala Ser Met Met Gly Leu Leu Thr Asn Leu Ala Asp Arg Glu Leu
340 345 350

gtt cac atg atc aac tgg gcg aag agg gtg cca ggc ttt gtg gat ttg 1402
Val His Met Ile Asn Trp Ala Lys Arg Val Pro Gly Phe Val Asp Leu
355 360 365 370

acc ctc cat gat cag gtc cac ctt cta gaa tgt gcc tgg cta gag atc 1450
Thr Leu His Asp Gln Val His Leu Leu Glu Cys Ala Trp Leu Glu Ile
375 380 385

ctg atg att ggt ctc gtc tgg cgc tcc atg gag cac cca gtg aag cta 1498
Leu Met Ile Gly Leu Val Trp Arg Ser Met Glu His Pro Val Lys Leu
390 395 400

ctg ttt gct cct aac ttg ctc ttg gac agg aac cag gga aaa tgt gta 1546
Leu Phe Ala Pro Asn Leu Leu Leu Asp Arg Asn Gln Gly Lys Cys Val
405 410 415

gag ggc atg gtg gag atc ttc gac atg ctg ctg gct aca tca tct cgg 1594
Glu Gly Met Val Glu Ile Phe Asp Met Leu Leu Ala Thr Ser Ser Arg
420 425 430

ttc cgc atg atg aat ctg cag gga gag gag ttt gtg tgc ctc aaa tct 1642
Phe Arg Met Met Asn Leu Gln Gly Glu Glu Phe Val Cys Leu Lys Ser
435 440 445 450

att att ttg ctt aat tct gga gtg tac aca ttt ctg tcc agc acc ctg 1690
Ile Ile Leu Leu Asn Ser Gly Val Tyr Thr Phe Leu Ser Ser Thr Leu
455 460 465

aag tct ctg gaa gag aag gac cat atc cac cga gtc ctg gac aag atc 1738
Lys Ser Leu Glu Glu Lys Asp His Ile His Arg Val Leu Asp Lys Ile
470 475 480

aca gac act ttg atc cac ctg atg gcc aag gca ggc ctg acc ctg cag 1786
Thr Asp Thr Leu Ile His Leu Met Ala Lys Ala Gly Leu Thr Leu Gln
485 490 495

cag cag cac cag cgg ctg gcc cag ctc ctc ctc atc ctc tcc cac atc 1834
Gln Gln His Gln Arg Leu Ala Gln Leu Leu Leu Ile Leu Ser His Ile
500 505 510

agg cac atg agt aac aaa ggc atg gag cat ctg tac agc atg aag tgc 1882
Arg His Met Ser Asn Lys Gly Met Glu His Leu Tyr Ser Met Lys Cys
515 520 525 530

aag aac gtg gtg ccc ctc tat gac ctg ctg ctg gag atg ctg gac gcc 1930
Lys Asn Val Val Pro Leu Tyr Asp Leu Leu Leu Glu Met Leu Asp Ala
535 540 545

cac cgc cta cat gcg ccc act agc cgt gga ggg gca tcc gtg gag gag 1978
His Arg Leu His Ala Pro Thr Ser Arg Gly Gly Ala Ser Val Glu Glu
550 555 560

acg gac caa agc cac ttg gcc act gcg ggc tct act tca tcg cat tcc 2026
Thr Asp Gln Ser His Leu Ala Thr Ala Gly Ser Thr Ser Ser His Ser
565 570 575

ttg caa aag tat tac atc acg ggg gag gca gag ggt ttc cct gcc aca 2074
Leu Gln Lys Tyr Tyr Ile Thr Gly Glu Ala Glu Gly Phe Pro Ala Thr

580 585 590

gtc tga gagctccctg gc 2092
Val
595

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35 40 45

Pro Ala Val Tyr Asn Tyr Pro Glu Gly Ala Ala Tyr Glu Phe Asn Ala
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Ala Ala Ala Ala Asn Ala Gln Val Tyr Gly Gln Thr Gly Leu Pro Tyr
65 70 75 80

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

Phe Pro Pro Leu Asn Ser Val Ser Pro Ser Pro Leu Met Leu Leu His
100 105 110

Pro Pro Pro Gln Leu Ser Pro Phe Leu Gln Pro His Gly Gln Gln Val
115 120 125

Pro Tyr Tyr Leu Glu Asn Glu Pro Ser Gly Tyr Thr Val Arg Glu Ala
130 135 140

Gly Pro Pro Ala Phe Tyr Arg Pro Asn Ser Asp Asn Arg Arg Gln Gly
145 150 155 160

Gly Arg Glu Arg Leu Ala Ser Thr Asn Asp Lys Gly Ser Met Ala Met
165 170 175

Glu Ser Ala Lys Glu Thr Arg Tyr Cys Ala Val Cys Asn Asp Tyr Ala
180 185 190

Ser Gly Tyr His Tyr Gly Val Trp Ser Cys Glu Gly Cys Lys Ala Phe
195 200 205

Phe Lys Arg Ser Ile Gln Gly His Asn Asp Tyr Met Cys Pro Ala Thr
210 215 220

Asn Gln Cys Thr Ile Asp Lys Asn Arg Arg Lys Ser Cys Gln Ala Cys
225 230 235 240

Arg Leu Arg Lys Cys Tyr Glu Val Gly Met Met Lys Gly Gly Ile Arg
245 250 255

Lys Asp Arg Arg Gly Gly Arg Met Leu Lys His Lys Arg Gln Arg Asp
260 265 270

Asp Gly Glu Gly Arg Gly Glu Val Gly Ser Ala Gly Asp Met Arg Ala
275 280 285

Ala Asn Leu Trp Pro Ser Pro Leu Met Ile Lys Arg Ser Lys Lys Asn
290 295 300

Ser Leu Ala Leu Ser Leu Thr Ala Asp Gln Met Val Ser Ala Leu Leu
305 310 315 320

Asp Ala Glu Pro Pro Ile Leu Tyr Ser Glu Tyr Asp Pro Thr Arg Pro
325 330 335

Phe Ser Glu Ala Ser Met Met Gly Leu Leu Thr Asn Leu Ala Asp Arg
340 345 350

Glu Leu Val His Met Ile Asn Trp Ala Lys Arg Val Pro Gly Phe Val
355 360 365

Asp Leu Thr Leu His Asp Gln Val His Leu Leu Glu Cys Ala Trp Leu
370 375 380

Glu Ile Leu Met Ile Gly Leu Val Trp Arg Ser Met Glu His Pro Val
385 390 395 400

Lys Leu Leu Phe Ala Pro Asn Leu Leu Leu Asp Arg Asn Gln Gly Lys
405 410 415

Cys Val Glu Gly Met Val Glu Ile Phe Asp Met Leu Leu Ala Thr Ser
420 425 430

Ser Arg Phe Arg Met Met Asn Leu Gln Gly Glu Glu Phe Val Cys Leu
435 440 445

Lys Ser Ile Ile Leu Leu Asn Ser Gly Val Tyr Thr Phe Leu Ser Ser
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Thr Leu Lys Ser Leu Glu Glu Lys Asp His Ile His Arg Val Leu Asp
465 470 475 480

Lys Ile Thr Asp Thr Leu Ile His Leu Met Ala Lys Ala Gly Leu Thr
485 490 495

Leu Gln Gln Gln His Gln Arg Leu Ala Gln Leu Leu Leu Ile Leu Ser
500 505 510

His Ile Arg His Met Ser Asn Lys Gly Met Glu His Leu Tyr Ser Met
515 520 525

Lys Cys Lys Asn Val Val Pro Leu Tyr Asp Leu Leu Leu Glu Met Leu
530 535 540

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

Glu Glu Thr Asp Gln Ser His Leu Ala Thr Ala Gly Ser Thr Ser Ser
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Ala Thr Val
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tgatattcac tg atg gac tcc aaa gaa tca tta act cct ggt aga gaa gaa 171
Met Asp Ser Lys Glu Ser Leu Thr Pro Gly Arg Glu Glu
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aac ccc agc agt gtg ctt gct cag gag agg gga gat gtg atg gac ttc 219
Asn Pro Ser Ser Val Leu Ala Gln Glu Arg Gly Asp Val Met Asp Phe
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tat aaa acc cta aga gga gga gct act gtg aag gtt tct gcg tct tca 267
Tyr Lys Thr Leu Arg Gly Gly Ala Thr Val Lys Val Ser Ala Ser Ser
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ccc tca ctg gct gtc gct tct caa tca gac tcc aag cag cga aga ctt 315
Pro Ser Leu Ala Val Ala Ser Gln Ser Asp Ser Lys Gln Arg Arg Leu
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Leu Val Asp Phe Pro Lys Gly Ser Val Ser Asn Ala Gln Gln Pro Asp
65 70 75

ctg tcc aaa gca gtt tca ctc tca atg gga ctg tat atg gga gag aca 411
Leu Ser Lys Ala Val Ser Leu Ser Met Gly Leu Tyr Met Gly Glu Thr
80 85 90

gaa aca aaa gtg atg gga aat gac ctg gga ttc cca cag cag ggc caa 459
Glu Thr Lys Val Met Gly Asn Asp Leu Gly Phe Pro Gln Gln Gly Gln
95 100 105

atc agc ctt tcc tcg ggg gaa aca gac tta aag ctt ttg gaa gaa agc 507
Ile Ser Leu Ser Ser Gly Glu Thr Asp Leu Lys Leu Leu Glu Glu Ser
110 115 120 125

att gca aac ctc aat agg tcg acc agt gtt cca gag aac ccc aag agt 555
Ile Ala Asn Leu Asn Arg Ser Thr Ser Val Pro Glu Asn Pro Lys Ser
130 135 140

tca gca tcc act gct gtg tct gct gcc ccc aca gag aag gag ttt cca 603
Ser Ala Ser Thr Ala Val Ser Ala Ala Pro Thr Glu Lys Glu Phe Pro
145 150 155

aaa act cac tct gat gta tct tca gaa cag caa cat ttg aag ggc cag 651
Lys Thr His Ser Asp Val Ser Ser Glu Gln Gln His Leu Lys Gly Gln
160 165 170

act ggc acc aac ggt ggc aat gtg aaa ttg tat acc aca gac caa agc 699
Thr Gly Thr Asn Gly Gly Asn Val Lys Leu Tyr Thr Thr Asp Gln Ser
175 180 185

acc ttt gac att ttg cag gat ttg gag ttt tct tct ggg tcc cca ggt 747
Thr Phe Asp Ile Leu Gln Asp Leu Glu Phe Ser Ser Gly Ser Pro Gly
190 195 200 205

aaa gag acg aat gag agt cct tgg aga tca gac ctg ttg ata gat gaa 795
Lys Glu Thr Asn Glu Ser Pro Trp Arg Ser Asp Leu Leu Ile Asp Glu
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aac tgt ttg ctt tct cct ctg gcg gga gaa gac gat tca ttc ctt ttg 843
Asn Cys Leu Leu Ser Pro Leu Ala Gly Glu Asp Asp Ser Phe Leu Leu
225 230 235

gaa gga aac tcg aat gag gac tgc aag cct ctc att tta ccg gac act 891
Glu Gly Asn Ser Asn Glu Asp Cys Lys Pro Leu Ile Leu Pro Asp Thr
240 245 250

aaa ccc aaa att aag gat aat gga gat ctg gtt ttg tca agc ccc agt 939
Lys Pro Lys Ile Lys Asp Asn Gly Asp Leu Val Leu Ser Ser Pro Ser
255 260 265

aat gta aca ctg ccc caa gtg aaa aca gaa aaa gaa gat ttc atc gaa 987

Asn Val Thr Leu Pro Gln Val Lys Thr Glu Lys Glu Asp Phe Ile Glu
270 275 280 285

ctc tgc acc cct ggg gta att aag caa gag aaa ctg ggc aca gtt tac 1035
Leu Cys Thr Pro Gly Val Ile Lys Gln Glu Lys Leu Gly Thr Val Tyr
290 295 300

tgt cag gca agc ttt cct gga gca aat ata att ggt aat aaa atg tct 1083
Cys Gln Ala Ser Phe Pro Gly Ala Asn Ile Ile Gly Asn Lys Met Ser
305 310 315

gcc att tct gtt cat ggt gtg agt acc tct gga gga cag atg tac cac 1131
Ala Ile Ser Val His Gly Val Ser Thr Ser Gly Gly Gln Met Tyr His
320 325 330

tat gac atg aat aca gca tcc ctt tct caa cag cag gat cag aag cct 1179
Tyr Asp Met Asn Thr Ala Ser Leu Ser Gln Gln Gln Asp Gln Lys Pro
335 340 345

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Ile Phe Asn Val Ile Pro Pro Ile Pro Val Gly Ser Glu Asn Trp Asn
350 355 360 365

agg tgc caa gga tct gga gat gac aac ttg act tct ctg ggg act ctg 1275
Arg Cys Gln Gly Ser Gly Asp Asp Asn Leu Thr Ser Leu Gly Thr Leu
370 375 380

aac ttc cct ggt cga aca gtt ttt tct aat ggc tat tca agc ccc agc 1323
Asn Phe Pro Gly Arg Thr Val Phe Ser Asn Gly Tyr Ser Ser Pro Ser
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Met Arg Pro Asp Val Ser Ser Pro Pro Ser Ser Ser Ser Thr Ala Thr
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Gly Cys His Tyr Gly Val Leu Thr Cys Gly Ser Cys Lys Val Phe Phe
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450 455 460

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Asp Cys Ile Ile Asp Lys Ile Arg Arg Lys Asn Cys Pro Ala Cys Arg
465 470 475

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Tyr Arg Lys Cys Leu Gln Ala Gly Met Asn Leu Glu Ala Arg Lys Thr
480 485 490

aag aaa aaa ata aaa gga att cag cag gcc act aca gga gtc tca caa 1659
Lys Lys Lys Ile Lys Gly Ile Gln Gln Ala Thr Thr Gly Val Ser Gln
495 500 505

gaa acc tct gaa aat cct ggt aac aaa aca ata gtt cct gca acg tta 1707
Glu Thr Ser Glu Asn Pro Gly Asn Lys Thr Ile Val Pro Ala Thr Leu
510 515 520 525

cca caa ctc acc cct acc ctg gtg tca ctg ttg gag gtt att gaa cct 1755
Pro Gln Leu Thr Pro Thr Leu Val Ser Leu Leu Glu Val Ile Glu Pro
530 535 540

gaa gtg tta tat gca gga tat gat agc tct gtt cca gac tca act tgg 1803
Glu Val Leu Tyr Ala Gly Tyr Asp Ser Ser Val Pro Asp Ser Thr Trp
545 550 555

agg atc atg act acg ctc aac atg tta gga ggg cgg caa gtg att gca 1851
Arg Ile Met Thr Thr Leu Asn Met Leu Gly Gly Arg Gln Val Ile Ala
560 565 570

gca gtg aaa tgg gca aag gca ata cca ggt ttc agg aac tta cac ctg 1899
Ala Val Lys Trp Ala Lys Ala Ile Pro Gly Phe Arg Asn Leu His Leu
575 580 585

gat gac caa atg acc cta ctg cag tac tcc tgg atg ttt ctt atg gca 1947
Asp Asp Gln Met Thr Leu Leu Gln Tyr Ser Trp Met Phe Leu Met Ala
590 595 600 605

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Phe Ala Leu Gly Trp Arg Ser Tyr Arg Gln Ser Ser Ala Asn Leu Leu
610 615 620

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Cys Phe Ala Pro Asp Leu Ile Ile Asn Glu Gln Arg Met Thr Leu Pro
625 630 635

tgc atg tac gac caa tgt aaa cac atg ctg tat gtt tcc tct gag tta 2091
Cys Met Tyr Asp Gln Cys Lys His Met Leu Tyr Val Ser Ser Glu Leu
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cac agg ctt cag gta tct tat gaa gag tat ctc tgt atg aaa acc tta 2139
His Arg Leu Gln Val Ser Tyr Glu Glu Tyr Leu Cys Met Lys Thr Leu
655 660 665

ctg ctt ctc tct tca gtt cct aag gac ggt ctg aag agc caa gag cta 2187

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Phe Asp Glu Ile Arg Met Thr Tyr Ile Lys Glu Leu Gly Lys Ala Ile
690 695 700

gtc aag agg gaa gga aac tcc agc cag aac tgg cag cgg ttt tat caa 2283
Val Lys Arg Glu Gly Asn Ser Ser Gln Asn Trp Gln Arg Phe Tyr Gln
705 710 715

ctg aca aaa ctc ttg gat tct atg cat gaa gtg gtt gaa aat ctc ctt 2331
Leu Thr Lys Leu Leu Asp Ser Met His Glu Val Val Glu Asn Leu Leu
720 725 730

aac tat tgc ttc caa aca ttt ttg gat aag acc atg agt att gaa ttc 2379
Asn Tyr Cys Phe Gln Thr Phe Leu Asp Lys Thr Met Ser Ile Glu Phe
735 740 745

ccc gag atg tta gct gaa atc atc acc aat cag ata cca aaa tat tca 2427
Pro Glu Met Leu Ala Glu Ile Ile Thr Asn Gln Ile Pro Lys Tyr Ser
750 755 760 765

aat gga aat atc aaa aaa ctt ctg ttt cat caa aag tga ctgccttaat 2476
Asn Gly Asn Ile Lys Lys Leu Leu Phe His Gln Lys
770 775

aagaatggtt gccttaaaga aagtcgaatt aatagctttt attgtataaa ctatcagttt 2536

gtcctgtaga ggttttgttg ttttattttt tattgttttc atctgttgtt ttgttttaaa 2596

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gcttgtatag tgtaaaataa gaatgatttt tagatgagat tgttttatca tgacatgtta 4156

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

Ala Val Ala Ser Gln Ser Asp Ser Lys Gln Arg Arg Leu Leu Val Asp
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Phe Pro Lys Gly Ser Val Ser Asn Ala Gln Gln Pro Asp Leu Ser Lys
65 70 75 80

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

Ser Ser Gly Glu Thr Asp Leu Lys Leu Leu Glu Glu Ser Ile Ala Asn
115 120 125

Leu Asn Arg Ser Thr Ser Val Pro Glu Asn Pro Lys Ser Ser Ala Ser
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Thr Ala Val Ser Ala Ala Pro Thr Glu Lys Glu Phe Pro Lys Thr His

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

Asn Gly Gly Asn Val Lys Leu Tyr Thr Thr Asp Gln Ser Thr Phe Asp
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Ile Leu Gln Asp Leu Glu Phe Ser Ser Gly Ser Pro Gly Lys Glu Thr
195 200 205

Asn Glu Ser Pro Trp Arg Ser Asp Leu Leu Ile Asp Glu Asn Cys Leu
210 215 220

Leu Ser Pro Leu Ala Gly Glu Asp Asp Ser Phe Leu Leu Glu Gly Asn
225 230 235 240

Ser Asn Glu Asp Cys Lys Pro Leu Ile Leu Pro Asp Thr Lys Pro Lys
245 250 255

Ile Lys Asp Asn Gly Asp Leu Val Leu Ser Ser Pro Ser Asn Val Thr
260 265 270

Leu Pro Gln Val Lys Thr Glu Lys Glu Asp Phe Ile Glu Leu Cys Thr
275 280 285

Pro Gly Val Ile Lys Gln Glu Lys Leu Gly Thr Val Tyr Cys Gln Ala
290 295 300

Ser Phe Pro Gly Ala Asn Ile Ile Gly Asn Lys Met Ser Ala Ile Ser
305 310 315 320

Val His Gly Val Ser Thr Ser Gly Gly Gln Met Tyr His Tyr Asp Met
325 330 335

Asn Thr Ala Ser Leu Ser Gln Gln Gln Asp Gln Lys Pro Ile Phe Asn
340 345 350

Val Ile Pro Pro Ile Pro Val Gly Ser Glu Asn Trp Asn Arg Cys Gln
355 360 365

Gly Ser Gly Asp Asp Asn Leu Thr Ser Leu Gly Thr Leu Asn Phe Pro
370 375 380

Gly Arg Thr Val Phe Ser Asn Gly Tyr Ser Ser Pro Ser Met Arg Pro
385 390 395 400

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Pro Pro Lys Leu Cys Leu Val Cys Ser Asp Glu Ala Ser Gly Cys His
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435 440 445

Val Glu Gly Gln His Asn Tyr Leu Cys Ala Gly Arg Asn Asp Cys Ile
450 455 460

Ile Asp Lys Ile Arg Arg Lys Asn Cys Pro Ala Cys Arg Tyr Arg Lys
465 470 475 480

Cys Leu Gln Ala Gly Met Asn Leu Glu Ala Arg Lys Thr Lys Lys Lys
485 490 495

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

Trp Ala Lys Ala Ile Pro Gly Phe Arg Asn Leu His Leu Asp Asp Gln
580 585 590

Met Thr Leu Leu Gln Tyr Ser Trp Met Phe Leu Met Ala Phe Ala Leu
595 600 605

Gly Trp Arg Ser Tyr Arg Gln Ser Ser Ala Asn Leu Leu Cys Phe Ala
610 615 620

Pro Asp Leu Ile Ile Asn Glu Gln Arg Met Thr Leu Pro Cys Met Tyr
625 630 635 640

Asp Gln Cys Lys His Met Leu Tyr Val Ser Ser Glu Leu His Arg Leu
645 650 655

Gln Val Ser Tyr Glu Glu Tyr Leu Cys Met Lys Thr Leu Leu Leu Leu
660 665 670

Ser Ser Val Pro Lys Asp Gly Leu Lys Ser Gln Glu Leu Phe Asp Glu
675 680 685

Ile Arg Met Thr Tyr Ile Lys Glu Leu Gly Lys Ala Ile Val Lys Arg
690 695 700

Glu Gly Asn Ser Ser Gln Asn Trp Gln Arg Phe Tyr Gln Leu Thr Lys
705 710 715 720

Leu Leu Asp Ser Met His Glu Val Val Glu Asn Leu Leu Asn Tyr Cys
725 730 735

Phe Gln Thr Phe Leu Asp Lys Thr Met Ser Ile Glu Phe Pro Glu Met
740 745 750

Leu Ala Glu Ile Ile Thr Asn Gln Ile Pro Lys Tyr Ser Asn Gly Asn
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Ile Lys Lys Leu Leu Phe His Gln Lys
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Met Asp Leu Pro Val
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Gly Pro Gly Ala Ala Gly Pro Ser Asn Val Pro Ala Phe Leu Thr Lys
10 15 20

ctg tgg acc ctc gtg agc gac ccg gac acc gac gcg ctc atc tgc tgg 271
Leu Trp Thr Leu Val Ser Asp Pro Asp Thr Asp Ala Leu Ile Cys Trp
25 30 35

agc ccg agc ggg aac agc ttc cac gtg ttc gac cag ggc cag ttt gcc 319
Ser Pro Ser Gly Asn Ser Phe His Val Phe Asp Gln Gly Gln Phe Ala
40 45 50

aag gag gtg ctg ccc aag tac ttc aag cac aac aac atg gcc agc ttc 367
Lys Glu Val Leu Pro Lys Tyr Phe Lys His Asn Asn Met Ala Ser Phe
55 60 65

gtg cgg cag ctc aac atg tat ggc ttc cgg aaa gtg gtc cac atc gag 415
Val Arg Gln Leu Asn Met Tyr Gly Phe Arg Lys Val Val His Ile Glu
70 75 80 85

cag ggc ggc ctg gtc aag cca gag aga gac gac acg gag ttc cag cac 463
Gln Gly Gly Leu Val Lys Pro Glu Arg Asp Asp Thr Glu Phe Gln His

90 95 100

cca tgc ttc ctg cgt ggc cag gag cag ctc ctt gag aac atc aag agg 511
Pro Cys Phe Leu Arg Gly Gln Glu Gln Leu Leu Glu Asn Ile Lys Arg
105 110 115

aaa gtg acc agt gtg tcc acc ctg aag agt gaa gac ata aag atc cgc 559
Lys Val Thr Ser Val Ser Thr Leu Lys Ser Glu Asp Ile Lys Ile Arg
120 125 130

cag gac agc gtc acc aag ctg ctg acg gac gtg cag ctg atg aag ggg 607
Gln Asp Ser Val Thr Lys Leu Leu Thr Asp Val Gln Leu Met Lys Gly
135 140 145

aag cag gag tgc atg gac tcc aag ctc ctg gcc atg aag cat gag aat 655
Lys Gln Glu Cys Met Asp Ser Lys Leu Leu Ala Met Lys His Glu Asn
150 155 160 165

gag gct ctg tgg cgg gag gtg gcc agc ctt cgg cag aag cat gcc cag 703
Glu Ala Leu Trp Arg Glu Val Ala Ser Leu Arg Gln Lys His Ala Gln
170 175 180

caa cag aaa gtc gtc aac aag ctc att cag ttc ctg atc tca ctg gtg 751
Gln Gln Lys Val Val Asn Lys Leu Ile Gln Phe Leu Ile Ser Leu Val
185 190 195

cag tca aac cgg atc ctg ggg gtg aag aga aag atc ccc ctg atg ctg 799
Gln Ser Asn Arg Ile Leu Gly Val Lys Arg Lys Ile Pro Leu Met Leu
200 205 210

aac gac agt ggc tca gca cat tcc atg ccc aag tat agc cgg cag ttc 847
Asn Asp Ser Gly Ser Ala His Ser Met Pro Lys Tyr Ser Arg Gln Phe
215 220 225

tcc ctg gag cac gtc cac ggc tcg ggc ccc tac tcg gcc ccc tcc cca 895
Ser Leu Glu His Val His Gly Ser Gly Pro Tyr Ser Ala Pro Ser Pro
230 235 240 245

gcc tac agc agc tcc agc ctc tac gcc cct gat gct gtg gcc agc tct 943
Ala Tyr Ser Ser Ser Ser Leu Tyr Ala Pro Asp Ala Val Ala Ser Ser
250 255 260

gga ccc atc atc tcc gac atc acc gag ctg gct cct gcc agc ccc atg 991
Gly Pro Ile Ile Ser Asp Ile Thr Glu Leu Ala Pro Ala Ser Pro Met
265 270 275

gcc tcc ccc ggc ggg agc ata gac gag agg ccc cta tcc agc agc ccc 1039
Ala Ser Pro Gly Gly Ser Ile Asp Glu Arg Pro Leu Ser Ser Ser Pro
280 285 290

ctg gtg cgt gtc aag gag gag ccc ccc agc ccg cct cag agc ccc cgg 1087
Leu Val Arg Val Lys Glu Glu Pro Pro Ser Pro Pro Gln Ser Pro Arg
295 300 305

gta gag gag gcg agt ccc ggg cgc cca tct tcc gtg gac acc ctc ttg 1135
Val Glu Glu Ala Ser Pro Gly Arg Pro Ser Ser Val Asp Thr Leu Leu
310 315 320 325

tcc ccg acc gcc ctc att gac tcc atc ctg cgg gag agt gaa cct gcc 1183
Ser Pro Thr Ala Leu Ile Asp Ser Ile Leu Arg Glu Ser Glu Pro Ala
330 335 340

ccc gcc tcc gtc aca gcc ctc acg gac gcc agg ggc cac acg gac acc 1231
Pro Ala Ser Val Thr Ala Leu Thr Asp Ala Arg Gly His Thr Asp Thr
345 350 355

gag ggc cgg cct ccc tcc ccc ccg ccc acc tcc acc cct gaa aag tgc 1279
Glu Gly Arg Pro Pro Ser Pro Pro Pro Thr Ser Thr Pro Glu Lys Cys
360 365 370

ctc agc gta gcc tgc ctg gac aag aat gag ctc agt gac cac ttg gat 1327
Leu Ser Val Ala Cys Leu Asp Lys Asn Glu Leu Ser Asp His Leu Asp
375 380 385

gct atg gac tcc aac ctg gat aac ctg cag acc atg ctg agc agc cac 1375
Ala Met Asp Ser Asn Leu Asp Asn Leu Gln Thr Met Leu Ser Ser His
390 395 400 405

ggc ttc agc gtg gac acc agt gcc ctg ctg gac ctg ttc agc ccc tcg 1423
Gly Phe Ser Val Asp Thr Ser Ala Leu Leu Asp Leu Phe Ser Pro Ser
410 415 420

gtg acc gtg ccc gac atg agc ctg cct gac ctt gac agc agc ctg gcc 1471
Val Thr Val Pro Asp Met Ser Leu Pro Asp Leu Asp Ser Ser Leu Ala
425 430 435

agt atc caa gag ctc ctg tct ccc cag gag ccc ccc agg cct ccc gag 1519
Ser Ile Gln Glu Leu Leu Ser Pro Gln Glu Pro Pro Arg Pro Pro Glu
440 445 450

gca gag aac agc agc ccg gat tca ggg aag cag ctg gtg cac tac aca 1567
Ala Glu Asn Ser Ser Pro Asp Ser Gly Lys Gln Leu Val His Tyr Thr
455 460 465

gcg cag ccg ctg ttc ctg ctg gac ccc ggc tcc gtg gac acc ggg agc 1615
Ala Gln Pro Leu Phe Leu Leu Asp Pro Gly Ser Val Asp Thr Gly Ser
470 475 480 485

aac gac ctg ccg gtg ctg ttt gag ctg gga gag ggc tcc tac ttc tcc 1663
Asn Asp Leu Pro Val Leu Phe Glu Leu Gly Glu Gly Ser Tyr Phe Ser

490 495 500

gaa ggg gac ggc ttc gcc gag gac ccc acc atc tcc ctg ctg aca ggc 1711
Glu Gly Asp Gly Phe Ala Glu Asp Pro Thr Ile Ser Leu Leu Thr Gly
505 510 515

tcg gag cct ccc aaa gcc aag gac ccc act gtc tcc tag aggccccgga 1760
Ser Glu Pro Pro Lys Ala Lys Asp Pro Thr Val Ser
520 525

ggagctgggc cagccgccca cccccacccc cagtgcaggg ctggtcttgg ggaggcaggg 1820

cagcctcgcg gtcttgggca ctggtgggtc ggccgccata gccccagtag gacaaacggg 1880

ctcgggtctg ggcagcacct ctggtcagga gggtcaccct ggcctgccag tctgccttcc 1940

cccaaccccg tgtcctgtgg tttggttggg gcttcacagc cacacctgga ctgaccctgc 2000

aggttgttca tagtcagaat tgtattttgg atttttacac aactgtcccg ttccccgctc 2060

cacagagata cacagatata tacacacagt ggatggacgg acaagacagg cagagatcta 2120

taaacagaca ggctctaaaa aaaaaaaaaa aaaaaa 2156

<210> 16
<211> 529
<212> PRT
<213> Homo sapiens

<400> 16

Met Asp Leu Pro Val Gly Pro Gly Ala Ala Gly Pro Ser Asn Val Pro
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Ala Phe Leu Thr Lys Leu Trp Thr Leu Val Ser Asp Pro Asp Thr Asp
20 25 30

Ala Leu Ile Cys Trp Ser Pro Ser Gly Asn Ser Phe His Val Phe Asp
35 40 45

Gln Gly Gln Phe Ala Lys Glu Val Leu Pro Lys Tyr Phe Lys His Asn
50 55 60

Asn Met Ala Ser Phe Val Arg Gln Leu Asn Met Tyr Gly Phe Arg Lys
65 70 75 80

Val Val His Ile Glu Gln Gly Gly Leu Val Lys Pro Glu Arg Asp Asp
85 90 95

Thr Glu Phe Gln His Pro Cys Phe Leu Arg Gly Gln Glu Gln Leu Leu
100 105 110

Glu Asn Ile Lys Arg Lys Val Thr Ser Val Ser Thr Leu Lys Ser Glu
115 120 125

Asp Ile Lys Ile Arg Gln Asp Ser Val Thr Lys Leu Leu Thr Asp Val
130 135 140

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

Met Lys His Glu Asn Glu Ala Leu Trp Arg Glu Val Ala Ser Leu Arg
165 170 175

Gln Lys His Ala Gln Gln Gln Lys Val Val Asn Lys Leu Ile Gln Phe
180 185 190

Leu Ile Ser Leu Val Gln Ser Asn Arg Ile Leu Gly Val Lys Arg Lys
195 200 205

Ile Pro Leu Met Leu Asn Asp Ser Gly Ser Ala His Ser Met Pro Lys
210 215 220

Tyr Ser Arg Gln Phe Ser Leu Glu His Val His Gly Ser Gly Pro Tyr
225 230 235 240

Ser Ala Pro Ser Pro Ala Tyr Ser Ser Ser Ser Leu Tyr Ala Pro Asp
245 250 255

Ala Val Ala Ser Ser Gly Pro Ile Ile Ser Asp Ile Thr Glu Leu Ala
260 265 270

Pro Ala Ser Pro Met Ala Ser Pro Gly Gly Ser Ile Asp Glu Arg Pro
275 280 285

Leu Ser Ser Ser Pro Leu Val Arg Val Lys Glu Glu Pro Pro Ser Pro
290 295 300

Pro Gln Ser Pro Arg Val Glu Glu Ala Ser Pro Gly Arg Pro Ser Ser
305 310 315 320

Val Asp Thr Leu Leu Ser Pro Thr Ala Leu Ile Asp Ser Ile Leu Arg
325 330 335

Glu Ser Glu Pro Ala Pro Ala Ser Val Thr Ala Leu Thr Asp Ala Arg
340 345 350

Gly His Thr Asp Thr Glu Gly Arg Pro Pro Ser Pro Pro Pro Thr Ser
355 360 365

Thr Pro Glu Lys Cys Leu Ser Val Ala Cys Leu Asp Lys Asn Glu Leu
370 375 380

Ser Asp His Leu Asp Ala Met Asp Ser Asn Leu Asp Asn Leu Gln Thr
385 390 395 400

Met Leu Ser Ser His Gly Phe Ser Val Asp Thr Ser Ala Leu Leu Asp
405 410 415

Leu Phe Ser Pro Ser Val Thr Val Pro Asp Met Ser Leu Pro Asp Leu
420 425 430

Asp Ser Ser Leu Ala Ser Ile Gln Glu Leu Leu Ser Pro Gln Glu Pro
435 440 445

Pro Arg Pro Pro Glu Ala Glu Asn Ser Ser Pro Asp Ser Gly Lys Gln
450 455 460

Leu Val His Tyr Thr Ala Gln Pro Leu Phe Leu Leu Asp Pro Gly Ser
465 470 475 480

Val Asp Thr Gly Ser Asn Asp Leu Pro Val Leu Phe Glu Leu Gly Glu
485 490 495

Gly Ser Tyr Phe Ser Glu Gly Asp Gly Phe Ala Glu Asp Pro Thr Ile
500 505 510

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

Ser

<210> 17
<211> 2411
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<213> Homo sapiens

<220>
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<400> 17
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aatttggaat ccctgcgccg cgttaaca atg aag cag agt tcg aac gtg ccg 112
Met Lys Gln Ser Ser Asn Val Pro
1 5

gct ttc ctc agc aag ctg tgg acg ctt gtg gag gaa acc cac act aac 160
Ala Phe Leu Ser Lys Leu Trp Thr Leu Val Glu Glu Thr His Thr Asn
10 15 20

gag ttc atc acc tgg agc cag aat ggc caa agt ttt ctg gtc ttg gat 208
Glu Phe Ile Thr Trp Ser Gln Asn Gly Gln Ser Phe Leu Val Leu Asp
25 30 35 40

gag caa cga ttt gca aaa gaa att ctt ccc aaa tat ttc aag cac aat 256
Glu Gln Arg Phe Ala Lys Glu Ile Leu Pro Lys Tyr Phe Lys His Asn
45 50 55

aat atg gca agc ttt gtg agg caa ctg aat atg tat ggt ttc cgt aaa 304
Asn Met Ala Ser Phe Val Arg Gln Leu Asn Met Tyr Gly Phe Arg Lys
60 65 70

gta gta cat atc gac tct gga att gta aag caa gaa aga gat ggt cct 352
Val Val His Ile Asp Ser Gly Ile Val Lys Gln Glu Arg Asp Gly Pro
75 80 85

gta gaa ttt cag cat cct tac ttc aaa caa gga cag gat gac ttg ttg 400
Val Glu Phe Gln His Pro Tyr Phe Lys Gln Gly Gln Asp Asp Leu Leu
90 95 100

gag aac att aaa agg aag gtt tca tct tca aaa cca gaa gaa aat aaa 448
Glu Asn Ile Lys Arg Lys Val Ser Ser Ser Lys Pro Glu Glu Asn Lys
105 110 115 120

att cgt cag gaa gat tta aca aaa att ata agt agt gct cag aag gtt 496
Ile Arg Gln Glu Asp Leu Thr Lys Ile Ile Ser Ser Ala Gln Lys Val
125 130 135

cag ata aaa cag gaa act att gag tcc agg ctt tct gaa tta aaa agt 544
Gln Ile Lys Gln Glu Thr Ile Glu Ser Arg Leu Ser Glu Leu Lys Ser
140 145 150

gag aat gag tcc ctt tgg aag gag gtg tca gaa tta cga gca aag cat 592
Glu Asn Glu Ser Leu Trp Lys Glu Val Ser Glu Leu Arg Ala Lys His
155 160 165

gca caa cag caa caa gtt att cga aag att gtc cag ttt att gtt aca 640
Ala Gln Gln Gln Gln Val Ile Arg Lys Ile Val Gln Phe Ile Val Thr
170 175 180

ttg gtt caa aat aac caa ctt gtg agt tta aaa cgt aaa agg cct cta 688
Leu Val Gln Asn Asn Gln Leu Val Ser Leu Lys Arg Lys Arg Pro Leu
185 190 195 200

ctt cta aac act aat gga gcc caa aag aag aac ctg ttt cag cac ata 736
Leu Leu Asn Thr Asn Gly Ala Gln Lys Lys Asn Leu Phe Gln His Ile
205 210 215

gtc aaa gaa cca act gat aat cat cat cat aaa gtt cca cac agt agg 784
Val Lys Glu Pro Thr Asp Asn His His His Lys Val Pro His Ser Arg
220 225 230

act gaa ggt tta aag cca agg gag agg att tca gat gac atc att att 832
Thr Glu Gly Leu Lys Pro Arg Glu Arg Ile Ser Asp Asp Ile Ile Ile
235 240 245

tat gat gtt act gat gat aat gca gat gaa gaa aat atc cca gtt att 880
Tyr Asp Val Thr Asp Asp Asn Ala Asp Glu Glu Asn Ile Pro Val Ile
250 255 260

cca gaa act aat gag gat gtt ata tct gat ccc tcc aac tgt agc cag 928

Pro Glu Thr Asn Glu Asp Val Ile Ser Asp Pro Ser Asn Cys Ser Gln
265 270 275 280

tac cct gat att gtc atc gtt gaa gat gac aat gaa gat gag tat gca 976
Tyr Pro Asp Ile Val Ile Val Glu Asp Asp Asn Glu Asp Glu Tyr Ala
285 290 295

cct gtc att cag agt gga gag cag aat gaa cca gcc aga gaa tcc cta 1024
Pro Val Ile Gln Ser Gly Glu Gln Asn Glu Pro Ala Arg Glu Ser Leu
300 305 310

agt tca ggc agt gat ggc agc agc cct ctc atg tct agt gct gtc cag 1072
Ser Ser Gly Ser Asp Gly Ser Ser Pro Leu Met Ser Ser Ala Val Gln
315 320 325

cta aat ggc tca tcc agt ctg acc tca gaa gat cca gtg acc atg atg 1120
Leu Asn Gly Ser Ser Ser Leu Thr Ser Glu Asp Pro Val Thr Met Met
330 335 340

gat tcc att ttg aat gat aac atc aat ctt ttg gga aag gtt gag ctg 1168
Asp Ser Ile Leu Asn Asp Asn Ile Asn Leu Leu Gly Lys Val Glu Leu
345 350 355 360

ttg gat tat ctt gac agt att gac tgc agt tta gag gac ttc cag gcc 1216
Leu Asp Tyr Leu Asp Ser Ile Asp Cys Ser Leu Glu Asp Phe Gln Ala
365 370 375

atg cta tca gga aga caa ttt agc ata gac cca gat ctc ctg gtt gat 1264
Met Leu Ser Gly Arg Gln Phe Ser Ile Asp Pro Asp Leu Leu Val Asp
380 385 390

ctt ttc act agt tct gtg cag atg aat ccc aca gat tac atc aat aat 1312
Leu Phe Thr Ser Ser Val Gln Met Asn Pro Thr Asp Tyr Ile Asn Asn
395 400 405

aca aaa tct gag aat aaa gga tta gaa act acc aag aac aat gta gtt 1360
Thr Lys Ser Glu Asn Lys Gly Leu Glu Thr Thr Lys Asn Asn Val Val
410 415 420

cag cca gtt tcg gaa gag gga aga aaa tct aaa tcc aaa cca gat aag 1408
Gln Pro Val Ser Glu Glu Gly Arg Lys Ser Lys Ser Lys Pro Asp Lys
425 430 435 440

cag ctt atc cag tat acc gcc ttt cca ctt ctt gca ttc ctc gat ggg 1456
Gln Leu Ile Gln Tyr Thr Ala Phe Pro Leu Leu Ala Phe Leu Asp Gly
445 450 455

aac cct gct tct tct gtt gaa cag gcg agt aca aca gca tca tca gaa 1504
Asn Pro Ala Ser Ser Val Glu Gln Ala Ser Thr Thr Ala Ser Ser Glu
460 465 470

gtt ttg tcc tct gta gat aaa ccc ata gaa gtt gat gag ctt ctg gat 1552
Val Leu Ser Ser Val Asp Lys Pro Ile Glu Val Asp Glu Leu Leu Asp
475 480 485

agc agc cta gac cca gaa cca acc caa agt aag ctt gtt cgc ctg gag 1600
Ser Ser Leu Asp Pro Glu Pro Thr Gln Ser Lys Leu Val Arg Leu Glu
490 495 500

cca ttg act gaa gct gaa gct agt gaa gct aca ctg ttt tat tta tgt 1648
Pro Leu Thr Glu Ala Glu Ala Ser Glu Ala Thr Leu Phe Tyr Leu Cys
505 510 515 520

gaa ctt gct cct gca cct ctg gat agt gat atg cca ctt tta gat agc 1696
Glu Leu Ala Pro Ala Pro Leu Asp Ser Asp Met Pro Leu Leu Asp Ser
525 530 535

taa atccccagga agtggacttt acatgtatat attcatcaaa atgatgaact 1749

atttatttta aagtatcatt tggtactttt tttgtaaatt gctttgtttt gtttaatcag 1809

atactgtgga ataaaagcac cttttgcttt tctcactaac cacacactct tgcagagctt 1869

tcaggtgtta ctcagctgca tagttacgca gatgtaatgc acattattgg cgtatcttta 1929

agttggattc aaatggccat ttttctccaa ttttggtaaa ttggatatct ttttttaca 1989

aatacgacca ttaacctcag ttaaattttt gtttgttttc ctgtttgatg ctgtctattt 2049

gcattgagtg taagtcattt gaactaatgg tataactcct aaagcttctc tgctccagtt 2109

atttttatta aatatttttc acttggctta tttttaaaac tgggaacata aagtgcctgt 2169

atcttgtaaa acttcatttg tttcttttgg ttcagagaag ttcatttatg ttcaaagacg 2229

tttattcatg ttcaacagga aagacaaagt gtacgtgaat gctcgctgtc tgatagggtt 2289

ccagctccat atatatagaa agatcggggg tgggatggga tggagtgagc cccatccagt 2349

tagttggact agttttaaat aaaggttttc cggtttgtgt ttttttgaac catactgttt 2409

ag 2411

<210> 18
<211> 536
<212> PRT
<213> Homo sapiens

<400> 18

Met Lys Gln Ser Ser Asn Val Pro Ala Phe Leu Ser Lys Leu Trp Thr
1 5 10 15

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

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

Leu Pro Lys Tyr Phe Lys His Asn Asn Met Ala Ser Phe Val Arg Gln
50 55 60

Leu Asn Met Tyr Gly Phe Arg Lys Val Val His Ile Asp Ser Gly Ile
65 70 75 80

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

Lys Gln Gly Gln Asp Asp Leu Leu Glu Asn Ile Lys Arg Lys Val Ser
100 105 110

Ser Ser Lys Pro Glu Glu Asn Lys Ile Arg Gln Glu Asp Leu Thr Lys
115 120 125

Ile Ile Ser Ser Ala Gln Lys Val Gln Ile Lys Gln Glu Thr Ile Glu
130 135 140

Ser Arg Leu Ser Glu Leu Lys Ser Glu Asn Glu Ser Leu Trp Lys Glu
145 150 155 160

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

Lys Ile Val Gln Phe Ile Val Thr Leu Val Gln Asn Asn Gln Leu Val
180 185 190

Ser Leu Lys Arg Lys Arg Pro Leu Leu Leu Asn Thr Asn Gly Ala Gln

195 200 205

Lys Lys Asn Leu Phe Gln His Ile Val Lys Glu Pro Thr Asp Asn His
210 215 220

His His Lys Val Pro His Ser Arg Thr Glu Gly Leu Lys Pro Arg Glu
225 230 235 240

Arg Ile Ser Asp Asp Ile Ile Ile Tyr Asp Val Thr Asp Asp Asn Ala
245 250 255

Asp Glu Glu Asn Ile Pro Val Ile Pro Glu Thr Asn Glu Asp Val Ile
260 265 270

Ser Asp Pro Ser Asn Cys Ser Gln Tyr Pro Asp Ile Val Ile Val Glu
275 280 285

Asp Asp Asn Glu Asp Glu Tyr Ala Pro Val Ile Gln Ser Gly Glu Gln
290 295 300

Asn Glu Pro Ala Arg Glu Ser Leu Ser Ser Gly Ser Asp Gly Ser Ser
305 310 315 320

Pro Leu Met Ser Ser Ala Val Gln Leu Asn Gly Ser Ser Ser Leu Thr
325 330 335

Ser Glu Asp Pro Val Thr Met Met Asp Ser Ile Leu Asn Asp Asn Ile
340 345 350

Asn Leu Leu Gly Lys Val Glu Leu Leu Asp Tyr Leu Asp Ser Ile Asp
355 360 365

Cys Ser Leu Glu Asp Phe Gln Ala Met Leu Ser Gly Arg Gln Phe Ser
370 375 380

Ile Asp Pro Asp Leu Leu Val Asp Leu Phe Thr Ser Ser Val Gln Met
385 390 395 400

Asn Pro Thr Asp Tyr Ile Asn Asn Thr Lys Ser Glu Asn Lys Gly Leu
405 410 415

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

Lys Ser Lys Ser Lys Pro Asp Lys Gln Leu Ile Gln Tyr Thr Ala Phe
435 440 445

Pro Leu Leu Ala Phe Leu Asp Gly Asn Pro Ala Ser Ser Val Glu Gln
450 455 460

Ala Ser Thr Thr Ala Ser Ser Glu Val Leu Ser Ser Val Asp Lys Pro
465 470 475 480

Ile Glu Val Asp Glu Leu Leu Asp Ser Ser Leu Asp Pro Glu Pro Thr
485 490 495

Gln Ser Lys Leu Val Arg Leu Glu Pro Leu Thr Glu Ala Glu Ala Ser
500 505 510

Glu Ala Thr Leu Phe Tyr Leu Cys Glu Leu Ala Pro Ala Pro Leu Asp
515 520 525

Ser Asp Met Pro Leu Leu Asp Ser
530 535

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<213> Homo sapiens

<220>
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<222> (5)..(1396)

<400> 19
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Met Val Gln Glu Ala Pro Ala Ala Leu Pro Thr Glu Pro Gly Pro

1 5 10 15

agc ccc gtg cct gcc ttc ctc ggc aag cta tgg gcg ctg gtg ggg gac 97
Ser Pro Val Pro Ala Phe Leu Gly Lys Leu Trp Ala Leu Val Gly Asp
20 25 30

cca ggc aca gac cac ctg atc cgc tgg agc ccg agc ggg acc agt ttc 145
Pro Gly Thr Asp His Leu Ile Arg Trp Ser Pro Ser Gly Thr Ser Phe
35 40 45

ctc gta agc gac cag agc cgt ttc gcc aag gaa gtg ctg ccc cag tat 193
Leu Val Ser Asp Gln Ser Arg Phe Ala Lys Glu Val Leu Pro Gln Tyr
50 55 60

ttc aag cat agc aac atg gcg agc ttc gtg cgc caa ctc aac atg tac 241
Phe Lys His Ser Asn Met Ala Ser Phe Val Arg Gln Leu Asn Met Tyr
65 70 75

ggt ttt cgg aag gtg gtg agc atc gag cag ggc ggc ctg ctt agg ccg 289
Gly Phe Arg Lys Val Val Ser Ile Glu Gln Gly Gly Leu Leu Arg Pro
80 85 90 95

gag cgc gac cac gtc gag ttc cag cac ccg agc ttc gtg cgc ggc cgc 337
Glu Arg Asp His Val Glu Phe Gln His Pro Ser Phe Val Arg Gly Arg
100 105 110

gag cag cta ctg gag cgc gtg cgg cgc aag gtg ccc gcg ctg cgc ggc 385
Glu Gln Leu Leu Glu Arg Val Arg Arg Lys Val Pro Ala Leu Arg Gly
115 120 125

gac gac ggc cgc tgg cgc ccg gag gac ctg ggt cga cta ctg ggc gag 433
Asp Asp Gly Arg Trp Arg Pro Glu Asp Leu Gly Arg Leu Leu Gly Glu
130 135 140

gtg cag gct ttg cgg gga gtg cag gag agc acc gag gcg cgg ctg cgg 481
Val Gln Ala Leu Arg Gly Val Gln Glu Ser Thr Glu Ala Arg Leu Arg
145 150 155

gag ctc agg cag cag aac gag atc ttg tgg cgg gag gtg gtg aca ctt 529
Glu Leu Arg Gln Gln Asn Glu Ile Leu Trp Arg Glu Val Val Thr Leu
160 165 170 175

cgg cag agc cac ggt cag cag cac cgg gtc att ggc aag ctg atc cag 577
Arg Gln Ser His Gly Gln Gln His Arg Val Ile Gly Lys Leu Ile Gln
180 185 190

tgt ctc ttt ggg cca ctt cag gcg ggg ccg agc aat gca gga ggc aag 625
Cys Leu Phe Gly Pro Leu Gln Ala Gly Pro Ser Asn Ala Gly Gly Lys
195 200 205

aga aag ctg tcc ctg atg ctg gat gag ggg agc tca tgc cca aca cct 673
Arg Lys Leu Ser Leu Met Leu Asp Glu Gly Ser Ser Cys Pro Thr Pro
210 215 220

gcc aag ttc aac acc tgc cct cta cct ggt gcc ctt ctg cag gac ccc 721
Ala Lys Phe Asn Thr Cys Pro Leu Pro Gly Ala Leu Leu Gln Asp Pro
225 230 235

tac ttc atc cag tcg cct tct act tac agc ctc tcc cag aga caa att 769
Tyr Phe Ile Gln Ser Pro Ser Thr Tyr Ser Leu Ser Gln Arg Gln Ile
240 245 250 255

tgg gcc tta gcc ctc aca ggg cca ggg gcc cca tca tct ctg aca tcc 817
Trp Ala Leu Ala Leu Thr Gly Pro Gly Ala Pro Ser Ser Leu Thr Ser
260 265 270

cag aag act ctc cat ccc ctg agg gga cca ggc ttt ctc cct cca gtg 865
Gln Lys Thr Leu His Pro Leu Arg Gly Pro Gly Phe Leu Pro Pro Val
275 280 285

atg gca gga gcc ccc ccg cca ctg cct gtg gct gtg gtg cag gcc atc 913
Met Ala Gly Ala Pro Pro Pro Leu Pro Val Ala Val Val Gln Ala Ile
290 295 300

ctg gaa ggg aaa ggg agc ttc agc ccc gag ggg ccc agg aat gcc caa 961
Leu Glu Gly Lys Gly Ser Phe Ser Pro Glu Gly Pro Arg Asn Ala Gln
305 310 315

cag cct gaa cca ggg gat ccc agg gag ata cct gac agg ggg cct ctg 1009
Gln Pro Glu Pro Gly Asp Pro Arg Glu Ile Pro Asp Arg Gly Pro Leu
320 325 330 335

ggc ctg gaa agc ggg gac agg agc cca gag agt ctg ctg cct ccg atg 1057
Gly Leu Glu Ser Gly Asp Arg Ser Pro Glu Ser Leu Leu Pro Pro Met
340 345 350

ctg ctt cag ccc cct caa gaa agt gtg gaa cct gca ggg cct cta gat 1105
Leu Leu Gln Pro Pro Gln Glu Ser Val Glu Pro Ala Gly Pro Leu Asp
355 360 365

gtg ctg ggc ccc agt ctc caa ggg cga gaa tgg acc ctg atg gac ttg 1153
Val Leu Gly Pro Ser Leu Gln Gly Arg Glu Trp Thr Leu Met Asp Leu
370 375 380

gac atg gag ctg tcc ttg atg cag ccc ttg gtt cca gag cgg ggt gag 1201
Asp Met Glu Leu Ser Leu Met Gln Pro Leu Val Pro Glu Arg Gly Glu
385 390 395

cct gag ctg gcg gtc aag ggg tta aat tct cca agc cca ggg aag gac 1249
Pro Glu Leu Ala Val Lys Gly Leu Asn Ser Pro Ser Pro Gly Lys Asp

400 405 410 415

ccc acg ctc ggg gcc cca ctc ctg ctg gat gtc cag gcg gcc ttg gga 1297
Pro Thr Leu Gly Ala Pro Leu Leu Leu Asp Val Gln Ala Ala Leu Gly
420 425 430

ggc cca gcc ctg ggc ctg cct ggg gct tta acc att tat agc act cct 1345
Gly Pro Ala Leu Gly Leu Pro Gly Ala Leu Thr Ile Tyr Ser Thr Pro
435 440 445

gag agc cgg act gcc tcc tac ttg ggc ccg gaa gcc agt ccc tcc ccc 1393
Glu Ser Arg Thr Ala Ser Tyr Leu Gly Pro Glu Ala Ser Pro Ser Pro
450 455 460

taa gaccccgcgc ctctgaaggg gcttggaacc agtccgccgc tgcacatcct 1446

tcttggcttc ctggccgcct acgggggtga gcgaagcccc cactactaaa tggcctctct 1506

ccactacccc gactatccct gcacataaac tccgtttttt tttttcacc 1555

<210> 20
<211> 463
<212> PRT
<213> Homo sapiens

<400> 20

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

Pro Val Pro Ala Phe Leu Gly Lys Leu Trp Ala Leu Val Gly Asp Pro
20 25 30

Gly Thr Asp His Leu Ile Arg Trp Ser Pro Ser Gly Thr Ser Phe Leu
35 40 45

Val Ser Asp Gln Ser Arg Phe Ala Lys Glu Val Leu Pro Gln Tyr Phe
50 55 60

Lys His Ser Asn Met Ala Ser Phe Val Arg Gln Leu Asn Met Tyr Gly
65 70 75 80

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

Arg Asp His Val Glu Phe Gln His Pro Ser Phe Val Arg Gly Arg Glu
100 105 110

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

Asp Gly Arg Trp Arg Pro Glu Asp Leu Gly Arg Leu Leu Gly Glu Val
130 135 140

Gln Ala Leu Arg Gly Val Gln Glu Ser Thr Glu Ala Arg Leu Arg Glu
145 150 155 160

Leu Arg Gln Gln Asn Glu Ile Leu Trp Arg Glu Val Val Thr Leu Arg
165 170 175

Gln Ser His Gly Gln Gln His Arg Val Ile Gly Lys Leu Ile Gln Cys
180 185 190

Leu Phe Gly Pro Leu Gln Ala Gly Pro Ser Asn Ala Gly Gly Lys Arg
195 200 205

Lys Leu Ser Leu Met Leu Asp Glu Gly Ser Ser Cys Pro Thr Pro Ala
210 215 220

Lys Phe Asn Thr Cys Pro Leu Pro Gly Ala Leu Leu Gln Asp Pro Tyr
225 230 235 240

Phe Ile Gln Ser Pro Ser Thr Tyr Ser Leu Ser Gln Arg Gln Ile Trp
245 250 255

Ala Leu Ala Leu Thr Gly Pro Gly Ala Pro Ser Ser Leu Thr Ser Gln
260 265 270

Lys Thr Leu His Pro Leu Arg Gly Pro Gly Phe Leu Pro Pro Val Met
275 280 285

Ala Gly Ala Pro Pro Pro Leu Pro Val Ala Val Val Gln Ala Ile Leu
290 295 300

Glu Gly Lys Gly Ser Phe Ser Pro Glu Gly Pro Arg Asn Ala Gln Gln
305 310 315 320

Pro Glu Pro Gly Asp Pro Arg Glu Ile Pro Asp Arg Gly Pro Leu Gly
325 330 335

Leu Glu Ser Gly Asp Arg Ser Pro Glu Ser Leu Leu Pro Pro Met Leu
340 345 350

Leu Gln Pro Pro Gln Glu Ser Val Glu Pro Ala Gly Pro Leu Asp Val
355 360 365

Leu Gly Pro Ser Leu Gln Gly Arg Glu Trp Thr Leu Met Asp Leu Asp
370 375 380

Met Glu Leu Ser Leu Met Gln Pro Leu Val Pro Glu Arg Gly Glu Pro
385 390 395 400

Glu Leu Ala Val Lys Gly Leu Asn Ser Pro Ser Pro Gly Lys Asp Pro
405 410 415

Thr Leu Gly Ala Pro Leu Leu Leu Asp Val Gln Ala Ala Leu Gly Gly
420 425 430

Pro Ala Leu Gly Leu Pro Gly Ala Leu Thr Ile Tyr Ser Thr Pro Glu
435 440 445

Ser Arg Thr Ala Ser Tyr Leu Gly Pro Glu Ala Ser Pro Ser Pro
450 455 460

<210> 21
<211> 1550
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (95)..(1048)

<400> 21
tgccgccgtc ccgcccgcca gcgccccagc gaggaagcag cgcgcagccc gcggcccagc 60

gcacccgcag cagcgcccgc agctcgtccg cgcc atg ttc cag gcg gcc gag cgc 115
Met Phe Gln Ala Ala Glu Arg
1 5

ccc cag gag tgg gcc atg gag ggc ccc cgc gac ggg ctg aag aag gag 163
Pro Gln Glu Trp Ala Met Glu Gly Pro Arg Asp Gly Leu Lys Lys Glu
10 15 20

cgg cta ctg gac gac cgc cac gac agc ggc ctg gac tcc atg aaa gac 211
Arg Leu Leu Asp Asp Arg His Asp Ser Gly Leu Asp Ser Met Lys Asp
25 30 35

gag gag tac gag cag atg gtc aag gag ctg cag gag atc cgc ctc gag 259
Glu Glu Tyr Glu Gln Met Val Lys Glu Leu Gln Glu Ile Arg Leu Glu
40 45 50 55

ccg cag gag gtg ccg cgc ggc tcg gag ccc tgg aag cag cag ctc acc 307
Pro Gln Glu Val Pro Arg Gly Ser Glu Pro Trp Lys Gln Gln Leu Thr
60 65 70

gag gac ggg gac tcg ttc ctg cac ttg gcc atc atc cat gaa gaa aag 355
Glu Asp Gly Asp Ser Phe Leu His Leu Ala Ile Ile His Glu Glu Lys
75 80 85

gca ctg acc atg gaa gtg atc cgc cag gtg aag gga gac ctg gct ttc 403
Ala Leu Thr Met Glu Val Ile Arg Gln Val Lys Gly Asp Leu Ala Phe
90 95 100

ctc aac ttc cag aac aac ctg cag cag act cca ctc cac ttg gct gtg 451
Leu Asn Phe Gln Asn Asn Leu Gln Gln Thr Pro Leu His Leu Ala Val
105 110 115

atc acc aac cag cca gaa att gct gag gca ctt ctg gga gct ggc tgt 499
Ile Thr Asn Gln Pro Glu Ile Ala Glu Ala Leu Leu Gly Ala Gly Cys
120 125 130 135

gat cct gag ctc cga gac ttt cga gga aat acc ccc cta cac ctt gcc 547
Asp Pro Glu Leu Arg Asp Phe Arg Gly Asn Thr Pro Leu His Leu Ala
140 145 150

tgt gag cag ggc tgc ctg gcc agc gtg gga gtc ctg act cag tcc tgc 595
Cys Glu Gln Gly Cys Leu Ala Ser Val Gly Val Leu Thr Gln Ser Cys
155 160 165

acc acc ccg cac ctc cac tcc atc ctg aag gct acc aac tac aat ggc 643
Thr Thr Pro His Leu His Ser Ile Leu Lys Ala Thr Asn Tyr Asn Gly
170 175 180

cac acg tgt cta cac tta gcc tct atc cat ggc tac ctg ggc atc gtg 691
His Thr Cys Leu His Leu Ala Ser Ile His Gly Tyr Leu Gly Ile Val
185 190 195

gag ctt ttg gtg tcc ttg ggt gct gat gtc aat gct cag gag ccc tgt 739
Glu Leu Leu Val Ser Leu Gly Ala Asp Val Asn Ala Gln Glu Pro Cys
200 205 210 215

aat ggc cgg act gcc ctt cac ctc gca gtg gac ctg caa aat cct gac 787
Asn Gly Arg Thr Ala Leu His Leu Ala Val Asp Leu Gln Asn Pro Asp
220 225 230

ctg gtg tca ctc ctg ttg aag tgt ggg gct gat gtc aac aga gtt acc 835
Leu Val Ser Leu Leu Leu Lys Cys Gly Ala Asp Val Asn Arg Val Thr
235 240 245

tac cag ggc tat tct ccc tac cag ctc acc tgg ggc cgc cca agc acc 883
Tyr Gln Gly Tyr Ser Pro Tyr Gln Leu Thr Trp Gly Arg Pro Ser Thr
250 255 260

cgg ata cag cag cag ctg ggc cag ctg aca cta gaa aac ctt cag atg 931
Arg Ile Gln Gln Gln Leu Gly Gln Leu Thr Leu Glu Asn Leu Gln Met
265 270 275

ctg cca gag agt gag gat gag gag agc tat gac aca gag tca gag ttc 979
Leu Pro Glu Ser Glu Asp Glu Glu Ser Tyr Asp Thr Glu Ser Glu Phe
280 285 290 295

acg gag ttc aca gag gac gag ctg ccc tat gat gac tgt gtg ttt gga 1027
Thr Glu Phe Thr Glu Asp Glu Leu Pro Tyr Asp Asp Cys Val Phe Gly
300 305 310

ggc cag cgt ctg acg tta tga gtgcaaaggg gctgaaagaa catggacttg 1078
Gly Gln Arg Leu Thr Leu
315

tatatttgta caaaaaaaaa gttttatttt tctaaaaaaa gaaaaaagaa gaaaaaattt 1138

aaagggtgta cttatatcca cactgcacac tgcctagccc aaaacgtctt attgtggtag 1198

gatcagccct cattttgttg cttttgtgaa ctttttgtag gggacgagaa agatcattga 1258

aattctgaga aaacttcttt taaacctcac ctttgtgggg tttttggaga aggttatcaa 1318

aaatttcatg gaaggaccac attttatatt tattgtgctt cgagtgactg accccagtgg 1378

tatcctgtga catgtaacag ccaggagtgt taagcgttca gtgatgtggg gtgaaaagtt 1438

actacctgtc aaggtttgtg ttaccctcct gtaaatggtg tacataatgt attgttggta 1498

attattttgg tacttttatg atgtatattt attaaagaga ttttacaaa tg 1550

<210> 22
<211> 317
<212> PRT
<213> Homo sapiens

<400> 22

Met Phe Gln Ala Ala Glu Arg Pro Gln Glu Trp Ala Met Glu Gly Pro
1 5 10 15

Arg Asp Gly Leu Lys Lys Glu Arg Leu Leu Asp Asp Arg His Asp Ser
20 25 30

Gly Leu Asp Ser Met Lys Asp Glu Glu Tyr Glu Gln Met Val Lys Glu
35 40 45

Leu Gln Glu Ile Arg Leu Glu Pro Gln Glu Val Pro Arg Gly Ser Glu
50 55 60

Pro Trp Lys Gln Gln Leu Thr Glu Asp Gly Asp Ser Phe Leu His Leu
65 70 75 80

Ala Ile Ile His Glu Glu Lys Ala Leu Thr Met Glu Val Ile Arg Gln
85 90 95

Val Lys Gly Asp Leu Ala Phe Leu Asn Phe Gln Asn Asn Leu Gln Gln
100 105 110

Thr Pro Leu His Leu Ala Val Ile Thr Asn Gln Pro Glu Ile Ala Glu
115 120 125

Ala Leu Leu Gly Ala Gly Cys Asp Pro Glu Leu Arg Asp Phe Arg Gly
130 135 140

Asn Thr Pro Leu His Leu Ala Cys Glu Gln Gly Cys Leu Ala Ser Val
145 150 155 160

Gly Val Leu Thr Gln Ser Cys Thr Thr Pro His Leu His Ser Ile Leu
165 170 175

Lys Ala Thr Asn Tyr Asn Gly His Thr Cys Leu His Leu Ala Ser Ile
180 185 190

His Gly Tyr Leu Gly Ile Val Glu Leu Leu Val Ser Leu Gly Ala Asp
195 200 205

Val Asn Ala Gln Glu Pro Cys Asn Gly Arg Thr Ala Leu His Leu Ala
210 215 220

Val Asp Leu Gln Asn Pro Asp Leu Val Ser Leu Leu Leu Lys Cys Gly
225 230 235 240

Ala Asp Val Asn Arg Val Thr Tyr Gln Gly Tyr Ser Pro Tyr Gln Leu
245 250 255

Thr Trp Gly Arg Pro Ser Thr Arg Ile Gln Gln Gln Leu Gly Gln Leu
260 265 270

Thr Leu Glu Asn Leu Gln Met Leu Pro Glu Ser Glu Asp Glu Glu Ser
275 280 285

Tyr Asp Thr Glu Ser Glu Phe Thr Glu Phe Thr Glu Asp Glu Leu Pro
290 295 300

Tyr Asp Asp Cys Val Phe Gly Gly Gln Arg Leu Thr Leu
305 310 315

<210> 23
<211> 2880
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (142)..(2850)

<400> 23
gcttctggag ggaggcggca gcgacggagg agggggcttc tcagagaaag ggagggaggg 60

agccacccgg gtgaagatac agcagcctcc tgaactcccc cctcccaccc aggccgggac 120

ctgggggctc ctgccggatc c atg ggg gcg gcc agc tgc gag gat gag gag 171
Met Gly Ala Ala Ser Cys Glu Asp Glu Glu
1 5 10

ctg gaa ttt aag ctg gtg ttc ggg gag gaa aag gag gcc ccc ccg ctg 219
Leu Glu Phe Lys Leu Val Phe Gly Glu Glu Lys Glu Ala Pro Pro Leu
15 20 25

ggc gcg ggg gga ttg ggg gaa gaa ctg gac tca gag gat gcc ccg cca 267
Gly Ala Gly Gly Leu Gly Glu Glu Leu Asp Ser Glu Asp Ala Pro Pro
30 35 40

tgc tgc cgt ctg gcc ttg gga gag ccc cct ccc tat ggc gct gca cct 315
Cys Cys Arg Leu Ala Leu Gly Glu Pro Pro Pro Tyr Gly Ala Ala Pro
45 50 55

atc ggt att ccc cga cct cca ccc cct cgg cct ggc atg cat tcg cca 363
Ile Gly Ile Pro Arg Pro Pro Pro Pro Arg Pro Gly Met His Ser Pro
60 65 70

ccg ccg cga cca gcc ccc tca cct ggc acc tgg gag agc cag ccc gcc 411
Pro Pro Arg Pro Ala Pro Ser Pro Gly Thr Trp Glu Ser Gln Pro Ala
75 80 85 90

agg tcg gtg agg ctg gga gga cca gga ggg ggt gct ggg ggt gct ggg 459
Arg Ser Val Arg Leu Gly Gly Pro Gly Gly Gly Ala Gly Gly Ala Gly
95 100 105

ggt ggc cgt gtt ctc gag tgt ccc agc atc cgc atc acc tcc atc tct 507
Gly Gly Arg Val Leu Glu Cys Pro Ser Ile Arg Ile Thr Ser Ile Ser
110 115 120

ccc acg ccg gag ccg cca gca gcg ctg gag gac aac cct gat gcc tgg 555
Pro Thr Pro Glu Pro Pro Ala Ala Leu Glu Asp Asn Pro Asp Ala Trp
125 130 135

ggg gac ggc tct cct aga gat tac ccc cca cca gaa ggc ttt ggg ggc 603
Gly Asp Gly Ser Pro Arg Asp Tyr Pro Pro Pro Glu Gly Phe Gly Gly
140 145 150

tac aga gaa gca ggg gcc cag ggt ggg ggg gcc ttc ttc agc cca agc 651
Tyr Arg Glu Ala Gly Ala Gln Gly Gly Gly Ala Phe Phe Ser Pro Ser
155 160 165 170

cct ggc agc agc agc ctg tcc tcg tgg agc ttc ttc tcc gat gcc tct 699
Pro Gly Ser Ser Ser Leu Ser Ser Trp Ser Phe Phe Ser Asp Ala Ser
175 180 185

gac gag gca gcc ctg tat gca gcc tgc gac gag gtg gag tct gag cta 747
Asp Glu Ala Ala Leu Tyr Ala Ala Cys Asp Glu Val Glu Ser Glu Leu
190 195 200

aat gag gcg gcc tcc cgc ttt ggc ctg ggc tcc ccg ctg ccc tcg ccc 795
Asn Glu Ala Ala Ser Arg Phe Gly Leu Gly Ser Pro Leu Pro Ser Pro
205 210 215

cgg gcc tcc cct cgg cca tgg acc ccc gaa gat ccc tgg agc ctg tat 843
Arg Ala Ser Pro Arg Pro Trp Thr Pro Glu Asp Pro Trp Ser Leu Tyr
220 225 230

ggt cca agc ccc gga ggc cga ggg cca gag gat agc tgg cta ctc ctc 891
Gly Pro Ser Pro Gly Gly Arg Gly Pro Glu Asp Ser Trp Leu Leu Leu
235 240 245 250

agt gct cct ggg ccc acc cca gcc tcc ccg cgg cct gcc tct cca tgt 939
Ser Ala Pro Gly Pro Thr Pro Ala Ser Pro Arg Pro Ala Ser Pro Cys
255 260 265

ggc aag cgg cgc tat tcc agc tcg gga acc cca tct tca gcc tcc cca 987
Gly Lys Arg Arg Tyr Ser Ser Ser Gly Thr Pro Ser Ser Ala Ser Pro
270 275 280

gct ctg tcc cgc cgt ggc agc ctg ggg gaa gag ggg tct gag cca cct 1035
Ala Leu Ser Arg Arg Gly Ser Leu Gly Glu Glu Gly Ser Glu Pro Pro
285 290 295

cca cca ccc cca ttg cct ctg gcc cgg gac ccg ggc tcc cct ggt ccc 1083
Pro Pro Pro Pro Leu Pro Leu Ala Arg Asp Pro Gly Ser Pro Gly Pro
300 305 310

ttt gac tat gtg ggg gcc cca cca gct gag agc atc cct cag aag aca 1131
Phe Asp Tyr Val Gly Ala Pro Pro Ala Glu Ser Ile Pro Gln Lys Thr
315 320 325 330

cgg cgg act tcc agc gag cag gca gtg gct ctg cct cgg tct gag gag 1179
Arg Arg Thr Ser Ser Glu Gln Ala Val Ala Leu Pro Arg Ser Glu Glu
335 340 345

cct gcc tca tgc aat ggg aag ctg ccc ttg gga gca gag gag tct gtg 1227
Pro Ala Ser Cys Asn Gly Lys Leu Pro Leu Gly Ala Glu Glu Ser Val

350 355 360

gct cct cca gga ggt tcc cgg aag gag gtg gct ggc atg gac tac ctg 1275
Ala Pro Pro Gly Gly Ser Arg Lys Glu Val Ala Gly Met Asp Tyr Leu
365 370 375

gca gtg ccc tcc cca ctc gct tgg tcc aag gcc cgg att ggg gga cac 1323
Ala Val Pro Ser Pro Leu Ala Trp Ser Lys Ala Arg Ile Gly Gly His
380 385 390

agc cct atc ttc agg acc tct gcc cta ccc cca ctg gac tgg cct ctg 1371
Ser Pro Ile Phe Arg Thr Ser Ala Leu Pro Pro Leu Asp Trp Pro Leu
395 400 405 410

ccc agc caa tat gag cag ctg gag ctg agg atc gag gta cag cct aga 1419
Pro Ser Gln Tyr Glu Gln Leu Glu Leu Arg Ile Glu Val Gln Pro Arg
415 420 425

gcc cac cac cgg gcc cac tat gag aca gaa ggc agc cgt gga gct gtc 1467
Ala His His Arg Ala His Tyr Glu Thr Glu Gly Ser Arg Gly Ala Val
430 435 440

aaa gct gcc cct ggc ggt cac ccc gta gtc aag ctc cta ggc tac agt 1515
Lys Ala Ala Pro Gly Gly His Pro Val Val Lys Leu Leu Gly Tyr Ser
445 450 455

gag aag cca ctg acc cta cag atg ttc atc ggc act gca gat gaa agg 1563
Glu Lys Pro Leu Thr Leu Gln Met Phe Ile Gly Thr Ala Asp Glu Arg
460 465 470

aac ctg cgg cct cat gcc ttc tat cag gtg cac cgt atc aca ggc aag 1611
Asn Leu Arg Pro His Ala Phe Tyr Gln Val His Arg Ile Thr Gly Lys
475 480 485 490

atg gtg gcc acg gcc agc tat gaa gcc gta gtc agt ggc acc aag gtg 1659
Met Val Ala Thr Ala Ser Tyr Glu Ala Val Val Ser Gly Thr Lys Val
495 500 505

ttg gag atg act ctg ctg cct gag aac aac atg gcg gcc aac att gac 1707
Leu Glu Met Thr Leu Leu Pro Glu Asn Asn Met Ala Ala Asn Ile Asp
510 515 520

tgc gcg gga atc ctg aag ctt cgg aat tca gac att gag ctt cgg aag 1755
Cys Ala Gly Ile Leu Lys Leu Arg Asn Ser Asp Ile Glu Leu Arg Lys
525 530 535

ggt gag acg gac atc ggg cgc aaa aac aca cgt gta cgg ctg gtg ttc 1803
Gly Glu Thr Asp Ile Gly Arg Lys Asn Thr Arg Val Arg Leu Val Phe
540 545 550

cgg gta cac gtg ccc cag ggc ggc ggg aag gtc gtc tca gta cag gca 1851
Arg Val His Val Pro Gln Gly Gly Gly Lys Val Val Ser Val Gln Ala
555 560 565 570

gca tcg gtg ccc atc gag tgc tcc cag cgc tca gcc cag gag ctg ccc 1899
Ala Ser Val Pro Ile Glu Cys Ser Gln Arg Ser Ala Gln Glu Leu Pro
575 580 585

cag gtg gag gcc tac agc ccc agt gcc tgc tct gtg aga gga ggc gag 1947
Gln Val Glu Ala Tyr Ser Pro Ser Ala Cys Ser Val Arg Gly Gly Glu
590 595 600

gaa ctg gta ctg acc ggc tcc aac ttc ctg cca gac tcc aag gtg gtg 1995
Glu Leu Val Leu Thr Gly Ser Asn Phe Leu Pro Asp Ser Lys Val Val
605 610 615

ttc att gag agg ggt cct gat ggg aag ctg caa tgg gag gag gag gcc 2043
Phe Ile Glu Arg Gly Pro Asp Gly Lys Leu Gln Trp Glu Glu Glu Ala
620 625 630

aca gtg aac cga ctg cag agc aac gag gtg acg ctg acc ctg act gtc 2091
Thr Val Asn Arg Leu Gln Ser Asn Glu Val Thr Leu Thr Leu Thr Val
635 640 645 650

ccc gag tac agc aac aag agg gtt tcc cgg cca gtc cag gtc tac ttt 2139
Pro Glu Tyr Ser Asn Lys Arg Val Ser Arg Pro Val Gln Val Tyr Phe
655 660 665

tat gtc tcc aat ggg cgg agg aaa cgc agt cct acc cag agt ttc agg 2187
Tyr Val Ser Asn Gly Arg Arg Lys Arg Ser Pro Thr Gln Ser Phe Arg
670 675 680

ttt ctg cct gtg atc tgc aaa gag gag ccc cta ccg gac tca tct ctg 2235
Phe Leu Pro Val Ile Cys Lys Glu Glu Pro Leu Pro Asp Ser Ser Leu
685 690 695

cgg ggt ttc cct tca gca tcg gca acc ccc ttt ggc act gac atg gac 2283
Arg Gly Phe Pro Ser Ala Ser Ala Thr Pro Phe Gly Thr Asp Met Asp
700 705 710

ttc tca cca ccc agg ccc ccc tac ccc tcc tat ccc cat gaa gac cct 2331
Phe Ser Pro Pro Arg Pro Pro Tyr Pro Ser Tyr Pro His Glu Asp Pro
715 720 725 730

gct tgc gaa act cct tac cta tca gaa ggc ttc ggc tat ggc atg ccc 2379
Ala Cys Glu Thr Pro Tyr Leu Ser Glu Gly Phe Gly Tyr Gly Met Pro
735 740 745

cct ctg tac ccc cag acg ggg ccc cca cca tcc tac aga ccg ggc ctg 2427
Pro Leu Tyr Pro Gln Thr Gly Pro Pro Pro Ser Tyr Arg Pro Gly Leu

750 755 760

cgg atg ttc cct gag act agg ggt acc aca ggt tgt gcc caa cca cct 2475
Arg Met Phe Pro Glu Thr Arg Gly Thr Thr Gly Cys Ala Gln Pro Pro
765 770 775

gca gtt tcc ttc ctt ccc cgc ccc ttc cct agt gac ccg tat gga ggg 2523
Ala Val Ser Phe Leu Pro Arg Pro Phe Pro Ser Asp Pro Tyr Gly Gly
780 785 790

cgg ggc tcc tct ttc ccc ctg ggg ctg cca ttc tct ccg cca gcc ccc 2571
Arg Gly Ser Ser Phe Pro Leu Gly Leu Pro Phe Ser Pro Pro Ala Pro
795 800 805 810

ttt cgg ccg cct cct ctt cct gca tcc cca ccg ctt gaa ggc ccc ttc 2619
Phe Arg Pro Pro Pro Leu Pro Ala Ser Pro Pro Leu Glu Gly Pro Phe
815 820 825

cct tcc cag agt gat gtg cat ccc cta cct gct gag gga tac aat aag 2667
Pro Ser Gln Ser Asp Val His Pro Leu Pro Ala Glu Gly Tyr Asn Lys
830 835 840

gta ggg cca ggc tat ggc cct ggg gag ggg gct ccg gag cag gag aaa 2715
Val Gly Pro Gly Tyr Gly Pro Gly Glu Gly Ala Pro Glu Gln Glu Lys
845 850 855

tcc agg ggt ggc tac agc agc ggc ttt cga gac agt gtc cct atc cag 2763
Ser Arg Gly Gly Tyr Ser Ser Gly Phe Arg Asp Ser Val Pro Ile Gln
860 865 870

ggt atc acg ctg gag gaa gtg agt gag atc att ggc cga gac ctg agt 2811
Gly Ile Thr Leu Glu Glu Val Ser Glu Ile Ile Gly Arg Asp Leu Ser
875 880 885 890

ggc ttc cct gca cct cct gga gaa gag cct cct gcc tga accacgtgaa 2860
Gly Phe Pro Ala Pro Pro Gly Glu Glu Pro Pro Ala
895 900

ctgtcatcac ctggcaaccc 2880

<210> 24
<211> 902
<212> PRT
<213> Homo sapiens

<400> 24

Met Gly Ala Ala Ser Cys Glu Asp Glu Glu Leu Glu Phe Lys Leu Val
1 5 10 15

Phe Gly Glu Glu Lys Glu Ala Pro Pro Leu Gly Ala Gly Gly Leu Gly
20 25 30

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

Gly Glu Pro Pro Pro Tyr Gly Ala Ala Pro Ile Gly Ile Pro Arg Pro
50 55 60

Pro Pro Pro Arg Pro Gly Met His Ser Pro Pro Pro Arg Pro Ala Pro
65 70 75 80

Ser Pro Gly Thr Trp Glu Ser Gln Pro Ala Arg Ser Val Arg Leu Gly
85 90 95

Gly Pro Gly Gly Gly Ala Gly Gly Ala Gly Gly Gly Arg Val Leu Glu
100 105 110

Cys Pro Ser Ile Arg Ile Thr Ser Ile Ser Pro Thr Pro Glu Pro Pro
115 120 125

Ala Ala Leu Glu Asp Asn Pro Asp Ala Trp Gly Asp Gly Ser Pro Arg
130 135 140

Asp Tyr Pro Pro Pro Glu Gly Phe Gly Gly Tyr Arg Glu Ala Gly Ala
145 150 155 160

Gln Gly Gly Gly Ala Phe Phe Ser Pro Ser Pro Gly Ser Ser Ser Leu
165 170 175

Ser Ser Trp Ser Phe Phe Ser Asp Ala Ser Asp Glu Ala Ala Leu Tyr
180 185 190

Ala Ala Cys Asp Glu Val Glu Ser Glu Leu Asn Glu Ala Ala Ser Arg
195 200 205

Phe Gly Leu Gly Ser Pro Leu Pro Ser Pro Arg Ala Ser Pro Arg Pro
210 215 220

Trp Thr Pro Glu Asp Pro Trp Ser Leu Tyr Gly Pro Ser Pro Gly Gly
225 230 235 240

Arg Gly Pro Glu Asp Ser Trp Leu Leu Leu Ser Ala Pro Gly Pro Thr
245 250 255

Pro Ala Ser Pro Arg Pro Ala Ser Pro Cys Gly Lys Arg Arg Tyr Ser
260 265 270

Ser Ser Gly Thr Pro Ser Ser Ala Ser Pro Ala Leu Ser Arg Arg Gly
275 280 285

Ser Leu Gly Glu Glu Gly Ser Glu Pro Pro Pro Pro Pro Pro Leu Pro
290 295 300

Leu Ala Arg Asp Pro Gly Ser Pro Gly Pro Phe Asp Tyr Val Gly Ala
305 310 315 320

Pro Pro Ala Glu Ser Ile Pro Gln Lys Thr Arg Arg Thr Ser Ser Glu
325 330 335

Gln Ala Val Ala Leu Pro Arg Ser Glu Glu Pro Ala Ser Cys Asn Gly
340 345 350

Lys Leu Pro Leu Gly Ala Glu Glu Ser Val Ala Pro Pro Gly Gly Ser
355 360 365

Arg Lys Glu Val Ala Gly Met Asp Tyr Leu Ala Val Pro Ser Pro Leu
370 375 380

Ala Trp Ser Lys Ala Arg Ile Gly Gly His Ser Pro Ile Phe Arg Thr
385 390 395 400

Ser Ala Leu Pro Pro Leu Asp Trp Pro Leu Pro Ser Gln Tyr Glu Gln
405 410 415

Leu Glu Leu Arg Ile Glu Val Gln Pro Arg Ala His His Arg Ala His
420 425 430

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

His Pro Val Val Lys Leu Leu Gly Tyr Ser Glu Lys Pro Leu Thr Leu
450 455 460

Gln Met Phe Ile Gly Thr Ala Asp Glu Arg Asn Leu Arg Pro His Ala
465 470 475 480

Phe Tyr Gln Val His Arg Ile Thr Gly Lys Met Val Ala Thr Ala Ser
485 490 495

Tyr Glu Ala Val Val Ser Gly Thr Lys Val Leu Glu Met Thr Leu Leu
500 505 510

Pro Glu Asn Asn Met Ala Ala Asn Ile Asp Cys Ala Gly Ile Leu Lys
515 520 525

Leu Arg Asn Ser Asp Ile Glu Leu Arg Lys Gly Glu Thr Asp Ile Gly
530 535 540

Arg Lys Asn Thr Arg Val Arg Leu Val Phe Arg Val His Val Pro Gln
545 550 555 560

Gly Gly Gly Lys Val Val Ser Val Gln Ala Ala Ser Val Pro Ile Glu
565 570 575

Cys Ser Gln Arg Ser Ala Gln Glu Leu Pro Gln Val Glu Ala Tyr Ser
580 585 590

Pro Ser Ala Cys Ser Val Arg Gly Gly Glu Glu Leu Val Leu Thr Gly
595 600 605

Ser Asn Phe Leu Pro Asp Ser Lys Val Val Phe Ile Glu Arg Gly Pro
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Asp Gly Lys Leu Gln Trp Glu Glu Glu Ala Thr Val Asn Arg Leu Gln
625 630 635 640

Ser Asn Glu Val Thr Leu Thr Leu Thr Val Pro Glu Tyr Ser Asn Lys
645 650 655

Arg Val Ser Arg Pro Val Gln Val Tyr Phe Tyr Val Ser Asn Gly Arg
660 665 670

Arg Lys Arg Ser Pro Thr Gln Ser Phe Arg Phe Leu Pro Val Ile Cys
675 680 685

Lys Glu Glu Pro Leu Pro Asp Ser Ser Leu Arg Gly Phe Pro Ser Ala
690 695 700

Ser Ala Thr Pro Phe Gly Thr Asp Met Asp Phe Ser Pro Pro Arg Pro
705 710 715 720

Pro Tyr Pro Ser Tyr Pro His Glu Asp Pro Ala Cys Glu Thr Pro Tyr
725 730 735

Leu Ser Glu Gly Phe Gly Tyr Gly Met Pro Pro Leu Tyr Pro Gln Thr
740 745 750

Gly Pro Pro Pro Ser Tyr Arg Pro Gly Leu Arg Met Phe Pro Glu Thr
755 760 765

Arg Gly Thr Thr Gly Cys Ala Gln Pro Pro Ala Val Ser Phe Leu Pro
770 775 780

Arg Pro Phe Pro Ser Asp Pro Tyr Gly Gly Arg Gly Ser Ser Phe Pro
785 790 795 800

Leu Gly Leu Pro Phe Ser Pro Pro Ala Pro Phe Arg Pro Pro Pro Leu
805 810 815

Pro Ala Ser Pro Pro Leu Glu Gly Pro Phe Pro Ser Gln Ser Asp Val
820 825 830

His Pro Leu Pro Ala Glu Gly Tyr Asn Lys Val Gly Pro Gly Tyr Gly
835 840 845

Pro Gly Glu Gly Ala Pro Glu Gln Glu Lys Ser Arg Gly Gly Tyr Ser
850 855 860

Ser Gly Phe Arg Asp Ser Val Pro Ile Gln Gly Ile Thr Leu Glu Glu
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gcccagagac atg gag agt tgc tac aac cca ggt ctg gat ggt att att 289
Met Glu Ser Cys Tyr Asn Pro Gly Leu Asp Gly Ile Ile
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gaa tat gat gat ttc aaa ttg aac tcc tcc att gtg gaa ccc aag gag 337

Glu Tyr Asp Asp Phe Lys Leu Asn Ser Ser Ile Val Glu Pro Lys Glu
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Pro Ala Pro Glu Thr Ala Asp Gly Pro Tyr Leu Val Ile Val Glu Gln
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cct aag cag aga ggc ttc cga ttt cga tat ggc tgt gaa ggc ccc tcc 433
Pro Lys Gln Arg Gly Phe Arg Phe Arg Tyr Gly Cys Glu Gly Pro Ser
50 55 60

cat gga gga ctg ccc ggt gcc tcc agt gag aag ggc cga aag acc tat 481
His Gly Gly Leu Pro Gly Ala Ser Ser Glu Lys Gly Arg Lys Thr Tyr
65 70 75

ccc act gtc aag atc tgt aac tac gag gga cca gcc aag atc gag gtg 529
Pro Thr Val Lys Ile Cys Asn Tyr Glu Gly Pro Ala Lys Ile Glu Val
80 85 90

gac ctg gta aca cac agt gac cca cct cgt gct cat gcc cac agt ctg 577
Asp Leu Val Thr His Ser Asp Pro Pro Arg Ala His Ala His Ser Leu
95 100 105

gtg ggc aag caa tgc tcg gag ctg ggg atc tgc gcc gtt tct gtg ggg 625
Val Gly Lys Gln Cys Ser Glu Leu Gly Ile Cys Ala Val Ser Val Gly
110 115 120 125

ccc aag gac atg act gcc caa ttt aac aac ctg ggt gtc ctg cat gtg 673
Pro Lys Asp Met Thr Ala Gln Phe Asn Asn Leu Gly Val Leu His Val
130 135 140

act aag gag aac atg atg ggg act atg ata caa aaa ctt cag agg cag 721
Thr Lys Glu Asn Met Met Gly Thr Met Ile Gln Lys Leu Gln Arg Gln
145 150 155

cgg ctc cgc tct agg ccc cag ggc ctt acg gag gcc gag cag cgg gag 769
Arg Leu Arg Ser Arg Pro Gln Gly Leu Thr Glu Ala Glu Gln Arg Glu
160 165 170

ctg gag caa gag gcc aaa gaa ctg aag aag gtg atg gat ctg agt ata 817
Leu Glu Gln Glu Ala Lys Glu Leu Lys Lys Val Met Asp Leu Ser Ile
175 180 185

gtg cgg ctg cgc ttc tct gcc ttc ctt aga gcc agt gat ggc tcc ttc 865
Val Arg Leu Arg Phe Ser Ala Phe Leu Arg Ala Ser Asp Gly Ser Phe
190 195 200 205

tcc ctg ccc ctg aag cca gtc atc tcc cag ccc atc cat gac agc aaa 913
Ser Leu Pro Leu Lys Pro Val Ile Ser Gln Pro Ile His Asp Ser Lys
210 215 220

tct ccg ggg gca tca aac ctg aag att tct cga atg gac aag aca gca 961
Ser Pro Gly Ala Ser Asn Leu Lys Ile Ser Arg Met Asp Lys Thr Ala
225 230 235

ggc tct gtg cgg ggt gga gat gaa gtt tat ctg ctt tgt gac aag gtg 1009
Gly Ser Val Arg Gly Gly Asp Glu Val Tyr Leu Leu Cys Asp Lys Val
240 245 250

cag aaa gat gac att gag gtt cgg ttc tat gag gat gat gag aat gga 1057
Gln Lys Asp Asp Ile Glu Val Arg Phe Tyr Glu Asp Asp Glu Asn Gly
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tgg cag gcc ttt ggg gac ttc tct ccc aca gat gtg cat aaa cag tat 1105
Trp Gln Ala Phe Gly Asp Phe Ser Pro Thr Asp Val His Lys Gln Tyr
270 275 280 285

gcc att gtg ttc cgg aca ccc ccc tat cac aag atg aag att gag cgg 1153
Ala Ile Val Phe Arg Thr Pro Pro Tyr His Lys Met Lys Ile Glu Arg
290 295 300

cct gta aca gtg ttt ctg caa ctg aaa cgc aag cga gga ggg gac gtg 1201
Pro Val Thr Val Phe Leu Gln Leu Lys Arg Lys Arg Gly Gly Asp Val
305 310 315

tct gat tcc aaa cag ttc acc tat tac cct ctg gtg gaa gac aag gaa 1249
Ser Asp Ser Lys Gln Phe Thr Tyr Tyr Pro Leu Val Glu Asp Lys Glu
320 325 330

gag gtg cag cgg aag cgg agg aag gcc ttg ccc acc ttc tcc cag ccc 1297
Glu Val Gln Arg Lys Arg Arg Lys Ala Leu Pro Thr Phe Ser Gln Pro
335 340 345

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Phe Gly Gly Gly Ser His Met Gly Gly Gly Ser Gly Gly Ala Ala Gly
350 355 360 365

ggc tac gga gga gct gga gga ggt ggc agc ctc ggt ttc ttc ccc tcc 1393
Gly Tyr Gly Gly Ala Gly Gly Gly Gly Ser Leu Gly Phe Phe Pro Ser
370 375 380

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Ser Leu Ala Tyr Ser Pro Tyr Gln Ser Gly Ala Gly Pro Met Gly Cys
385 390 395

tac ccg gga ggc ggg ggc ggg gcg cag atg gcc gcc acg gtg ccc agc 1489
Tyr Pro Gly Gly Gly Gly Gly Ala Gln Met Ala Ala Thr Val Pro Ser
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agg gac tcc ggg gag gaa gcc gcg gag ccg agc gcc ccc tcc agg acc 1537

Arg Asp Ser Gly Glu Glu Ala Ala Glu Pro Ser Ala Pro Ser Arg Thr
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ccc cag tgc gac gcg cag gcc ccg gag atg ctg cag cga gct cga gag 1585
Pro Gln Cys Asp Ala Gln Ala Pro Glu Met Leu Gln Arg Ala Arg Glu
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Tyr Asn Ala Arg Leu Phe Gly Leu Ala Gln Arg Ser Ala Arg Ala Leu
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ctc gac tac ggc gtc acc gcg gac cgg cgc gcg ctg ctg gcg gga cag 1681
Leu Asp Tyr Gly Val Thr Ala Asp Arg Arg Ala Leu Leu Ala Gly Gln
465 470 475

cgc cac ctg ctg acg gcg cag gac gag aac gga gac aca cca ctg cac 1729
Arg His Leu Leu Thr Ala Gln Asp Glu Asn Gly Asp Thr Pro Leu His
480 485 490

cta gcc atc atc cac ggg cag acc agt gtc att gag cag ata gtc tat 1777
Leu Ala Ile Ile His Gly Gln Thr Ser Val Ile Glu Gln Ile Val Tyr
495 500 505

gtc atc cac cac gcc cag gac ctc ggc gtt gtc aac ctc acc aac cac 1825
Val Ile His His Ala Gln Asp Leu Gly Val Val Asn Leu Thr Asn His
510 515 520 525

ctg cac cag acg ccc ctg cac ctg gcg gtg atc acg ggg cag acg agt 1873
Leu His Gln Thr Pro Leu His Leu Ala Val Ile Thr Gly Gln Thr Ser
530 535 540

gtg gtg agc ttt ctg ctg cgg gta ggt gca gac cca gct ctg ctg gat 1921
Val Val Ser Phe Leu Leu Arg Val Gly Ala Asp Pro Ala Leu Leu Asp
545 550 555

cgg cat gga gac tca gcc atg cat ctg gcg ctg cgg gca ggc gct ggt 1969
Arg His Gly Asp Ser Ala Met His Leu Ala Leu Arg Ala Gly Ala Gly
560 565 570

gct cct gag ctg ctg cgt gca ctg ctt cag agt gga gct cct gct gtg 2017
Ala Pro Glu Leu Leu Arg Ala Leu Leu Gln Ser Gly Ala Pro Ala Val
575 580 585

ccc cag ctg ttg cat atg cct gac ttt gag gga ctg tat cca gta cac 2065
Pro Gln Leu Leu His Met Pro Asp Phe Glu Gly Leu Tyr Pro Val His
590 595 600 605

ctg gcg gtc cga gcc cga agc cct gag tgc ctg gat ctg ctg gtg gac 2113
Leu Ala Val Arg Ala Arg Ser Pro Glu Cys Leu Asp Leu Leu Val Asp
610 615 620

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Ser Gly Ala Glu Val Glu Ala Thr Glu Arg Gln Gly Gly Arg Thr Ala
625 630 635

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Leu His Leu Ala Thr Glu Met Glu Glu Leu Gly Leu Val Thr His Leu
640 645 650

gtc acc aag ctc cgg gcc aac gtg aac gct cgc acc ttt gcg gga aac 2257
Val Thr Lys Leu Arg Ala Asn Val Asn Ala Arg Thr Phe Ala Gly Asn
655 660 665

aca ccc ctg cac ctg gca gct gga ctg ggg tac ccg acc ctc acc cgc 2305
Thr Pro Leu His Leu Ala Ala Gly Leu Gly Tyr Pro Thr Leu Thr Arg
670 675 680 685

ctc ctt ctg aag gct ggt gct gac atc cat gct gaa aac gag gag ccc 2353
Leu Leu Leu Lys Ala Gly Ala Asp Ile His Ala Glu Asn Glu Glu Pro
690 695 700

ctg tgc cca ctg cct tca ccc cct acc tct gat agc gac tcg gac tct 2401
Leu Cys Pro Leu Pro Ser Pro Pro Thr Ser Asp Ser Asp Ser Asp Ser
705 710 715

gaa ggg cct gag aag gac acc cga agc agc ttc cgg ggc cac acg cct 2449
Glu Gly Pro Glu Lys Asp Thr Arg Ser Ser Phe Arg Gly His Thr Pro
720 725 730

ctt gac ctc act tgc agc acc aag gtg aag acc ttg ctg cta aat gct 2497
Leu Asp Leu Thr Cys Ser Thr Lys Val Lys Thr Leu Leu Leu Asn Ala
735 740 745

gct cag aac acc atg gag cca ccc ctg acc ccg ccc agc cca gca ggg 2545
Ala Gln Asn Thr Met Glu Pro Pro Leu Thr Pro Pro Ser Pro Ala Gly
750 755 760 765

ccg gga ctg tca ctt ggt gat aca gct ctg cag aac ctg gag cag ctg 2593
Pro Gly Leu Ser Leu Gly Asp Thr Ala Leu Gln Asn Leu Glu Gln Leu
770 775 780

cta gac ggg cca gaa gcc cag ggc agc tgg gca gag ctg gca gag cgt 2641
Leu Asp Gly Pro Glu Ala Gln Gly Ser Trp Ala Glu Leu Ala Glu Arg
785 790 795

ctg ggg ctg cgc agc ctg gta gac acg tac cga cag aca acc tca ccc 2689
Leu Gly Leu Arg Ser Leu Val Asp Thr Tyr Arg Gln Thr Thr Ser Pro
800 805 810

agt ggc agc ctc ctg cgc agc tac gag ctg gct ggc ggg gac ctg gca 2737

Ser Gly Ser Leu Leu Arg Ser Tyr Glu Leu Ala Gly Gly Asp Leu Ala
815 820 825

ggt cta ctg gag gcc ctg tct gac atg ggc cta gag gag gga gtg agg 2785
Gly Leu Leu Glu Ala Leu Ser Asp Met Gly Leu Glu Glu Gly Val Arg
830 835 840 845

ctg ctg agg ggt cca gaa acc cga gac aag ctg ccc agc aca aca gag 2833
Leu Leu Arg Gly Pro Glu Thr Arg Asp Lys Leu Pro Ser Thr Thr Glu
850 855 860

gtg aag gaa gac agt gcg tac ggg agc cag tca gtg gag cag aag gca 2881
Val Lys Glu Asp Ser Ala Tyr Gly Ser Gln Ser Val Glu Gln Lys Ala
865 870 875

gag aag ctg ggc cca ccc cct gag cca cca gga ggg ctc tgc cac ggg 2929
Glu Lys Leu Gly Pro Pro Pro Glu Pro Pro Gly Gly Leu Cys His Gly
880 885 890

cac ccc cag cct cag gtg cac tga cctgctgcct gcccccagcc cccttcccgg 2983
His Pro Gln Pro Gln Val His
895 900

acccccctgta cagcgtcccc acctatttca aatcttattt aacaccccac acccacccct 3043

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aaaaaaaaaa 3113

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Arg Gly Phe Arg Phe Arg Tyr Gly Cys Glu Gly Pro Ser His Gly Gly

50 55 60

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

Lys Ile Cys Asn Tyr Glu Gly Pro Ala Lys Ile Glu Val Asp Leu Val
85 90 95

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

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

Met Thr Ala Gln Phe Asn Asn Leu Gly Val Leu His Val Thr Lys Glu
130 135 140

Asn Met Met Gly Thr Met Ile Gln Lys Leu Gln Arg Gln Arg Leu Arg
145 150 155 160

Ser Arg Pro Gln Gly Leu Thr Glu Ala Glu Gln Arg Glu Leu Glu Gln
165 170 175

Glu Ala Lys Glu Leu Lys Lys Val Met Asp Leu Ser Ile Val Arg Leu
180 185 190

Arg Phe Ser Ala Phe Leu Arg Ala Ser Asp Gly Ser Phe Ser Leu Pro
195 200 205

Leu Lys Pro Val Ile Ser Gln Pro Ile His Asp Ser Lys Ser Pro Gly
210 215 220

Ala Ser Asn Leu Lys Ile Ser Arg Met Asp Lys Thr Ala Gly Ser Val
225 230 235 240

Arg Gly Gly Asp Glu Val Tyr Leu Leu Cys Asp Lys Val Gln Lys Asp
245 250 255

Asp Ile Glu Val Arg Phe Tyr Glu Asp Asp Glu Asn Gly Trp Gln Ala
260 265 270

Phe Gly Asp Phe Ser Pro Thr Asp Val His Lys Gln Tyr Ala Ile Val
275 280 285

Phe Arg Thr Pro Pro Tyr His Lys Met Lys Ile Glu Arg Pro Val Thr
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Val Phe Leu Gln Leu Lys Arg Lys Arg Gly Gly Asp Val Ser Asp Ser
305 310 315 320

Lys Gln Phe Thr Tyr Tyr Pro Leu Val Glu Asp Lys Glu Glu Val Gln
325 330 335

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

Gly Ser His Met Gly Gly Gly Ser Gly Gly Ala Ala Gly Gly Tyr Gly
355 360 365

Gly Ala Gly Gly Gly Gly Ser Leu Gly Phe Phe Pro Ser Ser Leu Ala
370 375 380

Tyr Ser Pro Tyr Gln Ser Gly Ala Gly Pro Met Gly Cys Tyr Pro Gly
385 390 395 400

Gly Gly Gly Gly Ala Gln Met Ala Ala Thr Val Pro Ser Arg Asp Ser
405 410 415

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

Asp Ala Gln Ala Pro Glu Met Leu Gln Arg Ala Arg Glu Tyr Asn Ala
435 440 445

Arg Leu Phe Gly Leu Ala Gln Arg Ser Ala Arg Ala Leu Leu Asp Tyr

450 455 460

Gly Val Thr Ala Asp Arg Arg Ala Leu Leu Ala Gly Gln Arg His Leu
465 470 475 480

Leu Thr Ala Gln Asp Glu Asn Gly Asp Thr Pro Leu His Leu Ala Ile
485 490 495

Ile His Gly Gln Thr Ser Val Ile Glu Gln Ile Val Tyr Val Ile His
500 505 510

His Ala Gln Asp Leu Gly Val Val Asn Leu Thr Asn His Leu His Gln
515 520 525

Thr Pro Leu His Leu Ala Val Ile Thr Gly Gln Thr Ser Val Val Ser
530 535 540

Phe Leu Leu Arg Val Gly Ala Asp Pro Ala Leu Leu Asp Arg His Gly
545 550 555 560

Asp Ser Ala Met His Leu Ala Leu Arg Ala Gly Ala Gly Ala Pro Glu
565 570 575

Leu Leu Arg Ala Leu Leu Gln Ser Gly Ala Pro Ala Val Pro Gln Leu
580 585 590

Leu His Met Pro Asp Phe Glu Gly Leu Tyr Pro Val His Leu Ala Val
595 600 605

Arg Ala Arg Ser Pro Glu Cys Leu Asp Leu Leu Val Asp Ser Gly Ala
610 615 620

Glu Val Glu Ala Thr Glu Arg Gln Gly Gly Arg Thr Ala Leu His Leu
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Ala Thr Glu Met Glu Glu Leu Gly Leu Val Thr His Leu Val Thr Lys
645 650 655

Leu Arg Ala Asn Val Asn Ala Arg Thr Phe Ala Gly Asn Thr Pro Leu
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His Leu Ala Ala Gly Leu Gly Tyr Pro Thr Leu Thr Arg Leu Leu Leu
675 680 685

Lys Ala Gly Ala Asp Ile His Ala Glu Asn Glu Glu Pro Leu Cys Pro
690 695 700

Leu Pro Ser Pro Pro Thr Ser Asp Ser Asp Ser Asp Ser Glu Gly Pro
705 710 715 720

Glu Lys Asp Thr Arg Ser Ser Phe Arg Gly His Thr Pro Leu Asp Leu
725 730 735

Thr Cys Ser Thr Lys Val Lys Thr Leu Leu Leu Asn Ala Ala Gln Asn
740 745 750

Thr Met Glu Pro Pro Leu Thr Pro Pro Ser Pro Ala Gly Pro Gly Leu
755 760 765

Ser Leu Gly Asp Thr Ala Leu Gln Asn Leu Glu Gln Leu Leu Asp Gly
770 775 780

Pro Glu Ala Gln Gly Ser Trp Ala Glu Leu Ala Glu Arg Leu Gly Leu
785 790 795 800

Arg Ser Leu Val Asp Thr Tyr Arg Gln Thr Thr Ser Pro Ser Gly Ser
805 810 815

Leu Leu Arg Ser Tyr Glu Leu Ala Gly Gly Asp Leu Ala Gly Leu Leu
820 825 830

Glu Ala Leu Ser Asp Met Gly Leu Glu Glu Gly Val Arg Leu Leu Arg
835 840 845

Gly Pro Glu Thr Arg Asp Lys Leu Pro Ser Thr Thr Glu Val Lys Glu

850 855 860

Asp Ser Ala Tyr Gly Ser Gln Ser Val Glu Gln Lys Ala Glu Lys Leu
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Pro Gln Val His
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Met Ala Ser Asn
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Ser Ser Ser Cys Pro Thr Pro Gly Gly Gly His Leu Asn Gly Tyr Pro
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Val Pro Pro Tyr Ala Phe Phe Phe Pro Pro Met Leu Gly Gly Leu Ser
25 30 35

ccg cca ggc gct ctg acc act ctc cag cac cag ctt cca gtt agt gga 258
Pro Pro Gly Ala Leu Thr Thr Leu Gln His Gln Leu Pro Val Ser Gly
40 45 50

tat agc aca cca tcc cca gcc acc att gag acc cag agc agc agt tct 306
Tyr Ser Thr Pro Ser Pro Ala Thr Ile Glu Thr Gln Ser Ser Ser Ser
55 60 65

gaa gag ata gtg ccc agc cct ccc tcg cca ccc cct cta ccc cgc atc 354
Glu Glu Ile Val Pro Ser Pro Pro Ser Pro Pro Pro Leu Pro Arg Ile

70 75 80

tac aag cct tgc ttt gtc tgt cag gac aag tcc tca ggc tac cac tat 402
Tyr Lys Pro Cys Phe Val Cys Gln Asp Lys Ser Ser Gly Tyr His Tyr
85 90 95 100

ggg gtc agc gcc tgt gag ggc tgc aag ggc ttc ttc cgc cgc agc atc 450
Gly Val Ser Ala Cys Glu Gly Cys Lys Gly Phe Phe Arg Arg Ser Ile
105 110 115

cag aag aac atg gtg tac acg tgt cac cgg gac aag aac tgc atc atc 498
Gln Lys Asn Met Val Tyr Thr Cys His Arg Asp Lys Asn Cys Ile Ile
120 125 130

aac aag gtg acc cgg aac cgc tgc cag tac tgc cga ctg cag aag tgc 546
Asn Lys Val Thr Arg Asn Arg Cys Gln Tyr Cys Arg Leu Gln Lys Cys
135 140 145

ttt gaa gtg ggc atg tcc aag gag tct gtg aga aac gac cga aac aag 594
Phe Glu Val Gly Met Ser Lys Glu Ser Val Arg Asn Asp Arg Asn Lys
150 155 160

aag aag aag gag gtg ccc aag ccc gag tgc tct gag agc tac acg ctg 642
Lys Lys Lys Glu Val Pro Lys Pro Glu Cys Ser Glu Ser Tyr Thr Leu
165 170 175 180

acg ccg gag gtg ggg gag ctc att gag aag gtg cgc aaa gcg cac cag 690
Thr Pro Glu Val Gly Glu Leu Ile Glu Lys Val Arg Lys Ala His Gln
185 190 195

gaa acc ttc cct gcc ctc tgc cag ctg ggc aaa tac act acg aac aac 738
Glu Thr Phe Pro Ala Leu Cys Gln Leu Gly Lys Tyr Thr Thr Asn Asn
200 205 210

agc tca gaa caa cgt gtc tct ctg gac att gac ctc tgg gac aag ttc 786
Ser Ser Glu Gln Arg Val Ser Leu Asp Ile Asp Leu Trp Asp Lys Phe
215 220 225

agt gaa ctc tcc acc aag tgc atc att aag act gtg gag ttc gcc aag 834
Ser Glu Leu Ser Thr Lys Cys Ile Ile Lys Thr Val Glu Phe Ala Lys
230 235 240

cag ctg ccc ggc ttc acc acc ctc acc atc gcc gac cag atc acc ctc 882
Gln Leu Pro Gly Phe Thr Thr Leu Thr Ile Ala Asp Gln Ile Thr Leu
245 250 255 260

ctc aag gct gcc tgc ctg gac atc ctg atc ctg cgg atc tgc acg cgg 930
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265 270 275

tac acg ccc gag cag gac acc atg acc ttc tcg gac ggg ctg acc ctg 978
Tyr Thr Pro Glu Gln Asp Thr Met Thr Phe Ser Asp Gly Leu Thr Leu
280 285 290

aac cgg acc cag atg cac aac gct ggc ttc ggc ccc ctc acc gac ctg 1026
Asn Arg Thr Gln Met His Asn Ala Gly Phe Gly Pro Leu Thr Asp Leu
295 300 305

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Val Phe Ala Phe Ala Asn Gln Leu Leu Pro Leu Glu Met Asp Asp Ala
310 315 320

gag acg ggg ctg ctc agc gcc atc tgc ctc atc tgc gga gac cgc cag 1122
Glu Thr Gly Leu Leu Ser Ala Ile Cys Leu Ile Cys Gly Asp Arg Gln
325 330 335 340

gac ctg gag cag ccg gac cgg gtg gac atg ctg cag gag ccg ctg ctg 1170
Asp Leu Glu Gln Pro Asp Arg Val Asp Met Leu Gln Glu Pro Leu Leu
345 350 355

gag gcg cta aag gtc tac gtg cgg aag cgg agg ccc agc cgc ccc cac 1218
Glu Ala Leu Lys Val Tyr Val Arg Lys Arg Arg Pro Ser Arg Pro His
360 365 370

atg ttc ccc aag atg cta atg aag att act gac ctg cga agc atc agc 1266
Met Phe Pro Lys Met Leu Met Lys Ile Thr Asp Leu Arg Ser Ile Ser
375 380 385

gcc aag ggg gct gag cgg gtg atc acg ctg aag atg gag atc ccg ggc 1314
Ala Lys Gly Ala Glu Arg Val Ile Thr Leu Lys Met Glu Ile Pro Gly
390 395 400

tcc atg ccg cct ctc atc cag gaa atg ttg gag aac tca gag ggc ctg 1362
Ser Met Pro Pro Leu Ile Gln Glu Met Leu Glu Asn Ser Glu Gly Leu
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Asp Thr Leu Ser Gly Gln Pro Gly Gly Gly Gly Arg Asp Gly Gly Gly
425 430 435

ctg gcc ccc ccg cca ggc agc tgt agc ccc agc ctc agc ccc agc tcc 1458
Leu Ala Pro Pro Pro Gly Ser Cys Ser Pro Ser Leu Ser Pro Ser Ser
440 445 450

aac aga agc agc ccg gcc acc cac tcc ccg tga ccgcccacgc cacatggaca 1511
Asn Arg Ser Ser Pro Ala Thr His Ser Pro
455 460

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gtccctgtgc cccccagttc tcctcctcag ccttttcctc ctcagttttc tctttaaaac 2231

tgtgaagtac taactttcca aggcctgcct tcccctcccc cccactggag aagccgccag 2291

ccccttctc cctctgcctg accactgggt gtggacggtg tggggcagcc ctgaaaggac 2351

aggctcctgg ccttggcact tgcctgcacc caccatgagg catggagcag ggcagagcaa 2411

gggccccggg acagagtttt cccagacctg gctcctcggc agagctgcct cccgtcaggg 2471

cccacatcat ctaggctccc cagcccccac tgtgaagggg ctggccaggg gcccgagctg 2531

cccccacccc cggcctcagc caccagcacc cccatagggc ccccagacac cacacacatg 2591

cgcgtgcgca cacacacaaa cacacacaca ctggacagta gatgggccga cacacacttg 2651

gcccgagttc ctccatttcc ctggcctgcc ccccaccccc aacctgtccc acccccgtgc 2711

cccctcctta ccccgcagga cgggcctaca gggggggtctc ccctcacccc tgcacccccа 2771

gctgggggag ctggctctgc cccgacctcc ttcaccaggg gttggggccc cttcccctgg 2831

agcccgtggg tgcacctgtt actgttgggc tttccactga gatctactgg ataaagaata 2891

aagttctatt tattct 2907

<210> 28
<211> 462
<212> PRT

<213> Homo sapiens

<400> 28

Met Ala Ser Asn Ser Ser Ser Cys Pro Thr Pro Gly Gly Gly His Leu
1 5 10 15

Asn Gly Tyr Pro Val Pro Pro Tyr Ala Phe Phe Phe Pro Pro Met Leu
20 25 30

Gly Gly Leu Ser Pro Pro Gly Ala Leu Thr Thr Leu Gln His Gln Leu
35 40 45

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

Ser Ser Ser Ser Glu Glu Ile Val Pro Ser Pro Pro Ser Pro Pro Pro
65 70 75 80

Leu Pro Arg Ile Tyr Lys Pro Cys Phe Val Cys Gln Asp Lys Ser Ser
85 90 95

Gly Tyr His Tyr Gly Val Ser Ala Cys Glu Gly Cys Lys Gly Phe Phe
100 105 110

Arg Arg Ser Ile Gln Lys Asn Met Val Tyr Thr Cys His Arg Asp Lys
115 120 125

Asn Cys Ile Ile Asn Lys Val Thr Arg Asn Arg Cys Gln Tyr Cys Arg
130 135 140

Leu Gln Lys Cys Phe Glu Val Gly Met Ser Lys Glu Ser Val Arg Asn
145 150 155 160

Asp Arg Asn Lys Lys Lys Lys Glu Val Pro Lys Pro Glu Cys Ser Glu
165 170 175

Ser Tyr Thr Leu Thr Pro Glu Val Gly Glu Leu Ile Glu Lys Val Arg
180 185 190

Lys Ala His Gln Glu Thr Phe Pro Ala Leu Cys Gln Leu Gly Lys Tyr
195 200 205

Thr Thr Asn Asn Ser Ser Glu Gln Arg Val Ser Leu Asp Ile Asp Leu
210 215 220

Trp Asp Lys Phe Ser Glu Leu Ser Thr Lys Cys Ile Ile Lys Thr Val
225 230 235 240

Glu Phe Ala Lys Gln Leu Pro Gly Phe Thr Thr Leu Thr Ile Ala Asp
245 250 255

Gln Ile Thr Leu Leu Lys Ala Ala Cys Leu Asp Ile Leu Ile Leu Arg
260 265 270

Ile Cys Thr Arg Tyr Thr Pro Glu Gln Asp Thr Met Thr Phe Ser Asp
275 280 285

Gly Leu Thr Leu Asn Arg Thr Gln Met His Asn Ala Gly Phe Gly Pro
290 295 300

Leu Thr Asp Leu Val Phe Ala Phe Ala Asn Gln Leu Leu Pro Leu Glu
305 310 315 320

Met Asp Asp Ala Glu Thr Gly Leu Leu Ser Ala Ile Cys Leu Ile Cys
325 330 335

Gly Asp Arg Gln Asp Leu Glu Gln Pro Asp Arg Val Asp Met Leu Gln
340 345 350

Glu Pro Leu Leu Glu Ala Leu Lys Val Tyr Val Arg Lys Arg Arg Pro
355 360 365

Ser Arg Pro His Met Phe Pro Lys Met Leu Met Lys Ile Thr Asp Leu
370 375 380

Arg Ser Ile Ser Ala Lys Gly Ala Glu Arg Val Ile Thr Leu Lys Met
385 390 395 400

Glu Ile Pro Gly Ser Met Pro Pro Leu Ile Gln Glu Met Leu Glu Asn
405 410 415

Ser Glu Gly Leu Asp Thr Leu Ser Gly Gln Pro Gly Gly Gly Gly Arg
420 425 430

Asp Gly Gly Gly Leu Ala Pro Pro Pro Gly Ser Cys Ser Pro Ser Leu
435 440 445

Ser Pro Ser Ser Asn Arg Ser Ser Pro Ala Thr His Ser Pro
450 455 460

<210> 29
<211> 3119
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (496)..(1815)

<400> 29
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tccgagcagg gtttgtctgg gcaccgtcgg ggtaggatcc ggaacgcatt cggaaggctt 180

tttgcaagca tttacttgga aggagaactt gggatctttc tgggaacccc ccgccccggc 240

tggattggcc gagcaagcct ggaaaatggt aaatgatcat ttggatcaat tacaggcttt 300

tagctggctt gtctgtcata attcatgatt cggggctggg aaaaagacca acagcctacg 360

tgccaaaaaa ggggcagagt ttgatggagt tgggtggact tttctatgcc atttgcctcc 420

acacctagag gataagcact tttgcagaca ttcagtgcaa gggagatcat gtttgactgt 480

atggatgttc tgtca gtg agt cct ggg caa atc ctg gat ttc tac act gcg 531
Val Ser Pro Gly Gln Ile Leu Asp Phe Tyr Thr Ala
1 5 10

agt ccg tct tcc tgc atg ctc cag gag aaa gct ctc aaa gca tgc ttc 579
Ser Pro Ser Ser Cys Met Leu Gln Glu Lys Ala Leu Lys Ala Cys Phe
15 20 25

agt gga ttg acc caa acc gaa tgg cag cat cgg cac act gct caa tca 627
Ser Gly Leu Thr Gln Thr Glu Trp Gln His Arg His Thr Ala Gln Ser
30 35 40

att gaa aca cag agc acc agc tct gag gaa ctc gtc cca agc ccc cca 675
Ile Glu Thr Gln Ser Thr Ser Ser Glu Glu Leu Val Pro Ser Pro Pro
45 50 55 60

tct cca ctt cct ccc cct cga gtg tac aaa ccc tgc ttc gtc tgc cag 723
Ser Pro Leu Pro Pro Pro Arg Val Tyr Lys Pro Cys Phe Val Cys Gln
65 70 75

gac aaa tca tca ggg tac cac tat ggg gtc agc gcc tgt gag gga tgt 771
Asp Lys Ser Ser Gly Tyr His Tyr Gly Val Ser Ala Cys Glu Gly Cys
80 85 90

aag ggc ttt ttc cgc aga agt att cag aag aat atg att tac act tgt 819
Lys Gly Phe Phe Arg Arg Ser Ile Gln Lys Asn Met Ile Tyr Thr Cys
95 100 105

cac cga gat aag aac tgt gtt att aat aaa gtc acc agg aat cga tgc 867
His Arg Asp Lys Asn Cys Val Ile Asn Lys Val Thr Arg Asn Arg Cys
110 115 120

caa tac tgt cga ctc cag aag tgc ttt gaa gtg gga atg tcc aaa gaa 915
Gln Tyr Cys Arg Leu Gln Lys Cys Phe Glu Val Gly Met Ser Lys Glu
125 130 135 140

tct gtc agg aat gac agg aac aag aaa aag aag gag act tcg aag caa 963
Ser Val Arg Asn Asp Arg Asn Lys Lys Lys Lys Glu Thr Ser Lys Gln
145 150 155

gaa tgc aca gag agc tat gaa atg aca gct gag ttg gac gat ctc aca 1011
Glu Cys Thr Glu Ser Tyr Glu Met Thr Ala Glu Leu Asp Asp Leu Thr
160 165 170

gag aag atc cga aaa gct cac cag gaa act ttc cct tca ctc tgc cag 1059
Glu Lys Ile Arg Lys Ala His Gln Glu Thr Phe Pro Ser Leu Cys Gln
175 180 185

ctg ggt aaa tac acc acg aat tcc agt gct gac cat cga gtc cga ctg 1107
Leu Gly Lys Tyr Thr Thr Asn Ser Ser Ala Asp His Arg Val Arg Leu
190 195 200

gac ctg ggc ctc tgg gac aaa ttc agt gaa ctg gcc acc aag tgc att 1155

Asp Leu Gly Leu Trp Asp Lys Phe Ser Glu Leu Ala Thr Lys Cys Ile
205 210 215 220

att aag atc gtg gag ttt gct aaa cgt ctg cct ggt ttc act ggc ttg 1203
Ile Lys Ile Val Glu Phe Ala Lys Arg Leu Pro Gly Phe Thr Gly Leu
225 230 235

acc atc gca gac caa att acc ctg ctg aag gcc gcc tgc ctg gac atc 1251
Thr Ile Ala Asp Gln Ile Thr Leu Leu Lys Ala Ala Cys Leu Asp Ile
240 245 250

ctg att ctt aga att tgc acc agg tat acc cca gaa caa gac acc atg 1299
Leu Ile Leu Arg Ile Cys Thr Arg Tyr Thr Pro Glu Gln Asp Thr Met
255 260 265

act ttc tca gac ggc ctt acc cta aat cga act cag atg cac aat gct 1347
Thr Phe Ser Asp Gly Leu Thr Leu Asn Arg Thr Gln Met His Asn Ala
270 275 280

gga ttt ggt cct ctg act gac ctt gtg ttc acc ttt gcc aac cag ctc 1395
Gly Phe Gly Pro Leu Thr Asp Leu Val Phe Thr Phe Ala Asn Gln Leu
285 290 295 300

ctg cct ttg gaa atg gat gac aca gaa aca ggc ctt ctc agt gcc atc 1443
Leu Pro Leu Glu Met Asp Asp Thr Glu Thr Gly Leu Leu Ser Ala Ile
305 310 315

tgc tta atc tgt gga gac cgc cag gac ctt gag gaa ccg aca aaa gta 1491
Cys Leu Ile Cys Gly Asp Arg Gln Asp Leu Glu Glu Pro Thr Lys Val
320 325 330

gat aag cta caa gaa cca ttg ctg gaa gca cta aaa att tat atc aga 1539
Asp Lys Leu Gln Glu Pro Leu Leu Glu Ala Leu Lys Ile Tyr Ile Arg
335 340 345

aaa aga cga ccc agc aag cct cac atg ttt cca aag atc tta atg aaa 1587
Lys Arg Arg Pro Ser Lys Pro His Met Phe Pro Lys Ile Leu Met Lys
350 355 360

atc aca gat ctc cgt agc atc agt gct aaa ggt gca gag cgt gta att 1635
Ile Thr Asp Leu Arg Ser Ile Ser Ala Lys Gly Ala Glu Arg Val Ile
365 370 375 380

acc ttg aaa atg gaa att cct gga tca atg cca cct ctc att caa gaa 1683
Thr Leu Lys Met Glu Ile Pro Gly Ser Met Pro Pro Leu Ile Gln Glu
385 390 395

atg ctg gag aat tct gaa gga cat gaa ccc ttg acc cca agt tca agt 1731
Met Leu Glu Asn Ser Glu Gly His Glu Pro Leu Thr Pro Ser Ser Ser
400 405 410

ggg aac aca gca gag cac agt cct agc atc tca ccc agc tca gtg gaa 1779
Gly Asn Thr Ala Glu His Ser Pro Ser Ile Ser Pro Ser Ser Val Glu
415 420 425

aac agt ggg gtc agt cag tca cca ctc gtg caa taa gacattttct 1825
Asn Ser Gly Val Ser Gln Ser Pro Leu Val Gln
430 435

agctacttca aacattcccc agtaccttca gttccaggat ttaaaatgca agaaaaaaca 1885

tttttactgc tgcttagttt ttggactgaa aagatattaa aactcaagaa ggaccaagaa 1945

gttttcatat gtatcaatat atatactcct cactgtgtaa cttacctaga aatacaaact 2005

tttccaattt taaaaaatca gccatttcat gcaaccagaa actagttaaa agcttctatt 2065

ttcctctttg aacactcaag atgcatggca aagacccagt caaaatgatt tacccctggt 2125

taagtttctg aagactttgt acatacagaa gtatggctct gttctttcta tactgtatgt 2185

ttggtgcttt ccttttgtct tgcatactca aaataaccat gacaccaagg ttatgaaata 2245

gactactgta cacgtctacc taggttcaaa aagataactg tcttgctttc atggaatagt 2305

caagacatca aggtaaggaa acaggactat tgacaggact attgtacagt atgacaagat 2365

aaggctgaag atattctact ttagttagta tggaagcttg tctttgctct ttctgatgct 2425

ctcaaactgc atcttttatt tcatgttgcc cagtaaaagt atacaaattc cctgcactag 2485

cagaagagaa ttctgtatca gtgtaactgc cagttcagtt aatcaaatgt catttgttca 2545

attgttaatg tcactttaaa ttaaaagtgg tttattactt gtttaatgac ataactacac 2605

agttagttaa aaaaaatttt tttacagtaa tgatagcctc caaggcagaa acacttttca 2665

gtgttaagtt tttgtttact tgttcacaag ccattaggga aatttcatgg gataattagc 2725

aggctggtct accactggac catgtaactc tagtgtcctt cctgattcat gcctgatatt 2785

gggatttttt tccagccctt cttgatgcca agggctaatt atattacatc ccaaagaaac 2845

aggcatagaa tctgcctcct ttgaccttgt tcaatcacta tgaagcagag tgaaagctgt 2905

ggtagagtgg ttaacagata caagtgtcag tttcttagtt ctcatttaag cactactgga 2965

attttttttt ttgatatatt agcaagtctg tgatgtactt tcactggctc tgtttgtaca 3025

ttgagattgt ttgtttaaca atgctttcta tgttcatata ctgtttacct ttttccatgg 3085

actctcctgg caaagaataa aatatattta tttt 3119

<210> 30
<211> 439
<212> PRT
<213> Homo sapiens

<400> 30

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

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

Gln Thr Glu Trp Gln His Arg His Thr Ala Gln Ser Ile Glu Thr Gln
35 40 45

Ser Thr Ser Ser Glu Glu Leu Val Pro Ser Pro Pro Ser Pro Leu Pro
50 55 60

Pro Pro Arg Val Tyr Lys Pro Cys Phe Val Cys Gln Asp Lys Ser Ser
65 70 75 80

Gly Tyr His Tyr Gly Val Ser Ala Cys Glu Gly Cys Lys Gly Phe Phe
85 90 95

Arg Arg Ser Ile Gln Lys Asn Met Ile Tyr Thr Cys His Arg Asp Lys
100 105 110

Asn Cys Val Ile Asn Lys Val Thr Arg Asn Arg Cys Gln Tyr Cys Arg
115 120 125

Leu Gln Lys Cys Phe Glu Val Gly Met Ser Lys Glu Ser Val Arg Asn
130 135 140

Asp Arg Asn Lys Lys Lys Lys Glu Thr Ser Lys Gln Glu Cys Thr Glu
145 150 155 160

Ser Tyr Glu Met Thr Ala Glu Leu Asp Asp Leu Thr Glu Lys Ile Arg
165 170 175

Lys Ala His Gln Glu Thr Phe Pro Ser Leu Cys Gln Leu Gly Lys Tyr
180 185 190

Thr Thr Asn Ser Ser Ala Asp His Arg Val Arg Leu Asp Leu Gly Leu
195 200 205

Trp Asp Lys Phe Ser Glu Leu Ala Thr Lys Cys Ile Ile Lys Ile Val
210 215 220

Glu Phe Ala Lys Arg Leu Pro Gly Phe Thr Gly Leu Thr Ile Ala Asp
225 230 235 240

Gln Ile Thr Leu Leu Lys Ala Ala Cys Leu Asp Ile Leu Ile Leu Arg
245 250 255

Ile Cys Thr Arg Tyr Thr Pro Glu Gln Asp Thr Met Thr Phe Ser Asp
260 265 270

Gly Leu Thr Leu Asn Arg Thr Gln Met His Asn Ala Gly Phe Gly Pro
275 280 285

Leu Thr Asp Leu Val Phe Thr Phe Ala Asn Gln Leu Leu Pro Leu Glu
290 295 300

Met Asp Asp Thr Glu Thr Gly Leu Leu Ser Ala Ile Cys Leu Ile Cys
305 310 315 320

Gly Asp Arg Gln Asp Leu Glu Glu Pro Thr Lys Val Asp Lys Leu Gln
325 330 335

Glu Pro Leu Leu Glu Ala Leu Lys Ile Tyr Ile Arg Lys Arg Arg Pro
340 345 350

Ser Lys Pro His Met Phe Pro Lys Ile Leu Met Lys Ile Thr Asp Leu

355 360 365

Arg Ser Ile Ser Ala Lys Gly Ala Glu Arg Val Ile Thr Leu Lys Met
370 375 380

Glu Ile Pro Gly Ser Met Pro Pro Leu Ile Gln Glu Met Leu Glu Asn
385 390 395 400

Ser Glu Gly His Glu Pro Leu Thr Pro Ser Ser Ser Gly Asn Thr Ala
405 410 415

Glu His Ser Pro Ser Ile Ser Pro Ser Ser Val Glu Asn Ser Gly Val
420 425 430

Ser Gln Ser Pro Leu Val Gln
435

<210> 31
<211> 2762
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (448)..(1458)

<400> 31
gtgacagaag tagtaggaag tgagctgttc agaggcagga gggtctattc tttgccaaag 60

gggggaccag aattccccat gcgagctgtt tgaggactgg gatgccgaga acgcgagcga 120

tccgagcagg gtttgtctgg gcaccgtcgg ggtaggatcc ggaacgcatt cggaaggctt 180

tttgcaagca tttacttgga aggagaactt gggatctttc tgggaacccc ccgccccggc 240

tggattggcc gagcaagcct ggaaaatgca attgaaacac agagcaccag ctctgaggaa 300

ctcgtcccaa gccccccatc tccacttcct ccccctcgag tgtacaaacc ctgcttcgtc 360

tgccaggaca aatcatcagg gtaccactat ggggtcagcg cctgtgaggg atgtaagggc 420

tttttccgca gaagtattca gaagaat atg att tac act tgt cac cga gat aag 474
Met Ile Tyr Thr Cys His Arg Asp Lys

1 5

aac tgt gtt att aat aaa gtc acc agg aat cga tgc caa tac tgt cga 522
Asn Cys Val Ile Asn Lys Val Thr Arg Asn Arg Cys Gln Tyr Cys Arg
10 15 20 25

ctc cag aag tgc ttt gaa gtg gga atg tcc aaa gaa tct gtc agg aat 570
Leu Gln Lys Cys Phe Glu Val Gly Met Ser Lys Glu Ser Val Arg Asn
30 35 40

gac agg aac aag aaa aag aag gag act tcg aag caa gaa tgc aca gag 618
Asp Arg Asn Lys Lys Lys Lys Glu Thr Ser Lys Gln Glu Cys Thr Glu
45 50 55

agc tat gaa atg aca gct gag ttg gac gat ctc aca gag aag atc cga 666
Ser Tyr Glu Met Thr Ala Glu Leu Asp Asp Leu Thr Glu Lys Ile Arg
60 65 70

aaa gct cac cag gaa act ttc cct tca ctc tgc cag ctg ggt aaa tac 714
Lys Ala His Gln Glu Thr Phe Pro Ser Leu Cys Gln Leu Gly Lys Tyr
75 80 85

acc acg aat tcc agt gct gac cat cga gtc cga ctg gac ctg ggc ctc 762
Thr Thr Asn Ser Ser Ala Asp His Arg Val Arg Leu Asp Leu Gly Leu
90 95 100 105

tgg gac aaa ttc agt gaa ctg gcc acc aag tgc att att aag atc gtg 810
Trp Asp Lys Phe Ser Glu Leu Ala Thr Lys Cys Ile Ile Lys Ile Val
110 115 120

gag ttt gct aaa cgt ctg cct ggt ttc act ggc ttg acc atc gca gac 858
Glu Phe Ala Lys Arg Leu Pro Gly Phe Thr Gly Leu Thr Ile Ala Asp
125 130 135

caa att acc ctg ctg aag gcc gcc tgc ctg gac atc ctg att ctt aga 906
Gln Ile Thr Leu Leu Lys Ala Ala Cys Leu Asp Ile Leu Ile Leu Arg
140 145 150

att tgc acc agg tat acc cca gaa caa gac acc atg act ttc tca gac 954
Ile Cys Thr Arg Tyr Thr Pro Glu Gln Asp Thr Met Thr Phe Ser Asp
155 160 165

ggc ctt acc cta aat cga act cag atg cac aat gct gga ttt ggt cct 1002
Gly Leu Thr Leu Asn Arg Thr Gln Met His Asn Ala Gly Phe Gly Pro
170 175 180 185

ctg act gac ctt gtg ttc acc ttt gcc aac cag ctc ctg cct ttg gaa 1050
Leu Thr Asp Leu Val Phe Thr Phe Ala Asn Gln Leu Leu Pro Leu Glu
190 195 200

atg gat gac aca gaa aca ggc ctt ctc agt gcc atc tgc tta atc tgt 1098
Met Asp Asp Thr Glu Thr Gly Leu Leu Ser Ala Ile Cys Leu Ile Cys
205 210 215

gga gac cgc cag gac ctt gag gaa ccg aca aaa gta gat aag cta caa 1146
Gly Asp Arg Gln Asp Leu Glu Glu Pro Thr Lys Val Asp Lys Leu Gln
220 225 230

gaa cca ttg ctg gaa gca cta aaa att tat atc aga aaa aga cga ccc 1194
Glu Pro Leu Leu Glu Ala Leu Lys Ile Tyr Ile Arg Lys Arg Arg Pro
235 240 245

agc aag cct cac atg ttt cca aag atc tta atg aaa atc aca gat ctc 1242
Ser Lys Pro His Met Phe Pro Lys Ile Leu Met Lys Ile Thr Asp Leu
250 255 260 265

cgt agc atc agt gct aaa ggt gca gag cgt gta att acc ttg aaa atg 1290
Arg Ser Ile Ser Ala Lys Gly Ala Glu Arg Val Ile Thr Leu Lys Met
270 275 280

gaa att cct gga tca atg cca cct ctc att caa gaa atg ctg gag aat 1338
Glu Ile Pro Gly Ser Met Pro Pro Leu Ile Gln Glu Met Leu Glu Asn
285 290 295

tct gaa gga cat gaa ccc ttg acc cca agt tca agt ggg aac aca gca 1386
Ser Glu Gly His Glu Pro Leu Thr Pro Ser Ser Ser Gly Asn Thr Ala
300 305 310

gag cac agt cct agc atc tca ccc agc tca gtg gaa aac agt ggg gtc 1434
Glu His Ser Pro Ser Ile Ser Pro Ser Ser Val Glu Asn Ser Gly Val
315 320 325

agt cag tca cca ctc gtg caa taa gacattttct agctacttca aacattcccc 1488
Ser Gln Ser Pro Leu Val Gln
330 335

agtaccttca gttccaggat ttaaaatgca agaaaaaaca tttttactgc tgcttagttt 1548

ttggactgaa aagatattaa aactcaagaa ggaccaagaa gttttcatat gtatcaatat 1608

atatactcct cactgtgtaa cttacctaga aatacaaact tttccaattt taaaaaatca 1668

gccatttcat gcaaccagaa actagttaaa agcttctatt ttcctctttg aacactcaag 1728

atgcatggca aagacccagt caaaatgatt tacccctggt taagtttctg aagactttgt 1788

acatacagaa gtatggctct gttctttcta tactgtatgt ttggtgcttt ccttttgtct 1848

tgcatactca aaataaccat gacaccaagg ttatgaaata gactactgta cacgtctacc 1908

taggttcaaa aagataactg tcttgctttc atggaatagt caagacatca aggtaaggaa 1968

acaggactat tgacaggact attgtacagt atgacaagat aaggctgaag atattctact 2028

ttagttagta tggaagcttg tctttgctct ttctgatgct ctcaaactgc atcttttatt 2088

tcatgttgcc cagtaaaagt atacaaattc cctgcactag cagaagagaa ttctgtatca 2148

gtgtaactgc cagttcagtt aatcaaatgt catttgttca attgttaatg tcactttaaa 2208

ttaaaagtgg tttattactt gtttaatgac ataactacac agttagttaa aaaaaatttt 2268

tttacagtaa tgatagcctc caaggcagaa acacttttca gtgttaagtt tttgtttact 2328

tgttcacaag ccattaggga aatttcatgg gataattagc aggctggtct accactggac 2388

catgtaactc tagtgtcctt cctgattcat gcctgatatt gggatttttt tccagccctt 2448

cttgatgcca agggctaatt atattacatc ccaaagaaac aggcatagaa tctgcctcct 2508

ttgaccttgt tcaatcacta tgaagcagag tgaaagctgt ggtagagtgg ttaacagata 2568

caagtgtcag tttcttagtt ctcatttaag cactactgga attttttttt ttgatatatt 2628

agcaagtctg tgatgtactt tcactggctc tgtttgtaca ttgagattgt ttgtttaaca 2688

atgctttcta tgttcatata ctgtttacct ttttccatgg actctcctgg caaagaataa 2748

aatatattta tttt 2762

<210> 32
<211> 336
<212> PRT
<213> Homo sapiens

<400> 32

Met Ile Tyr Thr Cys His Arg Asp Lys Asn Cys Val Ile Asn Lys Val
1 5 10 15

Thr Arg Asn Arg Cys Gln Tyr Cys Arg Leu Gln Lys Cys Phe Glu Val
20 25 30

Gly Met Ser Lys Glu Ser Val Arg Asn Asp Arg Asn Lys Lys Lys Lys
35 40 45

Glu Thr Ser Lys Gln Glu Cys Thr Glu Ser Tyr Glu Met Thr Ala Glu
50 55 60

Leu Asp Asp Leu Thr Glu Lys Ile Arg Lys Ala His Gln Glu Thr Phe
65 70 75 80

Pro Ser Leu Cys Gln Leu Gly Lys Tyr Thr Thr Asn Ser Ser Ala Asp
85 90 95

His Arg Val Arg Leu Asp Leu Gly Leu Trp Asp Lys Phe Ser Glu Leu
100 105 110

Ala Thr Lys Cys Ile Ile Lys Ile Val Glu Phe Ala Lys Arg Leu Pro
115 120 125

Gly Phe Thr Gly Leu Thr Ile Ala Asp Gln Ile Thr Leu Leu Lys Ala
130 135 140

Ala Cys Leu Asp Ile Leu Ile Leu Arg Ile Cys Thr Arg Tyr Thr Pro
145 150 155 160

Glu Gln Asp Thr Met Thr Phe Ser Asp Gly Leu Thr Leu Asn Arg Thr
165 170 175

Gln Met His Asn Ala Gly Phe Gly Pro Leu Thr Asp Leu Val Phe Thr
180 185 190

Phe Ala Asn Gln Leu Leu Pro Leu Glu Met Asp Asp Thr Glu Thr Gly
195 200 205

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

Glu Pro Thr Lys Val Asp Lys Leu Gln Glu Pro Leu Leu Glu Ala Leu
225 230 235 240

Lys Ile Tyr Ile Arg Lys Arg Arg Pro Ser Lys Pro His Met Phe Pro
245 250 255

Lys Ile Leu Met Lys Ile Thr Asp Leu Arg Ser Ile Ser Ala Lys Gly
260 265 270

Ala Glu Arg Val Ile Thr Leu Lys Met Glu Ile Pro Gly Ser Met Pro
275 280 285

Pro Leu Ile Gln Glu Met Leu Glu Asn Ser Glu Gly His Glu Pro Leu
290 295 300

Thr Pro Ser Ser Ser Gly Asn Thr Ala Glu His Ser Pro Ser Ile Ser
305 310 315 320

Pro Ser Ser Val Glu Asn Ser Gly Val Ser Gln Ser Pro Leu Val Gln
325 330 335

<210> 33
<211> 1576
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (200)..(1564)

<400> 33
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ttttggaggc ccagtgggca ggccaggcag ggcgggtacg gagcctccca ggctggggca 120

gtgggcatgg gcaggggctg tggctgaaga cctcgcccgc ccactgcaga ccccagggga 180

ctctcacacc gcagctgcc atg gcc acc aat aag gag cga ctc ttt gcg gct 232
Met Ala Thr Asn Lys Glu Arg Leu Phe Ala Ala
1 5 10

ggt gcc ctg ggg cct gga tct ggc tac cca ggg gca ggt ttc ccc ttc 280
Gly Ala Leu Gly Pro Gly Ser Gly Tyr Pro Gly Ala Gly Phe Pro Phe
15 20 25

gcc ttc cca ggg gca ctc agg ggg tct ccg cct ttc gag atg ctg agc 328
Ala Phe Pro Gly Ala Leu Arg Gly Ser Pro Pro Phe Glu Met Leu Ser
30 35 40

cct agc ttc cgg ggc ctg ggc cag cct gac ctc ccc aag gag atg gcc 376
Pro Ser Phe Arg Gly Leu Gly Gln Pro Asp Leu Pro Lys Glu Met Ala
45 50 55

tct ctg tcg gtg gag aca cag agc acc agc tca gag gag atg gtg ccc 424
Ser Leu Ser Val Glu Thr Gln Ser Thr Ser Ser Glu Glu Met Val Pro
60 65 70 75

agc tcg ccc tcg ccc cct ccg cct cct cgg gtc tac aag cca tgc ttc 472
Ser Ser Pro Ser Pro Pro Pro Pro Pro Arg Val Tyr Lys Pro Cys Phe
80 85 90

gtg tgc aat gac aag tcc tct ggc tac cac tat ggg gtc agc tct tgt 520
Val Cys Asn Asp Lys Ser Ser Gly Tyr His Tyr Gly Val Ser Ser Cys
95 100 105

gaa ggc tgc aag ggc ttc ttt cgc cga agc atc cag aag aac atg gtg 568
Glu Gly Cys Lys Gly Phe Phe Arg Arg Ser Ile Gln Lys Asn Met Val
110 115 120

tac acg tgt cac cgc gac aaa aac tgt atc atc aac aag gtg acc agg 616
Tyr Thr Cys His Arg Asp Lys Asn Cys Ile Ile Asn Lys Val Thr Arg
125 130 135

aat cgc tgc cag tac tgc cgg cta cag aag tgc ttc gaa gtg ggc atg 664
Asn Arg Cys Gln Tyr Cys Arg Leu Gln Lys Cys Phe Glu Val Gly Met
140 145 150 155

tcc aag gaa gct gtg cga aat gac cgg aac aag aag aag aaa gag gtg 712
Ser Lys Glu Ala Val Arg Asn Asp Arg Asn Lys Lys Lys Lys Glu Val
160 165 170

aag gaa gaa ggg tca cct gac agc tat gag ctg agc cct cag tta gaa 760
Lys Glu Glu Gly Ser Pro Asp Ser Tyr Glu Leu Ser Pro Gln Leu Glu
175 180 185

gag ctc atc acc aag gtc agc aaa gcc cat cag gag act ttc ccc tcg 808
Glu Leu Ile Thr Lys Val Ser Lys Ala His Gln Glu Thr Phe Pro Ser
190 195 200

ctc tgc cag ctg ggc aag tat acc acg aac tcc agt gca gac cac cgc 856
Leu Cys Gln Leu Gly Lys Tyr Thr Thr Asn Ser Ser Ala Asp His Arg
205 210 215

gtg cag ctg gat ctg ggg ctg tgg gac aag ttc agt gag ctg gct acc 904
Val Gln Leu Asp Leu Gly Leu Trp Asp Lys Phe Ser Glu Leu Ala Thr
220 225 230 235

aag tgc atc atc aag atc gtg gag ttt gcc aag cgg ttg cct ggc ttt 952

Lys Cys Ile Ile Lys Ile Val Glu Phe Ala Lys Arg Leu Pro Gly Phe
240 245 250

aca ggg ctc agc att gct gac cag atc act ctg ctc aaa gct gcc tgc 1000
Thr Gly Leu Ser Ile Ala Asp Gln Ile Thr Leu Leu Lys Ala Ala Cys
255 260 265

cta gat atc ctg atg ctg cgt atc tgc aca agg tac acc cca gag cag 1048
Leu Asp Ile Leu Met Leu Arg Ile Cys Thr Arg Tyr Thr Pro Glu Gln
270 275 280

gac acc atg acc ttc tcc gac ggg ctg acc ctg aac cgg acc cag atg 1096
Asp Thr Met Thr Phe Ser Asp Gly Leu Thr Leu Asn Arg Thr Gln Met
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cac aat gcc ggc ttc ggg ccc ctc aca gac ctt gtc ttt gcc ttt gct 1144
His Asn Ala Gly Phe Gly Pro Leu Thr Asp Leu Val Phe Ala Phe Ala
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Gly Gln Leu Leu Pro Leu Glu Met Asp Asp Thr Glu Thr Gly Leu Leu
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Ser Ala Ile Cys Leu Ile Cys Gly Asp Arg Met Asp Leu Glu Glu Pro
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gaa aaa gtg gac aag ctg cag gag cca ctg ctg gaa gcc ctg agg ctg 1288
Glu Lys Val Asp Lys Leu Gln Glu Pro Leu Leu Glu Ala Leu Arg Leu
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tac gcc cgg cgc cgg cgg ccc agc cag ccc tac atg ttc cca agg atg 1336
Tyr Ala Arg Arg Arg Arg Pro Ser Gln Pro Tyr Met Phe Pro Arg Met
365 370 375

cta atg aaa atc acc gac ctc cgg ggc atc agc act aag gga gct gaa 1384
Leu Met Lys Ile Thr Asp Leu Arg Gly Ile Ser Thr Lys Gly Ala Glu
380 385 390 395

agg gcc att act ctg aag atg gag att cca ggc ccg atg cct ccc tta 1432
Arg Ala Ile Thr Leu Lys Met Glu Ile Pro Gly Pro Met Pro Pro Leu
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atc cga gag atg ctg gag aac cct gaa atg ttt gag gat gac tcc tcg 1480
Ile Arg Glu Met Leu Glu Asn Pro Glu Met Phe Glu Asp Asp Ser Ser
415 420 425

cag cct ggt ccc cac ccc aat gcc tct agc gag gat gag gtt cct ggg 1528
Gln Pro Gly Pro His Pro Asn Ala Ser Ser Glu Asp Glu Val Pro Gly
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35 40 45

Leu Gly Gln Pro Asp Leu Pro Lys Glu Met Ala Ser Leu Ser Val Glu
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Thr Gln Ser Thr Ser Ser Glu Glu Met Val Pro Ser Ser Pro Ser Pro
65 70 75 80

Pro Pro Pro Pro Arg Val Tyr Lys Pro Cys Phe Val Cys Asn Asp Lys
85 90 95

Ser Ser Gly Tyr His Tyr Gly Val Ser Ser Cys Glu Gly Cys Lys Gly
100 105 110

Phe Phe Arg Arg Ser Ile Gln Lys Asn Met Val Tyr Thr Cys His Arg
115 120 125

Asp Lys Asn Cys Ile Ile Asn Lys Val Thr Arg Asn Arg Cys Gln Tyr
130 135 140

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

145 150 155 160

Arg Asn Asp Arg Asn Lys Lys Lys Lys Glu Val Lys Glu Glu Gly Ser
165 170 175

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

Val Ser Lys Ala His Gln Glu Thr Phe Pro Ser Leu Cys Gln Leu Gly
195 200 205

Lys Tyr Thr Thr Asn Ser Ser Ala Asp His Arg Val Gln Leu Asp Leu
210 215 220

Gly Leu Trp Asp Lys Phe Ser Glu Leu Ala Thr Lys Cys Ile Ile Lys
225 230 235 240

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

Ala Asp Gln Ile Thr Leu Leu Lys Ala Ala Cys Leu Asp Ile Leu Met
260 265 270

Leu Arg Ile Cys Thr Arg Tyr Thr Pro Glu Gln Asp Thr Met Thr Phe
275 280 285

Ser Asp Gly Leu Thr Leu Asn Arg Thr Gln Met His Asn Ala Gly Phe
290 295 300

Gly Pro Leu Thr Asp Leu Val Phe Ala Phe Ala Gly Gln Leu Leu Pro
305 310 315 320

Leu Glu Met Asp Asp Thr Glu Thr Gly Leu Leu Ser Ala Ile Cys Leu
325 330 335

Ile Cys Gly Asp Arg Met Asp Leu Glu Glu Pro Glu Lys Val Asp Lys
340 345 350

Leu Gln Glu Pro Leu Leu Glu Ala Leu Arg Leu Tyr Ala Arg Arg Arg
355 360 365

Arg Pro Ser Gln Pro Tyr Met Phe Pro Arg Met Leu Met Lys Ile Thr
370 375 380

Asp Leu Arg Gly Ile Ser Thr Lys Gly Ala Glu Arg Ala Ile Thr Leu
385 390 395 400

Lys Met Glu Ile Pro Gly Pro Met Pro Pro Leu Ile Arg Glu Met Leu
405 410 415

Glu Asn Pro Glu Met Phe Glu Asp Asp Ser Ser Gln Pro Gly Pro His
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ccgccgcgga aaggcgtc atg ccg ccc aaa acc ccc cga aaa acg gcc gcc 171
Met Pro Pro Lys Thr Pro Arg Lys Thr Ala Ala
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acc gcc gcc gct gcc gcc gcg gaa ccc ccg gca ccg ccg ccg ccg ccc 219
Thr Ala Ala Ala Ala Ala Ala Glu Pro Pro Ala Pro Pro Pro Pro Pro

15 20 25

cct cct gag gag gac cca gag cag gac agc ggc ccg gag gac ctg cct 267
Pro Pro Glu Glu Asp Pro Glu Gln Asp Ser Gly Pro Glu Asp Leu Pro
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ctc gtc agg ctt gag ttt gaa gaa aca gaa gaa cct gat ttt act gca 315
Leu Val Arg Leu Glu Phe Glu Glu Thr Glu Glu Pro Asp Phe Thr Ala
45 50 55

tta tgt cag aaa tta aag ata cca gat cat gtc aga gag aga gct tgg 363
Leu Cys Gln Lys Leu Lys Ile Pro Asp His Val Arg Glu Arg Ala Trp
60 65 70 75

tta act tgg gag aaa gtt tca tct gtg gat gga gta ttg gga ggt tat 411
Leu Thr Trp Glu Lys Val Ser Ser Val Asp Gly Val Leu Gly Gly Tyr
80 85 90

att caa aag aaa aag gaa ctg tgg gga atc tgt atc ttt att gca cga 459
Ile Gln Lys Lys Lys Glu Leu Trp Gly Ile Cys Ile Phe Ile Ala Arg
95 100 105

gtt gac cta gat gag atg tcg ttc act tta ctg agc tac aga aaa aca 507
Val Asp Leu Asp Glu Met Ser Phe Thr Leu Leu Ser Tyr Arg Lys Thr
110 115 120

tac gaa atc agt gtc cat aaa ttc ttt aac tta cta aaa gaa att gat 555
Tyr Glu Ile Ser Val His Lys Phe Phe Asn Leu Leu Lys Glu Ile Asp
125 130 135

acc agt acc aaa gtt gat aat gct atg tca aga ctg ttg aag aag tat 603
Thr Ser Thr Lys Val Asp Asn Ala Met Ser Arg Leu Leu Lys Lys Tyr
140 145 150 155

gat gta ttg ttt gca ctc ttc agc aaa ttg gaa agg aca tgt gaa ctt 651
Asp Val Leu Phe Ala Leu Phe Ser Lys Leu Glu Arg Thr Cys Glu Leu
160 165 170

ata tat ttg aca caa ccc agc agt tcg ata tct act gaa ata aat tct 699
Ile Tyr Leu Thr Gln Pro Ser Ser Ser Ile Ser Thr Glu Ile Asn Ser
175 180 185

gca ttg gtg cta aaa gtt tct tgg atc aca ttt tta tta gct aaa ggg 747
Ala Leu Val Leu Lys Val Ser Trp Ile Thr Phe Leu Leu Ala Lys Gly
190 195 200

gaa gta tta caa atg gaa gat gat ctg gtg att tca ttt cag tta atg 795
Glu Val Leu Gln Met Glu Asp Asp Leu Val Ile Ser Phe Gln Leu Met
205 210 215

cta tgt gtc ctt gac tat ttt att aaa ctc tca cct ccc atg ttg ctc 843
Leu Cys Val Leu Asp Tyr Phe Ile Lys Leu Ser Pro Pro Met Leu Leu
220 225 230 235

aaa gaa cca tat aaa aca gct gtt ata ccc att aat ggt tca cct cga 891
Lys Glu Pro Tyr Lys Thr Ala Val Ile Pro Ile Asn Gly Ser Pro Arg
240 245 250

aca ccc agg cga ggt cag aac agg agt gca cgg ata gca aaa caa cta 939
Thr Pro Arg Arg Gly Gln Asn Arg Ser Ala Arg Ile Ala Lys Gln Leu
255 260 265

gaa aat gat aca aga att att gaa gtt ctc tgt aaa gaa cat gaa tgt 987
Glu Asn Asp Thr Arg Ile Ile Glu Val Leu Cys Lys Glu His Glu Cys
270 275 280

aat ata gat gag gtg aaa aat gtt tat ttc aaa aat ttt ata cct ttt 1035
Asn Ile Asp Glu Val Lys Asn Val Tyr Phe Lys Asn Phe Ile Pro Phe
285 290 295

atg aat tct ctt gga ctt gta aca tct aat gga ctt cca gag gtt gaa 1083
Met Asn Ser Leu Gly Leu Val Thr Ser Asn Gly Leu Pro Glu Val Glu
300 305 310 315

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Asn Leu Ser Lys Arg Tyr Glu Glu Ile Tyr Leu Lys Asn Lys Asp Leu
320 325 330

gat cga aga tta ttt ttg gat cat gat aaa act ctt cag act gat tct 1179
Asp Arg Arg Leu Phe Leu Asp His Asp Lys Thr Leu Gln Thr Asp Ser
335 340 345

ata gac agt ttt gaa aca cag aga aca cca cga aaa agt aac ctt gat 1227
Ile Asp Ser Phe Glu Thr Gln Arg Thr Pro Arg Lys Ser Asn Leu Asp
350 355 360

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Glu Glu Val Asn Ile Ile Pro Pro His Thr Pro Val Arg Thr Val Met
365 370 375

aac act atc caa caa tta atg atg att tta aat tct gca agt gat caa 1323
Asn Thr Ile Gln Gln Leu Met Met Ile Leu Asn Ser Ala Ser Asp Gln
380 385 390 395

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Pro Ser Glu Asn Leu Ile Ser Tyr Phe Asn Asn Cys Thr Val Asn Pro
400 405 410

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Lys Glu Ser Ile Leu Lys Arg Val Lys Asp Ile Gly Tyr Ile Phe Lys

415 420 425

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Glu Lys Phe Ala Lys Ala Val Gly Gln Gly Cys Val Glu Ile Gly Ser
430 435 440

cag cga tac aaa ctt gga gtt cgc ttg tat tac cga gta atg gaa tcc 1515
Gln Arg Tyr Lys Leu Gly Val Arg Leu Tyr Tyr Arg Val Met Glu Ser
445 450 455

atg ctt aaa tca gaa gaa gaa cga tta tcc att caa aat ttt agc aaa 1563
Met Leu Lys Ser Glu Glu Glu Arg Leu Ser Ile Gln Asn Phe Ser Lys
460 465 470 475

ctt ctg aat gac aac att ttt cat atg tct tta ttg gcg tgc gct ctt 1611
Leu Leu Asn Asp Asn Ile Phe His Met Ser Leu Leu Ala Cys Ala Leu
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495 500 505

tct gga aca gat ttg tct ttc cca tgg att ctg aat gtg ctt aat tta 1707
Ser Gly Thr Asp Leu Ser Phe Pro Trp Ile Leu Asn Val Leu Asn Leu
510 515 520

aaa gcc ttt gat ttt tac aaa gtg atc gaa agt ttt atc aaa gca gaa 1755
Lys Ala Phe Asp Phe Tyr Lys Val Ile Glu Ser Phe Ile Lys Ala Glu
525 530 535

ggc aac ttg aca aga gaa atg ata aaa cat tta gaa cga tgt gaa cat 1803
Gly Asn Leu Thr Arg Glu Met Ile Lys His Leu Glu Arg Cys Glu His
540 545 550 555

cga atc atg gaa tcc ctt gca tgg ctc tca gat tca cct tta ttt gat 1851
Arg Ile Met Glu Ser Leu Ala Trp Leu Ser Asp Ser Pro Leu Phe Asp
560 565 570

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Leu Ile Lys Gln Ser Lys Asp Arg Glu Gly Pro Thr Asp His Leu Glu
575 580 585

tct gct tgt cct ctt aat ctt cct ctc cag aat aat cac act gca gca 1947
Ser Ala Cys Pro Leu Asn Leu Pro Leu Gln Asn Asn His Thr Ala Ala
590 595 600

gat atg tat ctt tct cct gta aga tct cca aag aaa aaa ggt tca act 1995
Asp Met Tyr Leu Ser Pro Val Arg Ser Pro Lys Lys Lys Gly Ser Thr
605 610 615

acg cgt gta aat tct act gca aat gca gag aca caa gca acc tca gcc 2043
Thr Arg Val Asn Ser Thr Ala Asn Ala Glu Thr Gln Ala Thr Ser Ala
620 625 630 635

ttc cag acc cag aag cca ttg aaa tct acc tct ctt tca ctg ttt tat 2091
Phe Gln Thr Gln Lys Pro Leu Lys Ser Thr Ser Leu Ser Leu Phe Tyr
640 645 650

aaa aaa gtg tat cgg cta gcc tat ctc cgg cta aat aca ctt tgt gaa 2139
Lys Lys Val Tyr Arg Leu Ala Tyr Leu Arg Leu Asn Thr Leu Cys Glu
655 660 665

cgc ctt ctg tct gag cac cca gaa tta gaa cat atc atc tgg acc ctt 2187
Arg Leu Leu Ser Glu His Pro Glu Leu Glu His Ile Ile Trp Thr Leu
670 675 680

ttc cag cac acc ctg cag aat gag tat gaa ctc atg aga gac agg cat 2235
Phe Gln His Thr Leu Gln Asn Glu Tyr Glu Leu Met Arg Asp Arg His
685 690 695

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Leu Asp Gln Ile Met Met Cys Ser Met Tyr Gly Ile Cys Lys Val Lys
700 705 710 715

aat ata gac ctt aaa ttc aaa atc att gta aca gca tac aag gat ctt 2331
Asn Ile Asp Leu Lys Phe Lys Ile Ile Val Thr Ala Tyr Lys Asp Leu
720 725 730

cct cat gct gtt cag gag aca ttc aaa cgt gtt ttg atc aaa gaa gag 2379
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735 740 745

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750 755 760

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Leu Lys Thr Asn Ile Leu Gln Tyr Ala Ser Thr Arg Pro Pro Thr Leu
765 770 775

tca cca ata cct cac att cct cga agc cct tac aag ttt cct agt tca 2523
Ser Pro Ile Pro His Ile Pro Arg Ser Pro Tyr Lys Phe Pro Ser Ser
780 785 790 795

ccc tta cgg att cct gga ggg aac atc tat att tca ccc ctg aag agt 2571
Pro Leu Arg Ile Pro Gly Gly Asn Ile Tyr Ile Ser Pro Leu Lys Ser
800 805 810

cca tat aaa att tca gaa ggt ctg cca aca cca aca aaa atg act cca 2619
Pro Tyr Lys Ile Ser Glu Gly Leu Pro Thr Pro Thr Lys Met Thr Pro

815 820 825

aga tca aga atc tta gta tca att ggt gaa tca ttc ggg act tct gag 2667
Arg Ser Arg Ile Leu Val Ser Ile Gly Glu Ser Phe Gly Thr Ser Glu
830 835 840

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Lys Phe Gln Lys Ile Asn Gln Met Val Cys Asn Ser Asp Arg Val Leu
845 850 855

aaa aga agt gct gaa gga agc aac cct cct aaa cca ctg aaa aaa cta 2763
Lys Arg Ser Ala Glu Gly Ser Asn Pro Pro Lys Pro Leu Lys Lys Leu
860 865 870 875

cgc ttt gat att gaa gga tca gat gaa gca gat gga agt aaa cat ctc 2811
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880 885 890

cca gga gag tcc aaa ttt cag cag aaa ctg gca gaa atg act tct act 2859
Pro Gly Glu Ser Lys Phe Gln Gln Lys Leu Ala Glu Met Thr Ser Thr
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910 915 920

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Asn Lys Glu Glu Lys
925

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35 40 45

Phe Glu Glu Thr Glu Glu Pro Asp Phe Thr Ala Leu Cys Gln Lys Leu
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Lys Ile Pro Asp His Val Arg Glu Arg Ala Trp Leu Thr Trp Glu Lys
65 70 75 80

Val Ser Ser Val Asp Gly Val Leu Gly Gly Tyr Ile Gln Lys Lys Lys
85 90 95

Glu Leu Trp Gly Ile Cys Ile Phe Ile Ala Arg Val Asp Leu Asp Glu
100 105 110

Met Ser Phe Thr Leu Leu Ser Tyr Arg Lys Thr Tyr Glu Ile Ser Val
115 120 125

His Lys Phe Phe Asn Leu Leu Lys Glu Ile Asp Thr Ser Thr Lys Val
130 135 140

Asp Asn Ala Met Ser Arg Leu Leu Lys Lys Tyr Asp Val Leu Phe Ala
145 150 155 160

Leu Phe Ser Lys Leu Glu Arg Thr Cys Glu Leu Ile Tyr Leu Thr Gln
165 170 175

Pro Ser Ser Ser Ile Ser Thr Glu Ile Asn Ser Ala Leu Val Leu Lys
180 185 190

Val Ser Trp Ile Thr Phe Leu Leu Ala Lys Gly Glu Val Leu Gln Met
195 200 205

Glu Asp Asp Leu Val Ile Ser Phe Gln Leu Met Leu Cys Val Leu Asp
210 215 220

Tyr Phe Ile Lys Leu Ser Pro Pro Met Leu Leu Lys Glu Pro Tyr Lys
225 230 235 240

Thr Ala Val Ile Pro Ile Asn Gly Ser Pro Arg Thr Pro Arg Arg Gly
245 250 255

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

Ile Ile Glu Val Leu Cys Lys Glu His Glu Cys Asn Ile Asp Glu Val
275 280 285

Lys Asn Val Tyr Phe Lys Asn Phe Ile Pro Phe Met Asn Ser Leu Gly
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Leu Val Thr Ser Asn Gly Leu Pro Glu Val Glu Asn Leu Ser Lys Arg
305 310 315 320

Tyr Glu Glu Ile Tyr Leu Lys Asn Lys Asp Leu Asp Arg Arg Leu Phe
325 330 335

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340 345 350

Thr Gln Arg Thr Pro Arg Lys Ser Asn Leu Asp Glu Glu Val Asn Ile
355 360 365

Ile Pro Pro His Thr Pro Val Arg Thr Val Met Asn Thr Ile Gln Gln
370 375 380

Leu Met Met Ile Leu Asn Ser Ala Ser Asp Gln Pro Ser Glu Asn Leu
385 390 395 400

Ile Ser Tyr Phe Asn Asn Cys Thr Val Asn Pro Lys Glu Ser Ile Leu
405 410 415

Lys Arg Val Lys Asp Ile Gly Tyr Ile Phe Lys Glu Lys Phe Ala Lys
420 425 430

Ala Val Gly Gln Gly Cys Val Glu Ile Gly Ser Gln Arg Tyr Lys Leu
435 440 445

Gly Val Arg Leu Tyr Tyr Arg Val Met Glu Ser Met Leu Lys Ser Glu
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Glu Glu Arg Leu Ser Ile Gln Asn Phe Ser Lys Leu Leu Asn Asp Asn
465 470 475 480

Ile Phe His Met Ser Leu Leu Ala Cys Ala Leu Glu Val Val Met Ala
485 490 495

Thr Tyr Ser Arg Ser Thr Ser Gln Asn Leu Asp Ser Gly Thr Asp Leu
500 505 510

Ser Phe Pro Trp Ile Leu Asn Val Leu Asn Leu Lys Ala Phe Asp Phe
515 520 525

Tyr Lys Val Ile Glu Ser Phe Ile Lys Ala Glu Gly Asn Leu Thr Arg
530 535 540

Glu Met Ile Lys His Leu Glu Arg Cys Glu His Arg Ile Met Glu Ser
545 550 555 560

Leu Ala Trp Leu Ser Asp Ser Pro Leu Phe Asp Leu Ile Lys Gln Ser
565 570 575

Lys Asp Arg Glu Gly Pro Thr Asp His Leu Glu Ser Ala Cys Pro Leu
580 585 590

Asn Leu Pro Leu Gln Asn Asn His Thr Ala Ala Asp Met Tyr Leu Ser
595 600 605

Pro Val Arg Ser Pro Lys Lys Lys Gly Ser Thr Thr Arg Val Asn Ser
610 615 620

Thr Ala Asn Ala Glu Thr Gln Ala Thr Ser Ala Phe Gln Thr Gln Lys
625 630 635 640

Pro Leu Lys Ser Thr Ser Leu Ser Leu Phe Tyr Lys Lys Val Tyr Arg
645 650 655

Leu Ala Tyr Leu Arg Leu Asn Thr Leu Cys Glu Arg Leu Leu Ser Glu
660 665 670

His Pro Glu Leu Glu His Ile Ile Trp Thr Leu Phe Gln His Thr Leu
675 680 685

Gln Asn Glu Tyr Glu Leu Met Arg Asp Arg His Leu Asp Gln Ile Met
690 695 700

Met Cys Ser Met Tyr Gly Ile Cys Lys Val Lys Asn Ile Asp Leu Lys
705 710 715 720

Phe Lys Ile Ile Val Thr Ala Tyr Lys Asp Leu Pro His Ala Val Gln
725 730 735

Glu Thr Phe Lys Arg Val Leu Ile Lys Glu Glu Glu Tyr Asp Ser Ile
740 745 750

Ile Val Phe Tyr Asn Ser Val Phe Met Gln Arg Leu Lys Thr Asn Ile
755 760 765

Leu Gln Tyr Ala Ser Thr Arg Pro Pro Thr Leu Ser Pro Ile Pro His
770 775 780

Ile Pro Arg Ser Pro Tyr Lys Phe Pro Ser Ser Pro Leu Arg Ile Pro
785 790 795 800

Gly Gly Asn Ile Tyr Ile Ser Pro Leu Lys Ser Pro Tyr Lys Ile Ser
805 810 815

Glu Gly Leu Pro Thr Pro Thr Lys Met Thr Pro Arg Ser Arg Ile Leu
820 825 830

Val Ser Ile Gly Glu Ser Phe Gly Thr Ser Glu Lys Phe Gln Lys Ile
835 840 845

Asn Gln Met Val Cys Asn Ser Asp Arg Val Leu Lys Arg Ser Ala Glu
850 855 860

Gly Ser Asn Pro Pro Lys Pro Leu Lys Lys Leu Arg Phe Asp Ile Glu
865 870 875 880

Gly Ser Asp Glu Ala Asp Gly Ser Lys His Leu Pro Gly Glu Ser Lys
885 890 895

Phe Gln Gln Lys Leu Ala Glu Met Thr Ser Thr Arg Thr Arg Met Gln
900 905 910

Lys Gln Lys Met Asn Asp Ser Met Asp Thr Ser Asn Lys Glu Glu Lys
915 920 925

<210> 37
<211> 4201
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (359)..(1885)

<400> 37
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gcagacggac agggggcgct gcgcgcggcc tggggcaacc cgggccacag gggcaggaaa 180

gtgagggccc aggtcggccc gggcgtgcag gggccccggg ttcgcagcgg cggccgcggc 240

agcgatagcg gcactagcag cagcgggagt gccgggttga gccgggaagc cgatggcggc 300

ggctgcggcg gctccgattc ctcgctgact gcccgtccgc cctcctgcat cgagcgcc 358

atg tta ccg acc caa gct ggg gcc gcg gcg gct ctg ggc cgg ggc tcg 406
Met Leu Pro Thr Gln Ala Gly Ala Ala Ala Ala Leu Gly Arg Gly Ser
1 5 10 15

gcc ctg ggg ggc agc ctg aac cgg acc ccg acg ggg cgg ccg ggc ggc 454
Ala Leu Gly Gly Ser Leu Asn Arg Thr Pro Thr Gly Arg Pro Gly Gly
20 25 30

ggc ggc ggg aca cgc ggg gct aac ggg ggc cgg gtc ccc ggg aat ggc 502
Gly Gly Gly Thr Arg Gly Ala Asn Gly Gly Arg Val Pro Gly Asn Gly
35 40 45

gcg ggg ctc ggg ccc ggc cgc ctg gag cgg gag gct gcg gca gcg gcg 550
Ala Gly Leu Gly Pro Gly Arg Leu Glu Arg Glu Ala Ala Ala Ala Ala
50 55 60

gca acc acc ccg gcg ccc acc gcg ggg gcc ctc tac agc ggc agc gag 598
Ala Thr Thr Pro Ala Pro Thr Ala Gly Ala Leu Tyr Ser Gly Ser Glu
65 70 75 80

ggc gac tcg gag tcg ggc gag gag gag gag ctg ggc gcc gag cgg cgc 646
Gly Asp Ser Glu Ser Gly Glu Glu Glu Glu Leu Gly Ala Glu Arg Arg
85 90 95

ggc ctg aag cgg agc ctg agc gag atg gag atc ggt atg gtg gtc ggt 694
Gly Leu Lys Arg Ser Leu Ser Glu Met Glu Ile Gly Met Val Val Gly
100 105 110

ggg ccc gag gcg tcg gca gcg gcc acc ggg ggc tac ggg ccg gtg agc 742
Gly Pro Glu Ala Ser Ala Ala Ala Thr Gly Gly Tyr Gly Pro Val Ser
115 120 125

ggc gcg gtg agc ggg gcc aag ccg ggt aag aag acc cgg ggc cgc gtg 790
Gly Ala Val Ser Gly Ala Lys Pro Gly Lys Lys Thr Arg Gly Arg Val
130 135 140

aag atc aag atg gag ttc atc gac aac aag ctg cgg cgc tac acg acc 838
Lys Ile Lys Met Glu Phe Ile Asp Asn Lys Leu Arg Arg Tyr Thr Thr
145 150 155 160

ttc agc aag agg aag acg ggc atc atg aag aag gcc tat gag ctg tcc 886
Phe Ser Lys Arg Lys Thr Gly Ile Met Lys Lys Ala Tyr Glu Leu Ser
165 170 175

acg ctg aca ggg aca cag gtg ctg ttg ctg gtg gcc agt gag aca ggc 934
Thr Leu Thr Gly Thr Gln Val Leu Leu Leu Val Ala Ser Glu Thr Gly
180 185 190

cat gtg tat acc ttt gcc acc cga aaa ctg cag ccc atg atc acc agt 982
His Val Tyr Thr Phe Ala Thr Arg Lys Leu Gln Pro Met Ile Thr Ser
195 200 205

gag acc ggc aag gca ctg att cag acc tgc ctc aac tcg cca gac tct 1030
Glu Thr Gly Lys Ala Leu Ile Gln Thr Cys Leu Asn Ser Pro Asp Ser
210 215 220

cca ccc cgt tca gac ccc aca aca gac cag aga atg agt gcc act ggc 1078
Pro Pro Arg Ser Asp Pro Thr Thr Asp Gln Arg Met Ser Ala Thr Gly
225 230 235 240

ttt gaa gag aca gat ctc acc tac cag gtg tcg gag tct gac agc agt 1126
Phe Glu Glu Thr Asp Leu Thr Tyr Gln Val Ser Glu Ser Asp Ser Ser
245 250 255

ggg gag acc aag gac aca ctg aag ccg gcg ttc aca gtc acc aac ctg 1174
Gly Glu Thr Lys Asp Thr Leu Lys Pro Ala Phe Thr Val Thr Asn Leu
260 265 270

ccg ggt aca acc tcc acc atc caa aca gca cct agc acc tct acc acc 1222
Pro Gly Thr Thr Ser Thr Ile Gln Thr Ala Pro Ser Thr Ser Thr Thr
275 280 285

atg caa gtc agc agc ggc ccc tcc ttt ccc atc acc aac tac ctg gca 1270
Met Gln Val Ser Ser Gly Pro Ser Phe Pro Ile Thr Asn Tyr Leu Ala
290 295 300

cca gtg tct gct agt gtc agc ccc agt gct gtc agc agt gcc aat ggg 1318
Pro Val Ser Ala Ser Val Ser Pro Ser Ala Val Ser Ser Ala Asn Gly
305 310 315 320

act gtg ctg aag agt aca ggc agc ggc cct gtc tcc tct ggg ggc ctt 1366
Thr Val Leu Lys Ser Thr Gly Ser Gly Pro Val Ser Ser Gly Gly Leu
325 330 335

atg cag ctg cct acc agc ttc acc ctc atg cct ggt ggg gca gtg gcc 1414
Met Gln Leu Pro Thr Ser Phe Thr Leu Met Pro Gly Gly Ala Val Ala
340 345 350

cag cag gtc cca gtg cag gcc att caa gtg cac cag gcc cca cag caa 1462
Gln Gln Val Pro Val Gln Ala Ile Gln Val His Gln Ala Pro Gln Gln
355 360 365

gcg tct ccc tcc cgt gac agc agc aca gac ctc acg cag acc tcc tcc 1510
Ala Ser Pro Ser Arg Asp Ser Ser Thr Asp Leu Thr Gln Thr Ser Ser
370 375 380

agc ggg aca gtg acg ctg ccc gcc acc atc atg acg tca tcc gtg ccc 1558

Ser Gly Thr Val Thr Leu Pro Ala Thr Ile Met Thr Ser Ser Val Pro
385 390 395 400

aca act gtg ggt ggc cac atg atg tac cct agc ccg cat gcg gtg atg 1606
Thr Thr Val Gly Gly His Met Met Tyr Pro Ser Pro His Ala Val Met
405 410 415

tat gcc ccc acc tcg ggc ctg ggt gat ggc agc ctc acc gtg ctg aat 1654
Tyr Ala Pro Thr Ser Gly Leu Gly Asp Gly Ser Leu Thr Val Leu Asn
420 425 430

gcc ttc tcc cag gca cca tcc acc atg cag gtg tca cac agc cag gtc 1702
Ala Phe Ser Gln Ala Pro Ser Thr Met Gln Val Ser His Ser Gln Val
435 440 445

cag gag cca ggt ggc gtc ccc cag gtg ttc ctg aca gca tca tct ggg 1750
Gln Glu Pro Gly Gly Val Pro Gln Val Phe Leu Thr Ala Ser Ser Gly
450 455 460

aca gtg cag atc cct gtt tca gca gtt cag ctc cac cag atg gct gtg 1798
Thr Val Gln Ile Pro Val Ser Ala Val Gln Leu His Gln Met Ala Val
465 470 475 480

ata ggg cag cag gcc ggg agc agc agc aac ctc acc gag cta cag gtg 1846
Ile Gly Gln Gln Ala Gly Ser Ser Ser Asn Leu Thr Glu Leu Gln Val
485 490 495

gtg aac ctg gac acc gcc cac agc acc aag agt gaa tga tccgcccgcc 1895
Val Asn Leu Asp Thr Ala His Ser Thr Lys Ser Glu
500 505

gccctggaca gatggcccaa gggatggcac cacttattta ttgttgcctt ttcacgtttt 1955

ctttacacac acgttgacgg gccgcaggag ggaggcgggg aggaggaacg ggcagccaca 2015

ggactgagcc ctctcactcc agccaaagaa atgggcctgc ctgcctccac ccgtcctccc 2075

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ggaccgtgcc ccacctcccc acacacaggc cttctgtggg gctgggcacc gtgtcctcct 2255

ctgaggaagc agttggggcc ctcttgccag cctccttgct gaccccaggt cagccctgtg 2315

tctgtcacag gctgggtcaa aagagccctg gctctgcccc tcaggggcc agctggggag 2375

atgggggctt cttcctcaca ctgctgtcct ctccccttc agctcctgag tagctgggcc 2435

tgtgcactgg gcaggttcct ggggccgcct gccctgcctt gccgctcccc ttggacctcc 2495

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aaaacaaatc tataaatata tatttttaaa atatttaact ttttttatg gcgtttttct 2675

cgtccccctc cctgcccaaa ctccccttcc ctggggagcc ctcaggctcc ccagaactgg 2735

ctgggcccct ggggacagag ccaccccatg agctcggggt ccaccagtgt gtgggggaga 2795

ttctgggttt gcccagtcct ggattgtttc caggagaaag ccgggggagg ggccctcagg 2855

ccattcccca acggggtggg gagggtgacc cacagctctg ggcctctttt tgcccttag 2915

ggctgttgct agggagaggg aagagggaga ccaaatgtcg gggttggggt gggagggcgt 2975

caggcagagg caactgactt catttgtgcc acacgcatgg gcattgcagc cttgcgctgt 3035

cccaggcatg cagctgcctg gggcccaagt tgcagtgagc agggtggggt ctgggagggg 3095

gtgagaggca ggaatggggg tcagaagaag tgggagcagc ttcttgggct gagtgcagcc 3155

aaaggggagc cagaaatggg cagttctccc agggagtgag cagctactgt aacttttta 3215

aattaagaca aaaagccttg aagaaaatga ctttattttt ctaagtgtaa cctcagtatt 3275

tatgtaattt gtacaggggc catgccccac ccccctcctc ccccttggg gtagaccttg 3335

agggtgggcc agcatagggg ggagggtctt ttaccctgtg tcagagccta ccttcaccac 3395

ctatatccag aaggggagct ttttcagaaa cagggcagca gtggggtgaa attttcttaa 3455

cccctaagac tgccttcagt aggaacaagc tggcttctgt gattaggtga agggatgggg 3515

gaagatttta tgcacagcct agttatcaag gggatgattt gccgacatgt ttgagaaccc 3575

cctaacctct aaccctcatt gctgtcttgc cccagtttgg ggtgccaaga tggaagtcac 3635

ctttctgggc tttctcctgg agactagctg gggcttatgg gtggctttca aggctggggc 3695

atggcaaatc aggggccaga gagcagggga gcttgggact caggtctgta actgcccagc 3755

ccctttctc tgctcttgtt tcactccacc atcactcact cactccccac tcccccaccc 3815

atggggagga gacctttgat gaattcttcc tctccttccc acaaaagaca gacccagtga 3875

gtgaatcagg caaagtgctt ataatgtgtg ttgtgtgagc gtggccttgg gaggacatgc 3935

gtgtgtcagg gatgagttga ggtgatattt ttatgtgcag cgacccttgg tgtttccctt 3995

cctcggtggc tctggggtat gtgtgtgtgg gtgtgtgcgc ctgagtgagt gtgtgtgctt 4055

gaatgtgagt gtgtatgtca gtggtttcta cttcccctgg gatgctgacc caggaatagt 4115

ggacatggtc acagtcctat gtacagagct ttcttttgta ttaaaaaaaa atactctttc 4175

aataaatgta tcatttttgt gcacag 4201

<210> 38
<211> 508
<212> PRT
<213> Homo sapiens

<400> 38

Met Leu Pro Thr Gln Ala Gly Ala Ala Ala Ala Leu Gly Arg Gly Ser
1 5 10 15

Ala Leu Gly Gly Ser Leu Asn Arg Thr Pro Thr Gly Arg Pro Gly Gly
20 25 30

Gly Gly Gly Thr Arg Gly Ala Asn Gly Gly Arg Val Pro Gly Asn Gly
35 40 45

Ala Gly Leu Gly Pro Gly Arg Leu Glu Arg Glu Ala Ala Ala Ala Ala
50 55 60

Ala Thr Thr Pro Ala Pro Thr Ala Gly Ala Leu Tyr Ser Gly Ser Glu
65 70 75 80

Gly Asp Ser Glu Ser Gly Glu Glu Glu Glu Leu Gly Ala Glu Arg Arg
85 90 95

Gly Leu Lys Arg Ser Leu Ser Glu Met Glu Ile Gly Met Val Val Gly
100 105 110

Gly Pro Glu Ala Ser Ala Ala Ala Thr Gly Gly Tyr Gly Pro Val Ser
115 120 125

Gly Ala Val Ser Gly Ala Lys Pro Gly Lys Lys Thr Arg Gly Arg Val

130 135 140

Lys Ile Lys Met Glu Phe Ile Asp Asn Lys Leu Arg Arg Tyr Thr Thr
145 150 155 160

Phe Ser Lys Arg Lys Thr Gly Ile Met Lys Lys Ala Tyr Glu Leu Ser
165 170 175

Thr Leu Thr Gly Thr Gln Val Leu Leu Leu Val Ala Ser Glu Thr Gly
180 185 190

His Val Tyr Thr Phe Ala Thr Arg Lys Leu Gln Pro Met Ile Thr Ser
195 200 205

Glu Thr Gly Lys Ala Leu Ile Gln Thr Cys Leu Asn Ser Pro Asp Ser
210 215 220

Pro Pro Arg Ser Asp Pro Thr Thr Asp Gln Arg Met Ser Ala Thr Gly
225 230 235 240

Phe Glu Glu Thr Asp Leu Thr Tyr Gln Val Ser Glu Ser Asp Ser Ser
245 250 255

Gly Glu Thr Lys Asp Thr Leu Lys Pro Ala Phe Thr Val Thr Asn Leu
260 265 270

Pro Gly Thr Thr Ser Thr Ile Gln Thr Ala Pro Ser Thr Ser Thr Thr
275 280 285

Met Gln Val Ser Ser Gly Pro Ser Phe Pro Ile Thr Asn Tyr Leu Ala
290 295 300

Pro Val Ser Ala Ser Val Ser Pro Ser Ala Val Ser Ser Ala Asn Gly
305 310 315 320

Thr Val Leu Lys Ser Thr Gly Ser Gly Pro Val Ser Ser Gly Gly Leu
325 330 335

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

Gln Gln Val Pro Val Gln Ala Ile Gln Val His Gln Ala Pro Gln Gln
355 360 365

Ala Ser Pro Ser Arg Asp Ser Ser Thr Asp Leu Thr Gln Thr Ser Ser
370 375 380

Ser Gly Thr Val Thr Leu Pro Ala Thr Ile Met Thr Ser Ser Val Pro
385 390 395 400

Thr Thr Val Gly Gly His Met Met Tyr Pro Ser Pro His Ala Val Met
405 410 415

Tyr Ala Pro Thr Ser Gly Leu Gly Asp Gly Ser Leu Thr Val Leu Asn
420 425 430

Ala Phe Ser Gln Ala Pro Ser Thr Met Gln Val Ser His Ser Gln Val
435 440 445

Gln Glu Pro Gly Gly Val Pro Gln Val Phe Leu Thr Ala Ser Ser Gly
450 455 460

Thr Val Gln Ile Pro Val Ser Ala Val Gln Leu His Gln Met Ala Val
465 470 475 480

Ile Gly Gln Gln Ala Gly Ser Ser Ser Asn Leu Thr Glu Leu Gln Val
485 490 495

Val Asn Leu Asp Thr Ala His Ser Thr Lys Ser Glu
500 505

<210> 39
<211> 4003
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (197)..(2449)

<400> 39
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gccatcctcg agagctgtct aggttaacgt tcgcactctg tgtatataac ctcgacagtc 120

ttggcaccta acgtgctgtg cgtagctgct cctttggttg aatccccagg cccttgttgg 180

ggcacaaggt ggcagg atg tct cag tgg tac gaa ctt cag cag ctt gac tca 232
Met Ser Gln Trp Tyr Glu Leu Gln Gln Leu Asp Ser
1 5 10

aaa ttc ctg gag cag gtt cac cag ctt tat gat gac agt ttt ccc atg 280
Lys Phe Leu Glu Gln Val His Gln Leu Tyr Asp Asp Ser Phe Pro Met
15 20 25

gaa atc aga cag tac ctg gca cag tgg tta gaa aag caa gac tgg gag 328
Glu Ile Arg Gln Tyr Leu Ala Gln Trp Leu Glu Lys Gln Asp Trp Glu
30 35 40

cac gct gcc aat gat gtt tca ttt gcc acc atc cgt ttt cat gac ctc 376
His Ala Ala Asn Asp Val Ser Phe Ala Thr Ile Arg Phe His Asp Leu
45 50 55 60

ctg tca cag ctg gat gat caa tat agt cgc ttt tct ttg gag aat aac 424
Leu Ser Gln Leu Asp Asp Gln Tyr Ser Arg Phe Ser Leu Glu Asn Asn
65 70 75

ttc ttg cta cag cat aac ata agg aaa agc aag cgt aat ctt cag gat 472
Phe Leu Leu Gln His Asn Ile Arg Lys Ser Lys Arg Asn Leu Gln Asp
80 85 90

aat ttt cag gaa gac cca atc cag atg tct atg atc att tac agc tgt 520
Asn Phe Gln Glu Asp Pro Ile Gln Met Ser Met Ile Ile Tyr Ser Cys
95 100 105

ctg aag gaa gaa agg aaa att ctg gaa aac gcc cag aga ttt aat cag 568
Leu Lys Glu Glu Arg Lys Ile Leu Glu Asn Ala Gln Arg Phe Asn Gln
110 115 120

gct cag tcg ggg aat att cag agc aca gtg atg tta gac aaa cag aaa 616
Ala Gln Ser Gly Asn Ile Gln Ser Thr Val Met Leu Asp Lys Gln Lys
125 130 135 140

gag ctt gac agt aaa gtc aga aat gtg aag gac aag gtt atg tgt ata 664
Glu Leu Asp Ser Lys Val Arg Asn Val Lys Asp Lys Val Met Cys Ile

145 150 155

gag cat gaa atc aag agc ctg gaa gat tta caa gat gaa tat gac ttc 712
Glu His Glu Ile Lys Ser Leu Glu Asp Leu Gln Asp Glu Tyr Asp Phe
160 165 170

aaa tgc aaa acc ttg cag aac aga gaa cac gag acc aat ggt gtg gca 760
Lys Cys Lys Thr Leu Gln Asn Arg Glu His Glu Thr Asn Gly Val Ala
175 180 185

aag agt gat cag aaa caa gaa cag ctg tta ctc aag aag atg tat tta 808
Lys Ser Asp Gln Lys Gln Glu Gln Leu Leu Leu Lys Lys Met Tyr Leu
190 195 200

atg ctt gac aat aag aga aag gaa gta gtt cac aaa ata ata gag ttg 856
Met Leu Asp Asn Lys Arg Lys Glu Val Val His Lys Ile Ile Glu Leu
205 210 215 220

ctg aat gtc act gaa ctt acc cag aat gcc ctg att aat gat gaa cta 904
Leu Asn Val Thr Glu Leu Thr Gln Asn Ala Leu Ile Asn Asp Glu Leu
225 230 235

gtg gag tgg aag cgg aga cag cag agc gcc tgt att ggg ggg ccg ccc 952
Val Glu Trp Lys Arg Arg Gln Gln Ser Ala Cys Ile Gly Gly Pro Pro
240 245 250

aat gct tgc ttg gat cag ctg cag aac tgg ttc act ata gtt gcg gag 1000
Asn Ala Cys Leu Asp Gln Leu Gln Asn Trp Phe Thr Ile Val Ala Glu
255 260 265

agt ctg cag caa gtt cgg cag cag ctt aaa aag ttg gag gaa ttg gaa 1048
Ser Leu Gln Gln Val Arg Gln Gln Leu Lys Lys Leu Glu Glu Leu Glu
270 275 280

cag aaa tac acc tac gaa cat gac cct atc aca aaa aac aaa caa gtg 1096
Gln Lys Tyr Thr Tyr Glu His Asp Pro Ile Thr Lys Asn Lys Gln Val
285 290 295 300

tta tgg gac cgc acc ttc agt ctt ttc cag cag ctc att cag agc tcg 1144
Leu Trp Asp Arg Thr Phe Ser Leu Phe Gln Gln Leu Ile Gln Ser Ser
305 310 315

ttt gtg gtg gaa aga cag ccc tgc atg cca acg cac cct cag agg ccg 1192
Phe Val Val Glu Arg Gln Pro Cys Met Pro Thr His Pro Gln Arg Pro
320 325 330

ctg gtc ttg aag aca ggg gtc cag ttc act gtg aag ttg aga ctg ttg 1240
Leu Val Leu Lys Thr Gly Val Gln Phe Thr Val Lys Leu Arg Leu Leu
335 340 345

gtg aaa ttg caa gag ctg aat tat aat ttg aaa gtc aaa gtc tta ttt 1288
Val Lys Leu Gln Glu Leu Asn Tyr Asn Leu Lys Val Lys Val Leu Phe
350 355 360

gat aaa gat gtg aat gag aga aat aca gta aaa gga ttt agg aag ttc 1336
Asp Lys Asp Val Asn Glu Arg Asn Thr Val Lys Gly Phe Arg Lys Phe
365 370 375 380

aac att ttg ggc acg cac aca aaa gtg atg aac atg gag gag tcc acc 1384
Asn Ile Leu Gly Thr His Thr Lys Val Met Asn Met Glu Glu Ser Thr
385 390 395

aat ggc agt ctg gcg gct gaa ttt cgg cac ctg caa ttg aaa gaa cag 1432
Asn Gly Ser Leu Ala Ala Glu Phe Arg His Leu Gln Leu Lys Glu Gln
400 405 410

aaa aat gct ggc acc aga acg aat gag ggt cct ctc atc gtt act gaa 1480
Lys Asn Ala Gly Thr Arg Thr Asn Glu Gly Pro Leu Ile Val Thr Glu
415 420 425

gag ctt cac tcc ctt agt ttt gaa acc caa ttg tgc cag cct ggt ttg 1528
Glu Leu His Ser Leu Ser Phe Glu Thr Gln Leu Cys Gln Pro Gly Leu
430 435 440

gta att gac ctc gag acg acc tct ctg ccc gtt gtg gtg atc tcc aac 1576
Val Ile Asp Leu Glu Thr Thr Ser Leu Pro Val Val Val Ile Ser Asn
445 450 455 460

gtc agc cag ctc ccg agc ggt tgg gcc tcc atc ctt tgg tac aac atg 1624
Val Ser Gln Leu Pro Ser Gly Trp Ala Ser Ile Leu Trp Tyr Asn Met
465 470 475

ctg gtg gcg gaa ccc agg aat ctg tcc ttc ttc ctg act cca cca tgt 1672
Leu Val Ala Glu Pro Arg Asn Leu Ser Phe Phe Leu Thr Pro Pro Cys
480 485 490

gca cga tgg gct cag ctt tca gaa gtg ctg agt tgg cag ttt tct tct 1720
Ala Arg Trp Ala Gln Leu Ser Glu Val Leu Ser Trp Gln Phe Ser Ser
495 500 505

gtc acc aaa aga ggt ctc aat gtg gac cag ctg aac atg ttg gga gag 1768
Val Thr Lys Arg Gly Leu Asn Val Asp Gln Leu Asn Met Leu Gly Glu
510 515 520

aag ctt ctt ggt cct aac gcc agc ccc gat ggt ctc att ccg tgg acg 1816
Lys Leu Leu Gly Pro Asn Ala Ser Pro Asp Gly Leu Ile Pro Trp Thr
525 530 535 540

agg ttt tgt aag gaa aat ata aat gat aaa aat ttt ccc ttc tgg ctt 1864
Arg Phe Cys Lys Glu Asn Ile Asn Asp Lys Asn Phe Pro Phe Trp Leu

545 550 555

tgg att gaa agc atc cta gaa ctc att aaa aaa cac ctg ctc cct ctc 1912
Trp Ile Glu Ser Ile Leu Glu Leu Ile Lys Lys His Leu Leu Pro Leu
560 565 570

tgg aat gat ggg tgc atc atg ggc ttc atc agc aag gag cga gag cgt 1960
Trp Asn Asp Gly Cys Ile Met Gly Phe Ile Ser Lys Glu Arg Glu Arg
575 580 585

gcc ctg ttg aag gac cag cag ccg ggg acc ttc ctg ctg cgg ttc agt 2008
Ala Leu Leu Lys Asp Gln Gln Pro Gly Thr Phe Leu Leu Arg Phe Ser
590 595 600

gag agc tcc cgg gaa ggg gcc atc aca ttc aca tgg gtg gag cgg tcc 2056
Glu Ser Ser Arg Glu Gly Ala Ile Thr Phe Thr Trp Val Glu Arg Ser
605 610 615 620

cag aac gga ggc gaa cct gac ttc cat gcg gtt gaa ccc tac acg aag 2104
Gln Asn Gly Gly Glu Pro Asp Phe His Ala Val Glu Pro Tyr Thr Lys
625 630 635

aaa gaa ctt tct gct gtt act ttc cct gac atc att cgc aat tac aaa 2152
Lys Glu Leu Ser Ala Val Thr Phe Pro Asp Ile Ile Arg Asn Tyr Lys
640 645 650

gtc atg gct gct gag aat att cct gag aat ccc ctg aag tat ctg tat 2200
Val Met Ala Ala Glu Asn Ile Pro Glu Asn Pro Leu Lys Tyr Leu Tyr
655 660 665

cca aat att gac aaa gac cat gcc ttt gga aag tat tac tcc agg cca 2248
Pro Asn Ile Asp Lys Asp His Ala Phe Gly Lys Tyr Tyr Ser Arg Pro
670 675 680

aag gaa gca cca gag cca atg gaa ctt gat ggc cct aaa gga act gga 2296
Lys Glu Ala Pro Glu Pro Met Glu Leu Asp Gly Pro Lys Gly Thr Gly
685 690 695 700

tat atc aag act gag ttg att tct gtg tct gaa gtt cac cct tct aga 2344
Tyr Ile Lys Thr Glu Leu Ile Ser Val Ser Glu Val His Pro Ser Arg
705 710 715

ctt cag acc aca gac aac ctg ctc ccc atg tct cct gag gag ttt gac 2392
Leu Gln Thr Thr Asp Asn Leu Leu Pro Met Ser Pro Glu Glu Phe Asp
720 725 730

gag gtg tct cgg ata gtg ggc tct gta gaa ttc gac agt atg atg aac 2440
Glu Val Ser Arg Ile Val Gly Ser Val Glu Phe Asp Ser Met Met Asn
735 740 745

aca gta tag agcatgaatt tttttcatct tctctggcga cagttttcct 2489
Thr Val
750

tctcatctgt gattccctcc tgctactctg ttccttcaca tcctgtgttt ctagggaaat 2549

gaaagaaagg ccagcaaatt cgctgcaacc tgttgatagc aagtgaattt ttctctaact 2609

cagaaacatc agttactctg aagggcatca tgcatcttac tgaaggtaaa attgaaaggc 2669

attctctgaa gagtgggttt cacaagtgaa aaacatccag atacacccaa agtatcagga 2729

cgagaatgag ggtcctttgg gaaaggagaa gttaagcaac atctagcaaa tgttatgcat 2789

aaagtcagtg cccaactgtt ataggttgtt ggataaatca gtggttattt agggaactgc 2849

ttgacgtagg aacggtaaat ttctgtggga gaattcttac atgttttctt tgctttaagt 2909

gtaactggca gttttccatt ggtttacctg tgaaatagtt caaagccaag tttatataca 2969

attatatcag tcctctttca aaggtagcca tcatggatct ggtaggggga aaatgtgtat 3029

tttattacat ctttcacatt ggctatttaa agacaaagac aaattctgtt tcttgagaag 3089

agaatattag ctttactgtt tgttatggct taatgacact agctaatatc aatagaagga 3149

tgtacatttc caaattcaca agttgtgttt gatatccaaa gctgaataca ttctgctttc 3209

atcttggtca catacaatta tttttacagt tctcccaagg gagttaggct attcacaacc 3269

actcattcaa aagttgaaat taaccataga tgtagataaa ctcagaaatt taattcatgt 3329

ttcttaaatg ggctactttg tccttttttgt tattagggtg gtatttagtc tattagccac 3389

aaaattggga aaggagtaga aaaagcagta actgacaact tgaataatac accagagata 3449

atatgagaat cagatcattt caaaactcat ttcctatgta actgcattga gaactgcata 3509

tgtttcgctg atatatgtgt ttttcacatt tgcgaatggt tccattctct ctcctgtact 3569

ttttccagac actttttga gtggatgatg tttcgtgaag tatactgtat ttttaccttt 3629

ttccttcctt atcactgaca caaaaagtag attaagagat gggtttgaca aggttcttcc 3689

cttttacata ctgctgtcta tgtggctgta tcttgttttt ccactactgc taccacaact 3749

atattatcat gcaaatgctg tattcttctt tggtggagat aaagatttct tgagttttgt 3809

tttaaaatta aagctaaagt atctgtattg cattaaatat aatatcgaca cagtgctttc 3869

cgtggcactg catacaatct gaggcctcct ctctcagttt ttatatagat ggcgagaacc 3929

taagtttcag ttgattttac aattgaaatg actaaaaaac aaagaagaca acattaaaaa 3989

caatattgtt tcta 4003

<210> 40
<211> 750
<212> PRT
<213> Homo sapiens

<400> 40

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Gln Val His Gln Leu Tyr Asp Asp Ser Phe Pro Met Glu Ile Arg Gln
20 25 30

Tyr Leu Ala Gln Trp Leu Glu Lys Gln Asp Trp Glu His Ala Ala Asn
35 40 45

Asp Val Ser Phe Ala Thr Ile Arg Phe His Asp Leu Leu Ser Gln Leu
50 55 60

Asp Asp Gln Tyr Ser Arg Phe Ser Leu Glu Asn Asn Phe Leu Leu Gln
65 70 75 80

His Asn Ile Arg Lys Ser Lys Arg Asn Leu Gln Asp Asn Phe Gln Glu
85 90 95

Asp Pro Ile Gln Met Ser Met Ile Ile Tyr Ser Cys Leu Lys Glu Glu
100 105 110

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

Asn Ile Gln Ser Thr Val Met Leu Asp Lys Gln Lys Glu Leu Asp Ser
130 135 140

Lys Val Arg Asn Val Lys Asp Lys Val Met Cys Ile Glu His Glu Ile
145 150 155 160

Lys Ser Leu Glu Asp Leu Gln Asp Glu Tyr Asp Phe Lys Cys Lys Thr
165 170 175

Leu Gln Asn Arg Glu His Glu Thr Asn Gly Val Ala Lys Ser Asp Gln
180 185 190

Lys Gln Glu Gln Leu Leu Leu Lys Lys Met Tyr Leu Met Leu Asp Asn
195 200 205

Lys Arg Lys Glu Val Val His Lys Ile Ile Glu Leu Leu Asn Val Thr
210 215 220

Glu Leu Thr Gln Asn Ala Leu Ile Asn Asp Glu Leu Val Glu Trp Lys
225 230 235 240

Arg Arg Gln Gln Ser Ala Cys Ile Gly Gly Pro Pro Asn Ala Cys Leu
245 250 255

Asp Gln Leu Gln Asn Trp Phe Thr Ile Val Ala Glu Ser Leu Gln Gln
260 265 270

Val Arg Gln Gln Leu Lys Lys Leu Glu Glu Leu Glu Gln Lys Tyr Thr
275 280 285

Tyr Glu His Asp Pro Ile Thr Lys Asn Lys Gln Val Leu Trp Asp Arg
290 295 300

Thr Phe Ser Leu Phe Gln Gln Leu Ile Gln Ser Ser Phe Val Val Glu
305 310 315 320

Arg Gln Pro Cys Met Pro Thr His Pro Gln Arg Pro Leu Val Leu Lys
325 330 335

Thr Gly Val Gln Phe Thr Val Lys Leu Arg Leu Leu Val Lys Leu Gln
340 345 350

Glu Leu Asn Tyr Asn Leu Lys Val Lys Val Leu Phe Asp Lys Asp Val
355 360 365

Asn Glu Arg Asn Thr Val Lys Gly Phe Arg Lys Phe Asn Ile Leu Gly
370 375 380

Thr His Thr Lys Val Met Asn Met Glu Glu Ser Thr Asn Gly Ser Leu
385 390 395 400

Ala Ala Glu Phe Arg His Leu Gln Leu Lys Glu Gln Lys Asn Ala Gly
405 410 415

Thr Arg Thr Asn Glu Gly Pro Leu Ile Val Thr Glu Glu Leu His Ser
420 425 430

Leu Ser Phe Glu Thr Gln Leu Cys Gln Pro Gly Leu Val Ile Asp Leu
435 440 445

Glu Thr Thr Ser Leu Pro Val Val Val Ile Ser Asn Val Ser Gln Leu
450 455 460

Pro Ser Gly Trp Ala Ser Ile Leu Trp Tyr Asn Met Leu Val Ala Glu
465 470 475 480

Pro Arg Asn Leu Ser Phe Phe Leu Thr Pro Pro Cys Ala Arg Trp Ala
485 490 495

Gln Leu Ser Glu Val Leu Ser Trp Gln Phe Ser Ser Val Thr Lys Arg
500 505 510

Gly Leu Asn Val Asp Gln Leu Asn Met Leu Gly Glu Lys Leu Leu Gly
515 520 525

Pro Asn Ala Ser Pro Asp Gly Leu Ile Pro Trp Thr Arg Phe Cys Lys
530 535 540

Glu Asn Ile Asn Asp Lys Asn Phe Pro Phe Trp Leu Trp Ile Glu Ser
545 550 555 560

Ile Leu Glu Leu Ile Lys Lys His Leu Leu Pro Leu Trp Asn Asp Gly
565 570 575

Cys Ile Met Gly Phe Ile Ser Lys Glu Arg Glu Arg Ala Leu Leu Lys
580 585 590

Asp Gln Gln Pro Gly Thr Phe Leu Leu Arg Phe Ser Glu Ser Ser Arg
595 600 605

Glu Gly Ala Ile Thr Phe Thr Trp Val Glu Arg Ser Gln Asn Gly Gly
610 615 620

Glu Pro Asp Phe His Ala Val Glu Pro Tyr Thr Lys Lys Glu Leu Ser
625 630 635 640

Ala Val Thr Phe Pro Asp Ile Ile Arg Asn Tyr Lys Val Met Ala Ala
645 650 655

Glu Asn Ile Pro Glu Asn Pro Leu Lys Tyr Leu Tyr Pro Asn Ile Asp
660 665 670

Lys Asp His Ala Phe Gly Lys Tyr Tyr Ser Arg Pro Lys Glu Ala Pro
675 680 685

Glu Pro Met Glu Leu Asp Gly Pro Lys Gly Thr Gly Tyr Ile Lys Thr
690 695 700

Glu Leu Ile Ser Val Ser Glu Val His Pro Ser Arg Leu Gln Thr Thr
705 710 715 720

Asp Asn Leu Leu Pro Met Ser Pro Glu Glu Phe Asp Glu Val Ser Arg
725 730 735

Ile Val Gly Ser Val Glu Phe Asp Ser Met Met Asn Thr Val
740 745 750

<210> 41
<211> 2607
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (197)..(2332)

<400> 41
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gccatcctcg agagctgtct aggttaacgt tcgcactctg tgtatataac ctcgacagtc 120

ttggcaccta acgtgctgtg cgtagctgct cctttggttg aatccccagg cccttgttgg 180

ggcacaaggt ggcagg atg tct cag tgg tac gaa ctt cag cag ctt gac tca 232
Met Ser Gln Trp Tyr Glu Leu Gln Gln Leu Asp Ser
1 5 10

aaa ttc ctg gag cag gtt cac cag ctt tat gat gac agt ttt ccc atg 280
Lys Phe Leu Glu Gln Val His Gln Leu Tyr Asp Asp Ser Phe Pro Met
15 20 25

gaa atc aga cag tac ctg gca cag tgg tta gaa aag caa gac tgg gag 328
Glu Ile Arg Gln Tyr Leu Ala Gln Trp Leu Glu Lys Gln Asp Trp Glu
30 35 40

cac gct gcc aat gat gtt tca ttt gcc acc atc cgt ttt cat gac ctc 376
His Ala Ala Asn Asp Val Ser Phe Ala Thr Ile Arg Phe His Asp Leu
45 50 55 60

ctg tca cag ctg gat gat caa tat agt cgc ttt tct ttg gag aat aac 424
Leu Ser Gln Leu Asp Asp Gln Tyr Ser Arg Phe Ser Leu Glu Asn Asn
65 70 75

ttc ttg cta cag cat aac ata agg aaa agc aag cgt aat ctt cag gat 472
Phe Leu Leu Gln His Asn Ile Arg Lys Ser Lys Arg Asn Leu Gln Asp
80 85 90

aat ttt cag gaa gac cca atc cag atg tct atg atc att tac agc tgt 520
Asn Phe Gln Glu Asp Pro Ile Gln Met Ser Met Ile Ile Tyr Ser Cys
95 100 105

ctg aag gaa gaa agg aaa att ctg gaa aac gcc cag aga ttt aat cag 568
Leu Lys Glu Glu Arg Lys Ile Leu Glu Asn Ala Gln Arg Phe Asn Gln
110 115 120

gct cag tcg ggg aat att cag agc aca gtg atg tta gac aaa cag aaa 616
Ala Gln Ser Gly Asn Ile Gln Ser Thr Val Met Leu Asp Lys Gln Lys
125 130 135 140

gag ctt gac agt aaa gtc aga aat gtg aag gac aag gtt atg tgt ata 664
Glu Leu Asp Ser Lys Val Arg Asn Val Lys Asp Lys Val Met Cys Ile
145 150 155

gag cat gaa atc aag agc ctg gaa gat tta caa gat gaa tat gac ttc 712
Glu His Glu Ile Lys Ser Leu Glu Asp Leu Gln Asp Glu Tyr Asp Phe
160 165 170

aaa tgc aaa acc ttg cag aac aga gaa cac gag acc aat ggt gtg gca 760
Lys Cys Lys Thr Leu Gln Asn Arg Glu His Glu Thr Asn Gly Val Ala
175 180 185

aag agt gat cag aaa caa gaa cag ctg tta ctc aag aag atg tat tta 808
Lys Ser Asp Gln Lys Gln Glu Gln Leu Leu Leu Lys Lys Met Tyr Leu
190 195 200

atg ctt gac aat aag aga aag gaa gta gtt cac aaa ata ata gag ttg 856
Met Leu Asp Asn Lys Arg Lys Glu Val Val His Lys Ile Ile Glu Leu
205 210 215 220

ctg aat gtc act gaa ctt acc cag aat gcc ctg att aat gat gaa cta 904
Leu Asn Val Thr Glu Leu Thr Gln Asn Ala Leu Ile Asn Asp Glu Leu
225 230 235

gtg gag tgg aag cgg aga cag cag agc gcc tgt att ggg ggg ccg ccc 952
Val Glu Trp Lys Arg Arg Gln Gln Ser Ala Cys Ile Gly Gly Pro Pro
240 245 250

aat gct tgc ttg gat cag ctg cag aac tgg ttc act ata gtt gcg gag 1000
Asn Ala Cys Leu Asp Gln Leu Gln Asn Trp Phe Thr Ile Val Ala Glu
255 260 265

agt ctg cag caa gtt cgg cag cag ctt aaa aag ttg gag gaa ttg gaa 1048
Ser Leu Gln Gln Val Arg Gln Gln Leu Lys Lys Leu Glu Glu Leu Glu
270 275 280

cag aaa tac acc tac gaa cat gac cct atc aca aaa aac aaa caa gtg 1096
Gln Lys Tyr Thr Tyr Glu His Asp Pro Ile Thr Lys Asn Lys Gln Val
285 290 295 300

tta tgg gac cgc acc ttc agt ctt ttc cag cag ctc att cag agc tcg 1144
Leu Trp Asp Arg Thr Phe Ser Leu Phe Gln Gln Leu Ile Gln Ser Ser
305 310 315

ttt gtg gtg gaa aga cag ccc tgc atg cca acg cac cct cag agg ccg 1192

Phe Val Val Glu Arg Gln Pro Cys Met Pro Thr His Pro Gln Arg Pro
320 325 330

ctg gtc ttg aag aca ggg gtc cag ttc act gtg aag ttg aga ctg ttg 1240
Leu Val Leu Lys Thr Gly Val Gln Phe Thr Val Lys Leu Arg Leu Leu
335 340 345

gtg aaa ttg caa gag ctg aat tat aat ttg aaa gtc aaa gtc tta ttt 1288
Val Lys Leu Gln Glu Leu Asn Tyr Asn Leu Lys Val Lys Val Leu Phe
350 355 360

gat aaa gat gtg aat gag aga aat aca gta aaa gga ttt agg aag ttc 1336
Asp Lys Asp Val Asn Glu Arg Asn Thr Val Lys Gly Phe Arg Lys Phe
365 370 375 380

aac att ttg ggc acg cac aca aaa gtg atg aac atg gag gag tcc acc 1384
Asn Ile Leu Gly Thr His Thr Lys Val Met Asn Met Glu Glu Ser Thr
385 390 395

aat ggc agt ctg gcg gct gaa ttt cgg cac ctg caa ttg aaa gaa cag 1432
Asn Gly Ser Leu Ala Ala Glu Phe Arg His Leu Gln Leu Lys Glu Gln
400 405 410

aaa aat gct ggc acc aga acg aat gag ggt cct ctc atc gtt act gaa 1480
Lys Asn Ala Gly Thr Arg Thr Asn Glu Gly Pro Leu Ile Val Thr Glu
415 420 425

gag ctt cac tcc ctt agt ttt gaa acc caa ttg tgc cag cct ggt ttg 1528
Glu Leu His Ser Leu Ser Phe Glu Thr Gln Leu Cys Gln Pro Gly Leu
430 435 440

gta att gac ctc gag acg acc tct ctg ccc gtt gtg gtg atc tcc aac 1576
Val Ile Asp Leu Glu Thr Thr Ser Leu Pro Val Val Val Ile Ser Asn
445 450 455 460

gtc agc cag ctc ccg agc ggt tgg gcc tcc atc ctt tgg tac aac atg 1624
Val Ser Gln Leu Pro Ser Gly Trp Ala Ser Ile Leu Trp Tyr Asn Met
465 470 475

ctg gtg gcg gaa ccc agg aat ctg tcc ttc ttc ctg act cca cca tgt 1672
Leu Val Ala Glu Pro Arg Asn Leu Ser Phe Phe Leu Thr Pro Pro Cys
480 485 490

gca cga tgg gct cag ctt tca gaa gtg ctg agt tgg cag ttt tct tct 1720
Ala Arg Trp Ala Gln Leu Ser Glu Val Leu Ser Trp Gln Phe Ser Ser
495 500 505

gtc acc aaa aga ggt ctc aat gtg gac cag ctg aac atg ttg gga gag 1768
Val Thr Lys Arg Gly Leu Asn Val Asp Gln Leu Asn Met Leu Gly Glu
510 515 520

aag ctt ctt ggt cct aac gcc agc ccc gat ggt ctc att ccg tgg acg 1816
Lys Leu Leu Gly Pro Asn Ala Ser Pro Asp Gly Leu Ile Pro Trp Thr
525 530 535 540

agg ttt tgt aag gaa aat ata aat gat aaa aat ttt ccc ttc tgg ctt 1864
Arg Phe Cys Lys Glu Asn Ile Asn Asp Lys Asn Phe Pro Phe Trp Leu
545 550 555

tgg att gaa agc atc cta gaa ctc att aaa aaa cac ctg ctc cct ctc 1912
Trp Ile Glu Ser Ile Leu Glu Leu Ile Lys Lys His Leu Leu Pro Leu
560 565 570

tgg aat gat ggg tgc atc atg ggc ttc atc agc aag gag cga gag cgt 1960
Trp Asn Asp Gly Cys Ile Met Gly Phe Ile Ser Lys Glu Arg Glu Arg
575 580 585

gcc ctg ttg aag gac cag cag ccg ggg acc ttc ctg ctg cgg ttc agt 2008
Ala Leu Leu Lys Asp Gln Gln Pro Gly Thr Phe Leu Leu Arg Phe Ser
590 595 600

gag agc tcc cgg gaa ggg gcc atc aca ttc aca tgg gtg gag cgg tcc 2056
Glu Ser Ser Arg Glu Gly Ala Ile Thr Phe Thr Trp Val Glu Arg Ser
605 610 615 620

cag aac gga ggc gaa cct gac ttc cat gcg gtt gaa ccc tac acg aag 2104
Gln Asn Gly Gly Glu Pro Asp Phe His Ala Val Glu Pro Tyr Thr Lys
625 630 635

aaa gaa ctt tct gct gtt act ttc cct gac atc att cgc aat tac aaa 2152
Lys Glu Leu Ser Ala Val Thr Phe Pro Asp Ile Ile Arg Asn Tyr Lys
640 645 650

gtc atg gct gct gag aat att cct gag aat ccc ctg aag tat ctg tat 2200
Val Met Ala Ala Glu Asn Ile Pro Glu Asn Pro Leu Lys Tyr Leu Tyr
655 660 665

cca aat att gac aaa gac cat gcc ttt gga aag tat tac tcc agg cca 2248
Pro Asn Ile Asp Lys Asp His Ala Phe Gly Lys Tyr Tyr Ser Arg Pro
670 675 680

aag gaa gca cca gag cca atg gaa ctt gat ggc cct aaa gga act gga 2296
Lys Glu Ala Pro Glu Pro Met Glu Leu Asp Gly Pro Lys Gly Thr Gly
685 690 695 700

tat atc aag act gag ttg att tct gtg tct gaa gtg taagtgaaca 2342
Tyr Ile Lys Thr Glu Leu Ile Ser Val Ser Glu Val
705 710

cagaagagtg acatgtttac aaacctcaag ccagccttgc tcctggctgg ggcctgttga 2402

agatgcttgt attttacttt tccattgtaa ttgctatcgc catcacagct gaacttgttg 2462

agatccccgt gttactgcct atcagcattt tactacttta aaaaaaaaaa aaaaagccaa 2522

aaaccaaatt tgtatttaag gtatataaat tttcccaaaa ctgataccct ttgaaaaagt 2582

ataaataaaa tgagcaaaag ttgaa 2607

<210> 42
<211> 712
<212> PRT
<213> Homo sapiens

<400> 42

Met Ser Gln Trp Tyr Glu Leu Gln Gln Leu Asp Ser Lys Phe Leu Glu
1 5 10 15

Gln Val His Gln Leu Tyr Asp Asp Ser Phe Pro Met Glu Ile Arg Gln
20 25 30

Tyr Leu Ala Gln Trp Leu Glu Lys Gln Asp Trp Glu His Ala Ala Asn
35 40 45

Asp Val Ser Phe Ala Thr Ile Arg Phe His Asp Leu Leu Ser Gln Leu
50 55 60

Asp Asp Gln Tyr Ser Arg Phe Ser Leu Glu Asn Asn Phe Leu Leu Gln
65 70 75 80

His Asn Ile Arg Lys Ser Lys Arg Asn Leu Gln Asp Asn Phe Gln Glu
85 90 95

Asp Pro Ile Gln Met Ser Met Ile Ile Tyr Ser Cys Leu Lys Glu Glu
100 105 110

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

Asn Ile Gln Ser Thr Val Met Leu Asp Lys Gln Lys Glu Leu Asp Ser

130 135 140

Lys Val Arg Asn Val Lys Asp Lys Val Met Cys Ile Glu His Glu Ile
145 150 155 160

Lys Ser Leu Glu Asp Leu Gln Asp Glu Tyr Asp Phe Lys Cys Lys Thr
165 170 175

Leu Gln Asn Arg Glu His Glu Thr Asn Gly Val Ala Lys Ser Asp Gln
180 185 190

Lys Gln Glu Gln Leu Leu Leu Lys Lys Met Tyr Leu Met Leu Asp Asn
195 200 205

Lys Arg Lys Glu Val Val His Lys Ile Ile Glu Leu Leu Asn Val Thr
210 215 220

Glu Leu Thr Gln Asn Ala Leu Ile Asn Asp Glu Leu Val Glu Trp Lys
225 230 235 240

Arg Arg Gln Gln Ser Ala Cys Ile Gly Gly Pro Pro Asn Ala Cys Leu
245 250 255

Asp Gln Leu Gln Asn Trp Phe Thr Ile Val Ala Glu Ser Leu Gln Gln
260 265 270

Val Arg Gln Gln Leu Lys Lys Leu Glu Glu Leu Glu Gln Lys Tyr Thr
275 280 285

Tyr Glu His Asp Pro Ile Thr Lys Asn Lys Gln Val Leu Trp Asp Arg
290 295 300

Thr Phe Ser Leu Phe Gln Gln Leu Ile Gln Ser Ser Phe Val Val Glu
305 310 315 320

Arg Gln Pro Cys Met Pro Thr His Pro Gln Arg Pro Leu Val Leu Lys
325 330 335

Thr Gly Val Gln Phe Thr Val Lys Leu Arg Leu Leu Val Lys Leu Gln
340 345 350

Glu Leu Asn Tyr Asn Leu Lys Val Lys Val Leu Phe Asp Lys Asp Val
355 360 365

Asn Glu Arg Asn Thr Val Lys Gly Phe Arg Lys Phe Asn Ile Leu Gly
370 375 380

Thr His Thr Lys Val Met Asn Met Glu Glu Ser Thr Asn Gly Ser Leu
385 390 395 400

Ala Ala Glu Phe Arg His Leu Gln Leu Lys Glu Gln Lys Asn Ala Gly
405 410 415

Thr Arg Thr Asn Glu Gly Pro Leu Ile Val Thr Glu Glu Leu His Ser
420 425 430

Leu Ser Phe Glu Thr Gln Leu Cys Gln Pro Gly Leu Val Ile Asp Leu
435 440 445

Glu Thr Thr Ser Leu Pro Val Val Val Ile Ser Asn Val Ser Gln Leu
450 455 460

Pro Ser Gly Trp Ala Ser Ile Leu Trp Tyr Asn Met Leu Val Ala Glu
465 470 475 480

Pro Arg Asn Leu Ser Phe Phe Leu Thr Pro Pro Cys Ala Arg Trp Ala
485 490 495

Gln Leu Ser Glu Val Leu Ser Trp Gln Phe Ser Ser Val Thr Lys Arg
500 505 510

Gly Leu Asn Val Asp Gln Leu Asn Met Leu Gly Glu Lys Leu Leu Gly
515 520 525

Pro Asn Ala Ser Pro Asp Gly Leu Ile Pro Trp Thr Arg Phe Cys Lys

530 535 540

Glu Asn Ile Asn Asp Lys Asn Phe Pro Phe Trp Leu Trp Ile Glu Ser
545 550 555 560

Ile Leu Glu Leu Ile Lys Lys His Leu Leu Pro Leu Trp Asn Asp Gly
565 570 575

Cys Ile Met Gly Phe Ile Ser Lys Glu Arg Glu Arg Ala Leu Leu Lys
580 585 590

Asp Gln Gln Pro Gly Thr Phe Leu Leu Arg Phe Ser Glu Ser Ser Arg
595 600 605

Glu Gly Ala Ile Thr Phe Thr Trp Val Glu Arg Ser Gln Asn Gly Gly
610 615 620

Glu Pro Asp Phe His Ala Val Glu Pro Tyr Thr Lys Lys Glu Leu Ser
625 630 635 640

Ala Val Thr Phe Pro Asp Ile Ile Arg Asn Tyr Lys Val Met Ala Ala
645 650 655

Glu Asn Ile Pro Glu Asn Pro Leu Lys Tyr Leu Tyr Pro Asn Ile Asp
660 665 670

Lys Asp His Ala Phe Gly Lys Tyr Tyr Ser Arg Pro Lys Glu Ala Pro
675 680 685

Glu Pro Met Glu Leu Asp Gly Pro Lys Gly Thr Gly Tyr Ile Lys Thr
690 695 700

Glu Leu Ile Ser Val Ser Glu Val
705 710

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<211> 3281
<212> DNA

<213> Homo sapiens

<220>
<221> CDS
<222> (38)..(2590)

<400> 43
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Met Ala Gln Trp Glu Met
1 5

ctg cag aat ctt gac agc ccc ttt cag gat cag ctg cac cag ctt tac 103
Leu Gln Asn Leu Asp Ser Pro Phe Gln Asp Gln Leu His Gln Leu Tyr
10 15 20

tcg cac agc ctc ctg cct gtg gac att cga cag tac ttg gct gtc tgg 151
Ser His Ser Leu Leu Pro Val Asp Ile Arg Gln Tyr Leu Ala Val Trp
25 30 35

att gaa gac cag aac tgg cag gaa gct gca ctt ggg agt gat gat tcc 199
Ile Glu Asp Gln Asn Trp Gln Glu Ala Ala Leu Gly Ser Asp Asp Ser
40 45 50

aag gct acc atg cta ttc ttc cac ttc ttg gat cag ctg aac tat gag 247
Lys Ala Thr Met Leu Phe Phe His Phe Leu Asp Gln Leu Asn Tyr Glu
55 60 65 70

tgt ggc cgt tgc agc cag gac cca gag tcc ttg ttg ctg cag cac aat 295
Cys Gly Arg Cys Ser Gln Asp Pro Glu Ser Leu Leu Leu Gln His Asn
75 80 85

ttg cgg aaa ttc tgc cgg gac att cag ccc ttt tcc cag gat cct acc 343
Leu Arg Lys Phe Cys Arg Asp Ile Gln Pro Phe Ser Gln Asp Pro Thr
90 95 100

cag ttg gct gag atg atc ttt aac ctc ctt ctg gaa gaa aaa aga att 391
Gln Leu Ala Glu Met Ile Phe Asn Leu Leu Leu Glu Glu Lys Arg Ile
105 110 115

ttg atc cag gct cag agg gcc caa ttg gaa caa gga gag cca gtt ctc 439
Leu Ile Gln Ala Gln Arg Ala Gln Leu Glu Gln Gly Glu Pro Val Leu
120 125 130

gaa aca cct gtg gag agc cag caa cat gag att gaa tcc cgg atc ctg 487
Glu Thr Pro Val Glu Ser Gln Gln His Glu Ile Glu Ser Arg Ile Leu
135 140 145 150

gat tta agg gct atg atg gag aag ctg gta aaa tcc atc agc caa ctg 535
Asp Leu Arg Ala Met Met Glu Lys Leu Val Lys Ser Ile Ser Gln Leu

155 160 165

aaa gac cag cag gat gtc ttc tgc ttc cga tat aag atc cag gcc aaa 583
Lys Asp Gln Gln Asp Val Phe Cys Phe Arg Tyr Lys Ile Gln Ala Lys
170 175 180

ggg aag aca ccc tct ctg gac ccc cat cag acc aaa gag cag aag att 631
Gly Lys Thr Pro Ser Leu Asp Pro His Gln Thr Lys Glu Gln Lys Ile
185 190 195

ctg cag gaa act ctc aat gaa ctg gac aaa agg aga aag gag gtg ctg 679
Leu Gln Glu Thr Leu Asn Glu Leu Asp Lys Arg Arg Lys Glu Val Leu
200 205 210

gat gcc tcc aaa gca ctg cta ggc cga tta act acc cta atc gag cta 727
Asp Ala Ser Lys Ala Leu Leu Gly Arg Leu Thr Thr Leu Ile Glu Leu
215 220 225 230

ctg ctg cca aag ttg gag gag tgg aag gcc cag cag caa aaa gcc tgc 775
Leu Leu Pro Lys Leu Glu Glu Trp Lys Ala Gln Gln Gln Lys Ala Cys
235 240 245

atc aga gct ccc att gac cac ggg ttg gaa cag ctg gag aca tgg ttc 823
Ile Arg Ala Pro Ile Asp His Gly Leu Glu Gln Leu Glu Thr Trp Phe
250 255 260

aca gct gga gca aag ctg ttg ttt cac ctg agg cag ctg ctg aag gag 871
Thr Ala Gly Ala Lys Leu Leu Phe His Leu Arg Gln Leu Leu Lys Glu
265 270 275

ctg aag gga ctg agt tgc ctg gtt agc tat cag gat gac cct ctg acc 919
Leu Lys Gly Leu Ser Cys Leu Val Ser Tyr Gln Asp Asp Pro Leu Thr
280 285 290

aaa ggg gtg gac cta cgc aac gcc cag gtc aca gag ttg cta cag cgt 967
Lys Gly Val Asp Leu Arg Asn Ala Gln Val Thr Glu Leu Leu Gln Arg
295 300 305 310

ctg ctc cac aga gcc ttt gtg gta gaa acc cag ccc tgc atg ccc caa 1015
Leu Leu His Arg Ala Phe Val Val Glu Thr Gln Pro Cys Met Pro Gln
315 320 325

act ccc cat cga ccc ctc atc ctc aag act ggc agc aag ttc acc gtc 1063
Thr Pro His Arg Pro Leu Ile Leu Lys Thr Gly Ser Lys Phe Thr Val
330 335 340

cga aca agg ctg ctg gtg aga ctc cag gaa ggc aat gag tca ctg act 1111
Arg Thr Arg Leu Leu Val Arg Leu Gln Glu Gly Asn Glu Ser Leu Thr
345 350 355

gtg gaa gtc tcc att gac agg aat cct cct caa tta caa ggc ttc cgg 1159
Val Glu Val Ser Ile Asp Arg Asn Pro Pro Gln Leu Gln Gly Phe Arg
360 365 370

aag ttc aac att ctg act tca aac cag aaa act ttg acc ccc gag aag 1207
Lys Phe Asn Ile Leu Thr Ser Asn Gln Lys Thr Leu Thr Pro Glu Lys
375 380 385 390

ggg cag agt cag ggt ttg att tgg gac ttt ggt tac ctg act ctg gtg 1255
Gly Gln Ser Gln Gly Leu Ile Trp Asp Phe Gly Tyr Leu Thr Leu Val
395 400 405

gag caa cgt tca ggt ggt tca gga aag ggc agc aat aag ggg cca cta 1303
Glu Gln Arg Ser Gly Gly Ser Gly Lys Gly Ser Asn Lys Gly Pro Leu
410 415 420

ggt gtg aca gag gaa ctg cac atc atc agc ttc acg gtc aaa tat acc 1351
Gly Val Thr Glu Glu Leu His Ile Ile Ser Phe Thr Val Lys Tyr Thr
425 430 435

tac cag ggt ctg aag cag gag ctg aaa acg gac acc ctc cct gtg gtg 1399
Tyr Gln Gly Leu Lys Gln Glu Leu Lys Thr Asp Thr Leu Pro Val Val
440 445 450

att att tcc aac atg aac cag ctc tca att gcc tgg gct tca gtt ctc 1447
Ile Ile Ser Asn Met Asn Gln Leu Ser Ile Ala Trp Ala Ser Val Leu
455 460 465 470

tgg ttc aat ttg ctc agc cca aac ctt cag aac cag cag ttc ttc tcc 1495
Trp Phe Asn Leu Leu Ser Pro Asn Leu Gln Asn Gln Gln Phe Phe Ser
475 480 485

aac ccc ccc aag gcc ccc tgg agc ttg ctg ggc cct gct ctc agt tgg 1543
Asn Pro Pro Lys Ala Pro Trp Ser Leu Leu Gly Pro Ala Leu Ser Trp
490 495 500

cag ttc tcc tcc tat gtt ggc cga ggc ctc aac tca gac cag ctg agc 1591
Gln Phe Ser Ser Tyr Val Gly Arg Gly Leu Asn Ser Asp Gln Leu Ser
505 510 515

atg ctg aga aac aag ctg ttc ggg cag aac tgt agg act gag gat cca 1639
Met Leu Arg Asn Lys Leu Phe Gly Gln Asn Cys Arg Thr Glu Asp Pro
520 525 530

tta ttg tcc tgg gct gac ttc act aag cga gag agc cct cct ggc aag 1687
Leu Leu Ser Trp Ala Asp Phe Thr Lys Arg Glu Ser Pro Pro Gly Lys
535 540 545 550

tta cca ttc tgg aca tgg ctg gac aaa att ctg gag ttg gta cat gac 1735
Leu Pro Phe Trp Thr Trp Leu Asp Lys Ile Leu Glu Leu Val His Asp

555 560 565

cac ctg aag gat ctc tgg aat gat gga cgc atc atg ggc ttt gtg agt 1783
His Leu Lys Asp Leu Trp Asn Asp Gly Arg Ile Met Gly Phe Val Ser
570 575 580

cgg agc cag gag cgc cgg ctg ctg aag aag acc atg tct ggc acc ttt 1831
Arg Ser Gln Glu Arg Arg Leu Leu Lys Lys Thr Met Ser Gly Thr Phe
585 590 595

cta ctg cgc ttc agt gaa tcg tca gaa ggg ggc att acc tgc tcc tgg 1879
Leu Leu Arg Phe Ser Glu Ser Ser Glu Gly Gly Ile Thr Cys Ser Trp
600 605 610

gtg gag cac cag gat gat gac aag gtg ctc atc tac tct gtg caa ccg 1927
Val Glu His Gln Asp Asp Asp Lys Val Leu Ile Tyr Ser Val Gln Pro
615 620 625 630

tac acg aag gag gtg ctg cag tca ctc ccg ctg act gaa atc atc cgc 1975
Tyr Thr Lys Glu Val Leu Gln Ser Leu Pro Leu Thr Glu Ile Ile Arg
635 640 645

cat tac cag ttg ctc act gag gag aat ata cct gaa aac cca ctg cgc 2023
His Tyr Gln Leu Leu Thr Glu Glu Asn Ile Pro Glu Asn Pro Leu Arg
650 655 660

ttc ctc tat ccc cga atc ccc cgg gat gaa gct ttt ggg tgc tac tac 2071
Phe Leu Tyr Pro Arg Ile Pro Arg Asp Glu Ala Phe Gly Cys Tyr Tyr
665 670 675

cag gag aaa gtt aat ctc cag gaa cgg agg aaa tac ctg aaa cac agg 2119
Gln Glu Lys Val Asn Leu Gln Glu Arg Arg Lys Tyr Leu Lys His Arg
680 685 690

ctc att gtg gtc tct aat aga cag gtg gat gaa ctg caa caa ccg ctg 2167
Leu Ile Val Val Ser Asn Arg Gln Val Asp Glu Leu Gln Gln Pro Leu
695 700 705 710

gag ctt aag cca gag cca gag ctg gag tca tta gag ctg gaa cta ggg 2215
Glu Leu Lys Pro Glu Pro Glu Leu Glu Ser Leu Glu Leu Glu Leu Gly
715 720 725

ctg gtg cca gag cca gag ctc agc ctg gac tta gag cca ctg ctg aag 2263
Leu Val Pro Glu Pro Glu Leu Ser Leu Asp Leu Glu Pro Leu Leu Lys
730 735 740

gca ggg ctg gat ctg ggg cca gag cta gag tct gtg ctg gag tcc act 2311
Ala Gly Leu Asp Leu Gly Pro Glu Leu Glu Ser Val Leu Glu Ser Thr
745 750 755

ctg gag cct gtg ata gag ccc aca cta tgc atg gta tca caa aca gtg 2359
Leu Glu Pro Val Ile Glu Pro Thr Leu Cys Met Val Ser Gln Thr Val
760 765 770

cca gag cca gac caa gga cct gta tca cag cca gtg cca gag cca gat 2407
Pro Glu Pro Asp Gln Gly Pro Val Ser Gln Pro Val Pro Glu Pro Asp
775 780 785 790

ttg ccc tgt gat ctg aga cat ttg aac act gag cca atg gaa atc ttc 2455
Leu Pro Cys Asp Leu Arg His Leu Asn Thr Glu Pro Met Glu Ile Phe
795 800 805

aga aac tgt gta aag att gaa gaa atc atg ccg aat ggt gac cca ctg 2503
Arg Asn Cys Val Lys Ile Glu Glu Ile Met Pro Asn Gly Asp Pro Leu
810 815 820

ttg gct ggc cag aac acc gtg gat gag gtt tac gtc tcc cgc ccc agc 2551
Leu Ala Gly Gln Asn Thr Val Asp Glu Val Tyr Val Ser Arg Pro Ser
825 830 835

cac ttc tac act gat gga ccc ttg atg cct tct gac ttc taggaaccac 2600
His Phe Tyr Thr Asp Gly Pro Leu Met Pro Ser Asp Phe
840 845 850

atttcctctg ttcttttcat atctctttgc ccttcctact cctcatagca tgatattgtt 2660

ctccaaggat gggaatcagg catgtgtccc ttccaagctg tgttaactgt tcaaactcag 2720

gcctgtgtga ctccattggg gtgagaggtg aaagcataac atgggtacag aggggacaac 2780

aatgaatcag aacagatgct gagccatagg tctaaatagg atcctggagg ctgcctgctg 2840

tgctgggagg tataggggtc ctgggggcag gccagggcag ttgacaggta cttggagggc 2900

tcagggcagt ggcttctttc cagtatggaa ggatttcaac attttaatag ttggttaggc 2960

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Gln Tyr Leu Ala Val Trp Ile Glu Asp Gln Asn Trp Gln Glu Ala Ala
35 40 45

Leu Gly Ser Asp Asp Ser Lys Ala Thr Met Leu Phe Phe His Phe Leu
50 55 60

Asp Gln Leu Asn Tyr Glu Cys Gly Arg Cys Ser Gln Asp Pro Glu Ser
65 70 75 80

Leu Leu Leu Gln His Asn Leu Arg Lys Phe Cys Arg Asp Ile Gln Pro
85 90 95

Phe Ser Gln Asp Pro Thr Gln Leu Ala Glu Met Ile Phe Asn Leu Leu
100 105 110

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

Gln Gly Glu Pro Val Leu Glu Thr Pro Val Glu Ser Gln Gln His Glu
130 135 140

Ile Glu Ser Arg Ile Leu Asp Leu Arg Ala Met Met Glu Lys Leu Val
145 150 155 160

Lys Ser Ile Ser Gln Leu Lys Asp Gln Gln Asp Val Phe Cys Phe Arg
165 170 175

Tyr Lys Ile Gln Ala Lys Gly Lys Thr Pro Ser Leu Asp Pro His Gln
180 185 190

Thr Lys Glu Gln Lys Ile Leu Gln Glu Thr Leu Asn Glu Leu Asp Lys
195 200 205

Arg Arg Lys Glu Val Leu Asp Ala Ser Lys Ala Leu Leu Gly Arg Leu
210 215 220

Thr Thr Leu Ile Glu Leu Leu Leu Pro Lys Leu Glu Glu Trp Lys Ala
225 230 235 240

Gln Gln Gln Lys Ala Cys Ile Arg Ala Pro Ile Asp His Gly Leu Glu
245 250 255

Gln Leu Glu Thr Trp Phe Thr Ala Gly Ala Lys Leu Leu Phe His Leu
260 265 270

Arg Gln Leu Leu Lys Glu Leu Lys Gly Leu Ser Cys Leu Val Ser Tyr
275 280 285

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

Thr Glu Leu Leu Gln Arg Leu Leu His Arg Ala Phe Val Val Glu Thr
305 310 315 320

Gln Pro Cys Met Pro Gln Thr Pro His Arg Pro Leu Ile Leu Lys Thr
325 330 335

Gly Ser Lys Phe Thr Val Arg Thr Arg Leu Leu Val Arg Leu Gln Glu
340 345 350

Gly Asn Glu Ser Leu Thr Val Glu Val Ser Ile Asp Arg Asn Pro Pro
355 360 365

Gln Leu Gln Gly Phe Arg Lys Phe Asn Ile Leu Thr Ser Asn Gln Lys
370 375 380

Thr Leu Thr Pro Glu Lys Gly Gln Ser Gln Gly Leu Ile Trp Asp Phe
385 390 395 400

Gly Tyr Leu Thr Leu Val Glu Gln Arg Ser Gly Gly Ser Gly Lys Gly
405 410 415

Ser Asn Lys Gly Pro Leu Gly Val Thr Glu Glu Leu His Ile Ile Ser
420 425 430

Phe Thr Val Lys Tyr Thr Tyr Gln Gly Leu Lys Gln Glu Leu Lys Thr
435 440 445

Asp Thr Leu Pro Val Val Ile Ile Ser Asn Met Asn Gln Leu Ser Ile
450 455 460

Ala Trp Ala Ser Val Leu Trp Phe Asn Leu Leu Ser Pro Asn Leu Gln
465 470 475 480

Asn Gln Gln Phe Phe Ser Asn Pro Pro Lys Ala Pro Trp Ser Leu Leu
485 490 495

Gly Pro Ala Leu Ser Trp Gln Phe Ser Ser Tyr Val Gly Arg Gly Leu
500 505 510

Asn Ser Asp Gln Leu Ser Met Leu Arg Asn Lys Leu Phe Gly Gln Asn
515 520 525

Cys Arg Thr Glu Asp Pro Leu Leu Ser Trp Ala Asp Phe Thr Lys Arg
530 535 540

Glu Ser Pro Pro Gly Lys Leu Pro Phe Trp Thr Trp Leu Asp Lys Ile
545 550 555 560

Leu Glu Leu Val His Asp His Leu Lys Asp Leu Trp Asn Asp Gly Arg
565 570 575

Ile Met Gly Phe Val Ser Arg Ser Gln Glu Arg Arg Leu Leu Lys Lys
580 585 590

Thr Met Ser Gly Thr Phe Leu Leu Arg Phe Ser Glu Ser Ser Glu Gly
595 600 605

Gly Ile Thr Cys Ser Trp Val Glu His Gln Asp Asp Asp Lys Val Leu
610 615 620

Ile Tyr Ser Val Gln Pro Tyr Thr Lys Glu Val Leu Gln Ser Leu Pro
625 630 635 640

Leu Thr Glu Ile Ile Arg His Tyr Gln Leu Leu Thr Glu Glu Asn Ile
645 650 655

Pro Glu Asn Pro Leu Arg Phe Leu Tyr Pro Arg Ile Pro Arg Asp Glu
660 665 670

Ala Phe Gly Cys Tyr Tyr Gln Glu Lys Val Asn Leu Gln Glu Arg Arg
675 680 685

Lys Tyr Leu Lys His Arg Leu Ile Val Val Ser Asn Arg Gln Val Asp
690 695 700

Glu Leu Gln Gln Pro Leu Glu Leu Lys Pro Glu Pro Glu Leu Glu Ser
705 710 715 720

Leu Glu Leu Glu Leu Gly Leu Val Pro Glu Pro Glu Leu Ser Leu Asp
725 730 735

Leu Glu Pro Leu Leu Lys Ala Gly Leu Asp Leu Gly Pro Glu Leu Glu
740 745 750

Ser Val Leu Glu Ser Thr Leu Glu Pro Val Ile Glu Pro Thr Leu Cys
755 760 765

Met Val Ser Gln Thr Val Pro Glu Pro Asp Gln Gly Pro Val Ser Gln
770 775 780

Pro Val Pro Glu Pro Asp Leu Pro Cys Asp Leu Arg His Leu Asn Thr
785 790 795 800

Glu Pro Met Glu Ile Phe Arg Asn Cys Val Lys Ile Glu Glu Ile Met
805 810 815

Pro Asn Gly Asp Pro Leu Leu Ala Gly Gln Asn Thr Val Asp Glu Val
820 825 830

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835 840 845

Ser Asp Phe
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ccccctcggc tcggagaggc ccttcggcct gagggagcct cgccgcccgt ccccggcaca 180

cgcgcagccc cggcctctcg gcctctgccg gagaaacagg atg gcc caa tgg aat 235
Met Ala Gln Trp Asn
1 5

cag cta cag cag ctt gac aca cgg tac ctg gag cag ctc cat cag ctc 283
Gln Leu Gln Gln Leu Asp Thr Arg Tyr Leu Glu Gln Leu His Gln Leu
10 15 20

tac agt gac agc ttc cca atg gag ctg cgg cag ttt ctg gcc cct tgg 331
Tyr Ser Asp Ser Phe Pro Met Glu Leu Arg Gln Phe Leu Ala Pro Trp
25 30 35

att gag agt caa gat tgg gca tat gcg gcc agc aaa gaa tca cat gcc 379
Ile Glu Ser Gln Asp Trp Ala Tyr Ala Ala Ser Lys Glu Ser His Ala
40 45 50

act ttg gtg ttt cat aat ctc ctg gga gag att gac cag cag tat agc 427
Thr Leu Val Phe His Asn Leu Leu Gly Glu Ile Asp Gln Gln Tyr Ser
55 60 65

cgc ttc ctg caa gag tcg aat gtt ctc tat cag cac aat cta cga aga 475
Arg Phe Leu Gln Glu Ser Asn Val Leu Tyr Gln His Asn Leu Arg Arg
70 75 80 85

atc aag cag ttt ctt cag agc agg tat ctt gag aag cca atg gag att 523
Ile Lys Gln Phe Leu Gln Ser Arg Tyr Leu Glu Lys Pro Met Glu Ile
90 95 100

gcc cgg att gtg gcc cgg tgc ctg tgg gaa gaa tca cgc ctt cta cag 571
Ala Arg Ile Val Ala Arg Cys Leu Trp Glu Glu Ser Arg Leu Leu Gln
105 110 115

act gca gcc act gcg gcc cag caa ggg ggc cag gcc aac cac ccc aca 619
Thr Ala Ala Thr Ala Ala Gln Gln Gly Gly Gln Ala Asn His Pro Thr
120 125 130

gca gcc gtg gtg acg gag aag cag cag atg ctg gag cag cac ctt cag 667
Ala Ala Val Val Thr Glu Lys Gln Gln Met Leu Glu Gln His Leu Gln
135 140 145

gat gtc cgg aag aga gtg cag gat cta gaa cag aaa atg aaa gtg gta 715
Asp Val Arg Lys Arg Val Gln Asp Leu Glu Gln Lys Met Lys Val Val
150 155 160 165

gag aat ctc cag gat gac ttt gat ttc aac tat aaa acc ctc aag agt 763
Glu Asn Leu Gln Asp Asp Phe Asp Phe Asn Tyr Lys Thr Leu Lys Ser
170 175 180

caa gga gac atg caa gat ctg aat gga aac aac cag tca gtg acc agg 811
Gln Gly Asp Met Gln Asp Leu Asn Gly Asn Asn Gln Ser Val Thr Arg
185 190 195

cag aag atg cag cag ctg gaa cag atg ctc act gcg ctg gac cag atg 859
Gln Lys Met Gln Gln Leu Glu Gln Met Leu Thr Ala Leu Asp Gln Met
200 205 210

cgg aga agc atc gtg agt gag ctg gcg ggg ctt ttg tca gcg atg gag 907
Arg Arg Ser Ile Val Ser Glu Leu Ala Gly Leu Leu Ser Ala Met Glu
215 220 225

tac gtg cag aaa act ctc acg gac gag gag ctg gct gac tgg aag agg 955

Tyr Val Gln Lys Thr Leu Thr Asp Glu Glu Leu Ala Asp Trp Lys Arg
230 235 240 245

cgg caa cag att gcc tgc att gga ggc ccg ccc aac atc tgc cta gat 1003
Arg Gln Gln Ile Ala Cys Ile Gly Gly Pro Pro Asn Ile Cys Leu Asp
250 255 260

cgg cta gaa aac tgg ata acg tca tta gca gaa tct caa ctt cag acc 1051
Arg Leu Glu Asn Trp Ile Thr Ser Leu Ala Glu Ser Gln Leu Gln Thr
265 270 275

cgt caa caa att aag aaa ctg gag gag ttg cac caa aaa gtt tcc tac 1099
Arg Gln Gln Ile Lys Lys Leu Glu Glu Leu His Gln Lys Val Ser Tyr
280 285 290

aaa ggg gac ccc att gta cag cac cgg ccg atg ctg gag gag agg atc 1147
Lys Gly Asp Pro Ile Val Gln His Arg Pro Met Leu Glu Glu Arg Ile
295 300 305

gtg gag ctg ttc aga aac tta atg aaa agt gcc ttt gtg gtg gag cgg 1195
Val Glu Leu Phe Arg Asn Leu Met Lys Ser Ala Phe Val Val Glu Arg
310 315 320 325

cag ccc tgc atg ccc atg cat cct gac cgg ccc ctc gtc atc aag acc 1243
Gln Pro Cys Met Pro Met His Pro Asp Arg Pro Leu Val Ile Lys Thr
330 335 340

ggc gtc cag ttc act act aaa gtc agg ttg ctg gtc aag ttc cct gag 1291
Gly Val Gln Phe Thr Thr Lys Val Arg Leu Leu Val Lys Phe Pro Glu
345 350 355

ttg aat tat cag ctt aaa att aaa gtg tgc att gac aaa gac tct ggg 1339
Leu Asn Tyr Gln Leu Lys Ile Lys Val Cys Ile Asp Lys Asp Ser Gly
360 365 370

gac gtt gca gct ctc aga gga tcc cgg aaa ttt aac att ctg ggc aca 1387
Asp Val Ala Ala Leu Arg Gly Ser Arg Lys Phe Asn Ile Leu Gly Thr
375 380 385

aac aca aaa gtg atg aac atg gaa gaa tcc aac aac ggc agc ctc tct 1435
Asn Thr Lys Val Met Asn Met Glu Glu Ser Asn Asn Gly Ser Leu Ser
390 395 400 405

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Ala Glu Phe Lys His Leu Thr Leu Arg Glu Gln Arg Cys Gly Asn Gly
410 415 420

ggc cga gcc aat tgt gat gct tcc ctg att gtg act gag gag ctg cac 1531
Gly Arg Ala Asn Cys Asp Ala Ser Leu Ile Val Thr Glu Glu Leu His
425 430 435

ctg atc acc ttt gag acc gag gtg tat cac caa ggt ctc aag att gac 1579
Leu Ile Thr Phe Glu Thr Glu Val Tyr His Gln Gly Leu Lys Ile Asp
440 445 450

cta gag acc cac tcc ttg tca gtt gtg gtg atc tcc aac atc tgt cag 1627
Leu Glu Thr His Ser Leu Ser Val Val Val Ile Ser Asn Ile Cys Gln
455 460 465

atg cca aat gcc tgg gcg tcc atc ctg tgg tac aac atg ctg acc aac 1675
Met Pro Asn Ala Trp Ala Ser Ile Leu Trp Tyr Asn Met Leu Thr Asn
470 475 480 485

aat ccc aag aat gtg aac ttc ttc act aag ccg cca att gga acc tgg 1723
Asn Pro Lys Asn Val Asn Phe Phe Thr Lys Pro Pro Ile Gly Thr Trp
490 495 500

gac caa gtg gcc gag gtg ctc agc tgg cag ttc tcg tcc acc acc aag 1771
Asp Gln Val Ala Glu Val Leu Ser Trp Gln Phe Ser Ser Thr Thr Lys
505 510 515

cgg ggg ctg agc atc gag cag ctg aca acg ctg gct gag aag ctc cta 1819
Arg Gly Leu Ser Ile Glu Gln Leu Thr Thr Leu Ala Glu Lys Leu Leu
520 525 530

ggg cct ggt gtg aac tac tca ggg tgt cag atc aca tgg gct aac ttc 1867
Gly Pro Gly Val Asn Tyr Ser Gly Cys Gln Ile Thr Trp Ala Asn Phe
535 540 545

tgc aaa gaa aac atg gct ggc aag ggc ttc tcc tac tgg gtc tgg cta 1915
Cys Lys Glu Asn Met Ala Gly Lys Gly Phe Ser Tyr Trp Val Trp Leu
550 555 560 565

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Asp Asn Ile Ile Asp Leu Val Lys Lys Tyr Ile Leu Ala Leu Trp Asn
570 575 580

gaa ggg tac atc atg ggt ttc atc agc aag gag cgg gag cgg gcc atc 2011
Glu Gly Tyr Ile Met Gly Phe Ile Ser Lys Glu Arg Glu Arg Ala Ile
585 590 595

ttg agc act aag ccc cca ggc acc ttc ctg ctg cgc ttc agt gaa agc 2059
Leu Ser Thr Lys Pro Pro Gly Thr Phe Leu Leu Arg Phe Ser Glu Ser
600 605 610

agc aaa gaa gga ggc gtc act ttc act tgg gtg gag aag gac atc agc 2107
Ser Lys Glu Gly Gly Val Thr Phe Thr Trp Val Glu Lys Asp Ile Ser
615 620 625

ggt aag acc cag atc cag tcc gtg gaa cca tac aca aag cag cag ctg 2155

Gly Lys Thr Gln Ile Gln Ser Val Glu Pro Tyr Thr Lys Gln Gln Leu
630 635 640 645

aac aac atg tca ttt gct gaa atc atc atg ggc tat aag atc atg gat 2203
Asn Asn Met Ser Phe Ala Glu Ile Ile Met Gly Tyr Lys Ile Met Asp
650 655 660

gct acc aat atc ctg ttg tct cca ctt gtc tat ctc tat cct gac att 2251
Ala Thr Asn Ile Leu Leu Ser Pro Leu Val Tyr Leu Tyr Pro Asp Ile
665 670 675

ccc aag gag gag gca ttc ggg aag tat tgt cgg cca gag agc cag gag 2299
Pro Lys Glu Glu Ala Phe Gly Lys Tyr Cys Arg Pro Glu Ser Gln Glu
680 685 690

cat cct gaa gct gac cca ggt agc gct gcc cca tac ctg aag acc aag 2347
His Pro Glu Ala Asp Pro Gly Ser Ala Ala Pro Tyr Leu Lys Thr Lys
695 700 705

ttt atc tgt gtg aca cca acg acc tgc agc aat acc att gac ctg ccg 2395
Phe Ile Cys Val Thr Pro Thr Thr Cys Ser Asn Thr Ile Asp Leu Pro
710 715 720 725

atg tcc ccc cgc gct tta gat tca ttg atg cag ttt gga aat aat ggt 2443
Met Ser Pro Arg Ala Leu Asp Ser Leu Met Gln Phe Gly Asn Asn Gly
730 735 740

gaa ggt gct gaa ccc tca gca gga ggg cag ttt gag tcc ctc acc ttt 2491
Glu Gly Ala Glu Pro Ser Ala Gly Gly Gln Phe Glu Ser Leu Thr Phe
745 750 755

gac atg gag ttg acc tcg gag tgc gct acc tcc ccc atg tga 2533
Asp Met Glu Leu Thr Ser Glu Cys Ala Thr Ser Pro Met
760 765 770

ggagctgaga acggaagctg cagaaagata cgactgaggc gcctacctgc attctgccac 2593

ccctcacaca gccaaacccc agatcatctg aaactactaa ctttgtggtt ccagattttt 2653

tttaatctcc tacttctgct atctttgagc aatctgggca cttttaaaaa tagagaaatg 2713

agtgaatgtg ggtgatctgc ttttatctaa atgcaaataa ggatgtgttc tctgagaccc 2773

atgatcaggg gatg 2787

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<400> 46

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Phe Leu Ala Pro Trp Ile Glu Ser Gln Asp Trp Ala Tyr Ala Ala Ser
35 40 45

Lys Glu Ser His Ala Thr Leu Val Phe His Asn Leu Leu Gly Glu Ile
50 55 60

Asp Gln Gln Tyr Ser Arg Phe Leu Gln Glu Ser Asn Val Leu Tyr Gln
65 70 75 80

His Asn Leu Arg Arg Ile Lys Gln Phe Leu Gln Ser Arg Tyr Leu Glu
85 90 95

Lys Pro Met Glu Ile Ala Arg Ile Val Ala Arg Cys Leu Trp Glu Glu
100 105 110

Ser Arg Leu Leu Gln Thr Ala Ala Thr Ala Ala Gln Gln Gly Gly Gln
115 120 125

Ala Asn His Pro Thr Ala Ala Val Val Thr Glu Lys Gln Gln Met Leu
130 135 140

Glu Gln His Leu Gln Asp Val Arg Lys Arg Val Gln Asp Leu Glu Gln
145 150 155 160

Lys Met Lys Val Val Glu Asn Leu Gln Asp Asp Phe Asp Phe Asn Tyr
165 170 175

Lys Thr Leu Lys Ser Gln Gly Asp Met Gln Asp Leu Asn Gly Asn Asn
180 185 190

Gln Ser Val Thr Arg Gln Lys Met Gln Gln Leu Glu Gln Met Leu Thr
195 200 205

Ala Leu Asp Gln Met Arg Arg Ser Ile Val Ser Glu Leu Ala Gly Leu
210 215 220

Leu Ser Ala Met Glu Tyr Val Gln Lys Thr Leu Thr Asp Glu Glu Leu
225 230 235 240

Ala Asp Trp Lys Arg Arg Gln Gln Ile Ala Cys Ile Gly Gly Pro Pro
245 250 255

Asn Ile Cys Leu Asp Arg Leu Glu Asn Trp Ile Thr Ser Leu Ala Glu
260 265 270

Ser Gln Leu Gln Thr Arg Gln Gln Ile Lys Lys Leu Glu Glu Leu His
275 280 285

Gln Lys Val Ser Tyr Lys Gly Asp Pro Ile Val Gln His Arg Pro Met
290 295 300

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

Phe Val Val Glu Arg Gln Pro Cys Met Pro Met His Pro Asp Arg Pro
325 330 335

Leu Val Ile Lys Thr Gly Val Gln Phe Thr Thr Lys Val Arg Leu Leu
340 345 350

Val Lys Phe Pro Glu Leu Asn Tyr Gln Leu Lys Ile Lys Val Cys Ile
355 360 365

Asp Lys Asp Ser Gly Asp Val Ala Ala Leu Arg Gly Ser Arg Lys Phe
370 375 380

Asn Ile Leu Gly Thr Asn Thr Lys Val Met Asn Met Glu Glu Ser Asn

385 390 395 400

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

Arg Cys Gly Asn Gly Gly Arg Ala Asn Cys Asp Ala Ser Leu Ile Val
420 425 430

Thr Glu Glu Leu His Leu Ile Thr Phe Glu Thr Glu Val Tyr His Gln
435 440 445

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

Ser Asn Ile Cys Gln Met Pro Asn Ala Trp Ala Ser Ile Leu Trp Tyr
465 470 475 480

Asn Met Leu Thr Asn Asn Pro Lys Asn Val Asn Phe Phe Thr Lys Pro
485 490 495

Pro Ile Gly Thr Trp Asp Gln Val Ala Glu Val Leu Ser Trp Gln Phe
500 505 510

Ser Ser Thr Thr Lys Arg Gly Leu Ser Ile Glu Gln Leu Thr Thr Leu
515 520 525

Ala Glu Lys Leu Leu Gly Pro Gly Val Asn Tyr Ser Gly Cys Gln Ile
530 535 540

Thr Trp Ala Asn Phe Cys Lys Glu Asn Met Ala Gly Lys Gly Phe Ser
545 550 555 560

Tyr Trp Val Trp Leu Asp Asn Ile Ile Asp Leu Val Lys Lys Tyr Ile
565 570 575

Leu Ala Leu Trp Asn Glu Gly Tyr Ile Met Gly Phe Ile Ser Lys Glu
580 585 590

Arg Glu Arg Ala Ile Leu Ser Thr Lys Pro Pro Gly Thr Phe Leu Leu
595 600 605

Arg Phe Ser Glu Ser Ser Lys Glu Gly Gly Val Thr Phe Thr Trp Val
610 615 620

Glu Lys Asp Ile Ser Gly Lys Thr Gln Ile Gln Ser Val Glu Pro Tyr
625 630 635 640

Thr Lys Gln Gln Leu Asn Asn Met Ser Phe Ala Glu Ile Ile Met Gly
645 650 655

Tyr Lys Ile Met Asp Ala Thr Asn Ile Leu Leu Ser Pro Leu Val Tyr
660 665 670

Leu Tyr Pro Asp Ile Pro Lys Glu Glu Ala Phe Gly Lys Tyr Cys Arg
675 680 685

Pro Glu Ser Gln Glu His Pro Glu Ala Asp Pro Gly Ser Ala Ala Pro
690 695 700

Tyr Leu Lys Thr Lys Phe Ile Cys Val Thr Pro Thr Thr Cys Ser Asn
705 710 715 720

Thr Ile Asp Leu Pro Met Ser Pro Arg Ala Leu Asp Ser Leu Met Gln
725 730 735

Phe Gly Asn Asn Gly Glu Gly Ala Glu Pro Ser Ala Gly Gly Gln Phe
740 745 750

Glu Ser Leu Thr Phe Asp Met Glu Leu Thr Ser Glu Cys Ala Thr Ser
755 760 765

Pro Met
770

<210> 47

<211> 2112
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (334)..(1806)

<400> 47
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tccgaagcta ctcccccagc acacagcccg ggacccacaa acccagcttg cccccagccc 120

tcccacctgc cactccctgg cccctcccac cggccgcccc ccttggcgcg ggcgcatggt 180

gtgaaaggcc aagtgctgag gcgggtatca tgggtgctgt gccctaggcc tgggtggcag 240

ggggtgggtg gcctgtgggt gtgccggggg ggccagtgtg cccaccccag tctcttggcg 300

tgctggaggg catcctggat ggaattgaag tga atg gaa cag aag cca agc aag 354
Met Glu Gln Lys Pro Ser Lys
1 5

gtg gag tgt ggg tca gac cca gag gag aac agt gcc agg tca cca gat 402
Val Glu Cys Gly Ser Asp Pro Glu Glu Asn Ser Ala Arg Ser Pro Asp
10 15 20

gga aag cga aaa aga aag aac ggc caa tgt tcc ctg aaa agc agc atg 450
Gly Lys Arg Lys Arg Lys Asn Gly Gln Cys Ser Leu Lys Ser Ser Met
25 30 35

tca ggg tat atc cct agt tac ctg gac aaa gac gag cag tgt gtc gtg 498
Ser Gly Tyr Ile Pro Ser Tyr Leu Asp Lys Asp Glu Gln Cys Val Val
40 45 50 55

tgt ggg gac aag gca act ggt tat cac tac cgc tgt atc act tgt gag 546
Cys Gly Asp Lys Ala Thr Gly Tyr His Tyr Arg Cys Ile Thr Cys Glu
60 65 70

ggc tgc aag ggc ttc ttt cgc cgc aca atc cag aag aac ctc cat ccc 594
Gly Cys Lys Gly Phe Phe Arg Arg Thr Ile Gln Lys Asn Leu His Pro
75 80 85

acc tat tcc tgc aaa tat gac agc tgc tgt gtc att gac aag atc acc 642
Thr Tyr Ser Cys Lys Tyr Asp Ser Cys Cys Val Ile Asp Lys Ile Thr
90 95 100

cgc aat cag tgc cag ctg tgc cgc ttc aag aag tgc atc gcc gtg gcc 690
Arg Asn Gln Cys Gln Leu Cys Arg Phe Lys Lys Cys Ile Ala Val Ala

105 110 115

atg gcc atg gac ttg gtt cta gat gac tcg aag cgg gtg gcc aag cgt 738
Met Ala Met Asp Leu Val Leu Asp Asp Ser Lys Arg Val Ala Lys Arg
120 125 130 135

aag ctg att gag cag aac cgg gag cgg cgg cgg aag gag gag atg atc 786
Lys Leu Ile Glu Gln Asn Arg Glu Arg Arg Arg Lys Glu Glu Met Ile
140 145 150

cga tca ctg cag cag cga cca gag ccc act cct gaa gag tgg gat ctg 834
Arg Ser Leu Gln Gln Arg Pro Glu Pro Thr Pro Glu Glu Trp Asp Leu
155 160 165

atc cac att gcc aca gag gcc cat cgc agc acc aat gcc cag ggc agc 882
Ile His Ile Ala Thr Glu Ala His Arg Ser Thr Asn Ala Gln Gly Ser
170 175 180

cat tgg aaa cag agg cgg aaa ttc ctg ccc gat gac att ggc cag tca 930
His Trp Lys Gln Arg Arg Lys Phe Leu Pro Asp Asp Ile Gly Gln Ser
185 190 195

ccc att gtc tcc atg ccg gac gga gac aag gtg gac ctg gaa gcc ttc 978
Pro Ile Val Ser Met Pro Asp Gly Asp Lys Val Asp Leu Glu Ala Phe
200 205 210 215

agc gag ttt acc aag atc atc acc ccg gcc atc acc cgt gtg gtg gac 1026
Ser Glu Phe Thr Lys Ile Ile Thr Pro Ala Ile Thr Arg Val Val Asp
220 225 230

ttt gcc aaa aaa ctg ccc atg ttc tcc gag ctg cct tgc gaa gac cag 1074
Phe Ala Lys Lys Leu Pro Met Phe Ser Glu Leu Pro Cys Glu Asp Gln
235 240 245

atc atc ctc ctg aag ggg tgc tgc atg gag atc atg tcc ctg cgg gcg 1122
Ile Ile Leu Leu Lys Gly Cys Cys Met Glu Ile Met Ser Leu Arg Ala
250 255 260

gct gtc cgc tac gac cct gag agc gac acc ctg acg ctg agt ggg gag 1170
Ala Val Arg Tyr Asp Pro Glu Ser Asp Thr Leu Thr Leu Ser Gly Glu
265 270 275

atg gct gtc aag cgg gag cag ctc aag aat ggc ggc ctg ggc gta gtc 1218
Met Ala Val Lys Arg Glu Gln Leu Lys Asn Gly Gly Leu Gly Val Val
280 285 290 295

tcc gac gcc atc ttc gaa ctg ggc aag tca ctc tct gcc ttt aac ctg 1266
Ser Asp Ala Ile Phe Glu Leu Gly Lys Ser Leu Ser Ala Phe Asn Leu
300 305 310

gat gac acg gaa gtg gct ctg ctg cag gct gtg ctg cta atg tca aca 1314
Asp Asp Thr Glu Val Ala Leu Leu Gln Ala Val Leu Leu Met Ser Thr
315 320 325

gac cgc tcg ggc ctg ctg tgt gtg gac aag atc gag aag agt cag gag 1362
Asp Arg Ser Gly Leu Leu Cys Val Asp Lys Ile Glu Lys Ser Gln Glu
330 335 340

gcg tac ctg ctg gcg ttc gag cac tac gtc aac cac cgc aaa cac aac 1410
Ala Tyr Leu Leu Ala Phe Glu His Tyr Val Asn His Arg Lys His Asn
345 350 355

att ccg cac ttc tgg ccc aag ctg ctg atg aag gag aga gaa gtg cag 1458
Ile Pro His Phe Trp Pro Lys Leu Leu Met Lys Glu Arg Glu Val Gln
360 365 370 375

agt tcg att ctg tac aag ggg gca gcg gca gaa ggc cgg ccg ggc ggg 1506
Ser Ser Ile Leu Tyr Lys Gly Ala Ala Ala Glu Gly Arg Pro Gly Gly
380 385 390

tca ctg ggc gtc cac ccg gaa gga cag cag ctt ctc gga atg cat gtt 1554
Ser Leu Gly Val His Pro Glu Gly Gln Gln Leu Leu Gly Met His Val
395 400 405

gtt cag ggt ccg cag gtc cgg cag ctt gag cag cag ctt ggt gaa gcg 1602
Val Gln Gly Pro Gln Val Arg Gln Leu Glu Gln Gln Leu Gly Glu Ala
410 415 420

gga agt ctc caa ggg ccg gtt ctt cag cac cag agc ccg aag agc ccg 1650
Gly Ser Leu Gln Gly Pro Val Leu Gln His Gln Ser Pro Lys Ser Pro
425 430 435

cag cag cgt ctc ctg gag ctg ctc cac cga agc gga att ctc cat gcc 1698
Gln Gln Arg Leu Leu Glu Leu Leu His Arg Ser Gly Ile Leu His Ala
440 445 450 455

cga gcg gtc tgt ggg gaa gac gac agc agt gag gcg gac tcc ccg agc 1746
Arg Ala Val Cys Gly Glu Asp Asp Ser Ser Glu Ala Asp Ser Pro Ser
460 465 470

tcc tct gag gag gaa ccg gag gtc tgc gag gac ctg gca ggc aat gca 1794
Ser Ser Glu Glu Glu Pro Glu Val Cys Glu Asp Leu Ala Gly Asn Ala
475 480 485

gcc tct ccc tga agccccccag aaggccgatg gggaaggaga aggagtgcca 1846
Ala Ser Pro
490

taccttctcc caggcctctg ccccaagagc aggaggtgcc tgaaagctgg gagcgtgggc 1906

tcagcagggc tggtcacctc ccatcccgta agaccacctt cccttcctca gcagccaaac 1966

atggccagac tcccttgctt tttgctgtgt agttccctct gcctgggatg cccttccccc 2026

tttctctgcc tggcaacatc ttacttgtcc tttgaggccc caactcaagt gtcacctcct 2086

tccccagctc ccccaggcag aaatag 2112

<210> 48
<211> 490
<212> PRT
<213> Homo sapiens

<400> 48

Met Glu Gln Lys Pro Ser Lys Val Glu Cys Gly Ser Asp Pro Glu Glu
1 5 10 15

Asn Ser Ala Arg Ser Pro Asp Gly Lys Arg Lys Arg Lys Asn Gly Gln
20 25 30

Cys Ser Leu Lys Ser Ser Met Ser Gly Tyr Ile Pro Ser Tyr Leu Asp
35 40 45

Lys Asp Glu Gln Cys Val Val Cys Gly Asp Lys Ala Thr Gly Tyr His
50 55 60

Tyr Arg Cys Ile Thr Cys Glu Gly Cys Lys Gly Phe Phe Arg Arg Thr
65 70 75 80

Ile Gln Lys Asn Leu His Pro Thr Tyr Ser Cys Lys Tyr Asp Ser Cys
85 90 95

Cys Val Ile Asp Lys Ile Thr Arg Asn Gln Cys Gln Leu Cys Arg Phe
100 105 110

Lys Lys Cys Ile Ala Val Ala Met Ala Met Asp Leu Val Leu Asp Asp
115 120 125

Ser Lys Arg Val Ala Lys Arg Lys Leu Ile Glu Gln Asn Arg Glu Arg
130 135 140

Arg Arg Lys Glu Glu Met Ile Arg Ser Leu Gln Gln Arg Pro Glu Pro
145 150 155 160

Thr Pro Glu Glu Trp Asp Leu Ile His Ile Ala Thr Glu Ala His Arg
165 170 175

Ser Thr Asn Ala Gln Gly Ser His Trp Lys Gln Arg Arg Lys Phe Leu
180 185 190

Pro Asp Asp Ile Gly Gln Ser Pro Ile Val Ser Met Pro Asp Gly Asp
195 200 205

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

Ala Ile Thr Arg Val Val Asp Phe Ala Lys Lys Leu Pro Met Phe Ser
225 230 235 240

Glu Leu Pro Cys Glu Asp Gln Ile Ile Leu Leu Lys Gly Cys Cys Met
245 250 255

Glu Ile Met Ser Leu Arg Ala Ala Val Arg Tyr Asp Pro Glu Ser Asp
260 265 270

Thr Leu Thr Leu Ser Gly Glu Met Ala Val Lys Arg Glu Gln Leu Lys
275 280 285

Asn Gly Gly Leu Gly Val Val Ser Asp Ala Ile Phe Glu Leu Gly Lys
290 295 300

Ser Leu Ser Ala Phe Asn Leu Asp Asp Thr Glu Val Ala Leu Leu Gln
305 310 315 320

Ala Val Leu Leu Met Ser Thr Asp Arg Ser Gly Leu Leu Cys Val Asp
325 330 335

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

Val Asn His Arg Lys His Asn Ile Pro His Phe Trp Pro Lys Leu Leu
355 360 365

Met Lys Glu Arg Glu Val Gln Ser Ser Ile Leu Tyr Lys Gly Ala Ala
370 375 380

Ala Glu Gly Arg Pro Gly Gly Ser Leu Gly Val His Pro Glu Gly Gln
385 390 395 400

Gln Leu Leu Gly Met His Val Val Gln Gly Pro Gln Val Arg Gln Leu
405 410 415

Glu Gln Gln Leu Gly Glu Ala Gly Ser Leu Gln Gly Pro Val Leu Gln
420 425 430

His Gln Ser Pro Lys Ser Pro Gln Gln Arg Leu Leu Glu Leu Leu His
435 440 445

Arg Ser Gly Ile Leu His Ala Arg Ala Val Cys Gly Glu Asp Asp Ser
450 455 460

Ser Glu Ala Asp Ser Pro Ser Ser Ser Glu Glu Glu Pro Glu Val Cys
465 470 475 480

Glu Asp Leu Ala Gly Asn Ala Ala Ser Pro
485 490

<210> 49
<211> 2521
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (136)..(1317)

<400> 49
ggcacgagcc accgtccagg gagcaggtag ctgctgggct ccggggacac tttgcgttcg 60

ggctgggagc gtgctttcca cgacggtgac acgcttccct ggattggcag ccagactgcc 120

ttccgggtca ctgcc atg gag gag ccg cag tca gat cct agc gtc gag ccc 171
Met Glu Glu Pro Gln Ser Asp Pro Ser Val Glu Pro
1 5 10

cct ctg agt cag gaa aca ttt tca gac cta tgg aaa cta ctt cct gaa 219
Pro Leu Ser Gln Glu Thr Phe Ser Asp Leu Trp Lys Leu Leu Pro Glu
15 20 25

aac aac gtt ctg tcc ccc ttg ccg tcc caa gca atg gat gat ttg atg 267
Asn Asn Val Leu Ser Pro Leu Pro Ser Gln Ala Met Asp Asp Leu Met
30 35 40

ctg tcc ccg gac gat att gaa caa tgg ttc act gaa gac cca ggt cca 315
Leu Ser Pro Asp Asp Ile Glu Gln Trp Phe Thr Glu Asp Pro Gly Pro
45 50 55 60

gat gaa gct ccc aga atg cca gag gct gct ccc cgc gtg gcc cct gca 363
Asp Glu Ala Pro Arg Met Pro Glu Ala Ala Pro Arg Val Ala Pro Ala
65 70 75

cca gca gct cct aca ccg gcg gcc cct gca cca gcc ccc tcc tgg ccc 411
Pro Ala Ala Pro Thr Pro Ala Ala Pro Ala Pro Ala Pro Ser Trp Pro
80 85 90

ctg tca tct tct gtc cct tcc cag aaa acc tac cag ggc agc tac ggt 459
Leu Ser Ser Ser Val Pro Ser Gln Lys Thr Tyr Gln Gly Ser Tyr Gly
95 100 105

ttc cgt ctg ggc ttc ttg cat tct ggg aca gcc aag tct gtg act tgc 507
Phe Arg Leu Gly Phe Leu His Ser Gly Thr Ala Lys Ser Val Thr Cys
110 115 120

acg tac tcc cct gcc ctc aac aag atg ttt tgc caa ctg gcc aag acc 555
Thr Tyr Ser Pro Ala Leu Asn Lys Met Phe Cys Gln Leu Ala Lys Thr
125 130 135 140

tgc cct gtg cag ctg tgg gtt gat tcc aca ccc ccg ccc ggc acc cgc 603
Cys Pro Val Gln Leu Trp Val Asp Ser Thr Pro Pro Pro Gly Thr Arg
145 150 155

gtc cgc gcc atg gcc atc tac aag cag tca cag cac atg acg gag gtt 651
Val Arg Ala Met Ala Ile Tyr Lys Gln Ser Gln His Met Thr Glu Val
160 165 170

gtg agg cgc tgc ccc cac cat gag cgc tgc tca gat agc gat ggt ctg 699

Val Arg Arg Cys Pro His His Glu Arg Cys Ser Asp Ser Asp Gly Leu
175 180 185

gcc cct cct cag cat ctt atc cga gtg gaa gga aat ttg cgt gtg gag 747
Ala Pro Pro Gln His Leu Ile Arg Val Glu Gly Asn Leu Arg Val Glu
190 195 200

tat ttg gat gac aga aac act ttt cga cat agt gtg gtg gtg ccc tat 795
Tyr Leu Asp Asp Arg Asn Thr Phe Arg His Ser Val Val Val Pro Tyr
205 210 215 220

gag ccg cct gag gtt ggc tct gac tgt acc acc atc cac tac aac tac 843
Glu Pro Pro Glu Val Gly Ser Asp Cys Thr Thr Ile His Tyr Asn Tyr
225 230 235

atg tgt aac agt tcc tgc atg ggc ggc atg aac cgg agg ccc atc ctc 891
Met Cys Asn Ser Ser Cys Met Gly Gly Met Asn Arg Arg Pro Ile Leu
240 245 250

acc atc atc aca ctg gaa gac tcc agt ggt aat cta ctg gga cgg aac 939
Thr Ile Ile Thr Leu Glu Asp Ser Ser Gly Asn Leu Leu Gly Arg Asn
255 260 265

agc ttt gag gtg cgt gtt tgt gcc tgt cct ggg aga gac cgg cgc aca 987
Ser Phe Glu Val Arg Val Cys Ala Cys Pro Gly Arg Asp Arg Arg Thr
270 275 280

gag gaa gag aat ctc cgc aag aaa ggg gag cct cac cac gag ctg ccc 1035
Glu Glu Glu Asn Leu Arg Lys Lys Gly Glu Pro His His Glu Leu Pro
285 290 295 300

cca ggg agc act aag cga gca ctg ccc aac aac acc agc tcc tct ccc 1083
Pro Gly Ser Thr Lys Arg Ala Leu Pro Asn Asn Thr Ser Ser Ser Pro
305 310 315

cag cca aag aag aaa cca ctg gat gga gaa tat ttc acc ctt cag atc 1131
Gln Pro Lys Lys Lys Pro Leu Asp Gly Glu Tyr Phe Thr Leu Gln Ile
320 325 330

cgt ggg cgt gag cgc ttc gag atg ttc cga gag ctg aat gag gcc ttg 1179
Arg Gly Arg Glu Arg Phe Glu Met Phe Arg Glu Leu Asn Glu Ala Leu
335 340 345

gaa ctc aag gat gcc cag gct ggg aag gag cca ggg ggg agc agg gct 1227
Glu Leu Lys Asp Ala Gln Ala Gly Lys Glu Pro Gly Gly Ser Arg Ala
350 355 360

cac tcc agc cac ctg aag tcc aaa aag ggt cag tct acc tcc cgc cat 1275
His Ser Ser His Leu Lys Ser Lys Lys Gly Gln Ser Thr Ser Arg His
365 370 375 380

aaa aaa ctc atg ttc aag aca gaa ggg cct gac tca gac tga 1317
Lys Lys Leu Met Phe Lys Thr Glu Gly Pro Asp Ser Asp
385 390

cattctccac ttcttgttcc ccactgacag cctcccaccc ccatctctcc ctcccctgcc 1377

attttgggtt ttgggtcttt gaacccttgc ttgcaatagg tgtgcgtcag aagcacccag 1437

gacttccatt tgctttgtcc cggggctcca ctgaacaagt tggcctgcac tggtgttttg 1497

ttgtggggag gaggatgggg agtaggacat accagcttag attttaaggt ttttactgtg 1557

agggatgttt gggagatgta agaaatgttc ttgcagttaa gggttagttt acaatcagcc 1617

acattctagg taggggccca cttcaccgta ctaaccaggg aagctgtccc tcactgttga 1677

attttctcta acttcaaggc ccatatctgt gaaatgctgg catttgcacc tacctcacag 1737

agtgcattgt gagggttaat gaaataatgt acatctggcc ttgaaaccac cttttattac 1797

atggggtcta gaacttgacc cccttgaggg tgcttgttcc ctctccctgt tggtcggtgg 1857

gttggtagtt tctacagttg ggcagctggt taggtagagg gagttgtcaa gtctctgctg 1917

gcccagccaa accctgtctg accacctctt ggtgaacctt agtacctaaa aggaaatctc 1977

accccatccc acaccctgga ggatttcatc tcttgtatat gatgatctgg atccaccaag 2037

acttgtttta tgctcagggt caatttcttt tttctttttt ttttttttt tctttttctt 2097

tgagactggg tctcgctttg ttgcccaggc tggagtggag tggcgtgatc ttggcttact 2157

gcagcctttg cctccccggc tcgagcagtc ctgcctcagc ctccggagta gctgggacca 2217

caggttcatg ccaccatggc cagccaactt ttgcatgttt tgtagagatg gggtctcaca 2277

gtgttgccca ggctggtctc aaactcctgg gctcaggcga tccacctgtc tcagcctccc 2337

agagtgctgg gattacaatt gtgagccacc acgtccagct ggaagggtca acatctttta 2397

cattctgcaa gcacatctgc attttcaccc caccttccc ctccttctcc ctttttatat 2457

cccatttta tatcgatctc ttattttaca ataaaacttt gctgccaaaa aaaaaaaaaa 2517

aaaa 2521

<210> 50
<211> 393

<212> PRT
<213> Homo sapiens

<400> 50

Met Glu Glu Pro Gln Ser Asp Pro Ser Val Glu Pro Pro Leu Ser Gln
1 5 10 15

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

Ser Pro Leu Pro Ser Gln Ala Met Asp Asp Leu Met Leu Ser Pro Asp
35 40 45

Asp Ile Glu Gln Trp Phe Thr Glu Asp Pro Gly Pro Asp Glu Ala Pro
50 55 60

Arg Met Pro Glu Ala Ala Pro Arg Val Ala Pro Ala Pro Ala Ala Pro
65 70 75 80

Thr Pro Ala Ala Pro Ala Pro Ala Pro Ser Trp Pro Leu Ser Ser Ser
85 90 95

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

Phe Leu His Ser Gly Thr Ala Lys Ser Val Thr Cys Thr Tyr Ser Pro
115 120 125

Ala Leu Asn Lys Met Phe Cys Gln Leu Ala Lys Thr Cys Pro Val Gln
130 135 140

Leu Trp Val Asp Ser Thr Pro Pro Pro Gly Thr Arg Val Arg Ala Met
145 150 155 160

Ala Ile Tyr Lys Gln Ser Gln His Met Thr Glu Val Val Arg Arg Cys
165 170 175

Pro His His Glu Arg Cys Ser Asp Ser Asp Gly Leu Ala Pro Pro Gln

180 185 190

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

Arg Asn Thr Phe Arg His Ser Val Val Val Pro Tyr Glu Pro Pro Glu
210 215 220

Val Gly Ser Asp Cys Thr Thr Ile His Tyr Asn Tyr Met Cys Asn Ser
225 230 235 240

Ser Cys Met Gly Gly Met Asn Arg Arg Pro Ile Leu Thr Ile Ile Thr
245 250 255

Leu Glu Asp Ser Ser Gly Asn Leu Leu Gly Arg Asn Ser Phe Glu Val
260 265 270

Arg Val Cys Ala Cys Pro Gly Arg Asp Arg Arg Thr Glu Glu Glu Asn
275 280 285

Leu Arg Lys Lys Gly Glu Pro His His Glu Leu Pro Pro Gly Ser Thr
290 295 300

Lys Arg Ala Leu Pro Asn Asn Thr Ser Ser Ser Pro Gln Pro Lys Lys
305 310 315 320

Lys Pro Leu Asp Gly Glu Tyr Phe Thr Leu Gln Ile Arg Gly Arg Glu
325 330 335

Arg Phe Glu Met Phe Arg Glu Leu Asn Glu Ala Leu Glu Leu Lys Asp
340 345 350

Ala Gln Ala Gly Lys Glu Pro Gly Gly Ser Arg Ala His Ser Ser His
355 360 365

Leu Lys Ser Lys Lys Gly Gln Ser Thr Ser Arg His Lys Lys Leu Met
370 375 380

Phe Lys Thr Glu Gly Pro Asp Ser Asp
385 390

<210> 51
<211> 1929
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(1929)

<400> 51
atg ctt agg ggt ccg ggg ccc ggg ctg ctg ctg ctg gcc gtc cag tgc 48
Met Leu Arg Gly Pro Gly Pro Gly Leu Leu Leu Leu Ala Val Gln Cys
1 5 10 15

ctg ggg aca gcg gtg ccc tcc acg gga gcc tcg aag agc aag agg cag 96
Leu Gly Thr Ala Val Pro Ser Thr Gly Ala Ser Lys Ser Lys Arg Gln
20 25 30

gct cag caa atg gtt cag ccc cag tcc ccg gtg gct gtc agt caa agc 144
Ala Gln Gln Met Val Gln Pro Gln Ser Pro Val Ala Val Ser Gln Ser
35 40 45

aag ccc ggt tgt tat gac aat gga aaa cac tat cag ata aat caa cag 192
Lys Pro Gly Cys Tyr Asp Asn Gly Lys His Tyr Gln Ile Asn Gln Gln
50 55 60

tgg gag cgg acc tac cta ggc aat gcg ttg gtt tgt act tgt tat gga 240
Trp Glu Arg Thr Tyr Leu Gly Asn Ala Leu Val Cys Thr Cys Tyr Gly
65 70 75 80

gga agc cga ggt ttt aac tgc gag agt aaa cct gaa gct gaa gag act 288
Gly Ser Arg Gly Phe Asn Cys Glu Ser Lys Pro Glu Ala Glu Glu Thr
85 90 95

tgc ttt gac aag tac act ggg aac act tac cga gtg ggt gac act tat 336
Cys Phe Asp Lys Tyr Thr Gly Asn Thr Tyr Arg Val Gly Asp Thr Tyr
100 105 110

gag cgt cct aaa gac tcc atg atc tgg gac tgt acc tgc atc ggg gct 384
Glu Arg Pro Lys Asp Ser Met Ile Trp Asp Cys Thr Cys Ile Gly Ala
115 120 125

ggg cga ggg aga ata agc tgt acc atc gca aac cgc tgc cat gaa ggg 432
Gly Arg Gly Arg Ile Ser Cys Thr Ile Ala Asn Arg Cys His Glu Gly

130 135 140

ggt cag tcc tac aag att ggt gac acc tgg agg aga cca cat gag act 480
Gly Gln Ser Tyr Lys Ile Gly Asp Thr Trp Arg Arg Pro His Glu Thr
145 150 155 160

ggt ggt tac atg tta gag tgt gtg tgt ctt ggt aat gga aaa gga gaa 528
Gly Gly Tyr Met Leu Glu Cys Val Cys Leu Gly Asn Gly Lys Gly Glu
165 170 175

tgg acc tgc aag ccc ata gct gag aag tgt ttt gat cat gct gct ggg 576
Trp Thr Cys Lys Pro Ile Ala Glu Lys Cys Phe Asp His Ala Ala Gly
180 185 190

act tcc tat gtg gtc gga gaa acg tgg gag aag ccc tac caa ggc tgg 624
Thr Ser Tyr Val Val Gly Glu Thr Trp Glu Lys Pro Tyr Gln Gly Trp
195 200 205

atg atg gta gat tgt act tgc ctg gga gaa ggc agc gga cgc atc act 672
Met Met Val Asp Cys Thr Cys Leu Gly Glu Gly Ser Gly Arg Ile Thr
210 215 220

tgc act tct aga aat aga tgc aac gat cag gac aca agg aca tcc tat 720
Cys Thr Ser Arg Asn Arg Cys Asn Asp Gln Asp Thr Arg Thr Ser Tyr
225 230 235 240

aga att gga gac acc tgg agc aag aag gat aat cga gga aac ctg ctc 768
Arg Ile Gly Asp Thr Trp Ser Lys Lys Asp Asn Arg Gly Asn Leu Leu
245 250 255

cag tgc atc tgc aca ggc aac ggc cga gga gag tgg aag tgt gag agg 816
Gln Cys Ile Cys Thr Gly Asn Gly Arg Gly Glu Trp Lys Cys Glu Arg
260 265 270

cac acc tct gtg cag acc aca tcg agc gga tct ggc ccc ttc acc gat 864
His Thr Ser Val Gln Thr Thr Ser Ser Gly Ser Gly Pro Phe Thr Asp
275 280 285

gtt cgt gca gct gtt tac caa ccg cag cct cac ccc cag cct cct ccc 912
Val Arg Ala Ala Val Tyr Gln Pro Gln Pro His Pro Gln Pro Pro Pro
290 295 300

tat ggc cac tgt gtc aca gac agt ggt gtg gtc tac tct gtg ggg atg 960
Tyr Gly His Cys Val Thr Asp Ser Gly Val Val Tyr Ser Val Gly Met
305 310 315 320

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Gln Trp Leu Lys Thr Gln Gly Asn Lys Gln Met Leu Cys Thr Cys Leu
325 330 335

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Gly Asn Gly Val Ser Cys Gln Glu Thr Ala Val Thr Gln Thr Tyr Gly
340 345 350

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355 360 365

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Arg Thr Asp Ser Thr Thr Ser Asn Tyr Glu Gln Asp Gln Lys Tyr Ser
370 375 380

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Phe Cys Thr Asp His Thr Val Leu Val Gln Thr Arg Gly Gly Asn Ser
385 390 395 400

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Asn Gly Ala Leu Cys His Phe Pro Phe Leu Tyr Asn Asn His Asn Tyr
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Thr Thr Gln Asn Tyr Asp Ala Asp Gln Lys Phe Gly Phe Cys Pro Met
435 440 445

gct gcc cac gag gaa atc tgc aca acc aat gaa ggg gtc atg tac cgc 1392
Ala Ala His Glu Glu Ile Cys Thr Thr Asn Glu Gly Val Met Tyr Arg
450 455 460

att gga gat cag tgg gat aag cag cat gac atg ggt cac atg atg agg 1440
Ile Gly Asp Gln Trp Asp Lys Gln His Asp Met Gly His Met Met Arg
465 470 475 480

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Cys Thr Cys Val Gly Asn Gly Arg Gly Glu Trp Thr Cys Ile Ala Tyr
485 490 495

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Ser Gln Leu Arg Asp Gln Cys Ile Val Asp Asp Ile Thr Tyr Asn Val
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Asn Asp Thr Phe His Lys Arg His Glu Glu Gly His Met Leu Asn Cys
515 520 525

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Thr Cys Phe Gly Gln Gly Arg Gly Arg Trp Lys Cys Asp Pro Val Asp

530 535 540

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Gln Cys Gln Asp Ser Glu Thr Gly Thr Phe Tyr Gln Ile Gly Asp Ser
545 550 555 560

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Trp Glu Lys Tyr Val His Gly Val Arg Tyr Gln Cys Tyr Cys Tyr Gly
565 570 575

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Arg Gly Ile Gly Glu Trp His Cys Gln Pro Leu Gln Thr Tyr Pro Ser
580 585 590

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Ser Ser Gly Pro Val Glu Val Phe Ile Thr Glu Thr Pro Ser Gln Pro
595 600 605

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625 630 635 640

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35 40 45

Lys Pro Gly Cys Tyr Asp Asn Gly Lys His Tyr Gln Ile Asn Gln Gln
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Trp Glu Arg Thr Tyr Leu Gly Asn Ala Leu Val Cys Thr Cys Tyr Gly
65 70 75 80

Gly Ser Arg Gly Phe Asn Cys Glu Ser Lys Pro Glu Ala Glu Glu Thr
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Cys Phe Asp Lys Tyr Thr Gly Asn Thr Tyr Arg Val Gly Asp Thr Tyr
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Glu Arg Pro Lys Asp Ser Met Ile Trp Asp Cys Thr Cys Ile Gly Ala
115 120 125

Gly Arg Gly Arg Ile Ser Cys Thr Ile Ala Asn Arg Cys His Glu Gly
130 135 140

Gly Gln Ser Tyr Lys Ile Gly Asp Thr Trp Arg Arg Pro His Glu Thr
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165 170 175

Trp Thr Cys Lys Pro Ile Ala Glu Lys Cys Phe Asp His Ala Ala Gly
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Thr Ser Tyr Val Val Gly Glu Thr Trp Glu Lys Pro Tyr Gln Gly Trp
195 200 205

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210 215 220

Cys Thr Ser Arg Asn Arg Cys Asn Asp Gln Asp Thr Arg Thr Ser Tyr
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Arg Ile Gly Asp Thr Trp Ser Lys Lys Asp Asn Arg Gly Asn Leu Leu
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Gln Cys Ile Cys Thr Gly Asn Gly Arg Gly Glu Trp Lys Cys Glu Arg
260 265 270

His Thr Ser Val Gln Thr Thr Ser Ser Gly Ser Gly Pro Phe Thr Asp
275 280 285

Val Arg Ala Ala Val Tyr Gln Pro Gln Pro His Pro Gln Pro Pro Pro
290 295 300

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370 375 380

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385 390 395 400

Asn Gly Ala Leu Cys His Phe Pro Phe Leu Tyr Asn Asn His Asn Tyr
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420 425 430

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435 440 445

Ala Ala His Glu Glu Ile Cys Thr Thr Asn Glu Gly Val Met Tyr Arg
450 455 460

Ile Gly Asp Gln Trp Asp Lys Gln His Asp Met Gly His Met Met Arg
465 470 475 480

Cys Thr Cys Val Gly Asn Gly Arg Gly Glu Trp Thr Cys Ile Ala Tyr
485 490 495

Ser Gln Leu Arg Asp Gln Cys Ile Val Asp Asp Ile Thr Tyr Asn Val
500 505 510

Asn Asp Thr Phe His Lys Arg His Glu Glu Gly His Met Leu Asn Cys
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Trp Glu Lys Tyr Val His Gly Val Arg Tyr Gln Cys Tyr Cys Tyr Gly
565 570 575

Arg Gly Ile Gly Glu Trp His Cys Gln Pro Leu Gln Thr Tyr Pro Ser
580 585 590

Ser Ser Gly Pro Val Glu Val Phe Ile Thr Glu Thr Pro Ser Gln Pro
595 600 605

Asn Ser His Pro Ile Gln Trp Asn Ala Pro Gln Pro Ser His Ile Ser
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gcacggcccc ctgactccgt ccagtattga tcgggagagc cggagcgagc tcttcgggga 240

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Leu Ala Ala Leu Cys Pro Ala Ser Arg Ala Leu Glu Glu Lys Lys Val
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Cys Gln Gly Thr Ser Asn Lys Leu Thr Gln Leu Gly Thr Phe Glu Asp
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His Phe Leu Ser Leu Gln Arg Met Phe Asn Asn Cys Glu Val Val Leu
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Gly Asn Leu Glu Ile Thr Tyr Val Gln Arg Asn Tyr Asp Leu Ser Phe
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Thr Val Glu Arg Ile Pro Leu Glu Asn Leu Gln Ile Ile Arg Gly Asn
95 100 105 110

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Met Tyr Tyr Glu Asn Ser Tyr Ala Leu Ala Val Leu Ser Asn Tyr Asp
115 120 125

gca aat aaa acc gga ctg aag gag ctg ccc atg aga aat tta cag gaa 672
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130 135 140

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

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275 280 285

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290 295 300

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305 310 315

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320 325 330

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385 390 395

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415 420 425 430

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560 565 570

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595 600 605

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625 630 635

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675 680 685

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690 695 700

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720 725 730

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735 740 745 750

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945 950 955

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agt cct aca gac tcc aac ttc tac cgt gcc ctg atg gat gaa gaa gac 3264
Ser Pro Thr Asp Ser Asn Phe Tyr Arg Ala Leu Met Asp Glu Glu Asp
995 1000 1005

atg gac gac gtg gtg gat gcc gac gag tac ctc atc cca cag cag 3309
Met Asp Asp Val Val Asp Ala Asp Glu Tyr Leu Ile Pro Gln Gln
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ggc ttc ttc agc agc ccc tcc acg tca cgg act ccc ctc ctg agc 3354
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Arg Asn Gly Leu Gln Ser Cys Pro Ile Lys Glu Asp Ser Phe Leu
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Gln Arg Tyr Ser Ser Asp Pro Thr Gly Ala Leu Thr Glu Asp Ser
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Ile Asp Asp Thr Phe Leu Pro Val Pro Glu Tyr Ile Asn Gln Ser
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Val Pro Lys Arg Pro Ala Gly Ser Val Gln Asn Pro Val Tyr His
1100 1105 1110

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Asn Gln Pro Leu Asn Pro Ala Pro Ser Arg Asp Pro His Tyr Gln
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Val Gln Pro Thr Cys Val Asn Ser Thr Phe Asp Ser Pro Ala His
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Trp Ala Gln Lys Gly Ser His Gln Ile Ser Leu Asp Asn Pro Asp
1160 1165 1170

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1175 1180 1185

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Thr Ile Gln Glu Val Ala Gly Tyr Val Leu Ile Ala Leu Asn Thr Val
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Glu Arg Ile Pro Leu Glu Asn Leu Gln Ile Ile Arg Gly Asn Met Tyr
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Tyr Glu Asn Ser Tyr Ala Leu Ala Val Leu Ser Asn Tyr Asp Ala Asn
115 120 125

Lys Thr Gly Leu Lys Glu Leu Pro Met Arg Asn Leu Gln Glu Ile Leu
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His Gly Ala Val Arg Phe Ser Asn Asn Pro Ala Leu Cys Asn Val Glu
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Ser Ile Gln Trp Arg Asp Ile Val Ser Ser Asp Phe Leu Ser Asn Met
165 170 175

Ser Met Asp Phe Gln Asn His Leu Gly Ser Cys Gln Lys Cys Asp Pro
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Ser Cys Pro Asn Gly Ser Cys Trp Gly Ala Gly Glu Glu Asn Cys Gln
195 200 205

Lys Leu Thr Lys Ile Ile Cys Ala Gln Gln Cys Ser Gly Arg Cys Arg
210 215 220

Gly Lys Ser Pro Ser Asp Cys Cys His Asn Gln Cys Ala Ala Gly Cys
225 230 235 240

Thr Gly Pro Arg Glu Ser Asp Cys Leu Val Cys Arg Lys Phe Arg Asp
245 250 255

Glu Ala Thr Cys Lys Asp Thr Cys Pro Pro Leu Met Leu Tyr Asn Pro
260 265 270

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

Ile Thr Gly Phe Leu Leu Ile Gln Ala Trp Pro Glu Asn Arg Thr Asp
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Leu His Ala Phe Glu Asn Leu Glu Ile Ile Arg Gly Arg Thr Lys Gln

420 425 430

His Gly Gln Phe Ser Leu Ala Val Val Ser Leu Asn Ile Thr Ser Leu
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Gly Leu Arg Ser Leu Lys Glu Ile Ser Asp Gly Asp Val Ile Ile Ser
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Gly Asn Lys Asn Leu Cys Tyr Ala Asn Thr Ile Asn Trp Lys Lys Leu
465 470 475 480

Phe Gly Thr Ser Gly Gln Lys Thr Lys Ile Ile Ser Asn Arg Gly Glu
485 490 495

Asn Ser Cys Lys Ala Thr Gly Gln Val Cys His Ala Leu Cys Ser Pro
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Glu Gly Cys Trp Gly Pro Glu Pro Arg Asp Cys Val Ser Cys Arg Asn
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Val Ser Arg Gly Arg Glu Cys Val Asp Lys Cys Asn Leu Leu Glu Gly
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Glu Cys Leu Pro Gln Ala Met Asn Ile Thr Cys Thr Gly Arg Gly Pro
565 570 575

Asp Asn Cys Ile Gln Cys Ala His Tyr Ile Asp Gly Pro His Cys Val
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Lys Thr Cys Pro Ala Gly Val Met Gly Glu Asn Asn Thr Leu Val Trp
595 600 605

Lys Tyr Ala Asp Ala Gly His Val Cys His Leu Cys His Pro Asn Cys
610 615 620

Thr Tyr Gly Cys Thr Gly Pro Gly Leu Glu Gly Cys Pro Thr Asn Gly
625 630 635 640

Pro Lys Ile Pro Ser Ile Ala Thr Gly Met Val Gly Ala Leu Leu Leu
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Leu Leu Val Val Ala Leu Gly Ile Gly Leu Phe Met Arg Arg Arg His
660 665 670

Ile Val Arg Lys Arg Thr Leu Arg Arg Leu Leu Gln Glu Arg Glu Leu
675 680 685

Val Glu Pro Leu Thr Pro Ser Gly Glu Ala Pro Asn Gln Ala Leu Leu
690 695 700

Arg Ile Leu Lys Glu Thr Glu Phe Lys Lys Ile Lys Val Leu Gly Ser
705 710 715 720

Gly Ala Phe Gly Thr Val Tyr Lys Gly Leu Trp Ile Pro Glu Gly Glu
725 730 735

Lys Val Lys Ile Pro Val Ala Ile Lys Glu Leu Arg Glu Ala Thr Ser
740 745 750

Pro Lys Ala Asn Lys Glu Ile Leu Asp Glu Ala Tyr Val Met Ala Ser
755 760 765

Val Asp Asn Pro His Val Cys Arg Leu Leu Gly Ile Cys Leu Thr Ser
770 775 780

Thr Val Gln Leu Ile Thr Gln Leu Met Pro Phe Gly Cys Leu Leu Asp
785 790 795 800

Tyr Val Arg Glu His Lys Asp Asn Ile Gly Ser Gln Tyr Leu Leu Asn
805 810 815

Trp Cys Val Gln Ile Ala Lys Gly Met Asn Tyr Leu Glu Asp Arg Arg

820 825 830

Leu Val His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Lys Thr Pro
835 840 845

Gln His Val Lys Ile Thr Asp Phe Gly Leu Ala Lys Leu Leu Gly Ala
850 855 860

Glu Glu Lys Glu Tyr His Ala Glu Gly Gly Lys Val Pro Ile Lys Trp
865 870 875 880

Met Ala Leu Glu Ser Ile Leu His Arg Ile Tyr Thr His Gln Ser Asp
885 890 895

Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe Gly Ser
900 905 910

Lys Pro Tyr Asp Gly Ile Pro Ala Ser Glu Ile Ser Ser Ile Leu Glu
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Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr Ile Asp Val Tyr
930 935 940

Met Ile Met Val Lys Cys Trp Met Ile Asp Ala Asp Ser Arg Pro Lys
945 950 955 960

Phe Arg Glu Leu Ile Ile Glu Phe Ser Lys Met Ala Arg Asp Pro Gln
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Arg Tyr Leu Val Ile Gln Gly Asp Glu Arg Met His Leu Pro Ser Pro
980 985 990

Thr Asp Ser Asn Phe Tyr Arg Ala Leu Met Asp Glu Glu Asp Met Asp
995 1000 1005

Asp Val Val Asp Ala Asp Glu Tyr Leu Ile Pro Gln Gln Gly Phe
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Lys Arg Pro Ala Gly Ser Val Gln Asn Pro Val Tyr His Asn Gln
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Pro Leu Asn Pro Ala Pro Ser Arg Asp Pro His Tyr Gln Asp Pro
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His Ser Thr Ala Val Gly Asn Pro Glu Tyr Leu Asn Thr Val Gln
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Gln Lys Gly Ser His Gln Ile Ser Leu Asp Asn Pro Asp Tyr Gln
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Gln Asp Phe Phe Pro Lys Glu Ala Lys Pro Asn Gly Ile Phe Lys
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Leu Leu Trp Gly Cys Ala Leu Ala Ala Ala Ala Ala Ala Gln Gly Lys
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Asn Asp Met Pro Ile Tyr Met Tyr Ser Val Cys Asn Val Met Ser Gly
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Glu Arg Ile Phe Ile Glu Leu Lys Phe Thr Val Arg Asp Cys Asn Ser
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Phe Pro Gly Gly Ala Ser Ser Cys Lys Glu Thr Phe Asn Leu Tyr Tyr
110 115 120

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Ala Glu Ser Asp Leu Asp Tyr Gly Thr Asn Phe Gln Lys Arg Leu Phe
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acc aag att gac acc att gcg ccc gat gag atc acc gtc agc agc gac 602
Thr Lys Ile Asp Thr Ile Ala Pro Asp Glu Ile Thr Val Ser Ser Asp
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Pro Leu Thr Arg Lys Gly Phe Tyr Leu Ala Phe Gln Asp Ile Gly Ala
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Cys Val Ala Leu Leu Ser Val Arg Val Tyr Tyr Lys Lys Cys Pro Glu
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205 210 215

gca cct tcc ctg gcc act gtg gcc ggc acc tgt gtg gac cat gcc gtg 842
Ala Pro Ser Leu Ala Thr Val Ala Gly Thr Cys Val Asp His Ala Val
220 225 230 235

gtg cca ccg ggg ggt gaa gag ccc cgt atg cac tgt gca gtg gat ggc 890
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240 245 250

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Pro His Tyr Leu Thr Ala Val Gly Met Gly Ala Lys Val Glu Leu Arg
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350 355 360

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365 370 375

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445 450 455

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510 515 520

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640 645 650

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Tyr Thr Glu Lys Gln Arg Val Asp Phe Leu Gly Glu Ala Gly Ile Met
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ggc cag ttc agc cac cac aac atc atc cgc cta gag ggc gtc atc tcc 2186
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685 690 695

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720 725 730

aac atg aac tat gtg cac cgt gac ctg gct gcc cgc aac atc ctc gtc 2378
Asn Met Asn Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val
735 740 745

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750 755 760

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Leu Glu Asp Asp Pro Glu Ala Thr Tyr Thr Thr Ser Gly Gly Lys Ile
765 770 775

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Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile Ser Tyr Arg Lys Phe Thr
780 785 790 795

tct gcc agc gac gtg tgg agc ttt ggc att gtc atg tgg gag gtg atg 2570
Ser Ala Ser Asp Val Trp Ser Phe Gly Ile Val Met Trp Glu Val Met
800 805 810

acc tat ggc gag cgg ccc tac tgg gag ttg tcc aac cac gag gtg atg 2618
Thr Tyr Gly Glu Arg Pro Tyr Trp Glu Leu Ser Asn His Glu Val Met
815 820 825

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Lys Ala Ile Asn Asp Gly Phe Arg Leu Pro Thr Pro Met Asp Cys Pro
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860 865 870 875

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880 885 890

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895 900 905

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910 915 920

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His Phe Met Ala Ala Gly Tyr Thr Ala Ile Glu Lys Val Val Gln Met
925 930 935

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940 945 950 955

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960 965 970

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Val Gly Ile Pro Ile
975

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Gly Lys Gly Trp Asp Leu Met Gln Asn Ile Met Asn Asp Met Pro Ile
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Glu Leu Lys Phe Thr Val Arg Asp Cys Asn Ser Phe Pro Gly Gly Ala
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Ser Ser Cys Lys Glu Thr Phe Asn Leu Tyr Tyr Ala Glu Ser Asp Leu
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130 135 140

Ile Ala Pro Asp Glu Ile Thr Val Ser Ser Asp Phe Glu Ala Arg His
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Val Lys Leu Asn Val Glu Glu Arg Ser Val Gly Pro Leu Thr Arg Lys
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180 185 190

Ser Val Arg Val Tyr Tyr Lys Lys Cys Pro Glu Leu Leu Gln Gly Leu
195 200 205

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Thr Val Ala Gly Thr Cys Val Asp His Ala Val Val Pro Pro Gly Gly
225 230 235 240

Glu Glu Pro Arg Met His Cys Ala Val Asp Gly Glu Trp Leu Val Pro
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Ile Gly Gln Cys Leu Cys Gln Ala Gly Tyr Glu Lys Val Glu Asp Ala
260 265 270

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

Asp Leu Glu Pro His Met Asn Tyr Thr Phe Thr Val Glu Ala Arg Asn
405 410 415

Gly Val Ser Gly Leu Val Thr Ser Arg Ser Phe Arg Thr Ala Ser Val
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Ser Ile Asn Gln Thr Glu Pro Pro Lys Val Arg Leu Glu Gly Arg Ser
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Glu Gly Gln Gly Ala Gly Ser Lys Val His Glu Phe Gln Thr Leu Ser
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Val Val Leu Leu Leu Val Leu Ala Gly Val Gly Phe Phe Ile His Arg
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Arg Arg Lys Asn Gln Arg Ala Arg Gln Ser Pro Glu Asp Val Tyr Phe
565 570 575

Ser Lys Ser Glu Gln Leu Lys Pro Leu Lys Thr Tyr Val Asp Pro His
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Thr Tyr Glu Asp Pro Asn Gln Ala Val Leu Lys Phe Thr Thr Glu Ile
595 600 605

His Pro Ser Cys Val Thr Arg Gln Lys Val Ile Gly Ala Gly Glu Phe
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Val Pro Val Ala Ile Lys Thr Leu Lys Ala Gly Tyr Thr Glu Lys Gln
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His Asn Ile Ile Arg Leu Glu Gly Val Ile Ser Lys Tyr Lys Pro Met
675 680 685

Met Ile Ile Thr Glu Tyr Met Glu Asn Gly Ala Leu Asp Lys Phe Leu
690 695 700

Arg Glu Lys Asp Gly Glu Phe Ser Val Leu Gln Leu Val Gly Met Leu
705 710 715 720

Arg Gly Ile Ala Ala Gly Met Lys Tyr Leu Ala Asn Met Asn Tyr Val
725 730 735

His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Asn Ser Asn Leu Val
740 745 750

Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Val Leu Glu Asp Asp Pro
755 760 765

Glu Ala Thr Tyr Thr Thr Ser Gly Gly Lys Ile Pro Ile Arg Trp Thr
770 775 780

Ala Pro Glu Ala Ile Ser Tyr Arg Lys Phe Thr Ser Ala Ser Asp Val
785 790 795 800

Trp Ser Phe Gly Ile Val Met Trp Glu Val Met Thr Tyr Gly Glu Arg
805 810 815

Pro Tyr Trp Glu Leu Ser Asn His Glu Val Met Lys Ala Ile Asn Asp
820 825 830

Gly Phe Arg Leu Pro Thr Pro Met Asp Cys Pro Ser Ala Ile Tyr Gln
835 840 845

Leu Met Met Gln Cys Trp Gln Gln Glu Arg Ala Arg Arg Pro Lys Phe
850 855 860

Ala Asp Ile Val Ser Ile Leu Asp Lys Leu Ile Arg Ala Pro Asp Ser
865 870 875 880

Leu Lys Thr Leu Ala Asp Phe Asp Pro Arg Val Ser Ile Arg Leu Pro
885 890 895

Ser Thr Ser Gly Ser Glu Gly Val Pro Phe Arg Thr Val Ser Glu Trp
900 905 910

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915 920 925

Gly Tyr Thr Ala Ile Glu Lys Val Val Gln Met Thr Asn Asp Asp Ile
930 935 940

Lys Arg Ile Gly Val Arg Leu Pro Gly His Gln Lys Arg Ile Ala Tyr
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Met Asp Cys Gln
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ctc tcc atc ctc ctc ctt ctc agc tgc tct gtt ctc gac agc ttc ggg 285
Leu Ser Ile Leu Leu Leu Leu Ser Cys Ser Val Leu Asp Ser Phe Gly
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Glu Leu Ile Pro Gln Pro Ser Asn Glu Val Asn Leu Leu Asp Ser Lys
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aca att caa ggg gag ctg ggc tgg atc tct tat cca tca cat ggg tgg 381
Thr Ile Gln Gly Glu Leu Gly Trp Ile Ser Tyr Pro Ser His Gly Trp
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gaa gag atc agt ggt gtg gat gaa cat tac aca ccc atc agg act tac 429
Glu Glu Ile Ser Gly Val Asp Glu His Tyr Thr Pro Ile Arg Thr Tyr
55 60 65

cag gtg tgc aat gtc atg gac cac agt caa aac aat tgg ctg aga aca 477
Gln Val Cys Asn Val Met Asp His Ser Gln Asn Asn Trp Leu Arg Thr
70 75 80

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Asn Trp Val Pro Arg Asn Ser Ala Gln Lys Ile Tyr Val Glu Leu Lys
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Phe Thr Leu Arg Asp Cys Asn Ser Ile Pro Leu Val Leu Gly Thr Cys
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Lys Glu Thr Phe Asn Leu Tyr Tyr Met Glu Ser Asp Asp Asp His Gly
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gtg aaa ttt cga gag cat cag ttt aca aag att gac acc att gca gct 669
Val Lys Phe Arg Glu His Gln Phe Thr Lys Ile Asp Thr Ile Ala Ala
135 140 145

gat gaa agt ttc act caa atg gat ctt ggg gac cgt att ctg aag ctc 717
Asp Glu Ser Phe Thr Gln Met Asp Leu Gly Asp Arg Ile Leu Lys Leu
150 155 160

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185 190 195

gta tac ttc aaa aag tgc cca ttt aca gtg aag aat ctg gct atg ttt 861
Val Tyr Phe Lys Lys Cys Pro Phe Thr Val Lys Asn Leu Ala Met Phe
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Ser Cys Val Asn Asn Ser Lys Glu Glu Asp Pro Pro Arg Met Tyr Cys
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245 250 255 260

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265 270 275

ttc tac aag gca ttg gat ggt aat atg aag tgt gct aag tgc ccg cct 1101
Phe Tyr Lys Ala Leu Asp Gly Asn Met Lys Cys Ala Lys Cys Pro Pro
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cac agt tct act cag gaa gat ggt tca atg aac tgc agg tgt gag aat 1149
His Ser Ser Thr Gln Glu Asp Gly Ser Met Asn Cys Arg Cys Glu Asn
295 300 305

aat tac ttc cgg gca gac aaa gac cct cca tcc atg gct tgt acc cga 1197
Asn Tyr Phe Arg Ala Asp Lys Asp Pro Pro Ser Met Ala Cys Thr Arg
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Pro Pro Ser Ser Pro Arg Asn Val Ile Ser Asn Ile Asn Glu Thr Ser
325 330 335 340

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Val Ile Leu Asp Trp Ser Trp Pro Leu Asp Thr Gly Gly Arg Lys Asp
345 350 355

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Val Thr Phe Asn Ile Ile Cys Lys Lys Cys Gly Trp Asn Ile Lys Gln
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Cys Glu Pro Cys Ser Pro Asn Val Arg Phe Leu Pro Arg Gln Phe Gly
375 380 385

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cct gac act ata tac gta ttc caa atc cga gcc cga aca gcc gct gga 1773
Pro Asp Thr Ile Tyr Val Phe Gln Ile Arg Ala Arg Thr Ala Ala Gly
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585 590 595

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Val Asp Pro His Thr Tyr Glu Asp Pro Thr Gln Ala Val His Glu Phe
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Ala Lys Glu Leu Asp Ala Thr Asn Ile Ser Ile Asp Lys Val Val Gly
615 620 625

gca ggt gaa ttt gga gag gtg tgc agt ggt cgc tta aaa ctt cct tca 2157
Ala Gly Glu Phe Gly Glu Val Cys Ser Gly Arg Leu Lys Leu Pro Ser
630 635 640

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Lys Lys Glu Ile Ser Val Ala Ile Lys Thr Leu Lys Val Gly Tyr Thr
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665 670 675

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Phe Asp His Pro Asn Ile Ile Arg Leu Glu Gly Val Val Thr Lys Ser
680 685 690

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Lys Pro Val Met Ile Val Thr Glu Tyr Met Glu Asn Gly Ser Leu Asp
695 700 705

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710 715 720

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Gly Met Leu Arg Gly Ile Ala Ser Gly Met Lys Tyr Leu Ser Asp Met
725 730 735 740

ggc tat gtt cac cga gac ctc gct gct cgg aac atc ttg atc aac agt 2493
Gly Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Ile Asn Ser
745 750 755

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Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Val Leu Glu
760 765 770

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Asp Asp Pro Glu Ala Ala Tyr Thr Thr Arg Gly Gly Lys Ile Pro Ile
775 780 785

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805 810 815 820

gga gag aga cca tac tgg gag atg tcc aat cag gat gta att aaa gct 2733
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825 830 835

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840 845 850

ttg tat cag ctg atg ctg gac tgc tgg cag aaa gac agg aac aac aga 2829
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855 860 865

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885 890 895 900

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935 940 945

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950 955 960

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Leu Asp Ser Lys Thr Ile Gln Gly Glu Leu Gly Trp Ile Ser Tyr Pro
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Ser His Gly Trp Glu Glu Ile Ser Gly Val Asp Glu His Tyr Thr Pro
50 55 60

Ile Arg Thr Tyr Gln Val Cys Asn Val Met Asp His Ser Gln Asn Asn
65 70 75 80

Trp Leu Arg Thr Asn Trp Val Pro Arg Asn Ser Ala Gln Lys Ile Tyr
85 90 95

Val Glu Leu Lys Phe Thr Leu Arg Asp Cys Asn Ser Ile Pro Leu Val
100 105 110

Leu Gly Thr Cys Lys Glu Thr Phe Asn Leu Tyr Tyr Met Glu Ser Asp
115 120 125

Asp Asp His Gly Val Lys Phe Arg Glu His Gln Phe Thr Lys Ile Asp
130 135 140

Thr Ile Ala Ala Asp Glu Ser Phe Thr Gln Met Asp Leu Gly Asp Arg

145 150 155 160

Ile Leu Lys Leu Asn Thr Glu Ile Arg Glu Val Gly Pro Val Asn Lys
165 170 175

Lys Gly Phe Tyr Leu Ala Phe Gln Asp Val Gly Ala Cys Val Ala Leu
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Glu Val Arg Gly Ser Cys Val Asn Asn Ser Lys Glu Glu Asp Pro Pro
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Arg Met Tyr Cys Ser Thr Glu Gly Glu Trp Leu Val Pro Ile Gly Lys
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Cys Ser Cys Asn Ala Gly Tyr Glu Glu Arg Gly Phe Met Cys Gln Ala
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Cys Arg Pro Gly Phe Tyr Lys Ala Leu Asp Gly Asn Met Lys Cys Ala
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Gly Arg Lys Asp Val Thr Phe Asn Ile Ile Cys Lys Lys Cys Gly Trp
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Arg Gln Phe Gly Leu Thr Asn Thr Thr Val Thr Val Thr Asp Leu Leu
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Ala His Thr Asn Tyr Thr Phe Glu Ile Asp Ala Val Asn Gly Val Ser
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Glu Leu Ser Ser Pro Pro Arg Gln Phe Ala Ala Val Ser Ile Thr Thr
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Ser Arg Asn Ser Ile Ser Leu Ser Trp Gln Glu Pro Glu His Pro Asn
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Val Thr Lys Ser Lys Pro Val Met Ile Val Thr Glu Tyr Met Glu Asn
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Ile Gln Leu Val Gly Met Leu Arg Gly Ile Ala Ser Gly Met Lys Tyr
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Leu Leu Ile Ala Gly Ser Ala Gly Ala Ala Pro Leu Pro Gln Thr Gly
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Lys His Asp His Phe Asp Glu Arg Ser Arg Gly His Leu Asp Glu Gly
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725 730 735

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740 745 750

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755 760 765

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770 775 780 785

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820 825 830

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835 840 845

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Pro Glu Asp Cys Leu His Gln Asp Ile Ser Pro Asp Ala Val Thr Val
850 855 860 865

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900 905 910

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930 935 940 945

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950 955 960

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980 985 990

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Pro Ser Val Gln Ser Pro Ala Glu Val Phe Thr Leu Ser Val Pro Asn
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Lys Ser Gln Val Ala Arg His Ser Leu Asn Tyr Ile Gln Glu Ile Gly
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Asn Gly Trp Phe Gly Lys Val Leu Leu Gly Glu Ile Tyr Thr Gly Thr
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Ser Val Ala Arg Val Ile Val Lys Glu Leu Lys Ala Ser Ala Asn Pro
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Lys Glu Gln Asp Thr Phe Leu Lys Asn Gly Glu Pro Tyr Tyr Ile Leu
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Gln His Pro Asn Ile Leu Gln Cys Val Gly Gln Cys Val Glu Ala Ile
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Pro Tyr Leu Leu Val Phe Glu Phe Cys Asp Leu Gly Asp Leu Lys Ala
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Tyr Leu Arg Ser Glu Gln Glu His Met Arg Gly Asp Ser Gln Thr Met
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Leu Leu Gln Arg Met Ala Cys Glu Val Ala Ala Gly Leu Ala Ala Met
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His Lys Leu His Phe Leu His Ser Asp Leu Ala Leu Arg Asn Cys Phe
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Pro Ser Val Ser Pro Gly Glu Pro Ser Pro Pro Ser Ile His Pro Gly
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Lys Ser Asp Leu Ile Val Arg Val Gly Asp Glu Ile Arg Leu Leu Cys
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Asn Thr Gly Lys Tyr Thr Cys Thr Asn Lys His Gly Leu Ser Asn Ser
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Ser Leu Tyr Gly Lys Glu Asp Asn Asp Thr Leu Val Arg Cys Pro Leu
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Thr Asp Pro Glu Val Thr Asn Tyr Ser Leu Lys Gly Cys Gln Gly Lys
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Thr Pro Leu Leu Ile Gly Phe Val Ile Val Ala Gly Met Met Cys Ile
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Ile Val Met Ile Leu Thr Tyr Lys Tyr Leu Gln Lys Pro Met Tyr Glu
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gta cag tgg aag gtt gtt gag gag ata aat gga aac aat tat gtt tac 1731
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Lys Ala Val Pro Val Val Ser Val Ser Lys Ala Ser Tyr Leu Leu Arg
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Glu Gly Glu Glu Phe Thr Val Thr Cys Thr Ile Lys Asp Val Ser Ser
225 230 235 240

Ser Val Tyr Ser Thr Trp Lys Arg Glu Asn Ser Gln Thr Lys Leu Gln
245 250 255

Glu Lys Tyr Asn Ser Trp His His Gly Asp Phe Asn Tyr Glu Arg Gln
260 265 270

Ala Thr Leu Thr Ile Ser Ser Ala Arg Val Asn Asp Ser Gly Val Phe
275 280 285

Met Cys Tyr Ala Asn Asn Thr Phe Gly Ser Ala Asn Val Thr Thr Thr

290 295 300

Leu Glu Val Val Asp Lys Gly Phe Ile Asn Ile Phe Pro Met Ile Asn
305 310 315 320

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

Tyr Glu Ala Phe Pro Lys Pro Glu His Gln Gln Trp Ile Tyr Met Asn
340 345 350

Arg Thr Phe Thr Asp Lys Trp Glu Asp Tyr Pro Lys Ser Glu Asn Glu
355 360 365

Ser Asn Ile Arg Tyr Val Ser Glu Leu His Leu Thr Arg Leu Lys Gly
370 375 380

Thr Glu Gly Gly Thr Tyr Thr Phe Leu Val Ser Asn Ser Asp Val Asn
385 390 395 400

Ala Ala Ile Ala Phe Asn Val Tyr Val Asn Thr Lys Pro Glu Ile Leu
405 410 415

Thr Tyr Asp Arg Leu Val Asn Gly Met Leu Gln Cys Val Ala Ala Gly
420 425 430

Phe Pro Glu Pro Thr Ile Asp Trp Tyr Phe Cys Pro Gly Thr Glu Gln
435 440 445

Arg Cys Ser Ala Ser Val Leu Pro Val Asp Val Gln Thr Leu Asn Ser
450 455 460

Ser Gly Pro Pro Phe Gly Lys Leu Val Val Gln Ser Ser Ile Asp Ser
465 470 475 480

Ser Ala Phe Lys His Asn Gly Thr Val Glu Cys Lys Ala Tyr Asn Asp
485 490 495

Val Gly Lys Thr Ser Ala Tyr Phe Asn Phe Ala Phe Lys Gly Asn Asn
500 505 510

Lys Glu Gln Ile His Pro His Thr Leu Phe Thr Pro Leu Leu Ile Gly
515 520 525

Phe Val Ile Val Ala Gly Met Met Cys Ile Ile Val Met Ile Leu Thr
530 535 540

Tyr Lys Tyr Leu Gln Lys Pro Met Tyr Glu Val Gln Trp Lys Val Val
545 550 555 560

Glu Glu Ile Asn Gly Asn Asn Tyr Val Tyr Ile Asp Pro Thr Gln Leu
565 570 575

Pro Tyr Asp His Lys Trp Glu Phe Pro Arg Asn Arg Leu Ser Phe Gly
580 585 590

Lys Thr Leu Gly Ala Gly Ala Phe Gly Lys Val Val Glu Ala Thr Ala
595 600 605

Tyr Gly Leu Ile Lys Ser Asp Ala Ala Met Thr Val Ala Val Lys Met
610 615 620

Leu Lys Pro Ser Ala His Leu Thr Glu Arg Glu Ala Leu Met Ser Glu
625 630 635 640

Leu Lys Val Leu Ser Tyr Leu Gly Asn His Met Asn Ile Val Asn Leu
645 650 655

Leu Gly Ala Cys Thr Ile Gly Gly Pro Thr Leu Val Ile Thr Glu Tyr
660 665 670

Cys Cys Tyr Gly Asp Leu Leu Asn Phe Leu Arg Arg Lys Arg Asp Ser
675 680 685

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

690 695 700

Asn Leu Leu His Ser Lys Glu Ser Ser Cys Ser Asp Ser Thr Asn Glu
705 710 715 720

Tyr Met Asp Met Lys Pro Gly Val Ser Tyr Val Val Pro Thr Lys Ala
725 730 735

Asp Lys Arg Arg Ser Val Arg Ile Gly Ser Tyr Ile Glu Arg Asp Val
740 745 750

Thr Pro Ala Ile Met Glu Asp Asp Glu Leu Ala Leu Asp Leu Glu Asp
755 760 765

Leu Leu Ser Phe Ser Tyr Gln Val Ala Lys Gly Met Ala Phe Leu Ala
770 775 780

Ser Lys Asn Cys Ile His Arg Asp Leu Ala Ala Arg Asn Ile Leu Leu
785 790 795 800

Thr His Gly Arg Ile Thr Lys Ile Cys Asp Phe Gly Leu Ala Arg Asp
805 810 815

Ile Lys Asn Asp Ser Asn Tyr Val Val Lys Gly Asn Ala Arg Leu Pro
820 825 830

Val Lys Trp Met Ala Pro Glu Ser Ile Phe Asn Cys Val Tyr Thr Phe
835 840 845

Glu Ser Asp Val Trp Ser Tyr Gly Ile Phe Leu Trp Glu Leu Phe Ser
850 855 860

Leu Gly Ser Ser Pro Tyr Pro Gly Met Pro Val Asp Ser Lys Phe Tyr
865 870 875 880

Lys Met Ile Lys Glu Gly Phe Arg Met Leu Ser Pro Glu His Ala Pro
885 890 895

Ala Glu Met Tyr Asp Ile Met Lys Thr Cys Trp Asp Ala Asp Pro Leu
900 905 910

Lys Arg Pro Thr Phe Lys Gln Ile Val Gln Leu Ile Glu Lys Gln Ile
915 920 925

Ser Glu Ser Thr Asn His Ile Tyr Ser Asn Leu Ala Asn Cys Ser Pro
930 935 940

Asn Arg Gln Lys Pro Val Val Asp His Ser Val Arg Ile Asn Ser Val
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Gly Ser Thr Ala Ser Ser Ser Gln Pro Leu Leu Val His Asp Asp Val
965 970 975

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ggtgtggccg cgaccgcaag ggcttttgtt gccgggtgga cccaacaggg atg ggc 176
Met Gly
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tgc tgg gga cag ctg ctg gtg tgg ttc gga gcc gcg ggc gcc att ctc 224
Cys Trp Gly Gln Leu Leu Val Trp Phe Gly Ala Ala Gly Ala Ile Leu
5 10 15

tgc tct agc ccg ggg tcc cag gag act ttt ctg cgg tcc tcg ccc ctg 272
Cys Ser Ser Pro Gly Ser Gln Glu Thr Phe Leu Arg Ser Ser Pro Leu
20 25 30

ccg ctg gca agt ccc agc ccc cgg gac ccg aaa gtc agc gcc ccg cct 320
Pro Leu Ala Ser Pro Ser Pro Arg Asp Pro Lys Val Ser Ala Pro Pro

35 40 45 50

agt atc ttg gag cca gcc tcc ccg ctg aat tct ccg ggc acc gag ggg 368
Ser Ile Leu Glu Pro Ala Ser Pro Leu Asn Ser Pro Gly Thr Glu Gly
55 60 65

tct tgg ctg ttt tct acc tgc ggg gcc agc ggc cgg cat ggg ccc aca 416
Ser Trp Leu Phe Ser Thr Cys Gly Ala Ser Gly Arg His Gly Pro Thr
70 75 80

cag aca caa tgt gac ggg gcg tac gcg ggg acc agc gtg gtg gtg acc 464
Gln Thr Gln Cys Asp Gly Ala Tyr Ala Gly Thr Ser Val Val Val Thr
85 90 95

gtg ggg gcc gcc ggg cag ctg aga ggc gtg cag ctg tgg cgc gtg ccg 512
Val Gly Ala Ala Gly Gln Leu Arg Gly Val Gln Leu Trp Arg Val Pro
100 105 110

ggc cct ggc cag tat ctg atc tca gcc tac gga gcc gcg ggc ggc aaa 560
Gly Pro Gly Gln Tyr Leu Ile Ser Ala Tyr Gly Ala Ala Gly Gly Lys
115 120 125 130

ggc gcc aag aac cac ctg tcg cgg gcg cat ggc gtc ttc gtc tca gca 608
Gly Ala Lys Asn His Leu Ser Arg Ala His Gly Val Phe Val Ser Ala
135 140 145

atc ttc tcc ctc ggt ctc ggg gag tcg ctg tac atc ctg gtg ggg cag 656
Ile Phe Ser Leu Gly Leu Gly Glu Ser Leu Tyr Ile Leu Val Gly Gln
150 155 160

cag gga gag gac gcc tgt ccc gga ggt agc ccg gag agc cag ctc gtc 704
Gln Gly Glu Asp Ala Cys Pro Gly Gly Ser Pro Glu Ser Gln Leu Val
165 170 175

tgc ctc ggg gag tct cga gcc gtt gaa gag cac gcg gcg atg gat ggg 752
Cys Leu Gly Glu Ser Arg Ala Val Glu Glu His Ala Ala Met Asp Gly
180 185 190

agc gaa ggg gtc ccg ggg tcg cgg cgc tgg gcg gga ggt ggc ggg ggt 800
Ser Glu Gly Val Pro Gly Ser Arg Arg Trp Ala Gly Gly Gly Gly Gly
195 200 205 210

ggc ggg ggc gcc acc tac gtt ttc cgg gtg cgc gct ggc gag ctg gaa 848
Gly Gly Gly Ala Thr Tyr Val Phe Arg Val Arg Ala Gly Glu Leu Glu
215 220 225

ccg ttg ctg gtg gcg gcc gga ggc ggc ggt cgg gcc tac ctg agg ccg 896
Pro Leu Leu Val Ala Ala Gly Gly Gly Gly Arg Ala Tyr Leu Arg Pro
230 235 240

cgg gac cga ggc cgg act cag gcc tcc ccc gag aaa ctg gag aac cgc 944
Arg Asp Arg Gly Arg Thr Gln Ala Ser Pro Glu Lys Leu Glu Asn Arg
245 250 255

tcg gag gcg ccc ggg agc ggc ggg aga ggc ggg gcg gca ggt ggt ggg 992
Ser Glu Ala Pro Gly Ser Gly Gly Arg Gly Gly Ala Ala Gly Gly Gly
260 265 270

ggc ggc tgg acg tcg cgg gct ccc tct ccg cag gcc ggc cgc tca ctg 1040
Gly Gly Trp Thr Ser Arg Ala Pro Ser Pro Gln Ala Gly Arg Ser Leu
275 280 285 290

cag gag ggg gcg gag ggc ggc cag ggc tgc tcc gag gct tgg gcg acc 1088
Gln Glu Gly Ala Glu Gly Gly Gln Gly Cys Ser Glu Ala Trp Ala Thr
295 300 305

ctt ggc tgg gcc gcg gcc ggc ggc ttc ggg ggc ggc ggc ggg gcc tgc 1136
Leu Gly Trp Ala Ala Ala Gly Gly Phe Gly Gly Gly Gly Gly Ala Cys
310 315 320

act gcg ggc gga ggc ggc ggc ggc tac agg ggg ggc gac gct tca gag 1184
Thr Ala Gly Gly Gly Gly Gly Gly Tyr Arg Gly Gly Asp Ala Ser Glu
325 330 335

act gac aac ctc tgg gct gat ggg gaa gat gga gta tcc ttc ata cac 1232
Thr Asp Asn Leu Trp Ala Asp Gly Glu Asp Gly Val Ser Phe Ile His
340 345 350

ccc agc agc gag ctc ttc ctg cag cct ctg gca gtc acc gag aac cac 1280
Pro Ser Ser Glu Leu Phe Leu Gln Pro Leu Ala Val Thr Glu Asn His
355 360 365 370

gga gag gta gag atc cga agg cac ctc aac tgc agt cac tgc cct ttg 1328
Gly Glu Val Glu Ile Arg Arg His Leu Asn Cys Ser His Cys Pro Leu
375 380 385

aga gac tgc caa tgg cag gca gag ctc cag ctg gct gaa tgc ctg tgc 1376
Arg Asp Cys Gln Trp Gln Ala Glu Leu Gln Leu Ala Glu Cys Leu Cys
390 395 400

cca gaa ggc atg gag cta gct gtg gat aac gtc acc tgc atg gac ctg 1424
Pro Glu Gly Met Glu Leu Ala Val Asp Asn Val Thr Cys Met Asp Leu
405 410 415

cac aag ccc cca ggc cct ctg gtt ctg atg gtg gct gtg gtg gca acc 1472
His Lys Pro Pro Gly Pro Leu Val Leu Met Val Ala Val Val Ala Thr
420 425 430

tca aca ctg agc ctc ctt atg gtg tgt ggg gtc ctg att ctg gtg aag 1520
Ser Thr Leu Ser Leu Leu Met Val Cys Gly Val Leu Ile Leu Val Lys

435 440 445 450

cag aag aag tgg cag ggc ctg cag gag atg agg ctg ccg agc cct gag 1568
Gln Lys Lys Trp Gln Gly Leu Gln Glu Met Arg Leu Pro Ser Pro Glu
455 460 465

ctt gag ctg agc aag ctt cga acc tct gcc atc agg aca gcc ccc aat 1616
Leu Glu Leu Ser Lys Leu Arg Thr Ser Ala Ile Arg Thr Ala Pro Asn
470 475 480

ccc tat tat tgc cag gtg ggg ctt ggc ccg gcc cag tcc tgg cct ctg 1664
Pro Tyr Tyr Cys Gln Val Gly Leu Gly Pro Ala Gln Ser Trp Pro Leu
485 490 495

cca cca ggt gtc acc gag gtt tcc cca gcc aat gtt act ctg ctc aga 1712
Pro Pro Gly Val Thr Glu Val Ser Pro Ala Asn Val Thr Leu Leu Arg
500 505 510

gcc ctg ggc cat ggt gcc ttt ggg gag gtg tat gag gga ctg gta att 1760
Ala Leu Gly His Gly Ala Phe Gly Glu Val Tyr Glu Gly Leu Val Ile
515 520 525 530

ggc ctt cct ggg gac tcc agt ccc ctg cag gta gct atc aag acc ctg 1808
Gly Leu Pro Gly Asp Ser Ser Pro Leu Gln Val Ala Ile Lys Thr Leu
535 540 545

cca gaa ctc tgc tcg cct cag gat gag ctg gat ttc ctc atg gag gcc 1856
Pro Glu Leu Cys Ser Pro Gln Asp Glu Leu Asp Phe Leu Met Glu Ala
550 555 560

ctc atc atc agc aag ttt cgc cat cag aac att gtg cgg tgt gtg ggg 1904
Leu Ile Ile Ser Lys Phe Arg His Gln Asn Ile Val Arg Cys Val Gly
565 570 575

ctc agc ctc agg gcc acc cct cgc ctc att ctg ctg gaa ctg atg tct 1952
Leu Ser Leu Arg Ala Thr Pro Arg Leu Ile Leu Leu Glu Leu Met Ser
580 585 590

gga ggg gac atg aag agt ttc ctg agg cac agt cgg cca cac ctg ggc 2000
Gly Gly Asp Met Lys Ser Phe Leu Arg His Ser Arg Pro His Leu Gly
595 600 605 610

cag cca tca cct ctg gtc atg cgg gac ctg ctg caa ctg gcc cag gac 2048
Gln Pro Ser Pro Leu Val Met Arg Asp Leu Leu Gln Leu Ala Gln Asp
615 620 625

ata gcc cag ggc tgc cac tac ctg gag gaa aat cac ttc atc cac agg 2096
Ile Ala Gln Gly Cys His Tyr Leu Glu Glu Asn His Phe Ile His Arg
630 635 640

gat att gcc gcc cgg aac tgc ctg ctg agc tgc gct gga ccc agc cga 2144
Asp Ile Ala Ala Arg Asn Cys Leu Leu Ser Cys Ala Gly Pro Ser Arg
645 650 655

gtg gcc aag att ggg gac ttt ggg atg gca cga gat atc tac cgg gcc 2192
Val Ala Lys Ile Gly Asp Phe Gly Met Ala Arg Asp Ile Tyr Arg Ala
660 665 670

agt tat tac cgc agg ggg gac cgg gcc ttg ctc cca gtc aag tgg atg 2240
Ser Tyr Tyr Arg Arg Gly Asp Arg Ala Leu Leu Pro Val Lys Trp Met
675 680 685 690

ccc cca gag gcc ttc ctg gag ggc atc ttc aca tcc aag aca gat tcc 2288
Pro Pro Glu Ala Phe Leu Glu Gly Ile Phe Thr Ser Lys Thr Asp Ser
695 700 705

tgg tct ttt ggg gtg ctg ctc tgg gag atc ttc tca ctg ggc tac atg 2336
Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe Ser Leu Gly Tyr Met
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ccc tat cct ggg cgc acc aac cag gag gtg ctg gac ttc gtc gtt gga 2384
Pro Tyr Pro Gly Arg Thr Asn Gln Glu Val Leu Asp Phe Val Val Gly
725 730 735

gga ggc cgg atg gac cct cct agg ggc tgc cca ggg cct gtg tac cgc 2432
Gly Gly Arg Met Asp Pro Pro Arg Gly Cys Pro Gly Pro Val Tyr Arg
740 745 750

atc atg acc cag tgt tgg cag cac gag cct gag ctc cgc cct agc ttt 2480
Ile Met Thr Gln Cys Trp Gln His Glu Pro Glu Leu Arg Pro Ser Phe
755 760 765 770

gcc agc atc ttg gag cgt ctg cag tac tgc act cag gac ccg gat gtg 2528
Ala Ser Ile Leu Glu Arg Leu Gln Tyr Cys Thr Gln Asp Pro Asp Val
775 780 785

ctg aat tca ctc ctg cca atg gag ctg ggg ccc acc cca gag gag gaa 2576
Leu Asn Ser Leu Leu Pro Met Glu Leu Gly Pro Thr Pro Glu Glu Glu
790 795 800

ggg act tct ggg ctg ggg aac aga tct ttg gag tgc cta aga ccc cca 2624
Gly Thr Ser Gly Leu Gly Asn Arg Ser Leu Glu Cys Leu Arg Pro Pro
805 810 815

cag ccc cag gaa ctg agt cca gag aag ttg aaa agc tgg gga ggt agc 2672
Gln Pro Gln Glu Leu Ser Pro Glu Lys Leu Lys Ser Trp Gly Gly Ser
820 825 830

cct ctt ggc ccc tgg ctg tcc tct ggc ctc aag ccc ctc aaa tcc agg 2720
Pro Leu Gly Pro Trp Leu Ser Ser Gly Leu Lys Pro Leu Lys Ser Arg

835 840 845 850

ggc ctc caa cct cag aac ctt tgg aat ccc act tat cgc tcc tga 2765
Gly Leu Gln Pro Gln Asn Leu Trp Asn Pro Thr Tyr Arg Ser
855 860

gccccaaggg gccctgaggg taaggactga ggcactgagg gtccctccct atactcctca 2825

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<400> 89

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Pro Leu Pro Leu Ala Ser Pro Ser Pro Arg Asp Pro Lys Val Ser Ala
35 40 45

Pro Pro Ser Ile Leu Glu Pro Ala Ser Pro Leu Asn Ser Pro Gly Thr
50 55 60

Glu Gly Ser Trp Leu Phe Ser Thr Cys Gly Ala Ser Gly Arg His Gly
65 70 75 80

Pro Thr Gln Thr Gln Cys Asp Gly Ala Tyr Ala Gly Thr Ser Val Val
85 90 95

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

Val Pro Gly Pro Gly Gln Tyr Leu Ile Ser Ala Tyr Gly Ala Ala Gly
115 120 125

Gly Lys Gly Ala Lys Asn His Leu Ser Arg Ala His Gly Val Phe Val
130 135 140

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

Gly Gln Gln Gly Glu Asp Ala Cys Pro Gly Gly Ser Pro Glu Ser Gln
165 170 175

Leu Val Cys Leu Gly Glu Ser Arg Ala Val Glu Glu His Ala Ala Met
180 185 190

Asp Gly Ser Glu Gly Val Pro Gly Ser Arg Arg Trp Ala Gly Gly Gly
195 200 205

Gly Gly Gly Gly Gly Ala Thr Tyr Val Phe Arg Val Arg Ala Gly Glu
210 215 220

Leu Glu Pro Leu Leu Val Ala Ala Gly Gly Gly Gly Arg Ala Tyr Leu
225 230 235 240

Arg Pro Arg Asp Arg Gly Arg Thr Gln Ala Ser Pro Glu Lys Leu Glu
245 250 255

Asn Arg Ser Glu Ala Pro Gly Ser Gly Gly Arg Gly Gly Ala Ala Gly
260 265 270

Gly Gly Gly Gly Trp Thr Ser Arg Ala Pro Ser Pro Gln Ala Gly Arg
275 280 285

Ser Leu Gln Glu Gly Ala Glu Gly Gly Gln Gly Cys Ser Glu Ala Trp
290 295 300

Ala Thr Leu Gly Trp Ala Ala Ala Gly Gly Phe Gly Gly Gly Gly Gly
305 310 315 320

Ala Cys Thr Ala Gly Gly Gly Gly Gly Gly Tyr Arg Gly Gly Asp Ala
325 330 335

Ser Glu Thr Asp Asn Leu Trp Ala Asp Gly Glu Asp Gly Val Ser Phe
340 345 350

Ile His Pro Ser Ser Glu Leu Phe Leu Gln Pro Leu Ala Val Thr Glu
355 360 365

Asn His Gly Glu Val Glu Ile Arg Arg His Leu Asn Cys Ser His Cys
370 375 380

Pro Leu Arg Asp Cys Gln Trp Gln Ala Glu Leu Gln Leu Ala Glu Cys
385 390 395 400

Leu Cys Pro Glu Gly Met Glu Leu Ala Val Asp Asn Val Thr Cys Met
405 410 415

Asp Leu His Lys Pro Pro Gly Pro Leu Val Leu Met Val Ala Val Val
420 425 430

Ala Thr Ser Thr Leu Ser Leu Leu Met Val Cys Gly Val Leu Ile Leu
435 440 445

Val Lys Gln Lys Lys Trp Gln Gly Leu Gln Glu Met Arg Leu Pro Ser
450 455 460

Pro Glu Leu Glu Leu Ser Lys Leu Arg Thr Ser Ala Ile Arg Thr Ala
465 470 475 480

Pro Asn Pro Tyr Tyr Cys Gln Val Gly Leu Gly Pro Ala Gln Ser Trp
485 490 495

Pro Leu Pro Pro Gly Val Thr Glu Val Ser Pro Ala Asn Val Thr Leu
500 505 510

Leu Arg Ala Leu Gly His Gly Ala Phe Gly Glu Val Tyr Glu Gly Leu
515 520 525

Val Ile Gly Leu Pro Gly Asp Ser Ser Pro Leu Gln Val Ala Ile Lys
530 535 540

Thr Leu Pro Glu Leu Cys Ser Pro Gln Asp Glu Leu Asp Phe Leu Met
545 550 555 560

Glu Ala Leu Ile Ile Ser Lys Phe Arg His Gln Asn Ile Val Arg Cys
565 570 575

Val Gly Leu Ser Leu Arg Ala Thr Pro Arg Leu Ile Leu Leu Glu Leu
580 585 590

Met Ser Gly Gly Asp Met Lys Ser Phe Leu Arg His Ser Arg Pro His
595 600 605

Leu Gly Gln Pro Ser Pro Leu Val Met Arg Asp Leu Leu Gln Leu Ala
610 615 620

Gln Asp Ile Ala Gln Gly Cys His Tyr Leu Glu Glu Asn His Phe Ile
625 630 635 640

His Arg Asp Ile Ala Ala Arg Asn Cys Leu Leu Ser Cys Ala Gly Pro
645 650 655

Ser Arg Val Ala Lys Ile Gly Asp Phe Gly Met Ala Arg Asp Ile Tyr
660 665 670

Arg Ala Ser Tyr Tyr Arg Arg Gly Asp Arg Ala Leu Leu Pro Val Lys
675 680 685

Trp Met Pro Pro Glu Ala Phe Leu Glu Gly Ile Phe Thr Ser Lys Thr
690 695 700

Asp Ser Trp Ser Phe Gly Val Leu Leu Trp Glu Ile Phe Ser Leu Gly
705 710 715 720

Tyr Met Pro Tyr Pro Gly Arg Thr Asn Gln Glu Val Leu Asp Phe Val
725 730 735

Val Gly Gly Gly Arg Met Asp Pro Pro Arg Gly Cys Pro Gly Pro Val
740 745 750

Tyr Arg Ile Met Thr Gln Cys Trp Gln His Glu Pro Glu Leu Arg Pro
755 760 765

Ser Phe Ala Ser Ile Leu Glu Arg Leu Gln Tyr Cys Thr Gln Asp Pro
770 775 780

Asp Val Leu Asn Ser Leu Leu Pro Met Glu Leu Gly Pro Thr Pro Glu
785 790 795 800

Glu Glu Gly Thr Ser Gly Leu Gly Asn Arg Ser Leu Glu Cys Leu Arg
805 810 815

Pro Pro Gln Pro Gln Glu Leu Ser Pro Glu Lys Leu Lys Ser Trp Gly
820 825 830

Gly Ser Pro Leu Gly Pro Trp Leu Ser Ser Gly Leu Lys Pro Leu Lys
835 840 845

Ser Arg Gly Leu Gln Pro Gln Asn Leu Trp Asn Pro Thr Tyr Arg Ser
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cagcgcgcac gggcg atg gcg aag gcg acg tcc ggt gcc gcg ggg ctg cgt 231
Met Ala Lys Ala Thr Ser Gly Ala Ala Gly Leu Arg
1 5 10

ctg ctg ttg ctg ctg ctg ctg ccg ctg cta ggc aaa gtg gca ttg ggc 279
Leu Leu Leu Leu Leu Leu Leu Pro Leu Leu Gly Lys Val Ala Leu Gly
15 20 25

ctc tac ttc tcg agg gat gct tac tgg gag aag ctg tat gtg gac cag 327
Leu Tyr Phe Ser Arg Asp Ala Tyr Trp Glu Lys Leu Tyr Val Asp Gln
30 35 40

gca gcc ggc acg ccc ttg ctg tac gtc cat gcc ctg cgg gac gcc cct 375
Ala Ala Gly Thr Pro Leu Leu Tyr Val His Ala Leu Arg Asp Ala Pro
45 50 55 60

gag gag gtg ccc agc ttc cgc ctg ggc cag cat ctc tac ggc acg tac 423
Glu Glu Val Pro Ser Phe Arg Leu Gly Gln His Leu Tyr Gly Thr Tyr
65 70 75

cgc aca cgg ctg cat gag aac aac tgg atc tgc atc cag gag gac acc 471
Arg Thr Arg Leu His Glu Asn Asn Trp Ile Cys Ile Gln Glu Asp Thr
80 85 90

ggc ctc ctc tac ctt aac cgg agc ctg gac cat agc tcc tgg gag aag 519
Gly Leu Leu Tyr Leu Asn Arg Ser Leu Asp His Ser Ser Trp Glu Lys
95 100 105

ctc agt gtc cgc aac cgc ggc ttt ccc ctg ctc acc gtc tac ctc aag 567
Leu Ser Val Arg Asn Arg Gly Phe Pro Leu Leu Thr Val Tyr Leu Lys
110 115 120

gtc ttc ctg tca ccc aca tcc ctt cgt gag ggc gag tgc cag tgg cca 615
Val Phe Leu Ser Pro Thr Ser Leu Arg Glu Gly Glu Cys Gln Trp Pro
125 130 135 140

ggc tgt gcc cgc gta tac ttc tcc ttc ttc aac acc tcc ttt cca gcc 663
Gly Cys Ala Arg Val Tyr Phe Ser Phe Phe Asn Thr Ser Phe Pro Ala
145 150 155

tgc agc tcc ctc aag ccc cgg gag ctc tgc ttc cca gag aca agg ccc 711
Cys Ser Ser Leu Lys Pro Arg Glu Leu Cys Phe Pro Glu Thr Arg Pro
160 165 170

tcc ttc cgc att cgg gag aac cga ccc cca ggc acc ttc cac cag ttc 759
Ser Phe Arg Ile Arg Glu Asn Arg Pro Pro Gly Thr Phe His Gln Phe
175 180 185

cgc ctg ctg cct gtg cag ttc ttg tgc ccc aac atc agc gtg gcc tac 807
Arg Leu Leu Pro Val Gln Phe Leu Cys Pro Asn Ile Ser Val Ala Tyr
190 195 200

agg ctc ctg gag ggt gag ggt ctg ccc ttc cgc tgc gcc ccg gac agc 855
Arg Leu Leu Glu Gly Glu Gly Leu Pro Phe Arg Cys Ala Pro Asp Ser
205 210 215 220

ctg gag gtg agc acg cgc tgg gcc ctg gac cgc gag cag cgg gag aag 903
Leu Glu Val Ser Thr Arg Trp Ala Leu Asp Arg Glu Gln Arg Glu Lys
225 230 235

tac gag ctg gtg gcc gtg tgc acc gtg cac gcc ggc gcg cgc gag gag 951
Tyr Glu Leu Val Ala Val Cys Thr Val His Ala Gly Ala Arg Glu Glu
240 245 250

gtg gtg atg gtg ccc ttc ccg gtg acc gtg tac gac gag gac gac tcg 999
Val Val Met Val Pro Phe Pro Val Thr Val Tyr Asp Glu Asp Asp Ser
255 260 265

gcg ccc acc ttc ccc gcg ggc gtc gac acc gcc agc gcc gtg gtg gag 1047
Ala Pro Thr Phe Pro Ala Gly Val Asp Thr Ala Ser Ala Val Val Glu
270 275 280

ttc aag cgg aag gag gac acc gtg gtg gcc acg ctg cgt gtc ttc gat 1095
Phe Lys Arg Lys Glu Asp Thr Val Val Ala Thr Leu Arg Val Phe Asp
285 290 295 300

gca gac gtg gta cct gca tca ggg gag ctg gtg agg cgg tac aca agc 1143
Ala Asp Val Val Pro Ala Ser Gly Glu Leu Val Arg Arg Tyr Thr Ser
305 310 315

acg ctg ctc ccc ggg gac acc tgg gcc cag cag acc ttc cgg gtg gaa 1191
Thr Leu Leu Pro Gly Asp Thr Trp Ala Gln Gln Thr Phe Arg Val Glu
320 325 330

cac tgg ccc aac gag acc tcg gtc cag gcc aac ggc agc ttc gtg cgg 1239
His Trp Pro Asn Glu Thr Ser Val Gln Ala Asn Gly Ser Phe Val Arg
335 340 345

gcg acc gta cat gac tat agg ctg gtt ctc aac cgg aac ctc tcc atc 1287

Ala Thr Val His Asp Tyr Arg Leu Val Leu Asn Arg Asn Leu Ser Ile
350 355 360

tcg gag aac cgc acc atg cag ctg gcg gtg ctg gtc aat gac tca gac 1335
Ser Glu Asn Arg Thr Met Gln Leu Ala Val Leu Val Asn Asp Ser Asp
365 370 375 380

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His Glu Asn Asn Trp Ile Cys Ile Gln Glu Asp Thr Gly Leu Leu Tyr
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Pro Ala Ser Gly Glu Leu Val Arg Arg Tyr Thr Ser Thr Leu Leu Pro
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Glu Thr Ser Val Gln Ala Asn Gly Ser Phe Val Arg Ala Thr Val His
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Thr Met Gln Leu Ala Val Leu Val Asn Asp Ser Asp Phe Gln Gly Pro
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Gly Ala Gly Val Leu Leu Leu His Phe Asn Val Ser Val Leu Pro Val
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Ser Leu His Leu Pro Ser Thr Tyr Ser Leu Ser Val Ser Arg Arg Ala
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Cys Ser Thr Leu Gly Val Val Thr Ser Ala Glu Asp Thr Ser Gly Ile
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gat gaa cca atg aat aac atc acc acg tct ctg ggc cag aca gca gaa 603
Asp Glu Pro Met Asn Asn Ile Thr Thr Ser Leu Gly Gln Thr Ala Glu
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Glu Glu Leu Gly Glu Cys Ala Phe Gly Lys Ile Tyr Lys Gly His Leu
480 485 490

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495 500 505

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Ser Arg Glu Ile Tyr Ser Ala Asp Tyr Tyr Arg Val Gln Ser Lys Ser

640 645 650

ttg ctg ccc att cgc tgg atg ccc cct gaa gcc atc atg tat ggc aaa 2379
Leu Leu Pro Ile Arg Trp Met Pro Pro Glu Ala Ile Met Tyr Gly Lys
655 660 665

ttc tct tct gat tca gat atc tgg tcc ttt ggg gtt gtc ttg tgg gag 2427
Phe Ser Ser Asp Ser Asp Ile Trp Ser Phe Gly Val Val Leu Trp Glu
670 675 680

att ttc agt ttt gga ctc cag cca tat tat gga ttc agt aac cag gaa 2475
Ile Phe Ser Phe Gly Leu Gln Pro Tyr Tyr Gly Phe Ser Asn Gln Glu
685 690 695 700

gtg att gag atg gtg aga aaa cgg cag ctc tta cca tgc tct gaa gac 2523
Val Ile Glu Met Val Arg Lys Arg Gln Leu Leu Pro Cys Ser Glu Asp
705 710 715

tgc cca ccc aga atg tac agc ctc atg aca gag tgc tgg aat gag att 2571
Cys Pro Pro Arg Met Tyr Ser Leu Met Thr Glu Cys Trp Asn Glu Ile
720 725 730

cct tct agg aga cca aga ttt aaa gat att cac gtc cgg ctt cgg tcc 2619
Pro Ser Arg Arg Pro Arg Phe Lys Asp Ile His Val Arg Leu Arg Ser
735 740 745

tgg gag gga ctc tca agt cac aca agc tct act act cct tca ggg gga 2667
Trp Glu Gly Leu Ser Ser His Thr Ser Ser Thr Thr Pro Ser Gly Gly
750 755 760

aat gcc acc aca cag aca acc tcc ctc agt gcc agc cca gtg agt aat 2715
Asn Ala Thr Thr Gln Thr Thr Ser Leu Ser Ala Ser Pro Val Ser Asn
765 770 775 780

ctc agt aac ccc aga tat cct aat tac atg ttc ccg agc cag ggt att 2763
Leu Ser Asn Pro Arg Tyr Pro Asn Tyr Met Phe Pro Ser Gln Gly Ile
785 790 795

aca cca cag ggc cag att gct ggt ttc att ggc ccg cca ata cct cag 2811
Thr Pro Gln Gly Gln Ile Ala Gly Phe Ile Gly Pro Pro Ile Pro Gln
800 805 810

aac cag cga ttc att ccc atc aat gga tac cca ata cct cct gga tat 2859
Asn Gln Arg Phe Ile Pro Ile Asn Gly Tyr Pro Ile Pro Pro Gly Tyr
815 820 825

gca gcg ttt cca gct gcc cac tac cag cca aca ggt cct ccc aga gtg 2907
Ala Ala Phe Pro Ala Ala His Tyr Gln Pro Thr Gly Pro Pro Arg Val
830 835 840

att cag cac tgc cca cct ccc aag agt cgg tcc cca agc agt gcc agt 2955
Ile Gln His Cys Pro Pro Pro Lys Ser Arg Ser Pro Ser Ser Ala Ser
845 850 855 860

ggg tcg act agc act ggc cat gtg act agc ttg ccc tca tca gga tcc 3003
Gly Ser Thr Ser Thr Gly His Val Thr Ser Leu Pro Ser Ser Gly Ser
865 870 875

aat cag gaa gca aat att cct tta cta cca cac atg tca att cca aat 3051
Asn Gln Glu Ala Asn Ile Pro Leu Leu Pro His Met Ser Ile Pro Asn
880 885 890

cat cct ggt gga atg ggt atc acc gtt ttt ggc aac aaa tct caa aaa 3099
His Pro Gly Gly Met Gly Ile Thr Val Phe Gly Asn Lys Ser Gln Lys
895 900 905

ccc tac aaa att gac tca aag caa gca tct tta cta gga gac gcc aat 3147
Pro Tyr Lys Ile Asp Ser Lys Gln Ala Ser Leu Leu Gly Asp Ala Asn
910 915 920

att cat gga cac acc gaa tct atg att tct gca gaa ctg taa 3189
Ile His Gly His Thr Glu Ser Met Ile Ser Ala Glu Leu
925 930 935

aatgcacaac ttttgtaaat gtggtataca ggacaaacta gacggccgta gaaaagattt 3249

atattcaaat gtttttatta aagtaaggtt ctcatttagc agacatcgca acaagtacct 3309

tctgtgaagt ttcactgtgt cttaccaagc aggacagaca ctcggccag 3358

<210> 93
<211> 937
<212> PRT
<213> Homo sapiens

<400> 93

Met His Arg Pro Arg Arg Arg Gly Thr Arg Pro Pro Leu Leu Ala Leu
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Leu Ala Ala Leu Leu Leu Ala Ala Arg Gly Ala Ala Ala Gln Glu Thr
20 25 30

Glu Leu Ser Val Ser Ala Glu Leu Val Pro Thr Ser Ser Trp Asn Ile
35 40 45

Ser Ser Glu Leu Asn Lys Asp Ser Tyr Leu Thr Leu Asp Glu Pro Met
50 55 60

Asn Asn Ile Thr Thr Ser Leu Gly Gln Thr Ala Glu Leu His Cys Lys
65 70 75 80

Val Ser Gly Asn Pro Pro Pro Thr Ile Arg Trp Phe Lys Asn Asp Ala
85 90 95

Pro Val Val Gln Glu Pro Arg Arg Leu Ser Phe Arg Ser Thr Ile Tyr
100 105 110

Gly Ser Arg Leu Arg Ile Arg Asn Leu Asp Thr Thr Asp Thr Gly Tyr
115 120 125

Phe Gln Cys Val Ala Thr Asn Gly Lys Glu Val Val Ser Ser Thr Gly
130 135 140

Val Leu Phe Val Lys Phe Gly Pro Pro Pro Thr Ala Ser Pro Gly Tyr
145 150 155 160

Ser Asp Glu Tyr Glu Glu Asp Gly Phe Cys Gln Pro Tyr Arg Gly Ile
165 170 175

Ala Cys Ala Arg Phe Ile Gly Asn Arg Thr Val Tyr Met Glu Ser Leu
180 185 190

His Met Gln Gly Glu Ile Glu Asn Gln Ile Thr Ala Ala Phe Thr Met
195 200 205

Ile Gly Thr Ser Ser His Leu Ser Asp Lys Cys Ser Gln Phe Ala Ile
210 215 220

Pro Ser Leu Cys His Tyr Ala Phe Pro Tyr Cys Asp Glu Thr Ser Ser
225 230 235 240

Val Pro Lys Pro Arg Asp Leu Cys Arg Asp Glu Cys Glu Ile Leu Glu
245 250 255

Asn Val Leu Cys Gln Thr Glu Tyr Ile Phe Ala Arg Ser Asn Pro Met
260 265 270

Ile Leu Met Arg Leu Lys Leu Pro Asn Cys Glu Asp Leu Pro Gln Pro
275 280 285

Glu Ser Pro Glu Ala Ala Asn Cys Ile Arg Ile Gly Ile Pro Met Ala
290 295 300

Asp Pro Ile Asn Lys Asn His Lys Cys Tyr Asn Ser Thr Gly Val Asp
305 310 315 320

Tyr Arg Gly Thr Val Ser Val Thr Lys Ser Gly Arg Gln Cys Gln Pro
325 330 335

Trp Asn Ser Gln Tyr Pro His Thr His Thr Phe Thr Ala Leu Arg Phe
340 345 350

Pro Glu Leu Asn Gly Gly His Ser Tyr Cys Arg Asn Pro Gly Asn Gln
355 360 365

Lys Glu Ala Pro Trp Cys Phe Thr Leu Asp Glu Asn Phe Lys Ser Asp
370 375 380

Leu Cys Asp Ile Pro Ala Cys Asp Ser Lys Asp Ser Lys Glu Lys Asn
385 390 395 400

Lys Met Glu Ile Leu Tyr Ile Leu Val Pro Ser Val Ala Ile Pro Leu
405 410 415

Ala Ile Ala Leu Leu Phe Phe Phe Ile Cys Val Cys Arg Asn Asn Gln
420 425 430

Lys Ser Ser Ser Ala Pro Val Gln Arg Gln Pro Lys His Val Arg Gly
435 440 445

Gln Asn Val Glu Met Ser Met Leu Asn Ala Tyr Lys Pro Lys Ser Lys
450 455 460

Ala Lys Glu Leu Pro Leu Ser Ala Val Arg Phe Met Glu Glu Leu Gly
465 470 475 480

Glu Cys Ala Phe Gly Lys Ile Tyr Lys Gly His Leu Tyr Leu Pro Gly
485 490 495

Met Asp His Ala Gln Leu Val Ala Ile Lys Thr Leu Lys Asp Tyr Asn
500 505 510

Asn Pro Gln Gln Trp Met Glu Phe Gln Gln Glu Ala Ser Leu Met Ala
515 520 525

Glu Leu His His Pro Asn Ile Val Cys Leu Leu Gly Ala Val Thr Gln
530 535 540

Glu Gln Pro Val Cys Met Leu Phe Glu Tyr Ile Asn Gln Gly Asp Leu
545 550 555 560

His Glu Phe Leu Ile Met Arg Ser Pro His Ser Asp Val Gly Cys Ser
565 570 575

Ser Asp Glu Asp Gly Thr Val Lys Ser Ser Leu Asp His Gly Asp Phe
580 585 590

Leu His Ile Ala Ile Gln Ile Ala Ala Gly Met Glu Tyr Leu Ser Ser
595 600 605

His Phe Phe Val His Lys Asp Leu Ala Ala Arg Asn Ile Leu Ile Gly
610 615 620

Glu Gln Leu His Val Lys Ile Ser Asp Leu Gly Leu Ser Arg Glu Ile
625 630 635 640

Tyr Ser Ala Asp Tyr Tyr Arg Val Gln Ser Lys Ser Leu Leu Pro Ile
645 650 655

Arg Trp Met Pro Pro Glu Ala Ile Met Tyr Gly Lys Phe Ser Ser Asp
660 665 670

Ser Asp Ile Trp Ser Phe Gly Val Val Leu Trp Glu Ile Phe Ser Phe
675 680 685

Gly Leu Gln Pro Tyr Tyr Gly Phe Ser Asn Gln Glu Val Ile Glu Met
690 695 700

Val Arg Lys Arg Gln Leu Leu Pro Cys Ser Glu Asp Cys Pro Pro Arg
705 710 715 720

Met Tyr Ser Leu Met Thr Glu Cys Trp Asn Glu Ile Pro Ser Arg Arg
725 730 735

Pro Arg Phe Lys Asp Ile His Val Arg Leu Arg Ser Trp Glu Gly Leu
740 745 750

Ser Ser His Thr Ser Ser Thr Thr Pro Ser Gly Gly Asn Ala Thr Thr
755 760 765

Gln Thr Thr Ser Leu Ser Ala Ser Pro Val Ser Asn Leu Ser Asn Pro
770 775 780

Arg Tyr Pro Asn Tyr Met Phe Pro Ser Gln Gly Ile Thr Pro Gln Gly
785 790 795 800

Gln Ile Ala Gly Phe Ile Gly Pro Pro Ile Pro Gln Asn Gln Arg Phe
805 810 815

Ile Pro Ile Asn Gly Tyr Pro Ile Pro Pro Gly Tyr Ala Ala Phe Pro
820 825 830

Ala Ala His Tyr Gln Pro Thr Gly Pro Pro Arg Val Ile Gln His Cys
835 840 845

Pro Pro Pro Lys Ser Arg Ser Pro Ser Ser Ala Ser Gly Ser Thr Ser
850 855 860

Thr Gly His Val Thr Ser Leu Pro Ser Ser Gly Ser Asn Gln Glu Ala
865 870 875 880

Asn Ile Pro Leu Leu Pro His Met Ser Ile Pro Asn His Pro Gly Gly
885 890 895

Met Gly Ile Thr Val Phe Gly Asn Lys Ser Gln Lys Pro Tyr Lys Ile
900 905 910

Asp Ser Lys Gln Ala Ser Leu Leu Gly Asp Ala Asn Ile His Gly His
915 920 925

Thr Glu Ser Met Ile Ser Ala Glu Leu
930 935