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SUPERINDUSTRIA Y COMERCIO
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DIVISION DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
E S D

COD 08

Ref SOLICITUD Nº 00024102
PATENTE COMPUESTOS PARA LA TERAPIA Y EL DIAGNÓSTICO DE CANCER DE PULMÓN Y MÉTODOS DE USO DE LOS MISMOS
FECHA DE SOLICITUD ABRIL 3 2000
SOLICITANTE CORIXA CORPORATION

ASUNTO PRESENTACION PRIORIDADES

DILIA RODRIGUEZ D ALEMAN en mi condición de apoderada de la sociedad solicitante en esta oportunidad por el presente escrito me permito presentar

1 Copia certificada de la prioridad estadoudinense reivindicada Nº 09/285 323 de Abril 2 de 1999

2 Copia certificada de la prioridad estadoudinense reivindicada Nº 09/370 838 de Agosto 9 de 1999

3 Copia certificada de la prioridad estadoudinense reivindicada Nº 09/476 235 de Diciembre 30 de 1999

4 Copia certificada de la prioridad estadoudinense reivindicada Nº 09/518 809 de Marzo 3 de 2000

- Traducción al Español de las mencionadas prioridades

Estas prioridades están siendo presentadas dentro del término de 3 meses que exige el Convenio de Paris toda vez que la solicitud fué radicada el 3 de Abril de 2 000

Ruego a usted continuar con el presente trámite

Señor Jefe

DILIA RODRIGUEZ D ALEMAN
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APPLICATION NUMBER: ***09/285,323***
FILING DATE: ***April 02, 1999***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

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Certifying Officer

TRADUCCION OFICIAL No. 2000/095
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April 12, 2000

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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for nonprovisional applications under 37 CFR § 1.53(b))

Attorney Docket No	210121.475
First Inventor or Application Identifier	Steven G. Reed
Title	COMPOUNDS FOR THERAPY AND DIAGNOSIS CANCER AND METHODS FOR THEIR USE
Express Mail Label No.	EL251273975US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Box Patent Application, Assistant Commissioner for, Washington, D.C. 20231

1. [ ] General Authorization Form & Fee Transmittal (Submit an original and a duplicate for fee processing)
2. [X] Specification [Total Pages] 63 (preferred arrangement set forth below)
   - Descriptive Title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings (if filed)
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
3. [ ] Drawing(s) (35 USC 113) [Total Sheets]
4. Oath or Declaration [Total Pages]
   a. [ ] Newly executed (original or copy)
   b. [ ] Copy from a prior application (37 CFR 1.63(d)) (for continuation/divisional with Box 17 completed)
      1 [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b)
5. [ ] Incorporation By Reference (useable if box 4b is checked) The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered to be part of the disclosure of the accompanying application and is hereby incorporated by reference therein
6. [ ] Microfiche Computer Program (App
7. Nucleotide and Amino Acid Sequence Su (if applicable, all necessary)
   a. [X] Computer-Readable Copy
   b. [X] Paper Copy (identical to compute
   c. [X] Statement verifying identity of abo

ACCOMPANYING APPLICATION P

8. [ ] Assignment Papers (cover sheet & doc
9. [ ] 37 CFR 3.73(b) Statement (when there is an assignee) [ ] Powe
10. [ ] English Translation Document (if app.
11. [ ] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copie
12. [ ] Preliminary Amendment
13. [X] Return Receipt Postcard
14. [ ] Small Entity Statement(s) [ ] Statement filed in pri Status still proper and
15. [ ] Certified Copy of Priority Document((if foreign priority is claimed)
16. [X] Other: Certificate of Express Mail

17. If a CONTINUING APPLICATION, check appropriate box and supply the requisite information below and in a preliminary amendment:
    [ ] Continuation [ ] Divisional [ ] Continuation-in-Part (CIP) of prior Application No
    Prior application information: Examiner Group / Art Unit

[ ] Claims the benefit of Provisional Application No

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Respectfully submitted,

TYPED or PRINTED NAME David J. Maki REGISTRATION NO. 31,392

SIGNATURE [signature] Date APRIL 2, 1999

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COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE

TECHNICAL FIELD

The present invention relates generally to compositions and method for the treatment of lung cancer. The invention is more specifically related t nucleotide sequences that are preferentially expressed in lung tumor tissue, togeth with polypeptides encoded by such nucleotide sequences. The inventive nucleotid sequences and polypeptides may be used in vaccines and pharmaceutic compositions for the treatment of lung cancer.

BACKGROUND OF THE INVENTION

Lung cancer is the primary cause of cancer death among both men ar women in the U.S., with an estimated 172,000 new cases being reported in 1994. Th five-year survival rate among all lung cancer patients, regardless of the stage disease at diagnosis, is only 13%. This contrasts with a five-year survival rate 46% among cases detected while the disease is still localized. However, only 16% lung cancers are discovered before the disease has spread.

Early detection is difficult since clinical symptoms are often not se until the disease has reached an advanced stage. Currently, diagnosis is aided by t use of chest x-rays, analysis of the type of cells contained in sputum and fiberop examination of the bronchial passages. Treatment regimens are determined by t type and stage of the cancer, and include surgery, radiation therapy and/ chemotherapy. In spite of considerable research into therapies for the disease, lu cancer remains difficult to treat.

Accordingly, there remains a need in the art for improved vaccin treatment methods and diagnostic techniques for lung cancer.

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SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compounds and method for the therapy of lung cancer. In a first aspect, isolated polynucleotides encodin lung tumor polypeptides are provided, such polynucleotides comprising a nucleotid sequence selected from the group consisting of: (a) sequences provided in SEQ II NO: 218-222 and 224-226; (b) sequences complementary to a sequence provided i SEQ ID NO: 218-222 and 224-226; and (b) variants of the sequences of (a) or (b).

In a second aspect, isolated polypeptides are provided that comprise a least an immunogenic portion of a lung tumor protein or a variant thereof. In specifi embodiments, such polypeptides comprise an amino acid sequence encoded by DNA sequence comprising a nucleotide sequence selected from the group consistin of (a) sequences recited in SEQ ID NO: 218-222 and 224-226; (b) sequenc complementary to a sequence provided in SEQ ID NO: 218-222 and 224-226; and (variants of the sequences of (a) and (b).

In related aspects, expression vectors comprising the inventi polynucleotides, together with host cells transformed or transfected with suc expression vectors are provided. In preferred embodiments, the host cells are selecte from the group consisting of *E. coli*, yeast and mammalian cells.

In another aspect, fusion proteins comprising a first and a secor inventive polypeptide or, alternatively, an inventive polypeptide and a known lu tumor antigen, are provided.

The present invention further provides pharmaceutical compositio comprising one or more of the above polypeptides, fusion proteins or polynucleotid and a physiologically acceptable carrier, together with vaccines comprising one more such polypeptides, fusion proteins or polynucleotides in combination with immune response enhancer.

In related aspects, the present invention provides methods f inhibiting the development of lung cancer in a patient, comprising administering t patient an effective amount of at least one of the above pharmaceutical compositio and/or vaccines.

In yet a further aspect of the present invention, methods are provide for detecting lung cancer in a patient, comprising: (a) contacting a biological sampl obtained from a patient with a binding agent that is capable of binding to polypeptide disclosed herein; and (b) detecting in the sample a protein or polypeptid that binds to the binding agent. In preferred embodiments, the binding agent is a antibody, most preferably a monoclonal antibody.

In related aspects, methods are provided for monitoring th progression of lung cancer in a patient, comprising: (a) contacting a biologic sample obtained from a patient with a binding agent that is capable of binding to on of the polypeptides disclosed herein; (b) determining in the sample an amount of protein or polypeptide that binds to the binding agent; (c) repeating steps (a) and (b and comparing the amounts of polypeptide detected in steps (b) and (c).

Within related aspects, the present invention provides antibodie preferably monoclonal antibodies, that bind to the inventive polypeptides, as well a diagnostic kits comprising such antibodies, and methods of using such antibodies t inhibit the development of lung cancer.

The present invention further provides methods for detecting lur cancer comprising: (a) obtaining a biological sample from a patient; (b) contactir the sample with a first and a second oligonucleotide primer in a polymerase cha reaction, at least one of the oligonucleotide primers being specific for polynucleotide that encodes one of the polypeptides disclosed herein; and (detecting in the sample a DNA sequence that amplifies in the presence of the first a second oligonucleotide primers. In a preferred embodiment, at least one of t oligonucleotide primers comprises at least about 10 contiguous nucleotides of polynucleotide comprising a sequence selected from the group consisting of SEQ I NO: 217-237.

In a further aspect, the present invention provides a method f detecting lung cancer in a patient comprising: (a) obtaining a biological sample fr the patient; (b) contacting the sample with an oligonucleotide probe specific for polynucleotide that encodes one of the polypeptides disclosed herein; and (

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detecting in the sample a DNA sequence that hybridizes to the oligonucleotide probe Preferably, the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide comprising a sequence selected from the group consisting of SEQ ID NO: 217-237. In related aspects, diagnostic kits comprising the above oligonucleotide probes or primers are provided.

In yet a further aspect, methods for the treatment of lung cancer in a patient are provided, the methods comprising obtaining PBMC from the patient incubating the PBMC with a polypeptide of the present invention (or a polynucleotide that encodes such a polypeptide) to provide incubated T cells and administering the incubated T cells to the patient. In present invention additionally provides method for the treatment of lung cancer that comprise incubating antigen presenting cells with a polypeptide of the present invention (or a polynucleotide that encodes such polypeptide) to provide incubated antigen presenting cells and administering the incubated antigen presenting cells to the patient. In certain embodiments, the antigen presenting cells are selected from the group consisting of dendritic cells and macrophages. Compositions for the treatment of lung cancer comprising T cells or antigen presenting cells that have been incubated with a polypeptide or polynucleotide of the present invention are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

SEQUENCE IDENTIFIERS

SEQ ID NO: 1 is the determined cDNA sequence for L363C1.cons

SEQ ID NO: 2 is the determined cDNA sequence for L263C2.cons

SEQ ID NO: 3 is the determined cDNA sequence for L263C2c

SEQ ID NO: 4 is the determined cDNA sequence for L263C1.cons

SEQ ID NO: 5 is the determined cDNA sequence for L263C1b

SEQ ID NO: 6 is the determined cDNA sequence for L164C2.cons

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SEQ ID NO: 7 is the determined cDNA sequence for L164C1.cons

SEQ ID NO: 8 is the determined cDNA sequence for L366C1a

SEQ ID NO: 9 is the determined cDNA sequence for L260C1.cons

SEQ ID NO: 10 is the determined cDNA sequence for L163C1c

SEQ ID NO: 11 is the determined cDNA sequence for L163C1b

SEQ ID NO: 12 is the determined cDNA sequence for L255C1.cons

SEQ ID NO: 13 is the determined cDNA sequence for L255C1b

SEQ ID NO: 14 is the determined cDNA sequence for L355C1.cons

SEQ ID NO: 15 is the determined cDNA sequence for L366C1.cons

SEQ ID NO: 16 is the determined cDNA sequence for L163C1a

SEQ ID NO: 17 is the determined cDNA sequence for LT86-1

SEQ ID NO: 18 is the determined cDNA sequence for LT86-2

SEQ ID NO: 19 is the determined cDNA sequence for LT86-3

SEQ ID NO: 20 is the determined cDNA sequence for LT86-4

SEQ ID NO: 21 is the determined cDNA sequence for LT86-5

SEQ ID NO: 22 is the determined cDNA sequence for LT86-6

SEQ ID NO: 23 is the determined cDNA sequence for LT86-7

SEQ ID NO: 24 is the determined cDNA sequence for LT86-8

SEQ ID NO: 25 is the determined cDNA sequence for LT86-9

SEQ ID NO: 26 is the determined cDNA sequence for LT86-10

SEQ ID NO: 27 is the determined cDNA sequence for LT86-11

SEQ ID NO: 28 is the determined cDNA sequence for LT86-12

SEQ ID NO: 29 is the determined cDNA sequence for LT86-13

SEQ ID NO: 30 is the determined cDNA sequence for LT86-14

SEQ ID NO: 31 is the determined cDNA sequence for LT86-15

SEQ ID NO: 32 is the predicted amino acid sequence for LT86-1

SEQ ID NO: 33 is the predicted amino acid sequence for LT86-2

SEQ ID NO: 34 is the predicted amino acid sequence for LT86-3

SEQ ID NO: 35 is the predicted amino acid sequence for LT86-4

SEQ ID NO: 36 is the predicted amino acid sequence for LT86-5

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SEQ ID NO: 37 is the predicted amino acid sequence for LT86-6

SEQ ID NO: 38 is the predicted amino acid sequence for LT86-7

SEQ ID NO: 39 is the predicted amino acid sequence for LT86-8

SEQ ID NO: 40 is the predicted amino acid sequence for LT86-9

SEQ ID NO: 41 is the predicted amino acid sequence for LT86-10

SEQ ID NO: 42 is the predicted amino acid sequence for LT86-11

SEQ ID NO: 43 is the predicted amino acid sequence for LT86-12

SEQ ID NO: 44 is the predicted amino acid sequence for LT86-13

SEQ ID NO: 45 is the predicted amino acid sequence for LT86-14

SEQ ID NO: 46 is the predicted amino acid sequence for LT86-15

SEQ ID NO: 47 is a $(dT)_{12}AG$ primer

SEQ ID NO: 48 is a primer

SEQ ID NO: 49 is the determined 5' cDNA sequence for L86S-3

SEQ ID NO: 50 is the determined 5' cDNA sequence for L86S-12

SEQ ID NO: 51 is the determined 5' cDNA sequence for L86S-16

SEQ ID NO: 52 is the determined 5' cDNA sequence for L86S-25

SEQ ID NO: 53 is the determined 5' cDNA sequence for L86S-36

SEQ ID NO: 54 is the determined 5' cDNA sequence for L86S-40

SEQ ID NO: 55 is the determined 5' cDNA sequence for L86S-46

SEQ ID NO: 56 is the predicted amino acid sequence for L86S-3

SEQ ID NO: 57 is the predicted amino acid sequence for L86S-12

SEQ ID NO: 58 is the predicted amino acid sequence for L86S-16

SEQ ID NO: 59 is the predicted amino acid sequence for L86S-25

SEQ ID NO: 60 is the predicted amino acid sequence for L86S-36

SEQ ID NO: 61 is the predicted amino acid sequence for L86S-40

SEQ ID NO: 62 is the predicted amino acid sequence for L86S-46

SEQ ID NO: 63 is the determined 5' cDNA sequence for L86S-30

SEQ ID NO: 64 is the determined 5' cDNA sequence for L86S-41

SEQ ID NO: 65 is the predicted amino acid sequence from the 5' end of LT86-9

SEQ ID NO: 66 is the determined extended cDNA sequence for LT86-4

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SEQ ID NO: 67 is the predicted extended amino acid sequence for LT86-4

SEQ ID NO: 68 is the determined 5' cDNA sequence for LT86-20

SEQ ID NO: 69 is the determined 3' cDNA sequence for LT86-21

SEQ ID NO: 70 is the determined 5' cDNA sequence for LT86-22

SEQ ID NO: 71 is the determined 5' cDNA sequence for LT86-26

SEQ ID NO: 72 is the determined 5' cDNA sequence for LT86-27

SEQ ID NO: 73 is the predicted amino acid sequence for LT86-20

SEQ ID NO: 74 is the predicted amino acid sequence for LT86-21

SEQ ID NO: 75 is the predicted amino acid sequence for LT86-22

SEQ ID NO: 76 is the predicted amino acid sequence for LT86-26

SEQ ID NO: 77 is the predicted amino acid sequence for LT86-27

SEQ ID NO: 78 is the determined extended cDNA sequence for L86S-12

SEQ ID NO: 79 is the determined extended cDNA sequence for L86S-36

SEQ ID NO: 80 is the determined extended cDNA sequence for L86S-46

SEQ ID NO: 81 is the predicted extended amino acid sequence for L86S-12

SEQ ID NO: 82 is the predicted extended amino acid sequence for L86S-36

SEQ ID NO: 83 is the predicted extended amino acid sequence for L86S-46

SEQ ID NO: 84 is the determined 5'cDNA sequence for L86S-6

SEQ ID NO: 85 is the determined 5'cDNA sequence for L86S-11

SEQ ID NO: 86 is the determined 5'cDNA sequence for L86S-14

SEQ ID NO: 87 is the determined 5'cDNA sequence for L86S-29

SEQ ID NO: 88 is the determined 5'cDNA sequence for L86S-34

SEQ ID NO: 89 is the determined 5'cDNA sequence for L86S-39

SEQ ID NO: 90 is the determined 5'cDNA sequence for L86S-47

SEQ ID NO: 91 is the determined 5'cDNA sequence for L86S-49

SEQ ID NO: 92 is the determined 5'cDNA sequence for L86S-51

SEQ ID NO: 93 is the predicted amino acid sequence for L86S-6

SEQ ID NO: 94 is the predicted amino acid sequence for L86S-11

SEQ ID NO: 95 is the predicted amino acid sequence for L86S-14

SEQ ID NO: 96 is the predicted amino acid sequence for L86S-29

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SEQ ID NO: 97 is the predicted amino acid sequence for L86S-34

SEQ ID NO: 98 is the predicted amino acid sequence for L86S-39

SEQ ID NO: 99 is the predicted amino acid sequence for L86S-47

SEQ ID NO: 100 is the predicted amino acid sequence for L86S-49

SEQ ID NO: 101 is the predicted amino acid sequence for L86S-51

SEQ ID NO: 102 is the determined DNA sequence for SLT-T1

SEQ ID NO: 103 is the determined 5' cDNA sequence for SLT-T2

SEQ ID NO: 104 is the determined 5' cDNA sequence for SLT-T3

SEQ ID NO: 105 is the determined 5' cDNA sequence for SLT-T5

SEQ ID NO: 106 is the determined 5' cDNA sequence for SLT-T7

SEQ ID NO: 107 is the determined 5' cDNA sequence for SLT-T9

SEQ ID NO: 108 is the determined 5' cDNA sequence for SLT-T10

SEQ ID NO: 109 is the determined 5' cDNA sequence for SLT-T11

SEQ ID NO: 110 is the determined 5' cDNA sequence for SLT-T12

SEQ ID NO: 111 is the predicted amino acid sequence for SLT-T1

SEQ ID NO: 112 is the predicted amino acid sequence for SLT-T2

SEQ ID NO: 113 is the predicted amino acid sequence for SLT-T3

SEQ ID NO: 114 is the predicted amino acid sequence for SLT-T10

SEQ ID NO: 115 is the predicted amino acid sequence for SLT-T12

SEQ ID NO: 116 is the determined 5' cDNA sequence for SALT-T3

SEQ ID NO: 117 is the determined 5' cDNA sequence for SALT-T4

SEQ ID NO: 118 is the determined 5' cDNA sequence for SALT-T7

SEQ ID NO: 119 is the determined 5' cDNA sequence for SALT-T8

SEQ ID NO: 120 is the determined 5' cDNA sequence for SALT-T9

SEQ ID NO: 121 is the predicted amino acid sequence for SALT-T3

SEQ ID NO: 122 is the predicted amino acid sequence for SALT-T4

SEQ ID NO: 123 is the predicted amino acid sequence for SALT-T7

SEQ ID NO: 124 is the predicted amino acid sequence for SALT-T8

SEQ ID NO: 125 is the predicted amino acid sequence for SALT-T9

SEQ ID NO: 126 is the determined cDNA sequence for PSLT-1

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SEQ ID NO: 127 is the determined cDNA sequence for PSLT-2

SEQ ID NO: 128 is the determined cDNA sequence for PSLT-7

SEQ ID NO: 129 is the determined cDNA sequence for PSLT-13

SEQ ID NO: 130 is the determined cDNA sequence for PSLT-27

SEQ ID NO: 131 is the determined cDNA sequence for PSLT-28

SEQ ID NO: 132 is the determined cDNA sequence for PSLT-30

SEQ ID NO: 133 is the determined cDNA sequence for PSLT-40

SEQ ID NO: 134 is the determined cDNA sequence for PSLT-69

SEQ ID NO: 135 is the determined cDNA sequence for PSLT-71

SEQ ID NO: 136 is the determined cDNA sequence for PSLT-73

SEQ ID NO: 137 is the determined cDNA sequence for PSLT-79

SEQ ID NO: 138 is the determined cDNA sequence for PSLT-03

SEQ ID NO: 139 is the determined cDNA sequence for PSLT-09

SEQ ID NO: 140 is the determined cDNA sequence for PSLT-011

SEQ ID NO: 141 is the determined cDNA sequence for PSLT-041

SEQ ID NO: 142 is the determined cDNA sequence for PSLT-62

SEQ ID NO: 143 is the determined cDNA sequence for PSLT-6

SEQ ID NO: 144 is the determined cDNA sequence for PSLT-37

SEQ ID NO: 145 is the determined cDNA sequence for PSLT-74

SEQ ID NO: 146 is the determined cDNA sequence for PSLT-010

SEQ ID NO: 147 is the determined cDNA sequence for PSLT-012

SEQ ID NO: 148 is the determined cDNA sequence for PSLT-037

SEQ ID NO: 149 is the determined 5' cDNA sequence for SAL-3

SEQ ID NO: 150 is the determined 5' cDNA sequence for SAL-24

SEQ ID NO: 151 is the determined 5' cDNA sequence for SAL-25

SEQ ID NO: 152 is the determined 5' cDNA sequence for SAL-33

SEQ ID NO: 153 is the determined 5' cDNA sequence for SAL-50

SEQ ID NO: 154 is the determined 5' cDNA sequence for SAL-57

SEQ ID NO: 155 is the determined 5' cDNA sequence for SAL-66

SEQ ID NO: 156 is the determined 5' cDNA sequence for SAL-82

SEQ ID NO: 157 is the determined 5' cDNA sequence for SAL-99

SEQ ID NO: 158 is the determined 5' cDNA sequence for SAL-104

SEQ ID NO: 159 is the determined 5' cDNA sequence for SAL-109

SEQ ID NO: 160 is the determined 5' cDNA sequence for SAL-5

SEQ ID NO: 161 is the determined 5' cDNA sequence for SAL-8

SEQ ID NO: 162 is the determined 5' cDNA sequence for SAL-12

SEQ ID NO: 163 is the determined 5' cDNA sequence for SAL-14

SEQ ID NO: 164 is the determined 5' cDNA sequence for SAL-16

SEQ ID NO: 165 is the determined 5' cDNA sequence for SAL-23

SEQ ID NO: 166 is the determined 5' cDNA sequence for SAL-26

SEQ ID NO: 167 is the determined 5' cDNA sequence for SAL-29

SEQ ID NO: 168 is the determined 5' cDNA sequence for SAL-32

SEQ ID NO: 169 is the determined 5' cDNA sequence for SAL-39

SEQ ID NO: 170 is the determined 5' cDNA sequence for SAL-42

SEQ ID NO: 171 is the determined 5' cDNA sequence for SAL-43

SEQ ID NO: 172 is the determined 5' cDNA sequence for SAL-44

SEQ ID NO: 173 is the determined 5' cDNA sequence for SAL-48

SEQ ID NO: 174 is the determined 5' cDNA sequence for SAL-68

SEQ ID NO: 175 is the determined 5' cDNA sequence for SAL-72

SEQ ID NO: 176 is the determined 5' cDNA sequence for SAL-77

SEQ ID NO: 177 is the determined 5' cDNA sequence for SAL-86

SEQ ID NO: 178 is the determined 5' cDNA sequence for SAL-88

SEQ ID NO: 179 is the determined 5' cDNA sequence for SAL-93

SEQ ID NO: 180 is the determined 5' cDNA sequence for SAL-100

SEQ ID NO: 181 is the determined 5' cDNA sequence for SAL-105

SEQ ID NO: 182 is the predicted amino acid sequence for SAL-3

SEQ ID NO: 183 is the predicted amino acid sequence for SAL-24

SEQ ID NO: 184 is a first predicted amino acid sequence for SAL-25

SEQ ID NO: 185 is a second predicted amino acid sequence for SAL-25

SEQ ID NO: 186 is the predicted amino acid sequence for SAL-33

SEQ ID NO: 187 is a first predicted amino acid sequence for SAL-50

SEQ ID NO: 188 is the predicted amino acid sequence for SAL-57

SEQ ID NO: 189 is a first predicted amino acid sequence for SAL-66

SEQ ID NO: 190 is a second predicted amino acid sequence for SAL-66

SEQ ID NO: 191 is the predicted amino acid sequence for SAL-82

SEQ ID NO: 192 is the predicted amino acid sequence for SAL-99

SEQ ID NO: 193 is the predicted amino acid sequence for SAL-104

SEQ ID NO: 194 is the predicted amino acid sequence for SAL-5

SEQ ID NO: 195 is the predicted amino acid sequence for SAL-8

SEQ ID NO: 196 is the predicted amino acid sequence for SAL-12

SEQ ID NO: 197 is the predicted amino acid sequence for SAL-14

SEQ ID NO: 198 is the predicted amino acid sequence for SAL-16

SEQ ID NO: 199 is the predicted amino acid sequence for SAL-23

SEQ ID NO: 200 is the predicted amino acid sequence for SAL-26

SEQ ID NO: 201 is the predicted amino acid sequence for SAL-29

SEQ ID NO: 202 is the predicted amino acid sequence for SAL-32

SEQ ID NO: 203 is the predicted amino acid sequence for SAL-39

SEQ ID NO: 204 is the predicted amino acid sequence for SAL-42

SEQ ID NO: 205 is the predicted amino acid sequence for SAL-43

SEQ ID NO: 206 is the predicted amino acid sequence for SAL-44

SEQ ID NO: 207 is the predicted amino acid sequence for SAL-48

SEQ ID NO: 208 is the predicted amino acid sequence for SAL-68

SEQ ID NO: 209 is the predicted amino acid sequence for SAL-72

SEQ ID NO: 210 is the predicted amino acid sequence for SAL-77

SEQ ID NO: 211 is the predicted amino acid sequence for SAL-86

SEQ ID NO: 212 is the predicted amino acid sequence for SAL-88

SEQ ID NO: 213 is the predicted amino acid sequence for SAL-93

SEQ ID NO: 214 is the predicted amino acid sequence for SAL-100

SEQ ID NO: 215 is the predicted amino acid sequence for SAL-105

SEQ ID NO: 216 is a second predicted amino acid sequence for SAL-50

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SEQ ID NO: 217 is the determined cDNA sequence for SSLT-4

SEQ ID NO: 218 is the determined cDNA sequence for SSLT-9

SEQ ID NO: 219 is the determined cDNA sequence for SSLT-10

SEQ ID NO: 220 is the determined cDNA sequence for SSLT-12

SEQ ID NO: 221 is the determined cDNA sequence for SSLT-19

SEQ ID NO: 222 is the determined cDNA sequence for SSLT-31

SEQ ID NO: 223 is the determined cDNA sequence for SSLT-38

SEQ ID NO: 224 is the determined cDNA sequence for LT4690-2

SEQ ID NO: 225 is the determined cDNA sequence for LT4690-3

SEQ ID NO: 226 is the determined cDNA sequence for LT4690-22

SEQ ID NO: 227 is the determined cDNA sequence for LT4690-24

SEQ ID NO: 228 is the determined cDNA sequence for LT4690-37

SEQ ID NO: 229 is the determined cDNA sequence for LT4690-39

SEQ ID NO: 230 is the determined cDNA sequence for LT4690-40

SEQ ID NO: 231 is the determined cDNA sequence for LT4690-41

SEQ ID NO: 232 is the determined cDNA sequence for LT4690-49

SEQ ID NO: 233 is the determined 3' cDNA sequence for LT4690-55

SEQ ID NO: 234 is the determined 5' cDNA sequence for LT4690-55

SEQ ID NO: 235 is the determined cDNA sequence for LT4690-59

SEQ ID NO: 236 is the determined cDNA sequence for LT4690-63

SEQ ID NO: 237 is the determined cDNA sequence for LT4690-71

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed compositions and methods for the therapy of lung cancer. The compositio described herein include polypeptides, fusion proteins and polynucleotides. Al included within the present invention are molecules (such as an antibody or fragm thereof) that bind to the inventive polypeptides. Such molecules are referred to her as "binding agents."

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In one embodiment, the inventive polypeptides comprise at least a portion of a protein that is expressed at a greater level in human lung tumor tissue than in normal lung tissue. Preferably, the level of RNA encoding the polypeptide is at least 2-fold higher in tumor tissue. Such polypeptides include, but are not limited to, polypeptides (and immunogenic portions thereof) encoded by the nucleotide sequences provided in SEQ ID NO: 1-16 and variants thereof.

In a second embodiment, the inventive polypeptides comprise at least a portion of a immunogenic lung tumor protein, including but not limited to polypeptides wherein the lung tumor protein includes an amino acid sequence encoded by a polynucleotide including a sequence selected from the group consisting of (a) nucleotide sequences recited in SEQ ID NO: 17-31, 49-55, 63,64, 66, 68-72, 78-80, 84-92 and 217-237, (b) the complements of said nucleotide sequences, and (c) variants of such sequences.

In a third embodiment, the inventive polypeptides comprise at least a portion of a lung tumor protein, including polypeptides wherein the lung tumor protein includes an amino acid sequence encoded by a polynucleotide including a sequence selected from the group consisting of (a) nucleotide sequences recited in SEQ ID NO: 102-110, 116-120 and 126-181, (b) the complements of said nucleotide sequences, and (c) variants of such sequences.

As used herein, the term "polypeptide" encompasses amino acid chains of any length, including full length proteins, wherein the amino acid residues are linked by covalent peptide bonds. Thus, a polypeptide comprising a portion of one of the above lung tumor proteins may consist entirely of the portion, or the portion may be present within a larger polypeptide that contains additional sequences. The additional sequences may be derived from the native protein or may be heterologous and such sequences may (but need not) be immunoreactive and/or antigenic. As detailed below, such polypeptides may be isolated from lung tumor tissue or prepared by synthetic or recombinant means.

As used herein, an "immunogenic portion" of a lung tumor protein is a portion that is capable of eliciting an immune response in a patient inflicted with lung

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cancer and as such binds to antibodies present within sera from a lung cancer patient Such immunogenic portions generally comprise at least about 5 amino acid residues. more preferably at least about 10, and most preferably at least about 20 amino acid residues. Immunogenic portions of the proteins described herein may be identified in antibody binding assays. Such assays may generally be performed using any of a variety of means known to those of ordinary skill in the art, as described, for example in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1988. For example, a polypeptide may be immobilized on a solid support (as described below) and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide Unbound sera may then be removed and bound antibodies detected using, for example, ^{125}I-labeled Protein A. Alternatively, a polypeptide may be used to generate monoclonal and polyclonal antibodies for use in detection of the polypeptide in blood or other fluids of lung cancer patients. Methods for preparing and identifying immunogenic portions of antigens of known sequence are well known in the art and include those summarized in Paul, *Fundamental Immunology*, 3rd ed., Raven Press 1993, pp. 243-247.

The term "polynucleotide(s)," as used herein, means a single or double stranded polymer of deoxyribonucleotide or ribonucleotide bases and includes DNA and corresponding RNA molecules, including HnRNA and mRNA molecules, both sense and anti-sense strands, and comprehends cDNA, genomic DNA and recombinant DNA, as well as wholly or partially synthesized polynucleotides. An HnRNA molecule contains introns and corresponds to a DNA molecule in a general one-to-one manner. An mRNA molecule corresponds to an HnRNA and DNA molecule from which the introns have been excised. A polynucleotide may consist an entire gene, or any portion thereof. Operable anti-sense polynucleotides may comprise a fragment of the corresponding polynucleotide, and the definition "polynucleotide" therefore includes all such operable anti-sense fragments.

The compositions and methods of the present invention also encompass variants of the above polypeptides and polynucleotides.

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A polypeptide "variant," as used herein, is a polypeptide that differs from the recited polypeptide only in conservative substitutions and/or modifications such that the antigenic properties of the polypeptide are retained. In a preferred embodiment, variant polypeptides differ from an identified sequence by substitution deletion or addition of five amino acids or fewer. Such variants may generally be identified by modifying one of the above polypeptide sequences, and evaluating the antigenic properties of the modified polypeptide using, for example, the representative procedures described herein. Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity (determined as described below) to the identified polypeptides.

As used herein, a "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. In general, the following groups of amino acids represent conservative changes: (1) ala, pro, gly glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys arg, his; and (5) phe, tyr, trp, his.

Variants may also, or alternatively, contain other modifications including the deletion or addition of amino acids that have minimal influence on the antigenic properties, secondary structure and hydropathic nature of the polypeptide. For example, a polypeptide may be conjugated to a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally direct transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (*e.g.*, poly-His), or to enhance binding of the polypeptide to a solid support. For example, polypeptide may be conjugated to an immunoglobulin Fc region.

A nucleotide "variant" is a sequence that differs from the recited nucleotide sequence in having one or more nucleotide deletions, substitutions additions. Such modifications may be readily introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis as taught, i

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example, by Adelman et al. (*DNA*. *2*:183, 1983). Nucleotide variants may be naturally occurring allelic variants, or non-naturally occurring variants. Variant nucleotide sequences preferably exhibit at least about 70%, more preferably at least about 80% and most preferably at least about 90% identity (determined as described below) to the recited sequence.

The lung tumor antigens provided by the present invention include variants that are encoded by DNA sequences which are substantially homologous to one or more of the DNA sequences specifically recited herein. "Substantial homology," as used herein, refers to DNA sequences that are capable of hybridizing under moderately stringent conditions. Suitable moderately stringent conditions include prewashing in a solution of 5X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0), hybridizing at 50°C-65°C, 5X SSC, overnight or, in the event of cross-specific homology, at 45°C with 0.5X SSC; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS. Such hybridizing DNA sequences are also within the scope of this invention, as are nucleotide sequences that, due to code degeneracy, encode an immunogenic polypeptide that is encoded by a hybridizing DNA sequence.

Two nucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acid residues in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M

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(1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-64: *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins D.G. and Sharp, P.M. (1989) Fast and sensitive multiple sequence alignments on a microcomputer *CABIOS 5*:151-153; Myers, E.W. and Muller W. (1988) Optima alignments in linear space *CABIOS 4*:11-17; Robinson, E.D. (1971) *Comb. Theo. 11*:105; Santou, N. Nes, M. (1987) The neighbor joining method. A new method fo reconstructing phylogenetic trees *Mol. Biol. Evol. 4*:406-425; Sneath, P.H.A. an Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numeric Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983 Rapid similarity searches of nucleic acid and protein data banks *Proc. Natl. Acad Sci. USA 80*:726-730.

Preferably, the "percentage of sequence identity" is determined b comparing two optimally aligned sequences over a window of comparison of at lea 20 positions, wherein the portion of the polynucleotide sequence in the compariso window may comprise additions or deletions (i.e. gaps) of 20 percent or less, usuall 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (whic does not comprise additions or deletions) for optimal alignment of the two sequence The percentage is calculated by determining the number of positions at which th identical nucleic acid bases or amino acid residue occurs in both sequences to yie the number of matched positions, dividing the number of matched positions by th total number of positions in the reference sequence (i.e. the window size) an multiplying the results by 100 to yield the percentage of sequence identity.

The lung tumor polypeptides of the present invention, an polynucleotides encoding such polypeptides, may be isolated from lung tumor tiss using any of a variety of methods well known in the art. For example, cDN molecules encoding polypeptides preferentially expressed in lung tumor tissue m be cloned on the basis of the lung tumor-specific expression of the correspondi

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mRNAs, using differential display PCR. This technique compares the amplified products from RNA templates prepared from normal lung and lung tumor tissue cDNA may be prepared by reverse transcription of RNA using a $(dT)_{12}AG$ primer Following amplification of the cDNA using a random primer, a band correspondin to an amplified product specific to the tumor RNA may be cut out from a silve stained gel and subcloned into a suitable vector. Examples of cDNA sequences tha may be isolated using this procedure include those provided in SEQ ID NO: 1-16.

cDNA molecules encoding immunogenic lung tumor polypeptide may be prepared by screening a cDNA expression library prepared from a lung tumo sample with sera from the same patient as the tumor sample, as described in detail i Example 2 below. Examples of cDNA sequences that may be isolated using thi procedure include those provided in SEQ ID NO: 17-31. Additional cDN molecules encoding lung tumor polypeptides may be obtained by screening such cDNA expression library with mouse anti-lung tumor serum as described below i Example 3. Examples of cDNA sequences that may thus be isolated are provided i SEQ ID NO: 49-55, 63, 64 and 126-148. cDNA sequences encoding lung tum antigens may also be isolated by screening of lung tumor cDNA libraries prepare from SCID mice with mouse anti-tumor sera, as described below in Example - Examples of cDNA sequences that may be isolated using this technique are provide in SEQ ID NO: 149-181 and 217-237.

A gene encoding a polypeptide described herein (or a portion thereo may, alternatively, be amplified from human genomic DNA, or from lung tum cDNA, via polymerase chain reaction. For this approach, sequence-specific prime may be designed based on the nucleotide sequences provided herein and may b purchased or synthesized. An amplified portion of a specific nucleotide sequence m then be used to isolate the full length gene from a human genomic DNA library from a lung tumor cDNA library, using well known techniques, such as tho described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spri Harbor Laboratories, Cold Spring Harbor, NY (1989).

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Once a DNA sequence encoding a polypeptide is obtained, the polypeptide may be produced recombinantly by inserting the DNA sequence into an expression vector and expressing the polypeptide in an appropriate host. Any of a variety of expression vectors known to those of ordinary skill in the art may be employed to express recombinant polypeptides of this invention. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a polynucleotide that encodes the recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO cells. The DNA sequences expressed in this manner may encode naturally occurring polypeptides, portions of naturally occurring polypeptides or other variants thereof. Supernatants from suitable host/vector systems which secrete the recombinant polypeptide may be first concentrated using a commercially available filter. The concentrate may then be applied to a suitable purification matrix such as an affinity matrix or ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify the recombinant polypeptide.

Such techniques may also be used to prepare polypeptides comprising portions or variants of the native polypeptides. Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids may be generated using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method where amino acids are sequentially added to a growing amino acid chain (see, for example, Merrifield, *J. Am. Chem. Soc.* *85*:2149-2146, 1963). Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

In general, regardless of the method of preparation, the polypeptides disclosed herein are prepared in an isolated, substantially pure form (*i.e.*, the polypeptides are homogenous as determined by amino acid composition and prima

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sequence analysis). Preferably, the polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. In certain preferred embodiments, described in more detail below, the substantially pure polypeptides are incorporated into pharmaceutical compositions or vaccines for use in one or more of the methods disclosed herein.

In a related aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, a polypeptide of the present invention and a known lung tumor antigen, together with variants of such fusion proteins. The fusion proteins of the present invention may (but need not include a linker peptide between the first and second polypeptides.

A DNA sequence encoding a fusion protein of the present invention is constructed using known recombinant DNA techniques to assemble separate DNA sequences encoding the first and second polypeptides into an appropriate expression vector. The 3' end of a DNA sequence encoding the first polypeptide is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide so that the reading frames of the sequences are in phase to permit mRNA translation of the two DNA sequences into a single fusion protein that retains the biological activity of both the first and the second polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptides by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene 40*:39–4

1985; Murphy et al., *Proc. Natl. Acad. Sci. USA 83*:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may be from 1 to about 50 amino acids in length. Peptide sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons require to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. *New Engl. J. Med.*, *336*:86-91 (1997)).

Polypeptides that comprise an immunogenic portion of a lung tumor protein may generally be used for therapy of lung cancer, wherein the polypeptide stimulates the patient's own immune response to lung tumor cells. The present invention thus provides methods for using one or more of the compounds described herein (which may be polypeptides, polynucleotides or fusion proteins) for immunotherapy of lung cancer in a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may be afflicted with disease or may be free of detectable disease. Accordingly, the compounds disclosed herein may be used to treat lung cancer or to inhibit the development of lung cancer. In a preferred embodiment, the compounds are administered either prior to or following surgical removal of primary tumors and/or treatment by administration radiotherapy and conventional chemotherapeutic drugs.

In these aspects, the inventive polypeptide is generally present within a pharmaceutical composition or a vaccine. Pharmaceutical compositions may

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comprise one or more polypeptides, each of which may contain one or more of the above sequences (or variants thereof), and a physiologically acceptable carrier. The vaccines may comprise one or more such polypeptides and an immune response enhancer, such as an adjuvant, biodegradable microsphere (*e.g.*, polylactic galactide or a liposome (into which the polypeptide is incorporated). Pharmaceutical compositions and vaccines may also contain other epitopes of lung tumor antigens either incorporated into a fusion protein as described above (*i.e.*, a single polypeptide that contains multiple epitopes) or present within a separate polypeptide.

Alternatively, a pharmaceutical composition or vaccine may contain DNA encoding one or more of the above polypeptides and/or fusion proteins, such that the polypeptide is generated *in situ*. In such pharmaceutical compositions and vaccines, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an epitope of a lung cell antigen on its cell surface. In a preferred embodiment, the DNA may be introduced using a viral expression system (*e.g.*, vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., *PNAS 86*:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci. 569*:86-103, 1989; Flexner et al., *Vaccine 8*:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,48 WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,24 WO 91/02805; Berkner, *Biotechniques 6*:616-627, 1988; Rosenfeld et al., *Scien 252*:431-434, 1991; Kolls et al., *PNAS 91*:215-219, 1994; Kass-Eisler et al., *PN 90*:11498-11502, 1993; Guzman et al., *Circulation 88*:2838-2848, 1993; and Guzm et al., *Cir. Res. 73*:1202-1207, 1993. Techniques for incorporating DNA into su expression systems are well known to those of ordinary skill in the art. The DN may also be "naked," as described, for example, in published PCT applicati

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WO 90/11092, and Ulmer et al., *Science 259*:1745-1749, 1993, reviewed by Cohen. *Science 259*:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

Routes and frequency of administration, as well as dosage, will vary from individual to individual and may parallel those currently being used in immunotherapy of other diseases. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g.*, intracutaneous, intramuscular intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Between and 10 doses may be administered over a 3-24 week period. Preferably, 4 doses are administered, at an interval of 3 months, and booster administrations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of polypeptide or DNA that is effective to raise an immune response (cellular and/or humoral) against lung tumor cells in treated patient. A suitable immune response is at least 10-50% above the basal (*i.e.* untreated) level. In general, the amount of polypeptide present in a dose (or produced *in situ* by the DNA in a dose) ranges from about 1 pg to about 100 mg per kg of host typically from about 10 pg to about 1 mg, and preferably from about 100 pg to about 1 μg. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.01 mL to about 5 mL.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a lipid, a wax and/or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and/or magnesium carbonate, may be employed. Biodegradable microspheres (*e.g.*, polylactic glycolic may also be employed as carriers for the pharmaceutical compositions of th

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invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Any of a variety of immune response enhancers may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism such as aluminum hydroxide or mineral oil, and a nonspecific stimulator of immune response, such as lipid A, *Bordella pertussis* or *Mycobacterium tuberculosis*. Such adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI), and Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ).

Within certain embodiments, polynucleotides of the present invention may be formulated so as to permit entry into a cell of a mammal, preferably a human and expression therein. Such formulations are particularly useful for therapeutic purposes. Those of skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cells, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (e.g. avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of skill in the art. A retroviral vector may additionally transfer or incorporate a targeting moiety, such as a gene that encodes for a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also be accomplished using an antibody, by methods know to those of ordinary skill in the art.

Polypeptides disclosed herein may also be employed in adoptive immunotherapy for the treatment of cancer. Adoptive immunotherapy may be broadly classified into either active or passive immunotherapy. In active immunotherapy, treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (for example, tumor vaccines, bacterial adjuvants, and cytokines).

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In passive immunotherapy, treatment involves the delivery of biologic reagents with established tumor-immune reactivity (such as effector cells o antibodies) that can directly or indirectly mediate antitumor effects and does no necessarily depend on an intact host immune system. Examples of effector cell include T lymphocytes (for example, CD8+ cytotoxic T-lymphocyte, CD4+ T-helper tumor-infiltrating lymphocytes), killer cells (Natural Killer cells, lymphokine-activated killer cells), B cells, or antigen presenting cells (such as dendritic cells an macrophages) expressing the disclosed antigens. The polypeptides disclosed herei may also be used to generate antibodies or anti-idiotypic antibodies (as in U.S. Paten No. 4,918,164), for passive immunotherapy.

The predominant method of procuring adequate numbers of T-cells fo adoptive immunotherapy is to grow immune T-cells *in vitro*. Culture conditions fo expanding single antigen-specific T-cells to several billion in number with retentio of antigen recognition *in vivo* are well known in the art. These *in vitro* cultur conditions typically utilize intermittent stimulation with antigen, often in th presence of cytokines, such as IL-2, and non-dividing feeder cells. As noted abov the immunoreactive polypeptides described herein may be used to rapidly expar antigen-specific T cell cultures in order to generate sufficient number of cells f immunotherapy. In particular, antigen-presenting cells, such as dendriti macrophage or B-cells, may be pulsed with immunoreactive polypeptides transfected with a polynucleotide sequence(s), using standard techniques well know in the art. For cultured T-cells to be effective in therapy, the cultured T-cells must able to grow and distribute widely and to survive long term *in vivo*. Studies ha demonstrated that cultured T-cells can be induced to grow *in vivo* and to survive lo term in substantial numbers by repeated stimulation with antigen supplemented w IL-2 (see, for example, Cheever et al. *Ibid*).

The polypeptides disclosed herein may also be employed to gener and/or isolate tumor-reactive T-cells, which can then be administered to the patie In one technique, antigen-specific T-cell lines may be generated by *in v* immunization with short peptides corresponding to immunogenic portions of

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disclosed polypeptides. The resulting antigen specific CD8+ CTL clones may be isolated from the patient, expanded using standard tissue culture techniques, and returned to the patient.

Alternatively, peptides corresponding to immunogenic portions of the polypeptides may be employed to generate tumor reactive T cell subsets by selective *in vitro* stimulation and expansion of autologous T cells to provide antigen-specific T cells which may be subsequently transferred to the patient as described, for example by Chang et al. *(Crit. Rev. Oncol. Hematol., 22*(3), 213, 1996).

In another embodiment, syngeneic or autologous dendritic cells may be pulsed with peptides corresponding to at least an immunogenic portion of a polypeptide disclosed herein. The resulting antigen-specific dendritic cells may either be transferred into a patient, or employed to stimulate T cells to provide antigen-specific T cells which may, in turn, be administered to a patient. The use of peptide-pulsed dendritic cells to generate antigen-specific T cells and the subsequent use of such antigen-specific T cells to eradicate tumors in a murine model has been demonstrated by Cheever et al. ("Therapy With Cultured T Cells: Principle Revisited," *Immunological Reviews, 157*:177, 1997).

Additionally vectors expressing the disclosed polynucleotides may be introduced into stem cells taken from the patient and clonally propagated *in vitro* for autologous transplant back into the same patient.

In one embodiment, cells of the immune system, such as T cells, may be isolated from the peripheral blood of a patient, using a commercially available cell separation system, such as CellPro Incorporated's (Bothell, WA) CEPRATE™ system (see U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/0628 WO 91/16116 and WO 92/07243). The separated cells are stimulated with one or more of the immunoreactive polypeptides contained within a delivery vehicle, such as a microsphere, to provide antigen-specific T cells. The population of tumor antigen specific T cells is then expanded using standard techniques and the cells are administered back to the patient.

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Polypeptides and fusion proteins of the present invention may also be used to generate binding agents, such as antibodies or fragments thereof, that are capable of detecting metastatic human lung tumors. Binding agents of the present invention may generally be prepared using methods known to those of ordinary skil. in the art, including the representative procedures described herein. Binding agents are capable of differentiating between patients with and without lung cancer, using the representative assays described herein. In other words, antibodies or othe binding agents raised against a lung tumor protein, or a suitable portion thereof, wil generate a signal indicating the presence of primary or metastatic lung cancer in a least about 20% of patients afflicted with the disease, and will generate a negativ signal indicating the absence of the disease in at least about 90% of individual without primary or metastatic lung cancer. Suitable portions of such lung tumo proteins are portions that are able to generate a binding agent that indicates th presence of primary or metastatic lung cancer in substantially all (*i.e.*, at least abou 80%, and preferably at least about 90%) of the patients for which lung cancer woul be indicated using the full length protein, and that indicate the absence of lung canc in substantially all of those samples that would be negative when tested with fu length protein. The representative assays described below, such as the two-antibo sandwich assay, may generally be employed for evaluating the ability of a bindir agent to detect metastatic human lung tumors.

The ability of a polypeptide prepared as described herein to genera antibodies capable of detecting primary or metastatic human lung tumors m generally be evaluated by raising one or more antibodies against the polypepti (using, for example, a representative method described herein) and determining t ability of such antibodies to detect such tumors in patients. This determination m be made by assaying biological samples from patients with and without primary metastatic lung cancer for the presence of a polypeptide that binds to the genera antibodies. Such test assays may be performed, for example, using a representati procedure described below. Polypeptides that generate antibodies capable detecting at least 20% of primary or metastatic lung tumors by such procedures

considered to be useful in assays for detecting primary or metastatic human lung tumors. Polypeptide specific antibodies may be used alone or in combination to improve sensitivity.

Polypeptides capable of detecting primary or metastatic human lung tumors may be used as markers for diagnosing lung cancer or for monitoring disease progression in patients. In one embodiment, lung cancer in a patient may be diagnosed by evaluating a biological sample obtained from the patient for the level of one or more of the above polypeptides, relative to a predetermined cut-off value. As used herein, suitable "biological samples" include blood, sera, urine and/or lung secretions.

The level of one or more of the above polypeptides may be evaluated using any binding agent specific for the polypeptide(s). A "binding agent," in the context of this invention, is any agent (such as a compound or a cell) that binds to polypeptide as described above. As used herein, "binding" refers to a noncovalent association between two separate molecules (each of which may be free (*i.e.*, in solution) or present on the surface of a cell or a solid support), such that a "complex" is formed. Such a complex may be free or immobilized (either covalently or noncovalently) on a support material. The ability to bind may generally be evaluated by determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind" in the context of the present invention when the binding constant for complex formation exceeds about 10^3 L/mol. The binding constant may be determined using methods well known to those of ordinary skill in the art.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome with or without a peptide component, an RNA molecule or a peptide. In a preferred embodiment, the binding partner is an antibody, or a fragment thereof. Such antibodies may be polyclonal, monoclonal. In addition, the antibodies may be single chain, chimeric, CDR-graf

or humanized. Antibodies may be prepared by the methods described herein and by other methods well known to those of skill in the art.

There are a variety of assay formats known to those of ordinary skill in the art for using a binding partner to detect polypeptide markers in a sample. *See. e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In a preferred embodiment, the assay involves the use of binding partner immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a second binding partner that contains a reporter group. Suitable second binding partners include antibodies that bind to the binding partner/polypeptide complex. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding partner after incubation of the binding partner with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding partner are indicative of the reactivity of the sample with the immobilized binding partner.

The solid support may be any material known to those of ordinary skill in the art to which the antigen may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the antigen and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount

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time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 μg, and preferably about 100 ng to about 1 μg, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see, e.g.,* Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a second antibody (containing a reporter group) capable of binding to a different site on the polypeptide is added. The amount of second antibody that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is that period of time that is sufficient to detect

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presence of polypeptide within a sample obtained from an individual with lung cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of abou 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid suppor with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The secon antibody, which contains a reporter group, may then be added to the solid support Preferred reporter groups include enzymes (such as horseradish peroxidase substrates, cofactors, inhibitors, dyes, radionuclides, luminescent groups, fluorescer groups and biotin. The conjugation of antibody to reporter group may be achieve using standard methods known to those of ordinary skill in the art.

The second antibody is then incubated with the immobilized antibody polypeptide complex for an amount of time sufficient to detect the boun polypeptide. An appropriate amount of time may generally be determined b assaying the level of binding that occurs over a period of time. Unbound secor antibody is then removed and bound second antibody is detected using the report group. The method employed for detecting the reporter group depends upon th nature of the reporter group. For radioactive groups, scintillation counting autoradiographic methods are generally appropriate. Spectroscopic methods may used to detect dyes, luminescent groups and fluorescent groups. Biotin may detected using avidin, coupled to a different reporter group (commonly a radioacti or fluorescent group or an enzyme). Enzyme reporter groups may generally detected by the addition of substrate (generally for a specific period of tim followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of lung cancer, the sig detected from the reporter group that remains bound to the solid support is genera compared to a signal that corresponds to a predetermined cut-off value. In c

preferred embodiment, the cut-off value is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without lung cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for lung cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for lung cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the antibody is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized antibody as the sample passes through the membrane. A second, labeled antibody then binds to the antibody-polypeptide complex as a solution containing the second antibody flows through the membrane. The detection of bound second antibody may then be performed as described above. In the strip test format, one end of the membrane to which antibody is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second antibody and to the area of immobilized antibody. Concentration of second antibody at the area of immobilized antibody indicates the presence of lung cancer. Typically, the concentration of second antibody at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negati

result. In general, the amount of antibody immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1 µg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the antigens or antibodies of the present invention. The above description are intended to be exemplary only.

In another embodiment, the above polypeptides may be used as markers for the progression of lung cancer. In this embodiment, assays as described above for the diagnosis of lung cancer may be performed over time, and the change in the level of reactive polypeptide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, lung cancer is progressing in those patients whom the level of polypeptide detected by the binding agent increases over time. In contrast, lung cancer is not progressing when the level of reactive polypeptide either remains constant or decreases with time.

Antibodies for use in the above methods may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In one such technique, an immunogen comprising the antigenic polypeptide is initially injected into any of a wide variety of mammals (*e.g.*, mice, rats, rabbits, sheep and goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and

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animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for the antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Monoclonal antibodies of the present invention may also be used as therapeutic reagents, to diminish or eliminate lung tumors. The antibodies may be used on their own (for instance, to inhibit metastases) or coupled to one or more

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therapeutic agents. Suitable agents in this regard include radionuclides. differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ^{90}Y, ^{123}I, ^{125}I, ^{131}I, ^{186}Re, ^{188}Re, ^{211}At, and ^{212}Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group such as an amino or sulfhydryl group, on one may be capable of reacting with carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amine groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use

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linker group which is cleavable during or upon internalization into a cell. A numbe of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, t Kohn et al.), by serum complement-mediated hydrolysis (*e.g.*, U.S. Paten No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (*e.g.*, U.S. Paten No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. I one embodiment, multiple molecules of an agent are coupled to one antibod molecule. In another embodiment, more than one type of agent may be coupled t one antibody. Regardless of the particular embodiment, immunoconjugates wit more than one agent may be prepared in a variety of ways. For example, more tha one agent may be coupled directly to an antibody molecule, or linkers which provid multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covale bonding either directly or via a linker group. Suitable carriers include proteins suc as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato et al.), peptides ar polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih et al A carrier may also bear an agent by noncovalent bonding or by encapsulation, such within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carrie specific for radionuclide agents include radiohalogenated small molecules a chelating compounds. For example, U.S. Patent No. 4,735,792 disclos representative radiohalogenated small molecules and their synthesis. A radionucli chelate may be formed from chelating compounds that include those containi nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxi radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. disclo representative chelating compounds and their synthesis.

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A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

Diagnostic reagents of the present invention may also comprise DNA sequences encoding one or more of the above polypeptides, or one or more portions thereof. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify lung tumor-specific cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for a polynucleotide encoding a lung tumor protein of the present invention. The presence of the amplified cDNA is then detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes specific for a polynucleotide encoding a lung tumor protein of the present invention may be used in a hybridization assay to detect the presence of an inventive polypeptide in a biological sample.

As used herein, the term "oligonucleotide primer/probe specific for a polynucleotide" means an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to the polynucleotide in question. Oligonucleotide primers and/or probes which may be usefully employed in the inventive diagnostic methods preferably have at least about 10-40 nucleotides. In a preferred embodiment, the oligonucleotide primers comprise at least about 10 contiguous nucleotides of a polynucleotide having a partial sequence selected from SEQ ID NO: 1-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120, 126-181 and 217-237. Preferably, oligonucleotide probes for use in the inventive diagnostic methods comprise at least about 15 contiguous oligonucleotides of a polynucleotide having a partial sequence provided in SEQ ID NO: 1-31, 49-55, 63, 64, 66, 68-72, 78-80, 84-92, 102-110, 116-120, 126-181 and 217-237. Techniques for both PCR based assays and hybridization assays are well known

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the art (see, for example, Mullis *et al. Ibid*; Ehrlich, *Ibid*). Primers or probes may thus be used to detect lung tumor-specific sequences in biological samples, including blood, semen, lung tissue and/or lung tumor tissue.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1

PREPARATION OF LUNG TUMOR-SPECIFIC cDNA SEQUENCES USING DIFFERENTIAL DISPLAY RT-PCR

This example illustrates the preparation of cDNA molecules encodin lung tumor-specific polypeptides using a differential display screen.

Tissue samples were prepared from breast tumor and normal tissue a patient with lung cancer that was confirmed by pathology after removal of sampl from the patient. Normal RNA and tumor RNA was extracted from the samples ar mRNA was isolated and converted into cDNA using a $(dT)_{12}AG$ (SEQ ID NO: 4 anchored 3' primer. Differential display PCR was then executed using a random chosen primer (SEQ ID NO: 48). Amplification conditions were standard buff containing 1.5 mM $MgCl_2$, 20 pmol of primer, 500 pmol dNTP and 1 unit of T: DNA polymerase (Perkin-Elmer, Branchburg, NJ). Forty cycles of amplificati were performed using 94 °C denaturation for 30 seconds, 42 °C annealing for minute and 72 °C extension for 30 seconds. Bands that were repeatedly observed be specific to the RNA fingerprint pattern of the tumor were cut out of a silver stain gel, subcloned into the pGEM-T vector (Promega, Madison, WI) and sequenced. T isolated 3' sequences are provided in SEQ ID NO: 1-16.

Comparison of these sequences to those in the public databases usi the BLASTN program, revealed no significant homologies to the sequences provic in SEQ ID NO: 1-11. To the best of the inventors' knowledge, none of the isola

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DNA sequences have previously been shown to be expressed at a greater level in human lung tumor tissue than in normal lung tissue.

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Example 2

USE OF PATIENT SERA TO IDENTIFY DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

This example illustrates the isolation of cDNA sequences encodin lung tumor antigens by expression screening of lung tumor samples with autologou patient sera.

A human lung tumor directional cDNA expression library wa constructed employing the Lambda ZAP Express expression system (Stratagene, L. Jolla, CA). Total RNA for the library was taken from a late SCID mouse passage human squamous epithelial lung carcinoma and poly A+ RNA was isolated using th Message Maker kit (Gibco BRL, Gaithersburg, MD). The resulting library wa screened using *E. coli*-absorbed autologous patient serum, as described in Sambroo et al., (*Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratorie Cold Spring Harbor, NY, 1989), with the secondary antibody being goat anti-huma IgG-A-M (H + L) conjugated with alkaline phosphatase, developed with NBT/BCI (Gibco BRL). Positive plaques expressing immunoreactive antigens were purifie. Phagemid from the plaques was rescued and the nucleotide sequences of the clon was determined.

Fifteen clones were isolated, referred to hereinafter as LT86-1 – LT8 15. The isolated cDNA sequences for LT86-1 – LT86-8 and LT86-10 - LT86-15 a provided in SEQ ID NO: 17-24 and 26-31, respectively, with the correspondi predicted amino acid sequences being provided in SEQ ID NO: 32-39 and 41– respectively. The determined cDNA sequence for LT86-9 is provided in SEQ NO: 25, with the corresponding predicted amino acid sequences from the 3' and ends being provided in SEQ ID NO: 40 and 65, respectively. These sequences w compared to those in the gene bank as described above. Clones LT86-3, LT86-(LT86-9, LT86-11 – LT86-13 and LT86-15 (SEQ ID NO: 19, 22-25, 27-29 and respectively) were found to show some homology to previously identified expres sequence tags (ESTs), with clones LT86-6, LT86-8, LT86-11, LT86-12 and LT86-

appearing to be similar or identical to each other. Clone LT86-3 was found to show some homology with a human transcription repressor. Clones LT86-6, 8, 9, 11, 12 and 15 were found to show some homology to a yeast RNA Pol II transcriptior regulation mediator. Clone LT86-13 was found to show some homology with a *C elegans* leucine aminopeptidase. Clone LT86-9 appears to contain two inserts, with the 5' sequence showing homology to the previously identified antisense sequence o interferon alpha-induced P27, and the 3' sequence being similar to LT86-6. Clon LT86-14 (SEQ ID NO: 30) was found to show some homology to the trithorax gen and has an "RGD" cell attachment sequence and a beta-Lactamase A site whicl functions in hydrolysis of penicillin. Clones LT86-1, LT86-2, LT86-4, LT86-5 an LT86-10 (SEQ ID NOS: 17, 18, 20, 21 and 26, respectively) were found to sho homology to previously identified genes. A subsequently determined extende cDNA sequence for LT86-4 is provided in SEQ ID NO: 66, with the correspondin predicted amino acid sequence being provided in SEQ ID NO: 67.

Subsequent studies led to the isolation of five additional clone referred to as LT86-20, LT86-21, LT86-22, LT86-26 and LT86-27. The determine 5' cDNA sequences for LT86-20, LT86-22, LT86-26 and LT86-27 are provided SEQ ID NO: 68 and 70-72, respectively, with the determined 3' cDNA sequences f LT86-21 being provided in SEQ ID NO: 69. The corresponding predicted ami acid sequences for LT86-20, LT86-21, LT86-22, LT86-26 and LT86-27 are provid in SEQ ID NO: 73-77, respectively. LT86-22 and LT86-27 were found to be high similar to each other. Comparison of these sequences to those in the gene bank described above, revealed no significant homologies to LT86-22 and LT86-2 LT86-20, LT86-21 and LT86-26 were found to show homology to previous identified genes.

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Example 3

USE OF MOUSE ANTISERA TO IDENTIFY DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by screening of lung tumor cDNA libraries with mouse anti-tumor sera.

A directional cDNA lung tumor expression library was prepared as described above in Example 2. Sera was obtained from SCID mice containing late passaged human squamous cell and adenocarcinoma tumors. These sera were pooled and injected into normal mice to produce anti-lung tumor serum. Approximately 200,000 PFUs were screened from the unamplified library using this antiserum. Using a goat anti-mouse IgG-A-M (H+L) alkaline phosphatase second antibody developed with NBT/BCIP (BRL Labs.), approximately 40 positive plaques were identified. Phage was purified and phagemid excised for 9 clones with inserts in pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined cDNA sequences for 7 of the isolated clones (hereinafter referred to as L86S-3, L86S-12, L86S-16, L86S-25, L86S-36, L86S-4 and L86S-46) are provided in SEQ ID NO: 49-55, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 56-62, respectively. The cDNA sequences for the remaining 2 clones (hereinafter referred to as L86S-30 and L86S-41) are provided in SEQ ID NO: 63 and 64. L86S-36 and L86S-46 were subsequently determined to represent the same gene. Comparison of these sequences with those in the public database as described above, revealed no significant homologies to clones L86S-30, L86S-36 and L86S-46 (SEQ ID NO: 63, 53 and 5 respectively). L86S-16 (SEQ ID NO: 51) was found to show some homology to EST previously identified in fetal lung and germ cell tumor. The remaining clones were found to show at least some degree of homology to previously identified human genes. Subsequently determined extended cDNA sequences for L86S-12, L86S- and L86S-46 are provided in SEQ ID NO: 78-80, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 81-8

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Subsequent studies led to the determination of 5' cDNA sequences for an additional nine clones, referred to as L86S-6, L86S-11, L86S-14, L86S-29, L86S-34, L86S-39, L86S-47, L86S-49 and L86S-51 (SEQ ID NO: 84-92, respectively) The corresponding predicted amino acid sequences are provided in SEQ ID NO: 93-101, respectively. L86S-30, L86S-39 and L86S-47 were found to be similar to each other. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to L86S-14. L86S-29 was found to show some homology to a previously identified EST. L86S-6, L86S-11, L86S-34, L86S-39, L86S-47, L86S-49 and L86S-51 were found to show some homology to previously identified genes.

In further studies, a directional cDNA library was constructed using Stratagene kit with a Lambda Zap Express vector. Total RNA for the library was isolated from two primary squamous lung tumors and poly A+ RNA was isolated using an oligo dT column. Antiserum was developed in normal mice using a pool of sera from three SCID mice implanted with human squamous lung carcinoma Approximately 700,000 PFUs were screened from the unamplified library with *E. coli* absorbed mouse anti-SCID tumor serum. Positive plaques were identified as described above. Phage was purified and phagemid excised for 180 clones with inserts in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined cDNA sequences for 23 of the isolated clones are provided in SEQ ID NO: 126-148. Comparison of these sequences with those in the public database as described above revealed no significant homologies to the sequences of SEQ ID NO: 139 and 143-148. The sequences of SEQ ID NO: 126-138 and 140-142 were found to show homology previously identified human polynucleotide sequences.

Example 4

USE OF MOUSE ANTISERA TO SCREEN LUNG TUMOR LIBRARIES PREPARED FROM SCID MICE

This example illustrates the isolation of cDNA sequences encodin lung tumor antigens by screening of lung tumor cDNA libraries prepared from SCII mice with mouse anti-tumor sera.

A directional cDNA lung tumor expression library was prepared usin a Stratagene kit with a Lambda Zap Express vector. Total RNA for the library wa taken from a late passaged lung adenocarcinoma grown in SCID mice. Poly A+ RN was isolated using a Message Maker Kit (Gibco BRL). Sera was obtained from tw SCID mice implanted with lung adenocarcinomas. These sera were pooled an injected into normal mice to produce anti-lung tumor serum. Approximately 700,00 PFUs were screened from the unamplified library with *E. coli*-absorbed mouse ant SCID tumor serum. Positive plaques were identified with a goat anti-mouse IgG-A M (H+L) alkaline phosphatase second antibody developed with NBT/BCIP (Gibc BRL). Phage was purified and phagemid excised for 100 clones with insert in pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined 5' cDNA sequences for 33 of the isolated clones a provided in SEQ ID NO: 149-181. The corresponding predicted amino ac sequences for SEQ ID NO: 149, 150, 152-154, 156-158 and 160-181 are provided SEQ ID NO: 182, 183, 186, 188-193 and 194-215, respectively. The clone of SE ID NO: 151 (referred to as SAL-25) was found to contain two open reading fram (ORFs). The predicted amino acid sequences encoded by these ORFs are provided SEQ ID NO: 184 and 185. The clone of SEQ ID NO: 153 (referred to as SAL-5 was found to contain two open reading frames encoding the predicted amino ac sequences of SEQ ID NO: 187 and 216. Similarly, the clone of SEQ ID NO: 1 (referred to as SAL-66) was found to contain two open reading frames encoding t predicted amino acid sequences of SEQ ID NO: 189 and 190. Comparison of t isolated sequences with those in the public database revealed no signific

homologies to the sequences of SEQ ID NO: 151, 153 and 154. The sequences of SEQ ID NO: 149, 152, 156, 157 and 158 were found to show some homology to previously isolated expressed sequence tags (ESTs). The sequences of SEQ ID NO: 150, 155 and 159-181 were found to show homology to sequences previously identified in humans.

Using the procedures described above, two directional cDNA libraries were prepared from two late passaged lung squamous carcinomas grown in SCID mice and screened with sera obtained from SCID mice implanted with human squamous lung carcinomas. The determined cDNA sequences for the isolated clones are provided in SEQ ID NO: 217-237. Comparison of these sequences with those in the public databases revealed no known homologies to the sequences of SEQ ID NO 219, 220, 225 and 226. The sequences of SEQ ID NO: 218, 221, 222 and 224 were found to show some homology to previously identified sequences of unknown function. The sequence of SEQ ID NO: 236 was found to show homology to known mouse mRNA sequence. The sequences of SEQ ID NO: 217, 223 and 227-237 showed some homology to known human DNA and/or RNA sequences.

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Example 5

DETERMINATION OF TISSUE SPECIFICITY OF LUNG TUMOR POLYPEPTIDES

Using gene specific primers, mRNA expression levels fc representative lung tumor polypeptides were examined in a variety of normal an tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumc tissues using Trizol reagent. First strand synthesis was carried out using 2 μg of tot RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42 °C fc one hour. The cDNA was then amplified by PCR with gene-specific primers. T ensure the semi-quantitative nature of the RT-PCR, β-actin was used as an intern control for each of the tissues examined. 1 μl of 1:30 dilution of cDNA w employed to enable the linear range amplification of the β-actin template and w sensitive enough to reflect the differences in the initial copy numbers. Using the conditions, the β-actin levels were determined for each reverse transcription reactic from each tissue. DNA contamination was minimized by DNase treatment and b assuring a negative PCR result when using first strand cDNA that was prepare without adding reverse transcriptase.

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mRNA Expression levels were examined in five different types o tumor tissue (lung squamous tumor from 3 patients, lung adenocarcinoma, prostat tumor colon tumor and breast tumor), and different normal tissues, including lun from four patients, prostate, brain, kidney, liver, ovary, skeletal muscle, skin, smal intestine, myocardium, retina and testes. L86S-46 was found to be expressed at hig levels in lung squamous tumor, colon tumor and prostate tumor, and was undetectabl in the other tissues examined. L86S-5 was found to be expressed in the lung tumc samples and in 2 out of 4 normal lung samples, but not in the other normal or tumc tissues tested. L86S-16 was found to be expressed in all tissues except normal liv and normal stomach. Using real-time PCR, L86S-46 was found to be over-expresse in lung squamous tissue and normal tonsil, with expression being low or undetectabl in all other tissues examined.

Example 6

ISOLATION OF DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

DNA sequences encoding antigens potentially involved in squamou cell lung tumor formation were isolated as follows.

A lung tumor directional cDNA expression library was constructe employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA Total RNA for the library was taken from a pool of two human squamous epitheli lung carcinomas and poly A+ RNA was isolated using oligo-dT cellulose (Gibc BRL, Gaithersburg, MD). Phagemid were rescued at random and the cDN sequences of isolated clones were determined.

The determined cDNA sequence for the clone SLT-T1 is provided i SEQ ID NO: 102, with the determined 5' cDNA sequences for the clones SLT-T SLT-T3, SLT-T5, SLT-T7, SLT-T9, SLT-T10, SLT-T11 and SLT-T12 beir provided in SEQ ID NO: 103-110, respectively. The corresponding predicted amir acid sequence for SLT-T1, SLT-T2, SLT-T3, SLT-T10 and SLT-T12 are provided SEQ ID NO: 111-115, respectively. Comparison of the sequences for SLT-T2, SL T3, SLT-T5, SLT-T7, SLT-T9 and SLT-T11 with those in the public databases described above, revealed no significant homologies. The sequences for SLT-T and SLT-T12 were found to show some homology to sequences previously identifi in humans.

The sequence of SLT-T1 was determined to show some homology tc PAC clone of unknown protein function. The cDNA sequence of SLT-T1 (SEQ I NO: 102) was found to contain a mutator (MUTT) domain. Such domains are kno to function in removal of damaged guanine from DNA that can cause A to transversions (see, for example, el-Deiry, W.S., 1997 *Curr. Opin. Oncol. 9*:79-8 Okamoto, K. et al. 1996 *Int. J. Cancer 65*:437-41; Wu, C. et al. 1995 *Bioche Biophys. Res. Commun. 214*:1239-45; Porter, D.W. et al. 1996 *Chem. Res. Toxic 9*:1375-81). SLT-T1 may thus be of use in the treatment, by gene therapy, of lu cancers caused by, or associated with, a disruption in DNA repair.

In further studies, DNA sequences encoding antigens potentially involved in adenocarcinoma lung tumor formation were isolated as follows. A human lung tumor-directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a late SCID mouse passaged human adenocarcinoma and poly A+ RNA was isolated using the Message Maker kit (Gibco BRL Gaithersburg, MD). Phagemid were rescued at random and the cDNA sequences of isolated clones were determined.

The determined 5' cDNA sequences for five isolated clones (referred to as SALT-T3, SALT-T4, SALT-T7, SALT-T8, and SALT-T9) are provided in SEQ ID NO: 116-120, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 121-125. SALT-T3 was found to show 98% identity to the previously identified human transducin-like enhancer protein TLE2. SALT-T4 appears to be the human homologue of the mouse H beta 58 gene. SALT-T7 was found to have 97% identity to human 3-mercaptopyruvate sulfurtransferase and SALT-T8 was found to show homology to human interferon-inducible protein 1-8U. SALT-T9 shows approximately 90% identity to human mucin MUC 5B.

Example 7

SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applie Biosystems Division 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide t provide a method of conjugation, binding to an immobilized surface, or labeling o the peptide. Cleavage of the peptides from the solid support may be carried out usin the following cleavage mixture: trifluoroaceti acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hour the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellet may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) an lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used t elute the peptides. Following lyophilization of the pure fractions, the peptides may b characterized using electrospray or other types of mass spectrometry and by amin acid analysis.

Example 8

ISOLATION AND CHARACTERIZATION OF DNA SEQUENCES ENCODIN LUNG TUMOR ANTIGENS BY T-CELL EXPRESSION CLONING

Lung tumor antigens may also be identified by T cell expressi cloning. One source of tumor specific T cells is from surgically excised tumors fr human patients.

A non-small cell lung carcinoma was minced and enzymatica digested for several hours to release tumor cells and infiltrating lymphocytes (tum infiltrating T cells, or TILs). The cells were washed in HBSS buffer and passed o a Ficoll (100%/75%/HBSS) discontinuous gradient to separate tumor cells a

lymphocytes from non-viable cells. Two bands were harvested from the interfaces the upper band at the 75%/HBSS interface contained predominantly tumor cells while the lower band at the 100%/75%/HBSS interface contained a majority o lymphocytes. The TILs were expanded in culture, either in 24-well plates witl culture media supplemented with 10 ng/ml IL-7 and 100 U/ml IL-2, or alternatively 24-well plates that have been pre-coated with the anti-CD3 monoclonal antibod OKT3. The resulting TIL cultures were analyzed by FACS to confirm that a hig percentage were CD8+ T cells (>90% of gated population) with only a sma percentage of CD4+ cells.

In addition, non-small cell lung carcinoma cells were expanded i culture using standard techniques to establish a tumor cell line, which was lat confirmed to be a lung carcinoma cell line by immunohistochemical analysis. Th tumor cell line was transduced with a retroviral vector to express human CD80, an characterized by FACS analysis to confirm high expression levels of CD80, an class I and II MHC molecules.

The specificity of the TIL lines to lung tumor was confirmed by INF- and/or TNF-α cytokine release assays. TIL cells from day 21 cultures were c cultured with either autologous or allogeneic tumor cells, EBV-immortalized LCL, control cell lines Daudi and K562, and the culture supernatant monitored by ELIS for the presence of cytokines. The TIL specifically recognized autologous tumor b not allogeneic tumor. In addition, there was no recognition of EBV-immortaliz LCL or the control cell lines, indicating that the TIL lines are tumor specific and a potentially recognizing a tumor antigen presented by autologous MHC molecules.

The characterized tumor-specific TIL lines were expanded to suitab numbers for T cell expression cloning using soluble anti-CD3 antibody in cultu with irradiated EBV transformed LCLs and PBL feeder cells in the presence of U/ml IL-2. Clones from the expanded TIL lines were generated by standard limiti dilution techniques. Specifically, TIL cells were seeded at 0.5 cells/well in a 96-w U bottom plate and stimulated with CD-80-transduced autologous tumor cells, EB transformed LCL, and PBL feeder cells in the presence of 50 U/ml IL-2. The

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clones were further analyzed for tumor specificity by ^{51}Cr microcytotoxicity and IFN γ bioassays. The MHC restriction element recognized by the TIL clones may b determined by antibody blocking studies.

CTL lines or clones prepared as described above may be employed t identify tumor specific antigens. For example, autologous fibroblasts or LCL from patient may be transfected or transduced with polynucleotide fragments derived fron a lung tumor cDNA library to generate target cells expressing tumor polypeptide The target cells expressing tumor polypeptides in the context of MHC will b recognized by the CTL line or clone, resulting in T-cell activation which can b monitored by cytokine detection assays. The tumor gene being expressed by th target cell and recognized by the tumor-specific CTL may then be isolated.

From the foregoing, it will be appreciated that, although specifi embodiments of the invention have been described herein for the purposes illustration, various modifications may be made without deviating from the spirit an scope of the invention.

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CLAIMS:

1. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO: 218-222 and 224-226;

(b) the complements of sequences provided in SEQ ID NO: 218 222 and 224-226; and

(c) variants of the sequences of (a) and (b).

2. An isolated polypeptide comprising an immunogenic portion of a lung tumor protein or a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide of claim 1.

3. An expression vector comprising the polynucleotide of claim 1

4. A host cell transformed with the expression vector of claim 3.

5. The host cell of claim 4 wherein the host cell is selected from the group consisting of *E. coli*, yeast and mammalian cell lines.

6. A pharmaceutical composition comprising the polypeptide of claim 2 and a physiologically acceptable carrier.

7. A vaccine comprising the polypeptide of claim 2 and an immune response enhancer.

8. The vaccine of claim 7 wherein the immune response enhancer is an adjuvant.

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9. A vaccine comprising the polynucleotide of claim 1 and an immune response enhancer.

10. The vaccine of claim 9 wherein the immune response enhancer is an adjuvant.

11. A pharmaceutical composition for the treatment of lung cancer comprising a polypeptide and a physiologically acceptable carrier, the polypeptide comprising an immunogenic portion of a lung protein or of a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 217, 223 and 227-237;

(b) sequences complementary to the sequences of SEQ ID NO: 217, 223 and 227-237; and

(c) variants of the sequences of (a) and (b).

12. A vaccine for the treatment of lung cancer comprising a polypeptide and an immune response enhancer, said polypeptide comprising a immunogenic portion of a lung protein or of a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 217, 223 and 227-237;

(b) sequences complementary to the sequences of SEQ ID NO: 217, 223 and 227-237; and

(c) variants of the sequences of (a) and (b).

13. A vaccine for the treatment of lung cancer comprising a polynucleotide and an immune response enhancer, the polynucleotide comprising a sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 217, 223 and 227-237;

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(b) sequences complementary to the sequences of SEQ ID NO: 217, 223 and 227-237; and

(c) variants of the sequences of (a) and (b).

14. A method for inhibiting the development of lung cancer in a patient, comprising administering to the patient an effective amount of the pharmaceutical composition of claims 6 or 11.

15. A method for inhibiting the development of lung cancer in a patient, comprising administering to the patient an effective amount of the vaccine of any one of claims 7, 9, 12 or 13.

16. A fusion protein comprising at least one polypeptide according to claim 2.

17. A fusion protein comprising at least two polypeptide according to claim 2.

18. A fusion protein comprising a polypeptide according to claim and a known lung tumor antigen.

19. A pharmaceutical composition comprising a fusion protein according to any one of claims 16-18 and a physiologically acceptable carrier.

20. A vaccine comprising a fusion protein according to any one claims 16-18 and an immune response enhancer.

21. The vaccine of claim 20 wherein the immune response enhancer is an adjuvant.

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22. A method for inhibiting the development of lung cancer in a patient, comprising administering to the patient an effective amount of the pharmaceutical composition of claim 19.

23. A method for inhibiting the development of lung cancer in a patient, comprising administering to the patient an effective amount of the vaccine of claim 20.

24. A method for detecting lung cancer in a patient, comprising:

(a) contacting a biological sample obtained from the patient with a binding agent which is capable of binding to a polypeptide, the polypeptide comprising an immunogenic portion of a lung tumor protein or a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a nucleotide sequence selected from the group consisting of sequences provided in SEQ ID NO: 217-237, the complements of said sequences and variants thereof; and

(b) detecting in the sample a polypeptide that binds to the binding agent, thereby detecting lung cancer in the patient.

25. The method of claim 24 wherein the binding agent is a monoclonal antibody.

26. The method of claim 25 wherein the binding agent is a polyclonal antibody.

27. A method for monitoring the progression of lung cancer in a patient, comprising:

(a) contacting a biological sample obtained from the patient with a binding agent that is capable of binding to a polypeptide, said polypeptide comprising an immunogenic portion of a lung tumor protein or a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising

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nucleotide sequence selected from the group consisting of sequences recited in SEQ ID NO: 217-237, the complements of said sequences and variants thereof;

(b) determining in the sample an amount of a polypeptide tha binds to the binding agent;

(c) repeating steps (a) and (b); and

(d) comparing the amount of polypeptide detected in steps (b) an (c) to monitor the progression of lung cancer in the patient.

28. A monoclonal antibody that binds to a polypeptide comprisin an immunogenic portion of a lung tumor protein or a variant thereof, wherein sai protein comprises an amino acid sequence encoded by a polynucleotide comprising nucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 218-222 and 224-226;

(b) the complements of nucleotide sequences recited in SEQ I NO: 218-222 and 224-226; and

(c) variants of the sequences of (a) and (b).

29. A method for inhibiting the development of lung cancer in patient, comprising administering to the patient a therapeutically effective amount a monoclonal antibody according to claim 28.

30. The method of claim 29 wherein the monoclonal antibody conjugated to a therapeutic agent.

31. A method for detecting lung cancer in a patient comprising:

(a) obtaining a biological sample from the patient;

(b) contacting the sample with at least two oligonucleotide prim in a polymerase chain reaction, wherein at least one of the oligonucleotides is speci for a polynucleotide encoding a polypeptide comprising an immunogenic portion o lung tumor protein or a variant thereof, said protein comprising an amino a sequence encoded by a polynucleotide comprising a nucleotide sequence selec

from the group consisting of sequences recited in SEQ ID NO: 217-237, the complements of said sequences and variants thereof; and

(c) detecting in the sample a DNA sequence that amplifies in the presence of the oligonucleotide primers, thereby detecting lung cancer.

32. The method of claim 31, wherein at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide comprising a sequence selected from SEQ ID NO: 217-237.

33. A diagnostic kit comprising:

(a) one or more monoclonal antibodies according to claim 28; and

(b) a detection reagent.

34. The kit of claim 33 wherein the monoclonal antibody is immobilized on a solid support.

35. The kit of claim 34 wherein the solid support comprises nitrocellulose, latex or a plastic material.

36. The kit of claim 33 wherein the detection reagent comprises a reporter group conjugated to a binding agent.

37. The kit of claim 36 wherein the binding agent is selected from the group consisting of anti-immunoglobulins, Protein G, Protein A and lectins.

38. The kit of claim 36 wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.

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39. A diagnostic kit comprising at least two oligonucleotide primers, at least one of the oligonucleotide primers being specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a lung tumor protein or a variant thereof, said protein comprising an amino acid sequence encoded by a polynucleotide comprising a nucleotide sequence selected from the group consisting of sequences recited in SEQ ID NO: 217-237, the complements of said sequences and variants thereof.

40. The diagnostic kit of claim 39 wherein at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide having a nucleotide sequence selected from the group consisting of sequences provided in SEQ ID NO: 217-237, the complements of said sequences and variants thereof.

41. A method for detecting lung cancer in a patient, comprising:

(a) obtaining a biological sample from the patient;

(b) contacting the biological sample with an oligonucleotide probe specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a lung tumor protein or a variant thereof, said protein comprising an amino acid sequence encoded by a polynucleotide comprising a nucleotide sequence selected from the group consisting of sequences recited in SEQ ID NO: 217-237, the complements of said nucleotide sequences and variants thereof; and

(c) detecting in the sample a DNA sequence that hybridizes to the oligonucleotide probe, thereby detecting lung cancer in the patient.

42. The method of claim 41 wherein the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide having a nucleotide sequence selected from the group consisting of sequences recited in SEQ ID NO: 217-237, the complements of said nucleotide sequences and variants thereof

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43. A diagnostic kit comprising an oligonucleotide probe specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a lung tumor protein or a variant thereof, said protein comprising an amino acid sequence encoded by a polynucleotide comprising a nucleotide sequence selected from the group consisting of sequences recited in SEQ ID NO: 217-237, the complements of said sequences and variants thereof.

44. The diagnostic kit of claim 43, wherein the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide having a nucleotide sequence selected from the group consisting of sequences recited in SEQ ID NO: 217-237, the complements of said sequences and variants thereof.

45. A method for treating lung cancer in a patient, comprising the steps of:

(a) obtaining peripheral blood cells from the patient;

(b) incubating the cells in the presence of at least one polypeptide of claim 2, such that T cells proliferate; and

(c) administering the proliferated T cells to the patient.

46. A method for treating lung cancer in a patient, comprising the steps of:

(a) obtaining peripheral blood cells from the patient;

(b) incubating the cells in the presence of at least one polynucleotide of claim 1, such that T cells proliferate; and

(c) administering to the patient the proliferated T cells.

47. The method of any one of claims 45 and 46 wherein the step incubating the T cells is repeated one or more times.

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48. The method of any one of claims 45 and 46 wherein step (a) further comprises separating T cells from the peripheral blood cells, and the cells incubated in step (b) are the T cells.

49. The method of any one of claims 45 and 46 wherein step (a further comprises separating CD4+ cells or CD8+ cells from the peripheral bloo cells, and the cells proliferated in step (b) are CD4+ or CD8+ T cells.

50. The method of any one of claims 45 and 46 wherein step (b further comprises cloning one or more T cells that proliferated in the presence of th polypeptide.

51. A composition for the treatment of lung cancer in a patien comprising T cells proliferated in the presence of a polypeptide of claim 2, i combination with a pharmaceutically acceptable carrier.

52. A composition for the treatment of lung cancer in a patier comprising T cells proliferated in the presence of a polynucleotide of claim 1, combination with a pharmaceutically acceptable carrier.

53. A method for treating lung cancer in a patient, comprising t steps of:

(a) incubating antigen presenting cells in the presence of at le one polypeptide of claim 2; and

(b) administering to the patient the incubated antigen presenti cells.

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54. A method for treating lung cancer in a patient, comprising the steps of:

(a) incubating antigen presenting cells in the presence of at least one polynucleotide of claim 1; and

(b) administering to the patient the incubated antigen presenting cells.

55. The method of claims 53 or 54 wherein the antigen presenting cells are selected from the group consisting of dendritic cells and macrophage cells.

56. A composition for the treatment of lung cancer in a patient comprising antigen presenting cells incubated in the presence of a polypeptide of claim 2, in combination with a pharmaceutically acceptable carrier.

57. A composition for the treatment of lung cancer in a patient comprising antigen presenting cells incubated in the presence of a polynucleotide of claim 1, in combination with a pharmaceutically acceptable carrier.

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COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE

ABSTRACT OF THE DISCLOSURE

Compounds and methods for treating lung cancer are provided. Th inventive compounds include polypeptides containing at least a portion of a lun tumor protein. Vaccines and pharmaceutical compositions for immunotherapy o lung cancer comprising such polypeptides, or polynucleotides encoding suc polypeptides, are also provided, together with polynucleotides for preparing th inventive polypeptides.

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<110> Reed, Steven G.
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Mohamath, Roadoh

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<210> 8

69
329
336

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<211> 280
<212> DNA
<213> Homo sapien

<220>
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<222> (1)...(280)
<223> n = A,T,C or G

<400> 8
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<210> 9
<211> 449
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(449)
<223> n = A,T,C or G

<400> 9
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<210> 10
<211> 538
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(538)
<223> n = A,T,C or G

<400> 10
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<210> 11
<211> 543
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(543)
<223> n = A,T,C or G

<400> 11
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aaa 57

<210> 12
<211> 329
<212> DNA
<213> Homo sapien

<400> 12
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tgatgttcaa ggcaagttgc aagtcatcg 3

<210> 13
<211> 314
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(314)
<223> n = A,T,C or G

<400> 13
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3
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338

<210> 14
<211> 691
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(691)
<223> n = A,T,C or G

<400> 14
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<210> 15
<211> 355
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(355)
<223> n = A,T,C or G

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<210> 16
<211> 522
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(522)
<223> n = A,T,C or G

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<210> 17
<211> 317
<212> DNA
<213> Homo sapien

<400> 17
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<210> 18
<211> 392
<212> DNA
<213> Homo sapien

<400> 18
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<210> 19
<211> 2624
<212> DNA
<213> Homo sapien

<400> 19
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340

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<210> 20
<211> 488
<212> DNA
<213> Homo sapien

<400> 20
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<210> 21
<211> 391
<212> DNA
<213> Homo sapien

<400> 21
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<210> 22
<211> 1320
<212> DNA
<213> Homo sapien

<400> 22
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<210> 23
<211> 633
<212> DNA
<213> Homo sapien

<400> 23
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<210> 24
<211> 1328

342

<212> DNA
<213> Homo sapien

<400> 24

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<210> 25
<211> 1758
<212> DNA
<213> Homo sapien

<400> 25

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attggtggca cttcaaagat catgaagagc aagataaagt cagacctaaa gccaaaagga
aagaagaacc aagctctatt tttcagagac aacgtgtgga tgctttactt ttagacctca
gacaaaaatt tccacccaaa tttgtgcagc taaagcctgg agaaaagcct gttccagtgg 1
atcaaacaaa gaaagaggca gaacctatac cagaaactgt aaaacctgag gagaaggaga 1
ccacaaagaa tgtacaacag acagtgagtg ctaaaggccc ccctgaaaaa cggatgagac 1
ttcagtgagt actggacaaa agagaagcct ggaagactcc tcatgctagt tatcatacct 1
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gcgcttattt tttgaaagga tattaggccg gatgtggtgg ctcacgcctg taatcccagc 132
actttgggag gccatggcgg gtggatcact tgaggtcaga agttcaagac cagcctgacc 138
aatatggtga aaccccgtct ctactaaaaa tacaaaaatt agccgggcgt ggtggcgggc 144
gcccatagtc ccagctactc gggaggctga gacaggagac ttgcttgaac ccgggaggtg 150
gaggttgccc tgagctgatt atcatgctgt tgcactccag cttgggcgac agagcgagac 156
tttgtctcaa aaaagaagaa aagatattat tcccatcatg atttcttgtg aatatttgtt 162
atatgtcttc tgttaccttt cctctcccgg aattgagcaa cctacacact cacatgttta 168
ctggtagata tgtttaaaag caaataaagg tattggtata tattgcttca aaaaaaaaaa 174
aaaaaaaaaa aactcgag 175

<210> 26
<211> 493
<212> DNA
<213> Homo sapien

<400> 26
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acacgtcgag ccccgcacag gcaagggtcc ggaacttagc ccaaagcacg tttcccctgg 18
cagcgcagga gacgcccggc cgcgccgcgg cgcacgcccc cctctcctcc tttgttccgg 24
gggtcggcgg ccgctctcct gccagcgtcg ggatctcggc ccgcgggagc gggccgtcgg 30
gcgcagccgc gaagattccg ttggaactga cgcagagccg agtgcagaag atctgggtgc 36
ccgtggacca caggccctcg ttgcccagat cctgtgggcc aaagctgacc aactcccccg 42
ccgtcttcgt catggtgggc ctccccccgcc cggggcaaga cctacttctc cacgaaagct 48
tactcgctgc ctc 493

<210> 27
<211> 1331
<212> DNA
<213> Homo sapien

<400> 27
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tttgaacagt ggtagtgtcc tggattactt ttcagaaaga agtaatcctt tttatgacag 1
aacatgtaat aatgaagtgg tcaaaatgca gaggctaaca ttagaacact tgaatcagat 1
ggttggaatc gagtacatcc ttttgcatgc tcaagagccc attcttttca tcattcggaa 2
gcaacagcgg cagtcccctg cccaagttat cccactagct gattactata tcattgctgg 3
agtgatctat caggcaccag acttgggatc agttataaac tctagagtgc ttactgcagt 3
gcatggtatt cagtcagctt ttgatgaagc tatgtcatac tgtcgatatc atccttccaa 4
agggtattgg tggcacttca aagatcatga agagcaagat aaagtcagac ctaaagccaa 4
aaggaaagaa gaaccaagct ctatttttca gagacaacgt gtggatgctt tacttttaga 5
cctcagacaa aaatttccac ccaaatttgt gcagctaaag cctggagaaa agcctgttcc 6
agtggatcaa acaaagaaag aggcagaacc tataccagaa actgtaaaac ctgaggagaa 6
ggagaccaca aagaatgtac aacagacagt gagtgctaaa ggccccccctg aaaaacggat
gagacttcag tgagtactgg acaaaagaga agcctggaag actcctcatg ctagttatca
tacctcagta ctgtggctct tgagctttga agtactttat tgtaacctte ttatttgtat 8
ggaatgcgct tatttttga aaggatatta ggccggatgt ggtggctcac gcctgtaatc
ccagcacttt gggaggccat ggcgggtgga tcacttgagg tcagaagttc aagaccagcc
tgaccaatat ggtgaaaccc cgtctctact aaaaatacaa aaattagccg ggcgtggtgg 1
cgggcgccca tagtcccagc tactcgggag gctgagacag gagacttgct tgaacccggg 1
aggtggaggt tgccctgagc tgattatcat gctgttgcac tccagcttgg gcgacagagc 1
gagactttgt ctcaaaaaaa gaagaaaaga tattattccc atcatgattt cttgtgaata 1
tttgttatat gtcttctgta acctttcctc tcccggactt gagcaacctа cacactcaca 1
tgtttactgg tagatatgtt taaaagcaaa ataaaggtat tggtataaaa aaaaaaaaaa 1
aaaaactcga g 1

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<210> 28
<211> 1333
<212> DNA
<213> Homo sapien

<400> 28
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ctattttgaa cagtggtagt gtcctggatt acttttcaga aagaagtaat ccttttatg 12
acagaacatg taataatgaa gtggtcaaaa tgcagaggct aacattagaa cacttgaatc 18
agatggttgg aatcgagtac atcctttgc atgctcaaga gcccattctt ttcatcattc 24
ggaagcaaca gcggcagtcc cctgcccaag ttatcccact agctgattac tatatcattg 3C
ctggagtgat ctatcaggca ccagacttgg gatcagttat aaactctaga gtgcttactg 3E
cagtgcatgg tattcagtca gcttttgatg aagctatgtc atactgtcga tatcatcctt 4E
ccaaagggta ttggtggcac ttcaaagatc atgaagagca agataaagtc agacctaaag 4E
ccaaaaggaa agaagaacca agctctattt ttcagagaca acgtgtggat gctttacttt 5E
tagacctcag acaaaaattt ccacccaaat ttgtgcagct aaagcctgga gaaaagcctg 6C
ttccagtgga tcaaacaaag aaagaggcag aacctatacc agaaactgta aaacctgagg 6E
agaaggagac cacaaagaat gtacaacaga cagtgagtgc taaaggcccc cctgaaaaac 7E
ggatgagact tcagtgagta ctggacaaaa gagaagcctg gaagactcct catgctagtt 7E
atcatacctc agtactgtgg ctcttgagct ttgaagtact ttattgtaac cttcttattt 8E
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gtggcgggcg cccatagtcc cagctactcg ggaggctgag acaggagact tgcttgaacc 10
cgggaggtgg aggttgcgct gagctgatta tcatgctgtt gcactccagc ttgggcgaca 11
gagcgagact ttgtctcaaa aaagaagaaa agatattatt cccatcatga tttcttgtga 12
atatttgtga tatgtcttct gtaacctttc ctctcccgga cttgagcaac ctacacactc 12
acatgtttac tggtagatat gtttaaaagc aaaataaagg tatttgtata aaaaaaaaaa 13
aaaaaaactc gag 13

<210> 29
<211> 813
<212> DNA
<213> Homo sapien

<400> 29
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actggcccgg ggtctgggtc cacctggaca tcgctgctcc agtgcatgct ggcgagcgag :
ccacaggctt tggggtggct ctcctactgg ctcttttttgg ccgtgcctcc gaggacccgc :
tgctgaacct ggtatccccg ctggactgtg aggtggatgc ccaggaaggc gacaacatgg :
ggcgtgactc caagagacgg aggctcgtgt gagggctact tcccagctgg tgacacaggg
ttccttacct cattttgcac tgactgattt taagcaattg aaagattaac taactcttaa .
gatgagtttg gcttctcctt ctgtgcccag tggtgacagg agtgagccat tctttctctta .
gaagcagctt aggggcttgg tggggtctgg agaaaattgt cacagacccc ataggtctcc
atctgtaagc tctgtccctt gtcctccacc ctggtctttа gagccacctc aggtcaccct .
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taaccagccc tgggtagatg tgactggctg ttagggaccc cattctgtga agcaggagac
cctcacagct cccaccaacc cccagttcac ttgaagttga attaaatatg gccacaacat
aaaaaaaaaa aaaaaaaaaa aaaaaaactc gag

<210> 30
<211> 1316
<212> DNA

345

<213> Homo sapien

<400> 30

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gtggagtcaa atatactttt caccatcagg aaatatagtt gctcatgaaa actgtttgct 180
gtattcatca ggactggtgg agtgtgagac tcttgatcta cgtaatacaa ttagaaactt 240
tgatgtcaaa tctgtaaaga aagagatctg gagaggaaga agattgaaat gctcattctg 300
taacaaagga ggcgccaccg tggggtgtga tttatggttc tgtaagaaga gttaccacta 360
tgtctgtgcc aaaaaggacc aagcaattct tcaagttgat ggaaaccatg gaacttacaa 420
attattttgc ccagaacatt ctccagaaca agaagaggcc actgaaagtg ctgatgaccc 480
aagcatgaag aagaagagag gaaaaaacaa acgcctctca tcaggccctc ctgcacagcc 540
aaaaacgatg aaatgtagta acgccaaaag acatatgaca gaagagcctc atggtcacac 600
agatgcagct gtcaaatctc cttttcttaa gaaatgccag gaagcaggac ttcttactga 660
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tgcctcagag tcggactatg aagggatcga gaccttactg tttgactgtg gattatttaa 780
agacacacta agaaaattcc aagaagtaat caagagtaaa gcttgtgaat gggaagaaag 840
gcaaaggcag atgaagcagc agcttgaggc acttgcagac ttacaacaaa gcttgtgctc 900
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actgtgcatt gcacactgtt accatgggtt tatgctcact atcatatcac attgccaata 1260
tttagcacac ttaataaatg cttgtcaaaa cccaaaaaaa aaaaaaaaaa ctcgag 1315

<210> 31
<211> 1355
<212> DNA
<213> Homo sapien

<400> 31

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acagaacatg taataatgaa gtggtcaaaa tgcagaggct aacattagaa cacttgaatc 1
agatggttgg aatcgagtac atcctttgc atgctcaaga gcccattctt ttcatcattc 2
ggaagcaaca gcggcagtcc cctgcccaag ttatcccact agctgattac tatatcattg 3
ctggagtgat ctatcaggca ccagacttgg gatcagttat aaactctaga gtgcttactg 3
cagtgcatgg tattcagtca gcttttgatg aagctatgtc atactgtcga tatcatcctt 4
ccaaagggta ttggtggcac ttcaaagatc atgaagagca agataaagtc agacctaaag 4
ccaaaaggaa agaagaacca agctctattt ttcagagaca acgtgtggat gctttacttt 5
tagacctcag acaaaaattt ccacccaaat ttgtgcagct aaagcctgga gaaaagcctg 6
ttccagtgga tcaaacaaag aaagaggcag aacctatacc agaaactgta aaacctgagg 6
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ggatgagact tcagtgagta ctggacaaaa gagaagcctg gaagactcct catgctagtt
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gaacgagact ttgtctcaaa aaaagaagaa aagatattat tcccatcatg atttcttgtg 1
aatatttgtt atatgtcttc tggtaacctt tcctctcccg gacttgaagc aacctcacac 1
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaac tcgag 1

346

<210> 32
<211> 80
<212> PRT
<213> Homo sapien

<400> 32
Val Ser Arg Ile Arg Gly Gly Ala Lys Lys Arg Lys Lys Lys Ser Tyr
1 5 10 15
Thr Thr Pro Lys Lys Asp Lys His Gln Arg Lys Lys Val Gln Pro Ala
20 25 30
Val Leu Lys Tyr Tyr Lys Val Asp Glu Asn Gly Lys Ile Ser Cys Leu
35 40 45
Arg Arg Glu Cys Pro Ser Asp Glu Cys Gly Ala Gly Val Phe Met Ala
50 55 60
Ser His Phe Asp Arg His Tyr Cys Gly Lys Cys Cys Leu Thr His Cys
65 70 75 80

<210> 33
<211> 130
<212> PRT
<213> Homo sapien

<400> 33
Glu Ile Ser Asn Glu Val Arg Lys Phe Arg Thr Leu Thr Glu Leu Ile
1 5 10 15
Leu Asp Ala Gln Glu His Val Lys Asn Pro Tyr Lys Gly Lys Lys Leu
20 25 30
Lys Lys His Pro Asp Phe Pro Lys Lys Pro Leu Thr Pro Tyr Phe Arg
35 40 45
Phe Phe Met Glu Lys Arg Ala Lys Tyr Ala Lys Leu His Pro Gln Met
50 55 60
Ser Asn Leu Asp Leu Thr Lys Ile Leu Ser Lys Lys Tyr Lys Glu Leu
65 70 75 80
Pro Glu Lys Lys Lys Met Lys Tyr Val Pro Asp Phe Gln Arg Arg Glu
85 90 95
Thr Gly Val Arg Ala Lys Pro Gly Pro Ile Gln Gly Gly Ser Pro Pro
100 105 110
Pro Tyr Pro Glu Cys Gln Glu Ser Asp Ile Pro Glu Lys Pro Gln Asp
115 120 125
Pro Pro
130

<210> 34
<211> 506
<212> PRT
<213> Homo sapien

<400> 34
Asn Ser Glu Lys Glu Ile Pro Val Leu Asn Glu Leu Pro Val Pro Met
1 5 10 15
Val Ala Arg Tyr Ile Arg Ile Asn Pro Gln Ser Trp Phe Asp Asn Gly
20 25 30
Ser Ile Cys Met Arg Met Glu Ile Leu Gly Cys Pro Leu Pro Asp Pro
35 40 45

347

Asn Asn Tyr Tyr His Arg Arg Asn Glu Met Thr Thr Thr Asp Asp Leu
50 55 60
Asp Phe Lys His His Asn Tyr Lys Glu Met Arg Gln Leu Met Lys Val
65 70 75 80
Val Asn Glu Met Cys Pro Asn Ile Thr Arg Ile Tyr Asn Ile Gly Lys
85 90 95
Ser His Gln Gly Leu Lys Leu Tyr Ala Val Glu Ile Ser Asp His Pro
100 105 110
Gly Glu His Glu Val Gly Glu Pro Glu Phe His Tyr Ile Ala Gly Ala
115 120 125
His Gly Asn Glu Val Leu Gly Arg Glu Leu Leu Leu Leu Leu Leu His
130 135 140
Phe Leu Cys Gln Glu Tyr Ser Ala Gln Asn Ala Arg Ile Val Arg Leu
145 150 155 160
Val Glu Glu Thr Arg Ile His Ile Leu Pro Ser Leu Asn Pro Asp Gly
165 170 175
Tyr Glu Lys Ala Tyr Glu Gly Gly Ser Glu Leu Gly Gly Trp Ser Leu
180 185 190
Gly Arg Trp Thr His Asp Gly Ile Asp Ile Asn Asn Asn Phe Pro Asp
195 200 205
Leu Asn Ser Leu Leu Trp Glu Ala Glu Asp Gln Gln Asn Ala Pro Arg
210 215 220
Lys Val Pro Asn His Tyr Ile Ala Ile Pro Glu Trp Phe Leu Ser Glu
225 230 235 240
Asn Ala Thr Val Ala Thr Glu Thr Arg Ala Val Ile Ala Trp Met Glu
245 250 255
Lys Ile Pro Phe Val Leu Gly Gly Asn Leu Gln Gly Gly Glu Leu Val
260 265 270
Val Ala Tyr Pro Tyr Asp Met Val Arg Ser Leu Trp Lys Thr Gln Glu
275 280 285
His Thr Pro Thr Pro Asp Asp His Val Phe Arg Trp Leu Ala Tyr Ser
290 295 300
Tyr Ala Ser Thr His Arg Leu Met Thr Asp Ala Arg Arg Arg Val Cys
305 310 315 320
His Thr Glu Asp Phe Gln Lys Glu Glu Gly Thr Val Asn Gly Ala Ser
325 330 335
Trp His Thr Val Ala Gly Ser Leu Asn Asp Phe Ser Tyr Leu His Thr
340 345 350
Asn Cys Phe Glu Leu Ser Ile Tyr Val Gly Cys Asp Lys Tyr Pro His
355 360 365
Glu Ser Glu Leu Pro Glu Glu Trp Glu Asn Asn Arg Glu Ser Leu Ile
370 375 380
Val Phe Met Glu Gln Val His Arg Gly Ile Lys Gly Ile Val Arg Asp
385 390 395 400
Leu Gln Gly Lys Gly Ile Ser Asn Ala Val Ile Ser Val Glu Gly Val
405 410 415
Asn His Asp Ile Arg Thr Ala Ser Asp Gly Asp Tyr Trp Arg Leu Leu
420 425 430
Asn Pro Gly Glu Tyr Val Val Thr Ala Lys Ala Glu Gly Phe Ile Thr
435 440 445
Ser Thr Lys Asn Cys Met Val Gly Tyr Asp Met Gly Ala Thr Arg Cys
450 455 460
Asp Phe Thr Leu Thr Lys Thr Asn Leu Ala Arg Ile Arg Glu Ile Met
465 470 475 480
Glu Thr Phe Gly Lys Gln Pro Val Ser Leu Pro Ser Arg Arg Leu Lys

35
B
348

485 490 495
Leu Arg Gly Arg Lys Arg Arg Gln Arg Gly
500 505

<210> 35
<211> 96
<212> PRT
<213> Homo sapien

<400> 35
Met Asn Gly Glu Ala Asp Cys Pro Thr Asp Leu Glu Met Ala Ala Pro
1 5 10 15
Arg Gly Gln Asp Arg Trp Ser Gln Glu Asp Met Leu Thr Leu Leu Glu
20 25 30
Cys Met Lys Asn Asn Leu Pro Ser Asn Asp Ser Ser Gln Phe Lys Thr
35 40 45
Thr Gln Thr His Met Asp Arg Glu Lys Val Ala Leu Lys Asp Phe Ser
50 55 60
Gly Asp Met Cys Lys Leu Lys Trp Val Glu Ile Ser Asn Glu Val Arg
65 70 75 80
Lys Phe Arg Thr Leu Thr Glu Leu Ile Leu Asp Thr Gln Glu His Val
85 90 95

<210> 36
<211> 129
<212> PRT
<213> Homo sapien

<400> 36
Gly Ile Val Val Phe Ser Leu Gly Ser Met Val Ser Glu Ile Pro Glu
1 5 10 15
Lys Lys Ala Val Ala Ile Ala Asp Ala Leu Gly Lys Ile Pro Gln Thr
20 25 30
Val Leu Trp Arg Tyr Thr Gly Thr Arg Pro Ser Asn Leu Ala Asn Asn
35 40 45
Thr Ile Leu Val Gln Trp Leu Pro Gln Asn Asp Leu Leu Gly His Pro
50 55 60
Met Thr Arg Ala Phe Ile Thr His Ala Ser Ser His Gly Val Asn Glu
65 70 75 80
Ser Ile Cys Asn Gly Val Pro Met Val Met Ile Pro Leu Phe Gly Asp
85 90 95
Gln Met Asp Asn Ala Lys Arg Arg Glu Thr Lys Gly Ala Gly Val Thr
100 105 110
Leu Asn Val Leu Glu Met Thr Ser Glu Asp Leu Glu Asp Ala Leu Lys
115 120 125
Ser

<210> 37
<211> 238
<212> PRT
<213> Homo sapien

<400> 37
Asn Leu Leu Gly Ile Ser Trp Val Asp Ser Ser Trp Ile Pro Ile Leu

352
82
349

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 1               5                  10                  15
Asn Ser Gly Ser Val Leu Asp Tyr Phe Ser Glu Arg Ser Asn Pro Phe
            20                  25                  30
Tyr Asp Arg Thr Cys Asn Asn Glu Val Val Lys Met Gln Arg Leu Thr
        35                  40                  45
Leu Glu His Leu Asn Gln Met Val Gly Ile Glu Tyr Ile Leu Leu His
    50                  55                  60
Ala Gln Glu Pro Ile Leu Phe Ile Ile Arg Lys Gln Gln Arg Gln Ser
65                  70                  75                  80
Pro Ala Gln Val Ile Pro Leu Ala Asp Tyr Tyr Ile Ile Ala Gly Val
                85                  90                  95
Ile Tyr Gln Ala Pro Asp Leu Gly Ser Val Ile Asn Ser Arg Val Leu
            100                 105                 110
Thr Ala Val His Gly Ile Gln Ser Ala Phe Asp Glu Ala Met Ser Tyr
        115                 120                 125
Cys Arg Tyr His Pro Ser Lys Gly Tyr Trp Trp His Phe Lys Asp His
    130                 135                 140
Glu Glu Gln Asp Lys Val Arg Pro Lys Ala Lys Arg Lys Glu Glu Pro
145                 150                 155                 160
Ser Ser Ile Phe Gln Arg Gln Arg Val Asp Ala Leu Leu Leu Asp Leu
                165                 170                 175
Arg Gln Lys Phe Pro Pro Lys Phe Val Gln Leu Lys Pro Gly Glu Lys
            180                 185                 190
Pro Val Pro Val Asp Gln Thr Lys Lys Glu Ala Glu Pro Ile Pro Glu
        195                 200                 205
Thr Val Lys Pro Glu Glu Lys Glu Thr Thr Lys Asn Val Gln Gln Thr
    210                 215                 220
Val Ser Ala Lys Gly Pro Pro Glu Lys Arg Met Arg Leu Gln
225                 230                 235
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<210> 38
<211> 202
<212> PRT
<213> Homo sapien

<400> 38

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

<210> 39
<211> 243
<212> PRT
<213> Homo sapien

<400> 39
Val Asn Ala Leu Gly Ile Met Ala Ala Val Asp Ile Arg Asp Asn Leu
1 5 10 15
Leu Gly Ile Ser Trp Val Asp Ser Ser Trp Ile Pro Ile Leu Asn Ser
20 25 30
Gly Ser Val Leu Asp Tyr Phe Ser Glu Arg Ser Asn Pro Phe Tyr Asp
35 40 45
Arg Thr Cys Asn Asn Glu Val Val Lys Met Gln Arg Leu Thr Leu Glu
50 55 60
His Leu Asn Gln Met Val Gly Ile Glu Tyr Ile Leu Leu His Ala Gln
65 70 75 80
Glu Pro Ile Leu Phe Ile Ile Arg Lys Gln Gln Arg Gln Ser Pro Ala
85 90 95
Gln Val Ile Pro Leu Ala Asp Tyr Tyr Ile Ile Ala Gly Val Ile Tyr
100 105 110
Gln Ala Pro Asp Leu Gly Ser Val Ile Asn Ser Arg Val Leu Thr Ala
115 120 125
Val His Gly Ile Gln Ser Ala Phe Asp Glu Ala Met Ser Tyr Cys Arg
130 135 140
Tyr His Pro Ser Lys Gly Tyr Trp Trp His Phe Lys Asp His Glu Glu
145 150 155 160
Gln Asp Lys Val Arg Pro Lys Ala Lys Arg Lys Glu Glu Pro Ser Ser
165 170 175
Ile Phe Gln Arg Gln Arg Val Asp Ala Leu Leu Leu Asp Leu Arg Gln
180 185 190
Lys Ile Ser Thr Gln Ile Cys Ala Val Asp Gln Thr Lys Lys Glu Ala
195 200 205
Glu Pro Ile Pro Glu Thr Val Lys Pro Glu Glu Lys Glu Thr Thr Lys
210 215 220
Asn Val Gln Gln Thr Val Ser Ala Lys Gly Pro Pro Glu Lys Arg Met
225 230 235 240
Arg Leu Gln

<210> 40
<211> 245
<212> PRT
<213> Homo sapien

<400> 40
Ala Ala Val Asp Ile Arg Asp Asn Leu Leu Gly Ile Ser Trp Val Asp
1 5 10 15

354
354
351

SUBSTITUTE SHEET (RULE 26)

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

<210> 41
<211> 163
<212> PRT
<213> Homo sapien

<400> 41
Gly Glu Arg Gln Gly Leu Val Ala Arg Ala Arg Leu Ser Leu Arg Pro
1 5 10 15
Ser Ile Pro Glu Leu Ser Glu Arg Thr Ser Arg Pro Cys Arg Ala Ser
20 25 30
Pro Ala Ser Leu Pro Ser Gln His Thr Ser Ser Pro Ala Gln Ala Arg
35 40 45
Val Arg Asn Leu Ala Gln Ser Thr Phe Pro Leu Ala Ala Gln Glu Thr
50 55 60
Pro Gly Arg Ala Pro Ala His Ala Pro Leu Ser Ser Phe Val Pro Gly
65 70 75 80
Val Gly Gly Arg Ser Pro Ala Ser Val Gly Ile Ser Ala Pro Gly Gly
85 90 95
Gly Pro Ser Gly Ala Ala Ala Lys Ile Pro Leu Glu Leu Thr Gln Ser
100 105 110
Arg Val Gln Lys Ile Trp Val Pro Val Asp His Arg Pro Ser Leu Pro
115 120 125
Arg Ser Cys Gly Pro Lys Leu Thr Asn Ser Pro Ala Val Phe Val Met
130 135 140

355
BP
352

Val Gly Leu Pro Arg Pro Gly Gln Asp Leu Leu Leu His Glu Ser Leu
145 150 155 160
Leu Ala Ala

<210> 42
<211> 243
<212> PRT
<213> Homo sapien

<400> 42
Val Asp Ile Arg Asp Asn Leu Leu Gly Ile Ser Trp Val Asp Ser Ser
1 5 10 15
Trp Ile Pro Ile Leu Asn Ser Gly Ser Val Leu Asp Tyr Phe Ser Glu
20 25 30
Arg Ser Asn Pro Phe Tyr Asp Arg Thr Cys Asn Asn Glu Val Val Lys
35 40 45
Met Gln Arg Leu Thr Leu Glu His Leu Asn Gln Met Val Gly Ile Glu
50 55 60
Tyr Ile Leu Leu His Ala Gln Glu Pro Ile Leu Phe Ile Ile Arg Lys
65 70 75 80
Gln Gln Arg Gln Ser Pro Ala Gln Val Ile Pro Leu Ala Asp Tyr Tyr
85 90 95
Ile Ile Ala Gly Val Ile Tyr Gln Ala Pro Asp Leu Gly Ser Val Ile
100 105 110
Asn Ser Arg Val Leu Thr Ala Val His Gly Ile Gln Ser Ala Phe Asp
115 120 125
Glu Ala Met Ser Tyr Cys Arg Tyr His Pro Ser Lys Gly Tyr Trp Trp
130 135 140
His Phe Lys Asp His Glu Glu Gln Asp Lys Val Arg Pro Lys Ala Lys
145 150 155 160
Arg Lys Glu Glu Pro Ser Ser Ile Phe Gln Arg Gln Arg Val Asp Ala
165 170 175
Leu Leu Leu Asp Leu Arg Gln Lys Phe Pro Pro Lys Phe Val Gln Leu
180 185 190
Lys Pro Gly Glu Lys Pro Val Pro Val Asp Gln Thr Lys Lys Glu Ala
195 200 205
Glu Pro Ile Pro Glu Thr Val Lys Pro Glu Glu Lys Glu Thr Thr Lys
210 215 220
Asn Val Gln Gln Thr Val Ser Ala Lys Gly Pro Pro Glu Lys Arg Met
225 230 235 240
Arg Leu Gln

<210> 43
<211> 244
<212> PRT
<213> Homo sapien

<400> 43
Ala Val Asp Ile Arg Asp Asn Leu Leu Gly Ile Ser Trp Val Asp Ser
1 5 10 15
Ser Trp Ile Pro Ile Leu Asn Ser Gly Ser Val Leu Asp Tyr Phe Ser
20 25 30
Glu Arg Ser Asn Pro Phe Tyr Asp Arg Thr Cys Asn Asn Glu Val Val

353

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


      <210> 44
      <211> 109
      <212> PRT
      <213> Homo sapien

      <400> 44
Glu Leu His Phe Ser Glu Phe Thr Ser Ala Val Ala Asp Met Lys Asn
 1               5                  10                  15
Ser Val Ala Asp Arg Asp Asn Ser Pro Ser Ser Cys Ala Gly Leu Phe
            20                  25                  30
Ile Ala Ser His Ile Gly Phe Asp Trp Pro Gly Val Trp Val His Leu
        35                  40                  45
Asp Ile Ala Ala Pro Val His Ala Gly Glu Arg Ala Thr Gly Phe Gly
    50                  55                  60
Val Ala Leu Leu Leu Ala Leu Phe Gly Arg Ala Ser Glu Asp Pro Leu
65                  70                  75                  80
Leu Asn Leu Val Ser Pro Leu Asp Cys Glu Val Asp Ala Gln Glu Gly
                85                  90                  95
Asp Asn Met Gly Arg Asp Ser Lys Arg Arg Arg Leu Val
            100                 105


      <210> 45
      <211> 324
      <212> PRT
      <213> Homo sapien

      <400> 45
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Arg Arg Pro Val Met Ala Gln Glu Thr Ala Pro Pro Cys Gly Pro Val
1 5 10 15
Ser Arg Gly Asp Ser Pro Ile Ile Glu Lys Met Glu Lys Arg Thr Cys
20 25 30
Ala Leu Cys Pro Glu Gly His Glu Trp Ser Gln Ile Tyr Phe Ser Pro
35 40 45
Ser Gly Asn Ile Val Ala His Glu Asn Cys Leu Leu Tyr Ser Ser Gly
50 55 60
Leu Val Glu Cys Glu Thr Leu Asp Leu Arg Asn Thr Ile Arg Asn Phe
65 70 75 80
Asp Val Lys Ser Val Lys Lys Glu Ile Trp Arg Gly Arg Arg Leu Lys
85 90 95
Cys Ser Phe Cys Asn Lys Gly Gly Ala Thr Val Gly Cys Asp Leu Trp
100 105 110
Phe Cys Lys Lys Ser Tyr His Tyr Val Cys Ala Lys Lys Asp Gln Ala
115 120 125
Ile Leu Gln Val Asp Gly Asn His Gly Thr Tyr Lys Leu Phe Cys Pro
130 135 140
Glu His Ser Pro Glu Gln Glu Glu Ala Thr Glu Ser Ala Asp Asp Pro
145 150 155 160
Ser Met Lys Lys Lys Arg Gly Lys Asn Lys Arg Leu Ser Ser Gly Pro
165 170 175
Pro Ala Gln Pro Lys Thr Met Lys Cys Ser Asn Ala Lys Arg His Met
180 185 190
Thr Glu Glu Pro His Gly His Thr Asp Ala Ala Val Lys Ser Pro Phe
195 200 205
Leu Lys Lys Cys Gln Glu Ala Gly Leu Leu Thr Glu Leu Phe Glu His
210 215 220
Ile Leu Glu Asn Met Asp Ser Val His Gly Arg Leu Val Asp Glu Thr
225 230 235 240
Ala Ser Glu Ser Asp Tyr Glu Gly Ile Glu Thr Leu Leu Phe Asp Cys
245 250 255
Gly Leu Phe Lys Asp Thr Leu Arg Lys Phe Gln Glu Val Ile Lys Ser
260 265 270
Lys Ala Cys Glu Trp Glu Glu Arg Gln Arg Gln Met Lys Gln Gln Leu
275 280 285
Glu Ala Leu Ala Asp Leu Gln Gln Ser Leu Cys Ser Phe Gln Glu Asn
290 295 300
Gly Asp Leu Asp Cys Ser Ser Ser Thr Ser Gly Ser Leu Leu Pro Pro
305 310 315 320
Glu Asp His Gln

<210> 46
<211> 244
<212> PRT
<213> Homo sapien

<400> 46
Ala Val Asp Ile Arg Asp Asn Leu Leu Gly Ile Ser Trp Val Asp Ser
1 5 10 15
Ser Trp Ile Pro Ile Leu Asn Ser Gly Ser Val Leu Asp Tyr Phe Ser
20 25 30
Glu Arg Ser Asn Pro Phe Tyr Asp Arg Thr Cys Asn Asn Glu Val Val
35 40 45

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

<210> 47
<211> 14
<212> DNA
<213> Homo sapien

<400> 47
ttttttttt ttag

<210> 48
<211> 10
<212> DNA
<213> Homo sapien

<400> 48
cttcaacctc

<210> 49
<211> 496
<212> DNA
<213> Homo sapien

<400> 49
gcaccatgta ccgagcactt cggctcctcg cgcgctcgcg tcccctcgtg cgggctccag
ccgcagcctt agcttcggct cccggcttgg gtggcgcggc cgtgccctcg ttttggcctc
cgaacgcggc tcgaatggca agccaaaatt ccttccggat agaatatgat acctttggtg
aactaaaggt gccaaatgat aagtattatg gcgcccagac cgtgagatct acgatgaact
ttaagattgg aggtgtgaca gaacgcatgc caaccccagt tattaaagct tttggcatct
tgaagcgagc ggccgctgaa gtaaaccagg attatggtct tgatccaaag attgctaatg

356 59 359

caataatgaa ggcagcagat gaggtagctg aaggtaaatt aaatgatcat tttcctctcg 42
tggtatggca gactggatca ggaactcaga caaatatgaa tgtaaatgaa gtcattagcc 48
aatagagcaa ttgaaa 49

<210> 50
<211> 499
<212> DNA
<213> Homo sapien

<400> 50
agaaaaagtc tatgtttgca gaaatacaga tccaagacaa agacaggatg ggcactgctg 6
gaaaagttat taaatgcaaa gcagctgtgc tttgggagca gaagcaaccc ttctccattg 12
aggaaataga agttgcccca ccaaagacta aagaagttcg cattaagatt ttggccacag 18
gaatctgtcg cacagatgac catgtgataa aaggaacaat ggtgtccaag tttccagtga 24
ttgtgggaca tgaggcaact gggattgtag agagcattgg agaaggagtg actacagtga 30
aaccaggtga caaagtcatc cctctctttc tgccacaatg tagagaatgc aatgcttgtc 36
gcaacccaga tggcaacctt tgcattagga gcgatattac tggtcgtgga gtactggctg 42
atggcaccac cagatttaca tgcaagggcg aaccagtcca ccacttcatg aacaccagta 48
catttacgga gtacacagt 49

<210> 51
<211> 887
<212> DNA
<213> Homo sapien

<400> 51
gagtctgagc agaaaggaaa agcagccttg gcagccacgt tagaggaata caaagccaca
gtggccagtg accagataga gatgaatcgc ctgaaggctc agctggagaa tgaaaagcag 1
aaagtggcag agctgtattc tatccataac tctggagaca aatctgatat tcaggacctc 1
ctggagagtg tcaggctgga caaagaaaaa gcagagactt tggctagtag cttgcaggaa 2
gatctggctc atacccgaaa tgatgccaat cgattacagg atgccattgc taaggtagag 3
gatgaatacc gagccttcca agaagaagct aagaaacaaa ttgaagattt gaatatgacg 3
ttagaaaaat taagatcaga cctggatgaa aaagaaacag aaaggagtga catgaaagaa 4
accatctttg aacttgaaga tgaagtagaa caacatcgtg ctgtgaaact tcatgacaac 4
ctcattattt ctgatctaga gaatacagtt aaaaaactcc aggaccaaaa gcacgacatg 5
gaaagagaaa taaagacact ccacagaaga cttcgggaag aatctgcgga atggcggcag 6
tttcaggctg atctccagac tgcagtagtc attgcaaatg acattaaatc tgaagcccaa 6
gaggagattg gtgatctaaa gcgccggtta catgaggctc aagaaaaaaa tgagaaactc 7
acaaaagaat tggaggaaat aaagtcacgc aagcaagagg aggagcgagg cgggtataca 7
attacatgaa tgccgttgag agagatttgg cagccttaag gcagggaatg ggactgagta 8
gaaggtcctc gacttcctca gagccaactc ctacagtaaa aaccctc 8

<210> 52
<211> 491
<212> DNA
<213> Homo sapien

<400> 52
ggcacgagct tttccaaaaa tcatgctgct cctttctcta aagttcttac attttataga
aaggaacctt tcactcttga ggcctactac agctctcctc aggatttgcc ctatccagat
cctgctatag ctcagttttc agttcagaaa gtcactcctc agtctgatgg ctccagttca
aaagtgaaag tcaaagttcg agtaaatgtc catggcattt tcagtgtgtc cagtgcatct
ttagtggagg ttcacaagtc tgaggaaaat gaggagccaa tggaaacaga tcagaatgca
aaggaggaag agaagatgca agtggaccag gaggaaccac atgttgaaga gcaacagcag
cagacaccag gcagaaaata aggcagagtc tgaagaaatg gagacctctc aagctggatc

40
357 360

caaggataaa aagatggacc aaccacccca agccaagaag gcaaaagtga agaccagtac 48
tgtggacctg g 49

<210> 53
<211> 787
<212> DNA
<213> Homo sapien

<400> 53
aagcagttga gtaggcagaa aaaagaacct cttcattaag gattaaaatg tataggccag 6
cacgtgtaac ttcgacttca agatttctga atccatatgt agtatgtttc attgtcgtcg 12
caggggtagt gatcctggca gtcaccatag ctctacttgt ttacttttta gcttttgatc 18
aaaaatctta cttttatagg agcagttttc aactcctaaa tgttgaatat aatagtcagt 24
taaattcacc agctacacag gaatacagga ctttgagtgg aagaattgaa tctctgatta 30
ctaaaacatt caaagaatca aatttaagaa atcagttcat cagagctcat gttgccaaac 36
tgaggcaaga tggtagtggt gtgagagcgg atgttgtcat gaaatttcaa ttcactagaa 42
ataacaatgg agcatcaatg aaaagcagaa ttgagtctgt tttacgacaa atgctgaata 48
actctggaaa cctggaaata aacccttcaa ctgagataac atcacttact gaccaggctg 54
cagcaaattg gcttattaat gaatgtgggg ccggtccaga cctaataaca ttgtctgagc 60
agagaatcct tggaggcact gaggctgagg agggaagctg gccgtggcaa gtcagtctgc 66
ggctcaataa tgcccaccac tgtggaggca gcctgatcaa taacatgtgg atcctgacag 72
cagctcactg cttcagaagc aactctaatc ctcgtgactg gnttgccacg tctggtattt 78
ccacaac 78

<210> 54
<211> 386
<212> DNA
<213> Homo sapien

<400> 54
ggcattttca gtgtgtccag tgcatcttta gtggaggttc acaagtctga ggaaaatgag
gagccaatgg aaacagatca gaatgcaaag gaggaagaga agatgcaagt ggaccaggag 1
gaaccacatg ttgaagagca acagcagcag acaccagcag aaaataaggc agagtctgaa 1
gaaatggaga cctctcaagc tggatccaag gataaaaaga tggaccaacc accccaagcc 2
aagaaggcaa aagtgaagac cagtactgtg gacctgccaa tcgagaatca gctattatgg 3
cagatagaca gagagatgct caacttgtac attgaaaatg agggtaagat gatcatgcag 3
gataaactgg agaaggagcg gaatga 3

<210> 55
<211> 1462
<212> DNA
<213> Homo sapien

<400> 55
aagcagttga gtaggcagaa aaaagaacct cttcattaag gattaaaatg tataggccag
cacgtgtaac ttcgacttca agatttctga atccatatgt agtatgtttc attgtcgtcg
caggggtagt gatcctggca gtcaccatag ctctacttgt ttacttttta gcttttgatc
aaaaatctta cttttatagg agcagttttc aactcctaaa tgttgaatat aatagtcagt
taaattcacc agctacacag gaatacagga ctttgagtgg aagaattgaa tctctgatta
ctaaaacatt caaagaatca aatttaagaa atcagttcat cagagctcat gttgccaaac
tgaggcaaga tggtagtggt gtgagagcgg atgttgtcat gaaatttcaa ttcactagaa
ataacaatgg agcatcaatg aaaagcagaa ttgagtctgt tttacgacaa atgctgaata
actctggaaa cctggaaata aacccttcaa ctgagataac atcacttact gaccaggctg
cagcaaattg gcttattaat gaatgtgggg ccggtccaga cctaataaca ttgtctgagc
agagaatcct tggaggcact gaggctgagg agggaagctg gccgtggcaa gtcagtctgc

AH 358 3861

ggctcaataa tgcccaccac tgtggaggca gcctgatcaa taacatgtgg atcctgacag 72
cagctcactg cttcagagc aactctaatc ctcgtgactg gattgccacg tctggtattt 78
ccacaacatt tcctaaacta agaatgagag taagaaatat tttaattcat aacaattata 84
aatctgcaac tcatgaaaat gacattgcac ttgtgagact tgagaacagt gtcaccttta 90
ccaaagatat ccatagtgtg tgtctcccag ctgctaccca gaatattcca cctggctcta 96
ctgcttatgt aacaggatgg ggcgctcaag aatatgctgg ccacacagtt ccagagctaa 102
ggcaaggaca ggtcagaata ataagtaatg atgtatgtaa tgcaccacat agttataatg 108
gagccatctt gtctggaatg ctgtgtgctg gagtacctca aggtggagtg gacgcatgtc 114
agggtgactc tggtggccca ctagtacaag aagactcacg gcggctttgg tttattgtgg 120
ggatagtaag ctggggagat cagtgtggcc tgccggataa gccaggagtg tatactgcag 126
tgacagcata cattgactgg attaggcaac aaactgggat ctagtgcaac aagtgcatcc 132
ctgttgcaaa gtctgtatgc aggtgtgcct gtcttaaatt ccaaagcttt acatttcaac 138
tgaaaaagaa actagaaatg tcctaattta acatcttgtt acataaatat ggtttaacaa 144
aaaaaaaaaa aaaaaactcg ag 146

<210> 56
<211> 159
<212> PRT
<213> Homo sapien

<400> 56
Thr Met Tyr Arg Ala Leu Arg Leu Leu Ala Arg Ser Arg Pro Leu Val
1 5 10 15
Arg Ala Pro Ala Ala Ala Leu Ala Ser Ala Pro Gly Leu Gly Gly Ala
20 25 30
Ala Val Pro Ser Phe Trp Pro Pro Asn Ala Ala Arg Met Ala Ser Gln
35 40 45
Asn Ser Phe Arg Ile Glu Tyr Asp Thr Phe Gly Glu Leu Lys Val Pro
50 55 60
Asn Asp Lys Tyr Tyr Gly Ala Gln Thr Val Arg Ser Thr Met Asn Phe
65 70 75 80
Lys Ile Gly Gly Val Thr Glu Arg Met Pro Thr Pro Val Ile Lys Ala
85 90 95
Phe Gly Ile Leu Lys Arg Ala Ala Ala Glu Val Asn Gln Asp Tyr Gly
100 105 110
Leu Asp Pro Lys Ile Ala Asn Ala Ile Met Lys Ala Ala Asp Glu Val
115 120 125
Ala Glu Gly Lys Leu Asn Asp His Phe Pro Leu Val Val Trp Gln Thr
130 135 140
Gly Ser Gly Thr Gln Thr Asn Met Asn Val Asn Glu Val Ile Ser
145 150 155

<210> 57
<211> 165
<212> PRT
<213> Homo sapien

<400> 57
Lys Lys Ser Met Phe Ala Glu Ile Gln Ile Gln Asp Lys Asp Arg Met
1 5 10 15
Gly Thr Ala Gly Lys Val Ile Lys Cys Lys Ala Ala Val Leu Trp Glu
20 25 30
Gln Lys Gln Pro Phe Ser Ile Glu Glu Ile Glu Val Ala Pro Pro Lys
35 40 45
Thr Lys Glu Val Arg Ile Lys Ile Leu Ala Thr Gly Ile Cys Arg Thr

359

50 55 60
Asp Asp His Val Ile Lys Gly Thr Met Val Ser Lys Phe Pro Val Ile
65 70 75 80
Val Gly His Glu Ala Thr Gly Ile Val Glu Ser Ile Gly Glu Gly Val
85 90 95
Thr Thr Val Lys Pro Gly Asp Lys Val Ile Pro Leu Phe Leu Pro Gln
100 105 110
Cys Arg Glu Cys Asn Ala Cys Arg Asn Pro Asp Gly Asn Leu Cys Ile
115 120 125
Arg Ser Asp Ile Thr Gly Arg Gly Val Leu Ala Asp Gly Thr Thr Arg
130 135 140
Phe Thr Cys Lys Gly Glu Pro Val His His Phe Met Asn Thr Ser Thr
145 150 155 160
Phe Thr Glu Tyr Thr
165

<210> 58
<211> 259
<212> PRT
<213> Homo sapien

<400> 58
Glu Ser Glu Gln Lys Gly Lys Ala Ala Leu Ala Ala Thr Leu Glu Glu
1 5 10 15
Tyr Lys Ala Thr Val Ala Ser Asp Gln Ile Glu Met Asn Arg Leu Lys
20 25 30
Ala Gln Leu Glu Asn Glu Lys Gln Lys Val Ala Glu Leu Tyr Ser Ile
35 40 45
His Asn Ser Gly Asp Lys Ser Asp Ile Gln Asp Leu Leu Glu Ser Val
50 55 60
Arg Leu Asp Lys Glu Lys Ala Glu Thr Leu Ala Ser Ser Leu Gln Glu
65 70 75 80
Asp Leu Ala His Thr Arg Asn Asp Ala Asn Arg Leu Gln Asp Ala Ile
85 90 95
Ala Lys Val Glu Asp Glu Tyr Arg Ala Phe Gln Glu Glu Ala Lys Lys
100 105 110
Gln Ile Glu Asp Leu Asn Met Thr Leu Glu Lys Leu Arg Ser Asp Leu
115 120 125
Asp Glu Lys Glu Thr Glu Arg Ser Asp Met Lys Glu Thr Ile Phe Glu
130 135 140
Leu Glu Asp Glu Val Glu Gln His Arg Ala Val Lys Leu His Asp Asn
145 150 155 160
Leu Ile Ile Ser Asp Leu Glu Asn Thr Val Lys Lys Leu Gln Asp Gln
165 170 175
Lys His Asp Met Glu Arg Glu Ile Lys Thr Leu His Arg Arg Leu Arg
180 185 190
Glu Glu Ser Ala Glu Trp Arg Gln Phe Gln Ala Asp Leu Gln Thr Ala
195 200 205
Val Val Ile Ala Asn Asp Ile Lys Ser Glu Ala Gln Glu Glu Ile Gly
210 215 220
Asp Leu Lys Arg Arg Leu His Glu Ala Gln Glu Lys Asn Glu Lys Leu
225 230 235 240
Thr Lys Glu Leu Glu Glu Ile Lys Ser Arg Lys Gln Glu Glu Glu Arg
245 250 255
Gly Gly Tyr

93
365
360

<210> 59
<211> 125
<212> PRT
<213> Homo sapien

<400> 59

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Gly Thr Ser Phe Ser Lys Asn His Ala Ala Pro Phe Ser Lys Val Leu
 1               5                  10                  15
Thr Phe Tyr Arg Lys Glu Pro Phe Thr Leu Glu Ala Tyr Tyr Ser Ser
            20                  25                  30
Pro Gln Asp Leu Pro Tyr Pro Asp Pro Ala Ile Ala Gln Phe Ser Val
        35                  40                  45
Gln Lys Val Thr Pro Gln Ser Asp Gly Ser Ser Ser Lys Val Lys Val
    50                  55                  60
Lys Val Arg Val Asn Val His Gly Ile Phe Ser Val Ser Ser Ala Ser
65                  70                  75                  80
Leu Val Glu Val His Lys Ser Glu Glu Asn Glu Glu Pro Met Glu Thr
                85                  90                  95
Asp Gln Asn Ala Lys Glu Glu Glu Lys Met Gln Val Asp Gln Glu Glu
            100                 105                 110
Pro His Val Glu Glu Gln Gln Gln Gln Thr Pro Gly Arg
        115                 120                 125
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<210> 60
<211> 246
<212> PRT
<213> Homo sapien

<400> 60

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Met Tyr Arg Pro Ala Arg Val Thr Ser Thr Ser Arg Phe Leu Asn Pro
 1               5                  10                  15
Tyr Val Val Cys Phe Ile Val Val Ala Gly Val Val Ile Leu Ala Val
            20                  25                  30
Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
        35                  40                  45
Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
    50                  55                  60
Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65                  70                  75                  80
Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
                85                  90                  95
Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
            100                 105                 110
Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
        115                 120                 125
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
    130                 135                 140
Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145                 150                 155                 160
Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
                165                 170                 175
Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
            180                 185                 190
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361

Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
195 200 205
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
210 215 220
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225 230 235 240
Thr Ser Gly Ile Ser Thr
245

<210> 61
<211> 128
<212> PRT
<213> Homo sapien

<400> 61
Gly Ile Phe Ser Val Ser Ser Ala Ser Leu Val Glu Val His Lys Ser
1 5 10 15
Glu Glu Asn Glu Glu Pro Met Glu Thr Asp Gln Asn Ala Lys Glu Glu
20 25 30
Glu Lys Met Gln Val Asp Gln Glu Glu Pro His Val Glu Glu Gln Gln
35 40 45
Gln Gln Thr Pro Ala Glu Asn Lys Ala Glu Ser Glu Glu Met Glu Thr
50 55 60
Ser Gln Ala Gly Ser Lys Asp Lys Lys Met Asp Gln Pro Pro Gln Ala
65 70 75 80
Lys Lys Ala Lys Val Lys Thr Ser Thr Val Asp Leu Pro Ile Glu Asn
85 90 95
Gln Leu Leu Trp Gln Ile Asp Arg Glu Met Leu Asn Leu Tyr Ile Glu
100 105 110
Asn Glu Gly Lys Met Ile Met Gln Asp Lys Leu Glu Lys Glu Arg Asn
115 120 125

<210> 62
<211> 418
<212> PRT
<213> Homo sapien

<400> 62
Met Tyr Arg Pro Ala Arg Val Thr Ser Thr Ser Arg Phe Leu Asn Pro
1 5 10 15
Tyr Val Val Cys Phe Ile Val Val Ala Gly Val Val Ile Leu Ala Val
20 25 30
Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
35 40 45
Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
50 55 60
Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65 70 75 80
Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
85 90 95
Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
100 105 110
Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
115 120 125
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn

362

130 135 140
Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145 150 155 160
Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
165 170 175
Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
180 185 190
Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
195 200 205
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
210 215 220
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225 230 235 240
Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
245 250 255
Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
260 265 270
Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
275 280 285
His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
290 295 300
Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
305 310 315 320
Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
325 330 335
Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
340 345 350
Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
355 360 365
Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
370 375 380
Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
385 390 395 400
Val Tyr Thr Arg Val Thr Ala Tyr Ile Asp Trp Ile Arg Gln Gln Thr
405 410 415
Gly Ile

<210> 63
<211> 776
<212> DNA
<213> Homo sapien

<400> 63
cacagatggt gatagaggaa tccatcttgc agtcagataa agccctcact gatagagaga
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aacagaaatt acaggagcag ccagcaacag atggaggctc aagataagag tcgcaaggaa 1
aactagccaa ctgaaggaga agctgcagat ggagagagaa cacctactga gagagcagat 2
tatgatgttg gagcacacgc agaaggtcca aaatgattgg cttcatgaag gatttaagaa 3
gaagtatgag gagatgaatg cagagataag tcaatttaaa cgtatgattg atactacaaa 3
aaatgatgat actcccctgga ttgcacgaac cttggacaac cttgccgatg agctaactgc 4
aatattgtct gctcctgcta aattaattgg tcatggtgtc aaaggtgtga gctcactctt 4
taaaaagcat aagctcccct tttaaggata ttatagattg tacatatatg ctttggacta 5
tttttgatct gtatgttttt cattttcatt cagcaagttt ttttttttt tcagagtctt 6
actctgttgc ccaggctgga gtacagtggt gcaatctcag ctcactgcaa cctctgcctc 6

96
363

ctgggttcaa gagattcacc tgcctcagcc ccctagtagc tgggattata ggtgtacacc 72
accacaccca gctaattttt gtatttttag tagagatggg gtttcactat gttggc 77

<210> 64
<211> 160
<212> DNA
<213> Homo sapien

<400> 64
gcagcgctct cggttgcagt acccactgga aggacttagg cgctcgcgtg gacaccgcaa 6
gcccctcagt agcctcggcc caagaggcct gctttccact cgctagcccc gccgggggtc 12
cgtgtcctgt ctcggtggcc ggacccgggc ccgagcccga 16

<210> 65
<211> 72
<212> PRT
<213> Homo sapien

<400> 65
Leu Ser Ala Met Gly Phe Thr Ala Ala Gly Ile Ala Ser Ser Ser Ile
1 5 10 15
Ala Ala Lys Met Met Ser Ala Ala Ala Ile Ala Asn Gly Gly Gly Val
20 25 30
Ala Ser Gly Ser Leu Val Ala Thr Leu Gln Ser Leu Gly Ala Thr Gly
35 40 45
Leu Ser Gly Leu Thr Lys Phe Ile Leu Gly Ser Ile Gly Ser Ala Ile
50 55 60
Ala Ala Val Ile Ala Arg Phe Tyr
65 70

<210> 66
<211> 2581
<212> DNA
<213> Homo sapien

<400> 66
ctttcaaccc gcgctcgccg gctccagccc cgcgcgcccc caccccttgc cctccggcg
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gctggacagc tggaggatga acggagaagc cgactgcccc acagacctgg aaatggccgc 1
ccccaaaggc caagaccgtt ggtcccagga agacatgctg actttgctgg aatgcatgaa 2
gaacaacctt ccatccaatg acagctccaa gttcaaaacc accgaatcac acatggactg 3
ggaaaaagta gcatttaaag acttttctgg agacatgtgc aagctcaaat gggtggagat 3
ttctaatgag gtgaggaagt tccgtacatt gacagaattg atcctcgatg ctcaggaaca 4
tgttaaaaat ccttacaaag gcaaaaaact caagaaacac ccagacttcc caaagaagcc 4
cctgacccct tatttccgct tcttcatgga gaagcgggcc aagtatgcga aactccaccc 5
tgagatgagc aacctggacc taaccaagat tctgtccaag aaatacaagg agcttccgga 6
gaagaagaag atgaaatata ttcaggactt ccagagagag aaacaggagt tcgagcgaaa 6
cctggcccga ttcagggagg atcaccccga cctaatccag aatgccaaga aatcggacat 7
cccagagaag cccaaaaccc cccagcagct gtggtacacc cacgagaaga aggtgtatct 7
caaagtgcgg ccagatgcca ctacgaagga ggtgaaggac tccctgggga agcagtggtc 8
tcagctctcg gacaaaaaga ggctgaaatg gattcataag gccctggagc agcggaagga 9
gtacgaggag atcatgagag actatatcca gaagcaccca gagctgaaca tcagtgagga 9
gggtatcacc aagtccaccc tcaccaaggc cgaacgccag ctcaaggaca agtttgacgg 10
gcgacccacc aagccacctc cgaacagcta ctcgctgtac tgcgcagagc tcatggccaa 10
catgaaggac gtgcccagca cagagcgcat ggtgctgtgc agccagcagt ggaagctgct 11

gtcccagaag gagaaggacg cctatcacaa gaagtgtgat cagaaaaaga aagattacga 120
ggtggagctg ctccgtttcc tcgagagcct gcctgaggag gagcagcagc gggtcttggg 126
ggaagagaag atgctgaaca tcaacaagaa gcaggccacc agccccgcct ccaagaagcc 132
agcccaggaa gggggcaagg gcggctccga gaagcccaag cggccgtgt cggccatgtt 138
catcttctcg gaggagaaac ggcggcagct gcaggaggag cggcctgagc tctccgagag 144
cgagctgacc cgcctgctgg cccgaatgtg gaacgacctg tctgagaaga agaaggccaa 150
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cgttatcggc gactacctgg cccgcttcaa gaatgaccgg gtgaaggcct tgaaagccat 168
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ccagaagttc tcccaggagc tgctgtccaa tggggagctg aaccacctgc cgctgaagga 192
gcgcatggtg gagatcggca gtcgctggca gcgcatctcc cagagccaga aggagcacta 198
caaaaagctg gccgaggagc agcaaaagca gtacaaggtg cacctggacc tctgggttaa 204
gagcctgtct ccccaggacc gtgcagcata taaagagtac atctccaata aacgtaagag 210
catgaccaag ctgcgaggcc caaaccccaa atccagccgg actactctgc agtccaagtc 216
ggagtccgag gaggatgatg aagaggatga ggatgacgag gacgaggatg aagaagagga 222
agatgatgag aatggggact cctctgaaga tggcggcgac tcctctgagt ccagcagcga 228
ggacgagagc gaggatgggg atgagaatga agaggatgac gaggacgaag acgacgacga 234
ggatgacgat gaggatgaag ataatgagtc cgagggcagc agctccagct cctcctcctt 240
aggggactcc tcagactttg actccaactg aggcttagcc ccacccccagg ggagccaggg 246
agagcccagg agctcccctc cccaactgac caccttttgtt tcttccccat gttctgtccc 252
ttgccccccct ggcctccccc actttctttc tttctttaaa aaaaaaaaaa aaaaactcga 258
g 258

<210> 67
<211> 764
<212> PRT
<213> Homo sapien

<400> 67

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

365

```
                180                 185                 190
Ser Asp Ile Pro Glu Lys Pro Lys Thr Pro Gln Gln Leu Trp Tyr Thr
        195                 200                 205
His Glu Lys Lys Val Tyr Leu Lys Val Arg Pro Asp Ala Thr Thr Lys
    210                 215                 220
Glu Val Lys Asp Ser Leu Gly Lys Gln Trp Ser Gln Leu Ser Asp Lys
225                 230                 235                 240
Lys Arg Leu Lys Trp Ile His Lys Ala Leu Glu Gln Arg Lys Glu Tyr
                245                 250                 255
Glu Glu Ile Met Arg Asp Tyr Ile Gln Lys His Pro Glu Leu Asn Ile
            260                 265                 270
Ser Glu Glu Gly Ile Thr Lys Ser Thr Leu Thr Lys Ala Glu Arg Gln
        275                 280                 285
Leu Lys Asp Lys Phe Asp Gly Arg Pro Thr Lys Pro Pro Pro Asn Ser
    290                 295                 300
Tyr Ser Leu Tyr Cys Ala Glu Leu Met Ala Asn Met Lys Asp Val Pro
305                 310                 315                 320
Ser Thr Glu Arg Met Val Leu Cys Ser Gln Gln Trp Lys Leu Leu Ser
                325                 330                 335
Gln Lys Glu Lys Asp Ala Tyr His Lys Lys Cys Asp Gln Lys Lys Lys
            340                 345                 350
Asp Tyr Glu Val Glu Leu Leu Arg Phe Leu Glu Ser Leu Pro Glu Glu
        355                 360                 365
Glu Gln Gln Arg Val Leu Gly Glu Glu Lys Met Leu Asn Ile Asn Lys
    370                 375                 380
Lys Gln Ala Thr Ser Pro Ala Ser Lys Lys Pro Ala Gln Glu Gly Gly
385                 390                 395                 400
Lys Gly Gly Ser Glu Lys Pro Lys Arg Pro Val Ser Ala Met Phe Ile
                405                 410                 415
Phe Ser Glu Glu Lys Arg Arg Gln Leu Gln Glu Glu Arg Pro Glu Leu
            420                 425                 430
Ser Glu Ser Glu Leu Thr Arg Leu Leu Ala Arg Met Trp Asn Asp Leu
        435                 440                 445
Ser Glu Lys Lys Lys Ala Lys Tyr Lys Ala Arg Glu Ala Ala Leu Lys
    450                 455                 460
Ala Gln Ser Glu Arg Lys Pro Gly Gly Glu Arg Glu Glu Arg Gly Lys
465                 470                 475                 480
Leu Pro Glu Ser Pro Lys Arg Ala Glu Glu Ile Trp Gln Gln Ser Val
                485                 490                 495
Ile Gly Asp Tyr Leu Ala Arg Phe Lys Asn Asp Arg Val Lys Ala Leu
            500                 505                 510
Lys Ala Met Glu Met Thr Trp Asn Asn Met Glu Lys Lys Glu Lys Leu
        515                 520                 525
Met Trp Ile Lys Lys Ala Ala Glu Asp Gln Lys Arg Tyr Glu Arg Glu
    530                 535                 540
Leu Ser Glu Met Arg Ala Pro Pro Ala Ala Thr Asn Ser Ser Lys Lys
545                 550                 555                 560
Met Lys Phe Gln Gly Glu Pro Lys Lys Pro Pro Met Asn Gly Tyr Gln
                565                 570                 575
Lys Phe Ser Gln Glu Leu Leu Ser Asn Gly Glu Leu Asn His Leu Pro
            580                 585                 590
Leu Lys Glu Arg Met Val Glu Ile Gly Ser Arg Trp Gln Arg Ile Ser
        595                 600                 605
Gln Ser Gln Lys Glu His Tyr Lys Lys Leu Ala Glu Glu Gln Gln Lys
    610                 615                 620
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99
369
366

Gln Tyr Lys Val His Leu Asp Leu Trp Val Lys Ser Leu Ser Pro Gln
625 630 635 640
Asp Arg Ala Ala Tyr Lys Glu Tyr Ile Ser Asn Lys Arg Lys Ser Met
645 650 655
Thr Lys Leu Arg Gly Pro Asn Pro Lys Ser Ser Arg Thr Thr Leu Gln
660 665 670
Ser Lys Ser Glu Ser Glu Glu Asp Asp Glu Glu Asp Glu Asp Asp Glu
675 680 685
Asp Glu Asp Glu Glu Glu Glu Asp Asp Glu Asn Gly Asp Ser Ser Glu
690 695 700
Asp Gly Gly Asp Ser Ser Glu Ser Ser Ser Glu Asp Glu Ser Glu Asp
705 710 715 720
Gly Asp Glu Asn Glu Glu Asp Asp Glu Asp Glu Asp Asp Asp Glu Asp
725 730 735
Asp Asp Glu Asp Glu Asp Asn Glu Ser Glu Gly Ser Ser Ser Ser Ser
740 745 750
Ser Ser Leu Gly Asp Ser Ser Asp Phe Asp Ser Asn
755 760

<210> 68
<211> 434
<212> DNA
<213> Homo sapien

<400> 68
ctaagatgct ggatgctgaa gacatcgtcg gaactgcccg gccagatgag aaagccatta 6
tgacttatgt gtctagcttc tatcatgcct tctctggagc ccagaaggca gaaacagcag 1:
ccaatcgcat ctgcaaagtg ttggcggtca atcaagagaa cgagcagctt atggaagact 1:
atgagaagct ggccagtgat ctgttggagt ggatccgccg caccatccca tggctggaga 2
atcgggtgcc tgagaacacc atgcatgcca tgcagcagaa gctggaggac ttccgagact 3
atagacgcct gcacaagccg cccaaggtgc aggagaagtg ccagctggag atcaacttta 3
acacgctgca gaccaaactg cggctcagca accggcctgc cttcatgccc tccgagggca 4
ggatggtctc ggat 4

<210> 69
<211> 244
<212> DNA
<213> Homo sapien

<400> 69
aggcagcatg ctcgttgaga gtcatcacca ctccctaatc tcaagtacgc agggacacaa
acactgcgga aggccgcagg gtcctctgcc taggaaaacc agagaccttt gttcacttgt 1
ttatgtgctg accttcctc cactattgtc ctgtgaccct gccaaatccc cctttgtgag 1
aaacacccaa gaatgatcaa taaaaaataa attaatttag gaaaaaaaaa aaaaaaaact 2
cgag 2

<210> 70
<211> 437
<212> DNA
<213> Homo sapien

<400> 70
ctgggacggg agcgtccagc gggactcgaa ccccagatgt gaaggcgttt ctggaaagtc
cttggtccct ggatccagcg tcggccagcc cagagcccgt gccgcacatc cttgcgtcct 1
ccaggcagtg ggaccccgcg agctgcacgt ccctgggcac ggacaagtgt gaggcactgt 1

tggggctgtg ccaggtgcgg ggtgggctgc ccccttttctc agaaccttcc agcctggtgc 24(
cgtggccccc aggccggagt cttcctaagg ctgtgaggcc accccctgtcc tggcctccgt 30(
tctcgcagca gcagaccttg cccgtgatga gcggggaggc ccttggctgg ctgggccagg 36(
ctggttccct ggccatgggg gctgcacctc tgggggagcc agccaaggag gaccccatgc 42(
tggcgcagga agccggg 43

<210> 71
<211> 271
<212> DNA
<213> Homo sapien

<400> 71
gcgcagagtt ctgtcgtcca ccatcgagtg aggaagagag cattggttcc cctgagatag 6
aagagatggc tctcttcagt gcccagtctc catacattaa cccgatcatc ccctttactg 12
gaccaatcca aggagggctg caggagggac ttcaggtgac cctccagggg actaccgaga 18
gttttgcaca aaagtttgtg gtgaactttt cagaacagct tcaatggaga tgacttggcc 24
ttccacttca acccoggtta tgaggaagga g 27

<210> 72
<211> 290
<212> DNA
<213> Homo sapien

<400> 72
ccgagcccta cccggaggtc tccagaatcc ccaccgtcag gggatgcaac ggctccctgt 6
ctggtgccct ctcctgctgc gaggactcgg cccagggctc gggcccgccc aaggccccta 12
cggtggccga gggtcccagc tcctgccttc ggcggaacgt gatcagcgag agggagcgca 18
ggaagcggat gtcgttgagc tgtgagcgtc tgcgggccct gctgccccag ttcgatggcc 24
ggcgggagga catggcctcg gtcctggaga tgtctgttgc aattcctgcg 29

<210> 73
<211> 144
<212> PRT
<213> Homo sapien

<400> 73

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

101
327
368

<210> 74
<211> 64
<212> PRT
<213> Homo sapien

<400> 74

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Gly Ser Met Leu Val Glu Ser His His His Ser Leu Ile Ser Ser Thr
 1               5                  10                  15
Gln Gly His Lys His Cys Gly Arg Pro Gln Gly Pro Leu Pro Arg Lys
            20                  25                  30
Thr Arg Asp Leu Cys Ser Leu Val Tyr Val Leu Thr Phe Pro Pro Leu
        35                  40                  45
Leu Ser Cys Asp Pro Ala Lys Ser Pro Phe Val Arg Asn Thr Gln Glu
    50                  55                  60
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<210> 75
<211> 145
<212> PRT
<213> Homo sapien

<400> 75

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Gly Thr Gly Ala Ser Ser Gly Thr Arg Thr Pro Asp Val Lys Ala Phe
 1               5                  10                  15
Leu Glu Ser Pro Trp Ser Leu Asp Pro Ala Ser Ala Ser Pro Glu Pro
            20                  25                  30
Val Pro His Ile Leu Ala Ser Ser Arg Gln Trp Asp Pro Ala Ser Cys
        35                  40                  45
Thr Ser Leu Gly Thr Asp Lys Cys Glu Ala Leu Leu Gly Leu Cys Gln
    50                  55                  60
Val Arg Gly Gly Leu Pro Pro Phe Ser Glu Pro Ser Ser Leu Val Pro
65                  70                  75                  80
Trp Pro Pro Gly Arg Ser Leu Pro Lys Ala Val Arg Pro Pro Leu Ser
                85                  90                  95
Trp Pro Pro Phe Ser Gln Gln Gln Thr Leu Pro Val Met Ser Gly Glu
            100                 105                 110
Ala Leu Gly Trp Leu Gly Gln Ala Gly Ser Leu Ala Met Gly Ala Ala
        115                 120                 125
Pro Leu Gly Glu Pro Ala Lys Glu Asp Pro Met Leu Ala Gln Glu Ala
    130                 135                 140
Gly
145
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<210> 76
<211> 69
<212> PRT
<213> Homo sapien

<400> 76

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

402
375
369

50 55 60
Phe Val Val Asn Phe
65

<210> 77
<211> 96
<212> PRT
<213> Homo sapien

<400> 77
Glu Pro Tyr Pro Glu Val Ser Arg Ile Pro Thr Val Arg Gly Cys Asn
1 5 10 15
Gly Ser Leu Ser Gly Ala Leu Ser Cys Cys Glu Asp Ser Ala Gln Gly
20 25 30
Ser Gly Pro Pro Lys Ala Pro Thr Val Ala Glu Gly Pro Ser Ser Cys
35 40 45
Leu Arg Arg Asn Val Ile Ser Glu Arg Glu Arg Arg Lys Arg Met Ser
50 55 60
Leu Ser Cys Glu Arg Leu Arg Ala Leu Leu Pro Gln Phe Asp Gly Arg
65 70 75 80
Arg Glu Asp Met Ala Ser Val Leu Glu Met Ser Val Ala Ile Pro Ala
85 90 95

<210> 78
<211> 2076
<212> DNA
<213> Homo sapien

<400> 78
agaaaaagtc tatgtttgca gaaatacaga tccaagacaa agacaggatg ggcactgctg (
gaaaagttat taaatgcaaa gcagctgtgc tttgggagca gaagcaaccc ttctccattg 1.
aggaaataga agttgcccca ccaaagacta aagaagttcg catttaagatt ttggccacag 1·
gaatctgtcg cacagatgac catgtgataa aaggaacaat ggtgtccaag tttccagtga 2·
ttgtgggaca tgaggcaact gggattgtag agagcattgg agaaggagtg actacagtga 3
aaccaggtga caaagtcatc cctctctttc tgccacaatg tagagaatgc aatgcttgtc 3·
gcaacccaga tggcaacctt tgcattagga gcgatattac tggtcgtgga gtactggctg 4
atggcaccac cagatttaca tgcaagggca aaccagtcca ccacttcatg aacaccagta 4
catttaccga gtacacagtg gtggatgaat cttctgttgc taagattgat gatgcagctc 5
ctcctgagaa agtctgttta attggctgtg ggttttccac tggatatggc gctgctgtta 6
aaactggcaa ggtcaaacct ggttccactt gcgtcgtctt tggcctgaga ggagttggcc 6
tgtcagtcat catgggctgt aagtcagctg gtgcatctag gatcattggg attgacctca 7
acaaagacaa atttgagaag gccatggctg taggtgccac tgagtgtatc agtcccaagg 7
actctaccaa acccatcagt gaggtgctgt cagaaatgac aggcaacaac gtgggataca 8
cctttgaagt tattgggcat cttgaaacca tgattgatgc cctggcatcc tgccacatga 9
actatgggac cagcgtggtt gtaggagttc ctccatcagc caagatgctc acctatgacc 9
cgatgttgct cttcactgga cgcacatgga agggatgtgt ctttggaggt ttgaaaagca 10
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gacaaagcat tcgaacggtc ctgacgtttt gagatccaaa gtggcaggag gtctgtgttg 12
tcatggtgaa ctggagtttc tcttgtgaga gttccctcat ctgaaatcat gtatctgtct 12
cacaaataca agcataagta gaagatttgt tgaagacata gaacccttat aaagaattat 13
taacctttat aaacatttaa agtcttgtga gcacctggga attagtataa taacaatgtt 13
aatatttttg atttacattt tgtaaggcta taattgtatc ttttaagaaa acatacactt 14
ggatttctat gttgaaatgg agatttttaa gagttttaac cagctgctgc agatatatat 1!
ctcaaaacag atatagcgta taaagatata gtaaatgcat ctcctagagt aatattcact 1!

303
370

taacacattg aaactattat tttttagatt tgaatataaa tgtatttttt aaacacttgt 162(
tatgagttaa cttggattac attttgaaat cagttcattc catgatgcat attactggat 168(
tagattaaga aagacagaaa agattaaggg acgggcacat ttttcaacga ttaagaatca 174(
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cagcatatat taatatttta gaaaatattc cttttgtaat actgaatata aacatagagc 186
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<210> 79
<211> 2790
<212> DNA
<213> Homo sapien

<400> 79
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<210> 80
<211> 1460
<212> DNA
<213> Homo sapien

<400> 80
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acaaaaaaaa aaaaaaaaaa 146

<210> 81
<211> 386
<212> PRT
<213> Homo sapien

<400> 81
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20 25 30
Pro Phe Ser Ile Glu Glu Ile Glu Val Ala Pro Pro Lys Thr Lys Glu
35 40 45
Val Arg Ile Lys Ile Leu Ala Thr Gly Ile Cys Arg Thr Asp Asp His
50 55 60

105
375
372

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

<210> 82
<211> 418
<212> PRT
<213> Homo sapien

<400> 82
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Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
35 40 45

206
376
373

Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
50 55 60
Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65 70 75 80
Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
85 90 95
Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
100 105 110
Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
115 120 125
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
130 135 140
Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145 150 155 160
Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
165 170 175
Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
180 185 190
Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
195 200 205
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
210 215 220
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225 230 235 240
Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
245 250 255
Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
260 265 270
Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
275 280 285
His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
290 295 300
Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
305 310 315 320
Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
325 330 335
Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
340 345 350
Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
355 360 365
Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
370 375 380
Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
385 390 395 400
Val Tyr Thr Arg Val Thr Ala Tyr Leu Asp Trp Ile Arg Gln Gln Thr
405 410 415
Gly Ile

<210> 83
<211> 418
<212> PRT
<213> Homo sapien

<400> 83

107
377
374

SUBSTITUTE SHEET (RULE 26)

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Tyr Val Val Cys Phe Ile Val Val Ala Gly Val Val Ile Leu Ala Val
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Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
        35                  40                  45
Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
    50                  55                  60
Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65                  70                  75                  80
Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
                85                  90                  95
Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
            100                 105                 110
Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
        115                 120                 125
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
    130                 135                 140
Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145                 150                 155                 160
Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
                165                 170                 175
Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
            180                 185                 190
Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
        195                 200                 205
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
    210                 215                 220
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225                 230                 235                 240
Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
                245                 250                 255
Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
            260                 265                 270
Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
        275                 280                 285
His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
    290                 295                 300
Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
305                 310                 315                 320
Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
                325                 330                 335
Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
            340                 345                 350
Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
        355                 360                 365
Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
    370                 375                 380
Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
385                 390                 395                 400
Val Tyr Thr Arg Val Thr Ala Tyr Leu Asp Trp Ile Arg Gln Gln Thr
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Gly Ile
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103
375

<210> 84
<211> 489
<212> DNA
<213> Homo sapien

<400> 84
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aattacagag gagtttcatg gcactaagtc aagatattca gaaaacaata aagaagacag 18
cacgtcggga gcagcttatg agagaagaag ctgaacagaa acgtttaaaa actgtacttg 24
agctacagta tgttttggac aaattgggag atgatgaagt gcggactgac ctgaaacaag 30
gtttgaatgg agtgccaata ttgtccgaag aggagttgtc attgttggat gaattctata 36
agctagtaga ccctgaacgg gacatgagct tgaggttgaa tgaacagtat gaacatgcct 42
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aagttctaa 48

<210> 85
<211> 304
<212> DNA
<213> Homo sapien

<400> 85
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agctggagaa ggagaagagc gagatgaaga tggagatcga tgacctcgct tgtaacatgg 1
aggtcatctc caaatctaag ggaaaccttg agaagatgtg ccgcacactg gaggaccaag 2
tgagtgagct gaagacccag gaggaggaac agcagcggct gatcaatgaa ctgactgcgc 3
agag 3

<210> 86
<211> 296
<212> DNA
<213> Homo sapien

<400> 86
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tccatatgtt gtatgtttcc ttgtcctccc aggggttgtg atcctggcag tccccatagc 1
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actcccaaat gttgaatata atagtccgtt taattccccc gcttcaccgg gaattc :

<210> 87
<211> 904
<212> DNA
<213> Homo sapien

<400> 87
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acca 90

<210> 88
<211> 387
<212> DNA
<213> Homo sapien

<400> 88
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<210> 89
<211> 481
<212> DNA
<213> Homo sapien

<400> 89
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tgaaccagca agctatacag attcttgaaa agatttctca gccagtggtg gtggtggcca 1
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a 4

<210> 90
<211> 491
<212> DNA
<213> Homo sapien

<400> 90
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accagcaagc tatacagatt cttgaaaaga tttctcagcc agtggtggtg gtggccattg 1
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atgtgacgga c 4

110
380
377

<210> 91
<211> 488
<212> DNA
<213> Homo sapien

<400> 91
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ctgcttttaa ctctggtaaa gtggatattg ttgccatcaa tgaccccttc attgacctca 18
actacatggt ttacatgttc caatatgatt ccacccatgg caaattccat ggcaccgtcg 24
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acagcctc 48

<210> 92
<211> 384
<212> DNA
<213> Homo sapien

<400> 92
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ctgagaacgg gaagcttgtc atcaatggaa atcccatcac catcttccag gagcgagatc 3
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<210> 93
<211> 162
<212> PRT
<213> Homo sapien

<400> 93
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20 25 30
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35 40 45
Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln
50 55 60
Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu
65 70 75 80
Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp
85 90 95
Leu Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu
100 105 110Ser Leu Leu Asp
Phe Tyr Lys Leu Val Asp Pro Glu Arg Asp Met
115 120 125
Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp
130 135 140
Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys Gly Thr Thr Tyr Lys

HH
387
378

145 150 155 160
Val Leu

<210> 94
<211> 100
<212> PRT
<213> Homo sapien

<400> 94
Asp Leu Glu Glu Ala Thr Leu Gln His Glu Ala Thr Ala Ala Thr Leu
1 5 10 15
Arg Lys Lys His Ala Asp Ser Val Ala Glu Leu Gly Glu Gln Ile Asp
20 25 30
Asn Leu Gln Arg Val Lys Gln Lys Leu Glu Lys Glu Lys Ser Glu Met
35 40 45
Lys Met Glu Ile Asp Asp Leu Ala Cys Asn Met Glu Val Ile Ser Lys
50 55 60
Ser Lys Gly Asn Leu Glu Lys Met Cys Arg Thr Leu Glu Asp Gln Val
65 70 75 80
Ser Glu Leu Lys Thr Gln Glu Glu Glu Gln Gln Arg Leu Ile Asn Glu
85 90 95
Leu Thr Ala Gln
100

<210> 95
<211> 99
<212> PRT
<213> Homo sapien

<400> 95
Lys Ile Leu Pro Leu Asn Gly Asn Leu Gln Ala Val Glu Leu Gly Glu
1 5 10 15
Lys Arg Thr Ser Ser Leu Arg Ile Lys Met Phe Arg Ala Thr Arg Val
20 25 30
Thr Ser Thr Ser Arg Phe Leu Asn Pro Tyr Val Val Cys Phe Leu Val
35 40 45
Leu Pro Gly Val Val Ile Leu Ala Val Pro Ile Ala Leu Leu Val Tyr
50 55 60
Phe Leu Ala Phe Asp Gln Lys Ser Tyr Phe Tyr Trp Ser Asn Phe Pro
65 70 75 80
Leu Pro Asn Val Glu Tyr Asn Ser Pro Phe Asn Ser Pro Ala Ser Pro
85 90 95
Gly Ile Pro

<210> 96
<211> 257
<212> PRT
<213> Homo sapien

<400> 96
Val Gln Glu Thr Ile His Glu His Asn Lys Leu Ala Ala Asn Ser Asp
1 5 10 15
His Leu Met Gln Ile Gln Lys Cys Glu Leu Val Leu Ile His Thr Tyr

172
382
379

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                20                  25                  30
Pro Val Gly Glu Asp Ser Leu Val Ser Asp Arg Ser Lys Lys Glu Leu
            35                  40                  45
Ser Pro Val Leu Thr Ser Glu Val His Ser Val Arg Ala Gly Arg His
        50                  55                  60
Leu Ala Thr Lys Leu Asn Ile Leu Val Gln Gln His Phe Asp Leu Ala
65                  70                  75                  80
Ser Thr Thr Ile Thr Asn Ile Pro Met Lys Glu Glu Gln His Ala Asn
                85                  90                  95
Thr Ser Ala Asn Tyr Asp Val Glu Leu Leu His His Lys Asp Ala His
            100                 105                 110
Val Asp Phe Leu Lys Ser Gly Asp Ser His Leu Gly Gly Gly Ser Arg
        115                 120                 125
Glu Gly Ser Phe Lys Glu Thr Ile Thr Leu Lys Trp Cys Thr Pro Arg
    130                 135                 140
Thr Asn Asn Ile Glu Leu His Tyr Cys Thr Gly Ala Tyr Arg Ile Ser
145                 150                 155                 160
Pro Val Asp Val Asn Ser Arg Pro Ser Ser Cys Leu Thr Asn Phe Leu
                165                 170                 175
Leu Asn Gly Arg Ser Val Leu Leu Glu Gln Pro Arg Lys Ser Gly Ser
            180                 185                 190
Lys Val Ile Ser His Met Leu Ser Ser His Gly Gly Glu Ile Phe Leu
        195                 200                 205
His Val Leu Ser Ser Ser Arg Ser Ile Leu Glu Asp Pro Pro Ser Ile
    210                 215                 220
Ser Glu Gly Cys Gly Gly Arg Val Thr Asp Tyr Arg Ile Thr Asp Phe
225                 230                 235                 240
Gly Glu Phe Met Arg Gly Lys Gln Ile Asn Ser Phe Ser Thr Pro Gln
                245                 250                 255
Ile
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<210> 97
<211> 128
<212> PRT
<213> Homo sapien

<400> 97

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Ser Leu Pro Gln Phe Ala Val His Pro Glu Arg Ser Gly Leu Ala Asp
 1               5                  10                  15
Ser Gly Asp Gly Gly Asn Met Ser Val Ala Phe Ala Ala Pro Arg Gln
            20                  25                  30
Arg Gly Lys Gly Glu Ile Thr Pro Ala Ala Ile Gln Lys Met Leu Asp
        35                  40                  45
Asp Asn Asn His Leu Ile Gln Cys Ile Met Asp Ser Gln Asn Lys Gly
    50                  55                  60
Lys Thr Ser Glu Cys Ser Gln Tyr Gln Gln Met Leu His Thr Asn Leu
65                  70                  75                  80
Val Tyr Leu Ala Thr Ile Ala Asp Ser Asn Gln Asn Met Gln Ser Leu
                85                  90                  95
Leu Pro Ala Pro Pro Thr Gln Asn Met Pro Met Gly Pro Gly Gly Met
            100                 105                 110
Asn Gln Ser Gly Pro Pro Pro Pro Pro Arg Ser His Asn Met Pro Ser
        115                 120                 125
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HB 383 380

<210> 98
<211> 159
<212> PRT
<213> Homo sapien

<400> 98

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

<210> 99
<211> 147
<212> PRT
<213> Homo sapien

<400> 99

```
Met Glu Ser Gly Pro Lys Met Leu Ala Pro Val Cys Leu Val Glu Asn
 1               5                  10                  15
Asn Asn Glu Gln Leu Leu Val Asn Gln Gln Ala Ile Gln Ile Leu Glu
            20                  25                  30
Lys Ile Ser Gln Pro Val Val Val Val Ala Ile Val Gly Leu Tyr Arg
        35                  40                  45
Thr Gly Lys Ser Tyr Leu Met Asn His Leu Ala Gly Gln Asn His Gly
    50                  55                  60
Phe Pro Leu Gly Ser Thr Val Gln Ser Glu Thr Lys Gly Ile Trp Met
65                  70                  75                  80
Trp Cys Val Pro His Pro Ser Lys Pro Asn His Thr Leu Val Leu Leu
                85                  90                  95
Asp Thr Glu Gly Leu Gly Asp Val Glu Lys Gly Asp Pro Lys Asn Asp
            100                 105                 110
Ser Trp Ile Phe Ala Leu Ala Val Leu Leu Cys Ser Thr Phe Val Tyr
        115                 120                 125
Asn Ser Met Ser Thr Ile Asn His Gln Ala Leu Glu Gln Leu His Tyr
    130                 135                 140
Val Thr Asp
145
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<210> 100

114
384
381

<211> 124
<212> PRT
<213> Homo sapien

<400> 100

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

<210> 101
<211> 127
<212> PRT
<213> Homo sapien

<400> 101

```
Gln Ser Ala Ala Ser Ser Phe Ala Ser Pro Ala Glu Pro His Arg Ser
 1               5                  10                  15
Asp Thr Met Gly Lys Val Lys Val Gly Val Asn Gly Phe Gly Arg Ile
            20                  25                  30
Gly Arg Leu Val Thr Arg Ala Ala Phe Asn Ser Gly Lys Val Asp Ile
        35                  40                  45
Val Ala Ile Asn Asp Pro Phe Ile Asp Leu Asn Tyr Met Val Tyr Met
    50                  55                  60
Phe Gln Tyr Asp Ser Thr His Gly Lys Phe His Gly Thr Val Glu Ala
65                  70                  75                  80
Glu Asn Gly Lys Leu Val Ile Asn Gly Asn Pro Ile Thr Ile Phe Gln
                85                  90                  95
Glu Arg Asp Pro Ser Lys Ile Lys Trp Gly Asp Thr Gly Ala Glu Tyr
            100                 105                 110
Val Val Glu Ser Thr Gly Val Phe Thr Thr Met Glu Lys Ala Gly
        115                 120                 125
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<210> 102
<211> 1225
<212> DNA
<213> Homo sapien

<400> 102

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atggcggcgc ggtcgtcgtc ggggggtggcg gcggcagagg gggcggcggc cctggcggca
gcggagacgg cagccgtgac ggtggcagcg gcggcgcggg acctgggcct gggggaatga
ggcggccgcg gcgggccagc ggcggagccg tgtagcggag aagctccccc tccctgcttc
ccttggccga gccgggggcg cgcgcgcacg cggccgtcca gagcgggctc cccacccctc
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HF 385 382

gactcctgcg acccgcaccg cacccccacc cgggcccgga ggatgatgaa gctcaagtcg 30
aaccagaccc gcacctacga cggcgacggc tacaagaagc gggccgcatg cctgtgtttc 36
cgcagcgaga gcgaggagga ggtgctactc gtgagcagta gtcgccatcc agacagatgg 42
attgtccctg gaggaggcat ggagcccgag gaggagccaa gtgtggcagc agttcgtgaa 48
gtctgtgagg aggctggagt aaaagggaca ttgggaagat tagttggaat ttttgagaac 54
caggagagga agcacaggac gtatgtctat gtgctcattg tcactgaagt gctggaagac 60
tgggaagatt cagttaacat tggaaggaag agggaatggt ttaaaataga agacgccata 66
aaagtgctgc agtatcacaa acccgtgcag gcatcatatt ttgaaacatt gaggcaaggc 72
tactcagcca acaatggcac cccagtcgtg gccaccacat actcggtttc tgctcagagc 78
tcgatgtcag gcatcagatg actgaagact tcctgtaaga gaaatggaaa ttggaaacta 84
gactgaagtg caaatcttcc ctctcaccct ggctctttcc acttctcaca ggcctcctct 90
ttcaaataag gcatggtggg cagcaaagaa agggtgtatt gataatgttg ctgtttggtg 96
ttaagtgatg gggctttttc ttctgttttt attgagggtg ggggttgggt gtgtaatttg 102
taagtacttt tgtgcatgat ctgtccctcc ctcttcccac ccctgcagtc ctctgaagag 108
aggccaacag ccttcccctg ccttggattc tgaagtgttc ctgtttgtct tatcctggcc 114
ctggccagac gttttctttg atttttaatt ttttttttct attaaaagat accagtatga 120
gaaaaaaaaa aaaaaaaaac tcgag 125

<210> 103
<211> 741
<212> DNA
<213> Homo sapien

<400> 103
agaaacctca atcggattca gcaaaggaat ggtgttatta tcactacata ccaaatgtta
atcaataact ggcagcaact ttcaagcttt aggggccaag agtttgtgtg ggactatgtc 1
atcctcgatg aagcacataa aataaaaacc tcatctacta agtcagcaat atgtgctcgt 1
gctattcctg caagtaatcg cctcctcctc acaggaaccc caatccagaa taatttacaa 2
gaactatggt ccctatttga ttttgcttgt caagggtccc tgctgggaac attaaaaact 3
tttaagatgg agtatgaaaa tcctattact agagcaagag agaaggatgc taccccagga 3
gaaaaagcct tgggatttaa aatatctgaa aacttaatgg caatcataaa accctatttt 4
ctcaggagga ctaaagaaga cgtacagaag aaaaagtcaa gcaacccaga ggccagactt 4
aatgaaaaga atccagatgt tgatgccatt tgtgaaatgc cttccctttc caggagaaat 5
gatttaatta tttggatacg acttgtgcct ttacaagaag aaatatacag gaaatttgtg 6
tctttagatc atatcaagga gttgctaatg gagacgcgct caccttggc tgagctaggt 6
gtcttaaaga agctgtgtga tcatcctagg ctgctgtctg cacgggcttg ttgtttgcta 7
aatcttggga cattctctgc t 7

<210> 104
<211> 321
<212> DNA
<213> Homo sapien

<400> 104
ttgctctgcg tcatcaaaga caccaaactg ctgtgctata aaagttccaa ggaccagcag
cctcagatgg aactgccact ccaaggctgt aacattacgt acatcccgaa agacagcaaa 1
aagaagaagc acgagctgaa gattactcag cagggcacgg acccgcttgt tctcgccgtc 1
cagagcaagg aacaggccga gcagtggctg aaggtgatca aagaagccta cagtggttgt 2
agtggccccg tggattcaga gtgtcctcct ccaccaagct ccccggtgca caaggcagaa 3
ctggagaaga aactgtcttc a 3

<210> 105
<211> 389
<212> DNA
<213> Homo sapien

H6
286
383

<400> 105
cagcactggc cacactataa aattcaggtt cagaaaaaca gggtaagtca cagacagcaa 6
cgcttccagc atttattttc tttgcaccca tgggcaattt gagaaaattt acctttagaa 12
cgaactctgt taaaggtaca gacagtacaa tacttttttat tcagaaggtt tctgcataaa 18
ggtgatagtc ttttgactta atatattatt gtctcctgcc ttgtgtttct ggaatgaatg 24
aaggtcatta tttagaagat aatctgggtt gtatttgtgt cgtcagattg aatttttcatt 30
gcacatgcta cttaatgtct ttaccaaata ataacaaagg gaaagaaaac caaatataga 36
tgtataataa ggaaaagctg gcctataga 38

<210> 106
<211> 446
<212> DNA
<213> Homo sapien

<400> 106
gccacatttg ccctggtcat agtttaaaca ccaggtcctg tgtcacatct ttttggtgcc 6
acaagtatca ctccattgtt cagagagtaa tgtattagtt ctgcccaatt cattcttcac 12
ttttatttct tccatttcat tagcatttat atcagctcaa gaagttaagg ttagaaaatt 18
ttccacttca aattttcagt acagaaatgt gctgtgatgt ttgacaagac tatttcatag 24
taagtgagtt aatgtttatt ggcctctgct ctcctctgtg tcagacctag gaagcctgag 30
gattacttag ttgttctgtc tctgggtcca caggcagaat ttggcccatc caaagactgg 36
ccaagtgcca aaaaaaggcc tgattaggcc ctgaaattca gtgaaattct gcctgaagaa 42
acctcttatt gaatttgaaa accata 44

<210> 107
<211> 467
<212> DNA
<213> Homo sapien

<400> 107
ccgccgctgc cgtcgccttc ctgggattgg agtctcgagc tttcttcgtt cgttcgccgg
cgggttcgcg ccccttctcgc gcctcggggc tgcgaggctg gggaaggggt tggaggggcc 1
tgttgatcgc cgcgtttaag ttgcgctcgg ggcggccatg tcggccggcg aggtcgagcg 1
cctagtgtcg gagctgagcg gcgggaccgg aggggatgag gaggaagagt ggctctatgg 2
cgatgaagat gaagttgaaa ggccagaaga agaaaatgcc agtgctaatc ctccatctgg 3
aattgaagat gaaactgctg aaaatggtgt accaaaaccg aaagtgactg agaccgaaga 3
tgatagtgat agtgacagcg atgatgatga agatgatgtg catgtcacta taggagacat 4
taaaacggga gcaccacagt atgggagtta tggtacagca cctgtaa 4

<210> 108
<211> 491
<212> DNA
<213> Homo sapien

<400> 108
gaaagataca acttccccaa cccaaacccg tttgtggagg acgacatgga taagaatgaa
atcgcctctg ttgcgtaccg ttaccgcagg tggaagcttg gagatgatat tgaccttatt
gtccgttgtg agcacgatgg cgtcatgact ggagccaacg gggaagtgtc cttcatcaac
atcaagacac tcaatgagtg ggattccagg cactgtaatg gcgttgactg gcgtcagaag
ctggactctc agcgaggggc tgtcattgcc acggagctga agaacaacag ctacaagttg
gcccggtgga cctgctgtgc tttgctggct ggatctgagt acctcaagct tggttatgtg
tctcggtacc acgtgaaaga ctcctcacgc cacgtcatcc taggcaccca gcagttcaag
cctaatgagt ttgccagcca gatcaacctg agcgtggaga atgcctgagg cattttacgc
tgcgtcattg a

383
384

<210> 109
<211> 489
<212> DNA
<213> Homo sapien

<400> 109
ctcagatagt actgaaccct ttatcaacta tgtttttca gtctgacaac caaggcggct 6
actaagtgac taaggggcag gtagtataca gtgtggataa gcaggacaaa ggggtgattc 12
acatcccagg caggacagag caggagatca tgagatttca tcactcagga tggcttgtga 18
tttattttat tttattcttt ttttttttg agatggagtc tcactcttgc ccaggctgga 24
gtgcagtggt gcgatcttgg ctcactgcaa cctctgcctc ctgggttcaa gcagttctcc 30
tgcctcagcc tcccaagtag ctgggattac aggcgtccgc caccatgccc agccaatttt 36
tgtacttta gtagagatgg ggtttcacca tgttggccag gctggtctcg aactcctgac 42
ctcaggtgat ccactcgcct cggcctccca aagtgctggg attataggca tgcgccacca 48
tgcccgggc 48

<210> 110
<211> 391
<212> DNA
<213> Homo sapien

<400> 110
gcggagtccg ctggctgacc cgagcgctgg tctccgccgg gaaccctggg gcatggagag
gtctgagtac ctcggccgcg gcgcacgctg catcgcggag ccaggctgcc gctgtcccag 1
tggagttcca ggagcaccac ctgagtgagg tgcagaatat ggcatctgag gagaagctgg 1
agcaggtgct gagttccatg aaggagaaca aagtggccat cattggaaag attcataccc 2
cgatggagta taaggggggag ctagcctcct atgatatgcg gctgaggcgt aagttggact 3
tatttgccaa cgtaatccat gtgaagtcac ttcctgggta tatgactcgg cacaacaatc 3
tagacctggt gatcattcga gagcagacag a 3

<210> 111
<211> 172
<212> PRT
<213> Homo sapien

<400> 111
Met Met Lys Leu Lys Ser Asn Gln Thr Arg Thr Tyr Asp Gly Asp Gly
1 5 10 15
Tyr Lys Lys Arg Ala Ala Cys Leu Cys Phe Arg Ser Glu Ser Glu Glu
20 25 30
Glu Val Leu Leu Val Ser Ser Ser Arg His Pro Asp Arg Trp Ile Val
35 40 45
Pro Gly Gly Gly Met Glu Pro Glu Glu Glu Pro Ser Val Ala Ala Val
50 55 60
Arg Glu Val Cys Glu Glu Ala Gly Val Lys Gly Thr Leu Gly Arg Leu
65 70 75 80
Val Gly Ile Phe Glu Asn Gln Glu Arg Lys His Arg Thr Tyr Val Tyr
85 90 95
Val Leu Ile Val Thr Glu Val Leu Glu Asp Trp Glu Asp Ser Val Asn
100 105 110
Ile Gly Arg Lys Arg Glu Trp Phe Lys Ile Glu Asp Ala Ile Lys Val
115 120 125
Leu Gln Tyr His Lys Pro Val Gln Ala Ser Tyr Phe Glu Thr Leu Arg
130 135 140

Gln Gly Tyr Ser Ala Asn Asn Gly Thr Pro Val Val Ala Thr Thr Tyr
145 150 155 160
Ser Val Ser Ala Gln Ser Ser Met Ser Gly Ile Arg
165 170

<210> 112
<211> 247
<212> PRT
<213> Homo sapien

<400> 112
Arg Asn Leu Asn Arg Ile Gln Gln Arg Asn Gly Val Ile Ile Thr Thr
1 5 10 15
Tyr Gln Met Leu Ile Asn Asn Trp Gln Gln Leu Ser Ser Phe Arg Gly
20 25 30
Gln Glu Phe Val Trp Asp Tyr Val Ile Leu Asp Glu Ala His Lys Ile
35 40 45
Lys Thr Ser Ser Thr Lys Ser Ala Ile Cys Ala Arg Ala Ile Pro Ala
50 55 60
Ser Asn Arg Leu Leu Leu Thr Gly Thr Pro Ile Gln Asn Asn Leu Gln
65 70 75 80
Glu Leu Trp Ser Leu Phe Asp Phe Ala Cys Gln Gly Ser Leu Leu Gly
85 90 95
Thr Leu Lys Thr Phe Lys Met Glu Tyr Glu Asn Pro Ile Thr Arg Ala
100 105 110
Arg Glu Lys Asp Ala Thr Pro Gly Glu Lys Ala Leu Gly Phe Lys Ile
115 120 125
Ser Glu Asn Leu Met Ala Ile Ile Lys Pro Tyr Phe Leu Arg Arg Thr
130 135 140
Lys Glu Asp Val Gln Lys Lys Lys Ser Ser Asn Pro Glu Ala Arg Leu
145 150 155 160
Asn Glu Lys Asn Pro Asp Val Asp Ala Ile Cys Glu Met Pro Ser Leu
165 170 175
Ser Arg Arg Asn Asp Leu Ile Ile Trp Ile Arg Leu Val Pro Leu Gln
180 185 190
Glu Glu Ile Tyr Arg Lys Phe Val Ser Leu Asp His Ile Lys Glu Leu
195 200 205
Leu Met Glu Thr Arg Ser Pro Leu Ala Glu Leu Gly Val Leu Lys Lys
210 215 220
Leu Cys Asp His Pro Arg Leu Leu Ser Ala Arg Ala Cys Cys Leu Leu
225 230 235 240
Asn Leu Gly Thr Phe Ser Ala
245

<210> 113
<211> 107
<212> PRT
<213> Homo sapien

<400> 113
Leu Leu Cys Val Ile Lys Asp Thr Lys Leu Leu Cys Tyr Lys Ser Ser
1 5 10 15
Lys Asp Gln Gln Pro Gln Met Glu Leu Pro Leu Gln Gly Cys Asn Ile
20 25 30
Thr Tyr Ile Pro Lys Asp Ser Lys Lys Lys Lys His Glu Leu Lys Ile

119
389
386

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35 40 45

Thr Gln Gln Gly Thr Asp Pro Leu Val Leu Ala Val Gln Ser Lys Glu
50 55 60
Gln Ala Glu Gln Trp Leu Lys Val Ile Lys Glu Ala Tyr Ser Gly Cys
65 70 75 80
Ser Gly Pro Val Asp Ser Glu Cys Pro Pro Pro Pro Ser Ser Pro Val
85 90 95
His Lys Ala Glu Leu Glu Lys Lys Leu Ser Ser
100 105

<210> 114
<211> 155
<212> PRT
<213> Homo sapien

<400> 114
Glu Arg Tyr Asn Phe Pro Asn Pro Asn Pro Phe Val Glu Asp Asp Met
1 5 10 15
Asp Lys Asn Glu Ile Ala Ser Val Ala Tyr Arg Tyr Arg Arg Trp Lys
20 25 30
Leu Gly Asp Asp Ile Asp Leu Ile Val Arg Cys Glu His Asp Gly Val
35 40 45
Met Thr Gly Ala Asn Gly Glu Val Ser Phe Ile Asn Ile Lys Thr Leu
50 55 60
Asn Glu Trp Asp Ser Arg His Cys Asn Gly Val Asp Trp Arg Gln Lys
65 70 75 80
Leu Asp Ser Gln Arg Gly Ala Val Ile Ala Thr Glu Leu Lys Asn Asn
85 90 95
Ser Tyr Lys Leu Ala Arg Trp Thr Cys Cys Ala Leu Leu Ala Gly Ser
100 105 110
Glu Tyr Leu Lys Leu Gly Tyr Val Ser Arg Tyr His Val Lys Asp Ser
115 120 125
Ser Arg His Val Ile Leu Gly Thr Gln Gln Phe Lys Pro Asn Glu Phe
130 135 140
Ala Ser Gln Ile Asn Leu Ser Val Glu Asn Ala
145 150 155

<210> 115
<211> 129
<212> PRT
<213> Homo sapien

<400> 115
Gly Val Arg Trp Leu Thr Arg Ala Leu Val Ser Ala Gly Asn Pro Gly
1 5 10 15
Ala Trp Arg Gly Leu Ser Thr Ser Ala Ala Ala His Ala Ala Ser Arg
20 25 30
Ser Gln Ala Ala Ala Val Pro Val Glu Phe Gln Glu His His Leu Ser
35 40 45
Glu Val Gln Asn Met Ala Ser Glu Glu Lys Leu Glu Gln Val Leu Ser
50 55 60
Ser Met Lys Glu Asn Lys Val Ala Ile Ile Gly Lys Ile His Thr Pro
65 70 75 80
Met Glu Tyr Lys Gly Glu Leu Ala Ser Tyr Asp Met Arg Leu Arg Arg
85 90 95

120
390
387

Lys Leu Asp Leu Phe Ala Asn Val Ile His Val Lys Ser Leu Pro Gly
100 105 110
Tyr Met Thr Arg His Asn Asn Leu Asp Leu Val Ile Ile Arg Glu Gln
115 120 125
Thr

<210> 116
<211> 550
<212> DNA
<213> Homo sapien

<400> 116
gaattcggca ccagcctcag agccccccag cccggctacc acccccctgcg gaaaggtacc 6
catctgcatt cctgcccgtc gggacctggt ggacagtcca gcctccttgg cctctagcct 12
tggctcaccg ctgcctagag ccaaggagct catcctgaat gaccttcccg ccagcactcc 18
tgcctccaaa tcctgtgact cctcccccgcc ccaggacgct tccacccccca ggcccagctc 24
ggccagtcac ctctgccagc ttgctgccaa gccagcacct tccacggaca gcgtcgccct 30
gaggagcccc ctgactctgt ccagtcccctt caccacgtcc ttcagcctgg gctcccacag 36
cactctcaac ggagacctct ccgtgcccag ctcctacgtc agcctccacc tgtccccccca 42
ggtcagcagc tctgtggtgt acggacgctc ccccgtgatg gcatttgagt ctcatcccca 48
tctccgaggg tcatccgtct cttcctccct acccagcatc cctgggggaa agccggccta 54
ctccttccac 55

<210> 117
<211> 154
<212> DNA
<213> Homo sapien

<400> 117
ttctgaggga aagccgagtg gagtgggcga cccggcggcg gtgacaatga gttttcttgg
aggcttttt ggtcccattt gtgagattga tgttgccctt aatgatgggg aaaccaggaa 1
aatggcagaa atgaaaactg aggatggcaa agta 1

<210> 118
<211> 449
<212> DNA
<213> Homo sapien

<400> 118
gaattcggca ccagggcccg cagcccgagt gtcgccgcca tggcttcgcc gcagctctgc
cgcgcgctgg tgtcggcgca atgggtggcg gaggcgctgc gggccccgcg cgctgggcag
cctctgcagc tgctggacgc ctcctggtac ctgccgaagc tggggcgcga cgcgcgacgc
gagttcgagg agcgccacat cccgggcgcc gctttcttcg acatcgacca gtgcagcgac
cgcacctcgc cctacgacca catgctgccc ggggccgagc atttcgcgga gtacgcaggc
cgcctgggcg tgggcgcggc cacccacgtc gtgatctacg acgccagcga ccagggcctc
tactccgccc cgcgcgtctg gtggatgttc cgcgccttcg gccaccacgc cgtgtcactg
cttgatggcg gcctccgcca ctggctgcg

<210> 119
<211> 642
<212> DNA
<213> Homo sapien

<400> 119

gaattcggca cgagcagtaa cccgaccgcc gctggtcttc gctggacacc atgaatcaca 60
ctgtccaaac cttcttctct cctgtcaaca gtggccagcc ccccaactat gagatgctca 120
aggaggagca cgaggtggct gtgctggggg cgccccacaa ccctgctccc ccgacgtcca 180
ccgtgatcca catccgcagc gagacctccg tgcccgacca tgtcgtctgg tccctgttca 240
acaccctctt catgaacccc tgctgcctgg gcttcatagc attcgcctac tccgtgaagt 300
ctagggacag gaagatggtt ggcgacgtga ccggggccca ggcctatgcc tccaccgcca 360
agtgcctgaa catctgggcc ctgattctgg gcatcctcat gaccattctg ctcatcgtca 420
tcccagtgct gatcttccag gcctatggat agatcaggag gcatcactga ggccaggagc 480
tctgcccatg acctgtatcc cacgtactcc aacttccatt cctcgccctg ccccccggagc 540
cgagtcctgt atcagccctt tatcctcaca cgcttttcta caatggcatt caataaagtg 600
cacgtgtttc tggtgaaaaa aaaaaaaaaa aaaaaactcg ag 642

<210> 120
<211> 603
<212> DNA
<213> Homo sapien

<400> 120
gaattcggca cgagccacaa cagccactac gactgcatcc actggatcca cggccacccc 60
gtcctccacc ccgggaacag ctccccctcc caaagtgctg accagcccgg ccaccacacc 120
catgtccacc atgtccacaa tccacacctc ctctactcca gagaccaccc acacctccac 180
agtgctgacc accacagcca ccatgacaag ggccaccaat tccacggcca cacctcctc 240
cactctgggg acgacccgga tcctcactga gctgaccaca acagccacta caactgcagc 300
cactggatcc acggccaccc tgtcctccac cccagggacc acctggatcc tcacagagcc 360
gagcactata gccaccgtga tggtgcccac cggttccacg gccaccgcct cctccactct 420
gggaacagct cacaccccca aagtggtgac caccatggcc actatgccca cagccactgc 480
ctccacggtt cccagctcgt ccaccgtggg gaccacccgc acccctgcag tgctccccag 540
cagcctgcca accttcagcg tgtccactgt gtcctcctca gtcctcacca ccctgagacc 600
cac 603

<210> 121
<211> 178
<212> PRT
<213> Homo sapien

<400> 121
Ser Glu Pro Pro Ser Pro Ala Thr Thr Pro Cys Gly Lys Val Pro Ile
1 5 10 15
Cys Ile Pro Ala Arg Arg Asp Leu Val Asp Ser Pro Ala Ser Leu Ala
20 25 30
Ser Ser Leu Gly Ser Pro Leu Pro Arg Ala Lys Glu Leu Ile Leu Asn
35 40 45
Asp Leu Pro Ala Ser Thr Pro Ala Ser Lys Ser Cys Asp Ser Ser Pro
50 55 60
Pro Gln Asp Ala Ser Thr Pro Arg Pro Ser Ser Ala Ser His Leu Cys
65 70 75 80
Gln Leu Ala Ala Lys Pro Ala Pro Ser Thr Asp Ser Val Ala Leu Arg
85 90 95
Ser Pro Leu Thr Leu Ser Ser Pro Phe Thr Thr Ser Phe Ser Leu Gly
100 105 110
Ser His Ser Thr Leu Asn Gly Asp Leu Ser Val Pro Ser Ser Tyr Val
115 120 125
Ser Leu His Leu Ser Pro Gln Val Ser Ser Ser Val Val Tyr Gly Arg
130 135 140
Ser Pro Val Met Ala Phe Glu Ser His Pro His Leu Arg Gly Ser Ser

AE 395 389

145 150 155 160
Val Ser Ser Ser Leu Pro Ser Ile Pro Gly Gly Lys Pro Ala Tyr Ser
165 170 175
Phe His

<210> 122
<211> 36
<212> PRT
<213> Homo sapien

<400> 122
Met Ser Phe Leu Gly Gly Phe Phe Gly Pro Ile Cys Glu Ile Asp Val
1 5 10 15
Ala Leu Asn Asp Gly Glu Thr Arg Lys Met Ala Glu Met Lys Thr Glu
20 25 30
Asp Gly Lys Val
35

<210> 123
<211> 136
<212> PRT
<213> Homo sapien

<400> 123
Met Ala Ser Pro Gln Leu Cys Arg Ala Leu Val Ser Ala Gln Trp Val
1 5 10 15
Ala Glu Ala Leu Arg Ala Pro Arg Ala Gly Gln Pro Leu Gln Leu Leu
20 25 30
Asp Ala Ser Trp Tyr Leu Pro Lys Leu Gly Arg Asp Ala Arg Arg Glu
35 40 45
Phe Glu Glu Arg His Ile Pro Gly Ala Ala Phe Phe Asp Ile Asp Gln
50 55 60
Cys Ser Asp Arg Thr Ser Pro Tyr Asp His Met Leu Pro Gly Ala Glu
65 70 75 80
His Phe Ala Glu Tyr Ala Gly Arg Leu Gly Val Gly Ala Ala Thr His
85 90 95
Val Val Ile Tyr Asp Ala Ser Asp Gln Gly Leu Tyr Ser Ala Pro Arg
100 105 110
Val Trp Trp Met Phe Arg Ala Phe Gly His His Ala Val Ser Leu Leu
115 120 125
Asp Gly Gly Leu Arg His Trp Leu
130 135

<210> 124
<211> 133
<212> PRT
<213> Homo sapien

<400> 124
Met Asn His Thr Val Gln Thr Phe Phe Ser Pro Val Asn Ser Gly Gln
1 5 10 15
Pro Pro Asn Tyr Glu Met Leu Lys Glu Glu His Glu Val Ala Val Leu
20 25 30
Gly Ala Pro His Asn Pro Ala Pro Pro Thr Ser Thr Val Ile His Ile

123
393
390

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

<210> 125
<211> 195
<212> PRT
<213> Homo sapien

<400> 125
Thr Thr Ala Thr Thr Thr Ala Ser Thr Gly Ser Thr Ala Thr Pro Ser
1 5 10 15
Ser Thr Pro Gly Thr Ala Pro Pro Pro Lys Val Leu Thr Ser Pro Ala
20 25 30
Thr Thr Pro Met Ser Thr Met Ser Thr Ile His Thr Ser Ser Thr Pro
35 40 45
Glu Thr Thr His Thr Ser Thr Val Leu Thr Thr Thr Ala Thr Met Thr
50 55 60
Arg Ala Thr Asn Ser Thr Ala Thr Pro Ser Ser Thr Leu Gly Thr Thr
65 70 75 80
Arg Ile Leu Thr Glu Leu Thr Thr Thr Ala Thr Thr Thr Ala Ala Thr
85 90 95
Gly Ser Thr Ala Thr Leu Ser Ser Thr Pro Gly Thr Thr Trp Ile Leu
100 105 110
Thr Glu Pro Ser Thr Ile Ala Thr Val Met Val Pro Thr Gly Ser Thr
115 120 125
Ala Thr Ala Ser Ser Thr Leu Gly Thr Ala His Thr Pro Lys Val Val
130 135 140
Thr Thr Met Ala Thr Met Pro Thr Ala Thr Ala Ser Thr Val Pro Ser
145 150 155 160
Ser Ser Thr Val Gly Thr Thr Arg Thr Pro Ala Val Leu Pro Ser Ser
165 170 175
Leu Pro Thr Phe Ser Val Ser Thr Val Ser Ser Ser Val Leu Thr Thr
180 185 190
Leu Arg Pro
195

<210> 126
<211> 509
<212> DNA
<213> Homo sapien

<400> 126
gaattcggca cgagccaagt acccccctgag gaatctgcag cctgcatctg agtacaccgt
atccctcgtg gccataaagg gcaaccaaga gagccccaaa gccactggag tctttaccac

391

actgcagcct gggagctcta ttccaccttа caacaccgag gtgactgaga ccaccattgt 18
gatcacatgg acgcctgctc caagaattgg ttttaagctg ggtgtacgac caagccaggg 24
aggagaggca ccacgagaag tgacttcaga ctcaggaagc atcgttgtgt ccggcttgac 30
tccaggagta gaatacgtct acaccatcca agtcctgaga gatggacagg aaagagatgc 36
gccaattgta aacaaagtgg tgacaccatt gtctccacca acaaacttgc atctggaggc 42
aaaccctgac actggagtgc tcacagtctc ctggagagga gcaccacccc agacattact 48
gggtatagaa ttaccacaac ccctacaaa 50

<210> 127
<211> 500
<212> DNA
<213> Homo sapien

<400> 127
gaattcggca cgagccactg atgtccgggg agtcagccag gagcttgggg aagggaagcg 6
cgcccccggg gccggtcccg gagggctcga tccgcatcta cagcatgagg ttctgcccgt 12
ttgctgagag gacgcgtcta gtcctgaagg ccaagggaat caggcatgaa gtcatcaata 18
tcaacctgaa aaataagcct gagtggttct ttaagaaaaa tccctttggt ctggtgccag 24
ttctggaaaa cagtcagggt cagctgatct acgagtctgc catcacctgt gagtacctgg 30
atgaagcata cccagggaag aagctgttgc cggatgaccc ctatgagaaa gcttgccaga 36
agatgatctt agagttgttt tctaaggtgc catccttggt aggaagcttt attagaagcc 42
aaaataaaga agactatgct ggcctaaaag aagaatttcg taaagaattt accaagctag 48
aggaggttct gactaataag 50

<210> 128
<211> 500
<212> DNA
<213> Homo sapien

<400> 128
agctttcctc tgctgccgct cggtcacgct tgtgcccgaa ggaggaaaca gtgacagacc
tggagactgc agttctctat ccttcacaca gctctttcac catgcctgga tcacttcctt 1
tgaatgcaga agcttgctgg ccaaaagatg tgggaattgt tgcccttgag atctattttc 1
cttctcaata tgttgatcaa gcagagttgg aaaaatatga tggtgtagat gctggaaagt 2
ataccattgg cttgggccag gccaagatgg gcttctgcac agatagagaa gatattaact 3
ctctttgcat gactgtggtt cagaatctta tggagagaaa taacctttcc tatgattgca 3
ttgggcggct ggaagttgga acagagacaa tcatcgacaa atcaaagtct gtgaagacta 4
atttgatgca gctgtttgaa gagtctggga atacagatat agaaggaatc gacacaacta 4
atgcatgcta tggaggcaca 5

<210> 129
<211> 497
<212> DNA
<213> Homo sapien

<400> 129
gaattcggca cgagcagagg tctccagagc cttctctctc ctgtgcaaaa tggcaactct
taaggaaaaa ctcattgcac cagttgcgga agaagaggca acagttccaa acaataagat 3
cactgtagtg ggtgttggac aagttggtat ggcgtgtgct atcagcattc tgggaaagtc 3
tctggctgat gaacttgctc ttgtggatgt tttggaagat aagcttaaag gagaaatgat 4
ggatctgcag catgggagct tatttcttca gacacctaaa attgtggcag ataaagatta 4
ttctgtgacc gccaattcta agattgtagt ggtaactgca ggagtccgtc agcaagaagg 5
ggagagtcgg ctcaatctgg tgcagagaaa tgttaatgtc ttcaaattca ttattcctca 5
gatcgtcaag tacagtcctg attgcatcat aattgtggtt tccaacccag tggacattct 6
tacgtatgtt acctgga 6

AS
395
392

<210> 130
<211> 383
<212> DNA
<213> Homo sapien

<400> 130
gaattcggca cgagggccgc ggctgccgac tgggtccccc gccgctgtcg ccaccatggc 6
tccgcaccgc cccgcgcccg cgctgctttg cgcgctgtcc ctggcgctgt gcgcgctgtc 12
gctgcccgtc cgcgcggcca ctgcgtcgcg gggggcgtcc caggcggggg cgccccaggg 18
gcgggtgccc gaggcgcggc ccaacagcat ggtggtggaa caccccgagt tcctcaaggc 24
agggaaggag cctggcctgc agatctggcg tgtggagaaa gttcgatctg gtggcccgtg 30
cccaccaacc tttatggaga cttcttcacg ggcgacgcct acgtcatcct gaagacagtg 36
cagcttaaga acggaaaatc ttg 38

<210> 131
<211> 509
<212> DNA
<213> Homo sapien

<400> 131
gaattcggca cgagagtcag ccgcatcttc ttttgcgtcg ccagccgagc cacatcgctc
agacaccatg gggaaggtga aggtcggagt caacggattt ggtcgtattg ggcgcctggt 1
caccagggct gcttttaact ctggtaaagt ggatattgtt gccatcaatg accccttcat 1
tgacctcaac tacatggttt acatgttcca atatgattcc acccatggca aattccatgg 2
caccgtcaag gctgagaacg ggaagcttgt catcaatgga aatcccatca ccatcttcca 3
ggagcgagat ccctccaaaa tcaagtgggg cgatgctggc gctgagtacg tcgtggagtc 3
cactggccgt cttcaccacc atggagaagg ctggggctca tttgcagggg ggagccaaaa 4
gggtcatcat ctctgccccc tctgctgacg ccccatgttt cgtcatgggt gtgaaccatg 4
agaagtatga caacagcctc aagatcatc 5

<210> 132
<211> 357
<212> DNA
<213> Homo sapien

<400> 132
gaattcggca cgagtaagaa gaagccccta gaccacagct ccacaccatg gactggacct
ggaggatcct cttcttggtg gcagcagcaa caggtgccca ctcccaggtg caactggtgc 1
aatctgggtc tgagttgaag aagcctgggg cctcagtgaa ggtttcctgc aaggcttctg 1
gacacatctt cagtatctat ggtttgaatt gggtgcgaca ggcccctggt caaggccttg 2
agtggatggg atggatcaaa gtcgacactg cgaacccaac gtatgcccag ggcttcacag 3
gacgatttgt cttctccctg gacacctctg tcagcacggc atatctgcag atcagca 3

<210> 133
<211> 468
<212> DNA
<213> Homo sapien

<400> 133
gaattcggca cgaggcgccc cgaacgtcc tcctgctgct ctcggcggcc ctggccctga
ccgagacctg ggccggctcc cactccatga ggtatttcga caccgccatg tcccggcccg
gccgcgggga gccccgcttc atctcagtgg gctacgtgga cgacacgcag ttcgtgaggt
tcgacagcga cgccgcgagt ccgagagagg agccgcgggc gccgtggata gagcaggagg
ggccggagta ttgggaccgg aacacacaga tcttcaagac caacacacag actgaccgag

726
396
393

agagcctgcg gaacctgcgc ggctactaca accagagcga ggccgggtct cacaccctcc 36
agagcatgta cggctgcgac gtggggccgg acgggcgcct cctccgcggg cataaccagt 42
acgcctacga cggcaaggat tacatcgccc tgaacgagga cctgcgct 46

<210> 134
<211> 214
<212> DNA
<213> Homo sapien

<400> 134
gaattcggca cgagctgcgt cctgctgagc tctgttctct ccagcacctc ccaacccact 6
agtgcctggt tctcttgctc caccaggaac aagccaccat gtctcgccag tcaagtgtgt 12
ccttccggag cgggggcagt cgtagcttca gcaccgcctc tgccatcacc acgtctgtct 18
cccgcaccag cttcacctcc gtgtcccggt ccgg 21

<210> 135
<211> 355
<212> DNA
<213> Homo sapien

<400> 135
gaattcggca cgaggtgaac aggacccgtc gccatgggcc gtgtgatccg tggacagagg
aagggcgccg ggtctgtgtt ccgcgcgcac gtgaagcacc gtaaaggcgc tgcgcgcctg 1
cgcgccgtgg atttcgctga gcggcacggc tacatcaagg gcatcgtcaa ggacatcatc 1
cacgacccgg gccgcggcgc gcccctcgcc aaggtggtct tccgggatcc gtatcggttt 2
aagaagcgga cggagctgtt cattgccgcc gagggcattc acacgggcca gtttgtgtat 3
tgcggcaaga aggcccagct caacattggc aatgtgctcc ctgtgggcac catgc 3

<210> 136
<211> 242
<212> DNA
<213> Homo sapien

<400> 136
gaattcggca cgagccagct cctaaccgcg agtgatccgc cagcctccgc ctcccgaggt
gcccggattg cagacggagt ctccttcact cagtgctcaa tggtgcccag gctggagtgc 1
agtggtgtga tctcggctcg ctacaacatc cacctcccag cagcctgcct tggcctccca 1
aagtgccgag attgcagctc tctgcccggc cgccaccct gtctgggaag tgaggatgct 2
gt 2

<210> 137
<211> 424
<212> DNA
<213> Homo sapien

<400> 137
gaattcggca cgagcccaga tcccgaggtc cgacagcgcc cggcccagat ccccacgcct
gccaggagca agccgagagc cagccggccg gcgcactccg actccgagca gtctctgtcc
ttcgacccga gccccgcgcc ctttccggga cccctgcccc gcgggcagcg ctgccaacct
gccggccatg gagacccccgt cccagcggcg cgccacccgc agcggggcgc aggccagctc
cactccgctg tcgcccaccc gcatcacccg gctgcaggag aaggaggacc tgcaggagct
caatgatcgc ttggcggtct acatcgaccg tgtgcgctcg ctggaaacgg agaacgcagg
gctgcgcctt cgcatcaccg agtctgaaga ggtggtcagc cgcgaggtgt ccggcatcaa
ggcc

394

<210> 138
<211> 448
<212> DNA
<213> Homo sapien

<400> 138
gaattcggca cgagcctgtg ttccaggagc cgaatcagaa atgtcatcct caggcacgcc 6
agacttacct gtcctactca ccgatttgaa gattcaatat actaagatct tcataaacaa 12
tgaatggcat gattcagtga gtggcaagaa atttcctgtc tttaatcctg caactgagga 18
ggagctctgc caggtagaag aaggagataa ggaggatgtt gacaaggcag tgaaggccgc 24
aagacaggct tttcagattg gatccccgtg gcgtactatg gatgcttccg agaggggcg 30
actattatac aagttggctg atttaatcga aagagatcgt ctgctgctgg ccgacaatgg 36
agtcaatgaa tggtggaaaa ctctattcca atgcatatct gaatgattta gcaggctgca 42
tcaaaacatt gcgctactgt gcaggttg 44

<210> 139
<211> 510
<212> DNA
<213> Homo sapien

<400> 139
gaattcggca cgaggttccg tgcagctcac ggagaagcga atggacaaag tcggcaagta
ccccaaggag ctgcgcaagt gctgcgagga cggcatgcgg gagaacccca tgaggttctc 1
gtgccagcgc cggacccgtt tcatctccct ggcgaggcgt gcaagaaggt cttcctggac 1
tgctgcaact acatcacaga gctgcggcgg cagcacgcgc gggccagcca cctggcctgc 2
caggagtaac ctggatgagg acatcattgc agaagagaac atcgtttccc gaagtgagtt 3
cccagagagc tggctgtgga acgttgagga cttgaaagag ccaccgaaaa atggaatctc 3
tacgaagctc atgaatatat ttttgaaaga ctccatcacc acgtgggaga ttctggctgt 4
gagcatgtcg gacaagaaag ggatctgtgt ggcagacccc ttcgaggtca cagtaatgca 4
ggacttcttc atcgacctgc ggctacccta 5

<210> 140
<211> 360
<212> DNA
<213> Homo sapien

<400> 140
gaattcggca cgagcggtaa ctaccccggc tgcgcacagc tcggcgctcc ttcccgctcc
ctcacacacc ggcctcagcc cgcaccggca gtagaagatg gtgaaagaaa caacttacta :
cgatgttttg ggggtcaaac ccaatgctac tcaggaagaa ttgaaaaagg cttataggaa
actggctttg aagtaccatc ctgataagaa cccaaatgaa ggagagaagt ttaaacagat :
ttctcaagct tacgaagttc tctctgatgc aaagaaaagg gaattatatg acaaaggagg .
agaacaggca attaaagagg gtggagcagg tggcggtttt ggctccccca tggacatctt

<210> 141
<211> 483
<212> DNA
<213> Homo sapien

<400> 141
gaattcggca cgagagcaga ggctgatctt tgctggaaaa cagctggaag atgggctgca
ccctgtctga ctacaacatc cagaaagagt ccaccctgca cctggtgctc cgtctcagag
gtgggatgca aatcttcgtg aagacactca ctggcaagac catcaccctt gaggtggagc
ccagtgacac catcgagaac gtcaaagcaa agatccagga caaggaaggc attcctcctg
accagcagag gttgatcttt gccggaaagc agctggaaga tgggcgcacc ctgtctgact

128
395

acaacatcca gaaagagtct accctgcacc tggtgctccg tctcagaggt gggatgcaga 36
tcttcgtgaa gaccctgact ggtaagacca tcaccctcga ggtggagccc agtgacacca 42
tcgagaatgt caaggcaaag atccaagata aggaaggcat tcctcctgat cagcagaggt 48
tga 48

<210> 142
<211> 500
<212> DNA
<213> Homo sapien

<400> 142
gaattcggca cgaggcggcg acgaccgccg ggagcgtgtg cagcggcggc ggcggaagtg 6
gccggcgagc ccggtccccg ccggcaccat gcttcccttg tcactgctga agacggctca 1:
gaatcacccc atgttggtgg agctgaaaaa tggggagacg tacaatggac acctggtgag 1:
ctgcgacaac tggatgaaca ttaacctgcg agaagtcatc tgcacgtcca gggacgggga 2-
caagttctgg cggatgcccg agtgctacat ccgcggcagc accatcaagt acctgcgcat 3(
ccccgacgag atcatcgaca tggtcaagga ggaggtggtg gccaagggcc gcggccgcgg 3:
aggcctgcag cagcagaagc agcagaaagg ccgcggcatg ggcggcgctg gccgaggtgt 4:
gtttggtggc cggggccgag gtgggatccc gggcacaggc agaagccagc cagagaagaa 4:
gcctggcaga caggcgggca 5

<210> 143
<211> 400
<212> DNA
<213> Homo sapien

<400> 143
gaattcggca cgagctcgga tgtcagcagg cgtcccaacc cagcaggaac tggctcaatt
ctcagaagaa agcgatcggc cccgaggcag gaaggccggc tccggtgcag ggcgcgccgc 1
ctgcgggctg cttcgggcca gggtcgaccc gagggccagc gcaagcagcg gcaacaggag 1
cgccaggagg acatgaggct ctgcctgcag tcagcaactt ggaatattca gacttcagac 2
cagcatcaca gattataacc ctccgtaaat catctgcatc ccagctccca tcaaaagcca 3
gcctgaagga cccatggaca cgtgactcca gtgttctcaa caacatctta gatcaagttg 3
gtttgcacaa catttgcatc tacttgggac aaagcaagaa 4

<210> 144
<211> 243
<212> DNA
<213> Homo sapien

<400> 144
gaattcggca cgagccagct cctaaccgcg agtgatccgc cagcctccgc ctccccgaggt
gcccggattg cagacggagt ctccttcact cagtgctcaa tggtgcccag gctggagtgc :
agtggtgtga tctcggctcg ctacaacatc cacctcccag cagcctgcct tggcctccca
aagtgccgag attgcagcct ctgcccggcc gtcaccccgt ctgggaagtg aggagcgttt .
ctg

<210> 145
<211> 450
<212> DNA
<213> Homo sapien

<400> 145
gaattcggca cgaggacagc aggaccgtgg aggccgcggc aggggtggca gtggtggcgg
cggcggcggc ggcggtggtg gttacaaccg cagcagtggt ggctatgaac ccagaggtcg

tggaggtggc cgtggaggca gaggtggcat gggcggaagt gacgtggtg gcttcaataa 18
atttggtggc cctcgggacc aaggatcacg tcatgactcc gaacaggata attcagacaa 24
caacaccatc tttgtgcaag gcctgggtga gaatgttaca attgagtctg tggctgatta 30
cttcaagcag attggtatta ttaagacaaa caagaaaacg ggacagccca tgattaattt 36
gtacacagac agggaaactg gcaagctgaa gggagaggca acggtctctt ttgatgaccc 42
accttcagct aaagcagcct attgactggt 45

<210> 146
<211> 451
<212> DNA
<213> Homo sapien

<400> 146
gaattcggca cgagccatcg agtccctgcc tttcgacttg cagagaaatg tctcgctgat 6
gcgggagatc gacgcgaaat accaagagat cctgaaggag ctagacgagt gctacgagcg 12
cttcagtcgc gagacagacg gggcgcagaa gcggcggatg ctgcactgtg tgcagcgcgc 18
gctgatccgc accaggagct gggcgacgag aagatccaga tcgtgagcca gatggtggag 24
ctggtggaga accgcacgcg gcaggtggac agccacgtgg agctgttcga ggcgcagcag 30
gagctgggcg acacagcggg caacagcggc aaggctggcg cggacaggcc caaaggcgag 36
gcggcagcgc aggctgacaa gcccaacagc aagcgctcac ggcggcagcg caacaacgag 42
aaccgtgaga acgcgtccag caaccacgac c 45

<210> 147
<211> 400
<212> DNA
<213> Homo sapien

<400> 147
gaattcggca cgagctcgga tgtcagcagg cgtcccaacc cagcaggaac tggctcaatt
ctcagaagaa agcgatcggc cccgaggcag gaaggccggc tccggtgcag ggcgcgccgc 1
ctgcgggctg cttcgggcca gggtcgaccc gagggccagc gcaagcagcg gcaacaggag 1
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30
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397

<213> Homo sapien

<400> 149

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EP 2 360 398

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<210> 157
<211> 2313
<212> DNA
<213> Homo sapien

<400> 157
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135
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402

403

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<210> 158
<211> 2114
<212> DNA
<213> Homo sapien

<400> 158
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gacacctcag cagcgcacca ggtggtttta ggagaaaact tgatagccac agccctttgt 18
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cgggagtact tcta 214

<210> 159
<211> 278

137
607
404

<212> DNA
<213> Homo sapien

<400> 159
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tgcagaatga gaatcactcc taaaataggt aatggtaaaa attaaattga caattacctc 18
tctctatgca gaaggaaata tcacctatat gacatcatca tcatctattg atacttgctg 24
gcagtgctaa taatggtttt aatgccaatt tgtaagaa 27

<210> 160
<211> 848
<212> DNA
<213> Homo sapien

<400> 160
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cttggtagga agctttatta gaagccaaaa taaagaagac tatgctggcc taaaagaagg
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<210> 161
<211> 432
<212> DNA
<213> Homo sapien

<400> 161
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ggaagggaag ggcccaagta aagcacagcg cgggagccta gagcacatga agctgatcct
gcgtgataag gagaaggagg tggaatgtca gcaggagcat atccatgaac tccaggagct
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<210> 162
<211> 433
<212> DNA
<213> Homo sapien

<400> 162
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D6
498
405

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tacagaaaag cagcatctgt tatagcaaaa tacccacaca aaataaagag tggagctgaa 30
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actggaaaat tacgtaaact ggaaaagatt cggcaggatg atacgagttc atccatcaat 42
ttcctgactc gag 43

<210> 163
<211> 432
<212> DNA
<213> Homo sapien

<400> 163
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ggacgccatg gaggagcccg accatggtgc cctgctgctg ctcccaggca ggcctcaccc 24
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ccccgctttc ctcacgccca gtccgacaaa gcggctctcc agcaagaagg tggcaaggta 42
cctgcaccag tc 44

<210> 164
<211> 395
<212> DNA
<213> Homo sapien

<400> 164
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ggttcctgaa aaaaaaaaaa aaaaaaaaac tcgag 3

<210> 165
<211> 503
<212> DNA
<213> Homo sapien

<400> 165
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agatggtgaa agaaacaact tactacgatg ttttgggggt caaacccaat gctactcagg :
aagaattgaa aaaggcttat aggaaactgg ccttgaagta ccatcctgat aagaacccaa :
atgaaggaga gaagtttaaa cagatttctc aagcttacga agttctctct gatgcaaaga :
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gttttggctc ccccatggac atctttgata tgtttttgg aggaggagga aggatgcaga
gagaaaggag aggtaaaaat gttgtacatc agctctcagt aaccctagaa gacttatata
atggtgcaac aagaaaactg gct

<210> 166
<211> 893
<212> DNA

<213> Homo sapien

<400> 166

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gctgggccag aggtgccaac atggggaaac tgaggctcgg ctcggaaggg tgagagtgag 12
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acaataaatt ttttttggtc aaatttaaaa aaaaaaaaaa aaaaaaactc gag 89

<210> 167
<211> 549
<212> DNA
<213> Homo sapien

<400> 167

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caatgatcgc ttggcggtct acatcgaccg tgtgcgctcg ctggaaacgg agaacgcagg 3
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gcgcaatac 5

<210> 168
<211> 547
<212> DNA
<213> Homo sapien

<400> 168

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<210> 169
<211> 547

<212> DNA
<213> Homo sapien

<400> 169
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aaacctc 547

<210> 170
<211> 838
<212> DNA
<213> Homo sapien

<400> 170
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cagcatgagg ttctgcccgt ttgctgagag gacgcgtcta gtcctgaagg ccaagggaat 1
caggcatgaa gtcatcaata tcaacctgaa aaataagcct gagtggttct ttaagaaaaa 2
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gctctactta cagaacagcc ctgaggcctg tgactatggg ctctgaaggg ggcaggagtc 7
agcaataaag ctatgtctga tattttcctt cactaaaaaa aaaaaaaaaa aactcgag 8

<210> 171
<211> 547
<212> DNA
<213> Homo sapien

<400> 171
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gcccagtgac accatcgaga atgtcaaggc aaagatccaa gataaggaag gcatccctcc
tgaccagcag aggctgatct ttgctggaaa acagctggaa gatgggcgca ccctgtctga
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catcgagaac gtcaaagcaa agatccagga caaggaaggc attcctcctg acgagcagag
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<210> 172
<211> 608

<212> DNA
<213> Homo sapien

<400> 172
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caccctcatc tacaatggtg ccctgccatg tcagtgcaac cctcaaggtt cactgagttc 12
tgagtgcaac cctcatggtg gtcagtgcct gtgcaagcct ggagtggttg ggcgccgctg 18
tgacctctgt gcccctggct actatggctt tggccccaca ggctgtcaag gcgcttgcct 24
gggctgccgt gatcacacag ggggtgagca ctgtgaaagg tgcattgctg gtttccacgg 30
ggacccacgg ctgccatatg ggggccagtg ccggccctgt ccctgtcctg aaggccctgg 36
gagccaacgg cactttgcta cttcttgcca ccaggatgaa tattcccagc agattgtgtg 42
ccactgccgg gcaggctata cggggctgcg atgtgaagct tgtgcccctg ggcactttgg 48
ggacccatca aggccaggtg gccggtgcca actgtgtgag tgcagtggga acattgaccc 54
aatggatcct gatgcctgtg acccccacac ggggcaatgc ctgcgctgtt tacaccacac 60
agagggtc 60

<210> 173
<211> 543
<212> DNA
<213> Homo sapien

<400> 173
gaattcggca ccagagatca tccgccagca gggtctggcc tcctacgact acgtgcgccg
ccgcctcacg gctgaggacc tgttcgaggc tcggatcatc tctctcgaga cctacaacct 1
gctccgggag ggcaccagga gcctccgtga ggctctcgag gcggagtccg cctggtgcta 1
cctctatggc acgggctccg tggctggtgt ctacctgccc ggttccaggc agacactgag 2
catctaccag gctctcaaga aagggctgct gagtgccgag gtggcccgcc tgctgctgga 3
ggcacaggca gccacaggct tcctgctgga cccggtgaag ggggaacggc tgactgtgga 3
tgaagctgtg cggaagggcc tcgtgggccc cgaactgcac gaccgcctgc tctcggctga 4
gcgggcggtc accggctacc gtgacccctа caccgagcag accatctcgc tcttccaggc 4
catgaagaag gaactgatcc ctactgagga ggccctgcgg ctgtggatgc ccagctggcc 5
acc 5

<210> 174
<211> 548
<212> DNA
<213> Homo sapien

<400> 174
gaattcggca cgagaaatgg cggcaggggt cgaagcggcg gcggaggtgg cggcgacgga
gatcaaaatg gaggaagaga gcggcgcgcc cggcgtgccg agcggcaacg gggctccggg
ccctaagggt gaaggagaac gacctgctca gaatgagaag aggaaggaga aaaacataaa
aagaggaggc aatcgctttg agccatatgc caatccaact aaaagataca gagccttcat
tacaaacata ccttttgatg tgaaatggca gtcacttaaa gacctggtta aagaaaaagt
tggtgaggta acatacgtgg agctcttaat ggacgctgaa ggaaagtcaa ggggatgtgc
tgttgttgaa ttcaagatgg aagagagcat gaaaaaagct gcggaagtcc taaacaagca
tagtctgagc ggaagaccac tgaaagtcaa agaagatcct gatggtgaac atgccaggag
agcaatgcaa aaggtgatgg ctacgactgg tgggatgggt atgggaccag gtggcccagg
aatgatta

<210> 175
<211> 604
<212> DNA
<213> Homo sapien

142
409

<400> 175
gaattcggca ccagaggacc tccaggacat gttcatcgtc cataccatcg aggagattga 6
gggcctgatc tcagcccatg accagttcaa gtccaccctg ccggacgccg atagggagcg 12
cgaggccatc ctggccatcc acaaggaggc ccagaggatc gctgagagca accacatcaa 18
gctgtcgggc agcaacccct acaccaccgt caccccgcaa atcatcaact ccaagtggga 24
gaaggtgcag cagctggtgc caaaacggga ccatgccctc ctggaggagc agagcaagca 30
gcagtccaac gagcacctgc gccgccagtt cgccagccag gccaatgttg tggggccctg 36
gatccagacc aagatggagg agatcgggcg catctccatt gagatgaacg ggaccctgga 42
ggaccagctg agccacctga agcagtatga acgcagcatc gtggactaca agcccaacct 48
ggacctgctg gagcagcagc accagcttat ccaggaggcc ctcatcttcg acaacaagca 54
caccaactat accatggagc acatccgcgt gggctgggag cagctgctca ccaccattgc 60
ccgg 60

<210> 176
<211> 486
<212> DNA
<213> Homo sapien

<400> 176
gaattcggca ccagccaagc tcactattga atccacgccg ttcaatgtcg cagaggggaa 6
ggaggttctt ctactcgccc acaacctgcc ccagaatcgt attggttaca gctggtacaa 12
aggcgaaaga gtggatggca acagtctaat tgtaggatat gtaataggaa ctcaacaagc 18
taccccaggg cccgcataca gtggtcgaga gacaatatac cccaatgcat ccctgctgat 24
ccagaacgtc acccagaatg acacaggatt ctatacccta caagtcataa agtcagatct 30
tgtgaatgaa gaagcaaccg gacagttcca tgtataccag gagctgccca agccctccat 36
ctccagcaac aactccaacc ccgtggagga caaggatgct gtggccttca cctgtgaacc 42
tgaggttcag aacacaacct acctgtggtg ggtaaatggt cagagcctcc cggtcagtcc 48
caaggc 54

<210> 177
<211> 387
<212> DNA
<213> Homo sapien

<400> 177
gaattcggca ccagggacag cagaccagac agtcacagca gccttgacaa aacgttcctg
gaactcaagc tcttctccac agaggaggac agagcagaca gcagagacca tggagtctcc 1
ctcggccccc ccccacagat ggtgcatccc ctggcagagg ctcctgctca cagcctcact 1
tctaaccttc tggaacccgc ccaccactgc caagctcact attgaatcca cgccgttcaa 2
tgtcgcagag gggaaggagg tgcttctact tgtccacaat ctgccccagc atctttttgg 3
ctacagctgg tacaaaggtg aaagagtgga tggcaaccgt caaattatag gatatgtaat 3
aggaactcaa caagctaccc cagggcc 3

<210> 178
<211> 440
<212> DNA
<213> Homo sapien

<400> 178
gaattcggca cgaggagaag cagaaaaaca aggaatttag ccagacttta gaaaatgaga
aaaatacctt actgagtcag atatcaacaa aggatggtga actaaaaatg cttcaggagg
aagtaaccaa aatgaacctg ttaaatccagc aaatccaaga agaactctct agagttacca
aactaaagga gacagcagaa gaagagaaag atgatttgga agagaggctt atgaatcaat
tagcagaact taatggaagc attgggaatt actgtcagga tgttacagat gcccaaataa
aaaatgagct attggaatct gaaatgaaga accttaaaaa gtgtgtgagt gaattggaag

aagaaaagca gcagttagtc aaggaaaaaa ctaaggtgga atcagaaata cgaaaggaat 42
atttggagaa aatacaaggt 44

<210> 179
<211> 443
<212> DNA
<213> Homo sapien

<400> 179
gaattcggca ccagcggggg gctacggcgg cggctacggc ggcgtcctga ccgcgtccga 6
cgggctgctg gcgggcaacg agaagctaac catgcagaac ctcaacgacc gcctggcctc 12
ctacctggac aaggtgcgcg ccctggaggc ggccaacggc gagctagagg tgaagatccg 18
cgactggtac cagaagcagg ggcctgggcc ctcccgcgac tacagccact actacacgac 24
catccaggac ctgcgggaca agattcttgg tgccaccatt gagaactcca ggattgtcct 30
gcagatcgac aacgcccgtc tggctgcaga tgacttccga accaagtttg agacggaaca 36
ggctctgcgc atgagcgtgg aggccgacat caacggcctg cgcagggtgc tggatgagct 42
gaccctggcc aggaccgacc tgg 45

<210> 180
<211> 403
<212> DNA
<213> Homo sapien

<400> 180
gaattcggca cgaggttatg agagtcgact tcaatgttcc tatgaagaac aaccagataa
caaacaacca gaggattaag gctgctgtcc caagcatcaa attctgcttg gacaatggag 1
ccaagtcggt agtccttatg agccacctag gccggcctga tggtgtgccc atgcctgaca 1
agtactcctt agagccagtt gctgtagaac tcagatctct gctgggcaag gatgttctgt 2
tcttgaagga ctgtgtaggc ccagaagtgg agaaagcctg tgccaaccca gctgctgggt 3
ctgtcatcct gctggagaac ctccgctttc atgtggagga agaagggaag ggaaaagatg 3
cttctgggaa caaggttaaa gccgagccag ccaaaataga agc 4

<210> 181
<211> 493
<212> DNA
<213> Homo sapien

<400> 181
gaattcggca ccagcagagg tctccagagc cttctctctc ctgtgcaaaa tggcaactct
taaggaaaaa ctcattgcac cagttgcgga agaagaggca acagttccaa acaataagat .
cactgtagtg ggtgttggac aagttggtat ggcgtgtgct atcagcattc tgggaaagtc
tctggctgat gaacttgctc ttgtggatgt tttggaagat aagcttaaag gagaaatgat .
ggatctgcag catgggagct tatttcttca gacacctaaa attgtggcag ataaagatta
ttctgtgacc gccaattcta agattgtagt ggtaactgca ggagtccgtc agcaagaagg
ggagagtcgg ctcaatctgg tgcagagaaa tgttaatgtc ttcaaattca ttattcctca
gatcgtcaag tacagtcctg attgcatcat aattgtggtt tccaacccag tggacattct
tacgtatgtt acc

<210> 182
<211> 209
<212> PRT
<213> Homo sapien

<400> 182
Ala Phe Ser Ser Asn Pro Lys Val Gln Val Glu Ala Ile Glu Gly Gly

4484
4/4
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WO 00/55350 PCT/US00/06599

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

<210> 183
<211> 255
<212> PRT
<213> Homo sapien

<400> 183

```
Met Ala Ala Gly Val Glu Ala Ala Ala Glu Val Ala Ala Thr Glu Pro
 1               5                  10                  15
Lys Met Glu Glu Glu Ser Gly Ala Pro Cys Val Pro Ser Gly Asn Gly
            20                  25                  30
Ala Pro Gly Pro Lys Gly Glu Glu Arg Pro Thr Gln Asn Glu Lys Arg
        35                  40                  45
Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr Ser
    50                  55                  60
Asn Pro Thr Lys Arg Tyr Arg Ala Phe Ile Thr Asn Ile Pro Phe Asp
65                  70                  75                  80
Val Lys Trp Gln Ser Leu Lys Asp Leu Val Lys Glu Lys Val Gly Glu
                85                  90                  95
Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg Gly
            100                 105                 110
Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala Ala
        115                 120                 125
Glu Val Leu Asn Lys His Ser Leu Ser Gly Arg Pro Leu Lys Val Lys
    130                 135                 140
Glu Asp Pro Asp Gly Glu His Ala Arg Arg Ala Met Gln Lys Ala Gly
145                 150                 155                 160
Arg Leu Gly Ser Thr Val Phe Val Ala Asn Leu Asp Tyr Lys Val Gly
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WO 00/22129 PCT/US99/23815

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

      <210> 184
      <211> 188
      <212> PRT
      <213> Homo sapien

      <400> 184
Leu Ser Gly Ser Cys Ile Arg Arg Glu Gln Thr Pro Glu Lys Glu Lys
 1               5                  10                  15
Gln Val Val Leu Phe Glu Glu Ala Ser Trp Thr Cys Thr Pro Ala Cys
            20                  25                  30
Gly Asp Glu Pro Arg Thr Val Ile Leu Leu Ser Ser Met Leu Ala Asp
        35                  40                  45
His Arg Leu Lys Leu Glu Asp Tyr Lys Asp Arg Leu Lys Ser Gly Glu
    50                  55                  60
His Leu Asn Pro Asp Gln Leu Glu Ala Val Glu Lys Tyr Glu Glu Val
65                  70                  75                  80
Leu His Asn Leu Glu Phe Ala Lys Glu Leu Gln Lys Thr Phe Ser Gly
                85                  90                  95
Leu Ser Leu Asp Leu Leu Lys Ala Gln Lys Lys Ala Gln Arg Arg Glu
            100                 105                 110
His Met Leu Lys Leu Glu Ala Glu Lys Lys Lys Leu Arg Thr Ile Leu
        115                 120                 125
Gln Val Gln Tyr Val Leu Gln Asn Leu Thr Gln Glu His Val Gln Lys
    130                 135                 140
Asp Phe Lys Gly Gly Leu Asn Gly Ala Val Tyr Leu Pro Ser Lys Glu
145                 150                 155                 160
Leu Asp Tyr Leu Ile Lys Phe Ser Lys Leu Thr Cys Pro Glu Arg Asn
                165                 170                 175
Glu Ser Leu Arg Gln Thr Leu Glu Gly Ser Thr Val
            180                 185

      <210> 185
      <211> 746
      <212> PRT
      <213> Homo sapien

      <400> 185
Asp Lys His Leu Lys Asp Leu Leu Ser Lys Leu Leu Asn Ser Gly Tyr
 1               5                  10                  15
Phe Glu Ser Ile Pro Val Pro Lys Asn Ala Lys Glu Lys Glu Val Pro
            20                  25                  30
Leu Glu Glu Glu Met Leu Ile Gln Ser Glu Lys Lys Thr Gln Leu Ser
        35                  40                  45
```

146
146
413

Lys Thr Glu Ser Val Lys Glu Ser Glu Ser Leu Met Glu Phe Ala Gln
50 55 60
Pro Glu Ile Gln Pro Gln Glu Phe Leu Asn Arg Arg Tyr Met Thr Glu
65 70 75 80
Val Asp Tyr Ser Asn Lys Gln Gly Glu Glu Gln Pro Trp Glu Ala Asp
85 90 95
Tyr Ala Arg Lys Pro Asn Leu Pro Lys Arg Trp Asp Met Leu Thr Glu
100 105 110
Pro Asp Gly Gln Glu Lys Lys Gln Glu Ser Phe Lys Ser Trp Glu Ala
115 120 125
Ser Gly Lys His Gln Glu Val Ser Lys Pro Ala Val Ser Leu Glu Gln
130 135 140
Arg Lys Gln Asp Thr Ser Lys Leu Arg Ser Thr Leu Pro Glu Glu Gln
145 150 155 160
Lys Lys Gln Glu Ile Ser Lys Ser Lys Pro Ser Pro Ser Gln Trp Lys
165 170 175
Gln Asp Thr Pro Lys Ser Lys Ala Gly Tyr Val Gln Glu Glu Gln Lys
180 185 190
Lys Gln Glu Thr Pro Lys Leu Trp Pro Val Gln Leu Gln Lys Glu Gln
195 200 205
Asp Pro Lys Lys Gln Thr Pro Lys Ser Trp Thr Pro Ser Met Gln Ser
210 215 220
Glu Gln Asn Thr Thr Lys Ser Trp Thr Thr Pro Met Cys Glu Glu Gln
225 230 235 240
Asp Ser Lys Gln Pro Glu Thr Pro Lys Ser Trp Glu Asn Asn Val Glu
245 250 255
Ser Gln Lys His Ser Leu Thr Ser Gln Ser Gln Ile Ser Pro Lys Ser
260 265 270
Trp Gly Val Ala Thr Ala Ser Leu Ile Pro Asn Asp Gln Leu Leu Pro
275 280 285
Arg Lys Leu Asn Thr Glu Pro Lys Asp Val Pro Lys Pro Val His Gln
290 295 300
Pro Val Gly Ser Ser Ser Thr Leu Pro Lys Asp Pro Val Leu Arg Lys
305 310 315 320
Glu Lys Leu Gln Asp Leu Met Thr Gln Ile Gln Gly Thr Cys Asn Phe
325 330 335
Met Gln Glu Ser Val Leu Asp Phe Asp Lys Pro Ser Ser Ala Ile Pro
340 345 350
Thr Ser Gln Pro Pro Ser Ala Thr Pro Gly Ser Pro Val Ala Ser Lys
355 360 365
Glu Gln Asn Leu Ser Ser Gln Ser Asp Phe Leu Gln Glu Pro Leu Gln
370 375 380
Val Phe Asn Val Asn Ala Pro Leu Pro Pro Arg Lys Glu Gln Glu Ile
385 390 395 400
Lys Glu Ser Pro Tyr Ser Pro Gly Tyr Asn Gln Ser Phe Thr Thr Ala
405 410 415
Ser Thr Gln Thr Pro Pro Gln Cys Gln Leu Pro Ser Ile His Val Glu
420 425 430
Gln Thr Val His Ser Gln Glu Thr Ala Ala Asn Tyr His Pro Asp Gly
435 440 445
Thr Ile Gln Val Ser Asn Gly Ser Leu Ala Phe Tyr Pro Ala Gln Thr
450 455 460
Asn Val Phe Pro Arg Pro Thr Gln Pro Phe Val Asn Ser Arg Gly Ser
465 470 475 480
Val Arg Gly Cys Thr Arg Gly Gly Arg Leu Ile Thr Asn Ser Tyr Arg

414

WO 00/12567 PCT/US99/19507

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                                485                 490                 495
Ser Pro Gly Gly Tyr Lys Gly Phe Asp Thr Tyr Arg Gly Leu Pro Ser
            500                 505                 510
Ile Ser Asn Gly Asn Tyr Ser Gln Leu Gln Phe Gln Ala Arg Glu Tyr
        515                 520                 525
Ser Gly Ala Pro Tyr Ser Gln Arg Asp Asn Phe Gln Gln Cys Tyr Lys
    530                 535                 540
Arg Gly Gly Thr Ser Gly Gly Pro Arg Ala Asn Ser Arg Ala Gly Trp
545                 550                 555                 560
Ser Asp Ser Ser Gln Val Ser Ser Pro Glu Arg Asp Asn Glu Thr Phe
                565                 570                 575
Asn Ser Gly Asp Ser Gly Gln Gly Asp Ser Arg Ser Met Thr Pro Val
            580                 585                 590
Asp Val Pro Val Thr Asn Pro Ala Ala Thr Ile Leu Pro Val His Val
        595                 600                 605
Tyr Pro Leu Pro Gln Gln Met Arg Val Ala Phe Ser Ala Ala Arg Thr
    610                 615                 620
Ser Asn Leu Ala Pro Gly Thr Leu Asp Gln Pro Ile Val Phe Asp Leu
625                 630                 635                 640
Leu Leu Asn Asn Leu Gly Glu Thr Phe Asp Leu Gln Leu Gly Arg Phe
                645                 650                 655
Asn Cys Pro Val Asn Gly Thr Tyr Val Phe Ile Phe His Met Leu Lys
            660                 665                 670
Leu Ala Val Asn Val Pro Leu Tyr Val Asn Leu Met Lys Asn Glu Glu
        675                 680                 685
Val Leu Val Ser Ala Tyr Ala Asn Asp Gly Ala Pro Asp His Glu Thr
    690                 695                 700
Ala Ser Asn His Ala Ile Leu Gln Leu Phe Gln Gly Asp Gln Ile Trp
705                 710                 715                 720
Leu Arg Leu His Arg Gly Ala Ile Tyr Gly Ser Ser Trp Lys Tyr Ser
                725                 730                 735
Thr Phe Ser Gly Tyr Leu Leu Tyr Gln Asp
            740                 745

        <210> 186
        <211> 705
        <212> PRT
        <213> Homo sapien

        <400> 186
Ala Leu Leu Asn Val Arg Gln Pro Pro Ser Thr Thr Thr Phe Val Leu
 1                  5                  10                  15
Asn Gln Ile Asn His Leu Pro Pro Leu Gly Ser Thr Ile Val Met Thr
            20                  25                  30
Lys Thr Pro Pro Val Thr Thr Asn Arg Gln Thr Ile Thr Leu Thr Lys
        35                  40                  45
Phe Ile Gln Thr Thr Ala Ser Thr Arg Pro Ser Val Ser Ala Pro Thr
    50                  55                  60
Val Arg Asn Ala Met Thr Ser Ala Pro Ser Lys Asp Gln Val Gln Leu
65                  70                  75                  80
Lys Asp Leu Leu Lys Asn Asn Ser Leu Asn Glu Leu Met Lys Leu Lys
                85                  90                  95
Pro Pro Ala Asn Ile Ala Gln Pro Val Ala Thr Ala Ala Thr Asp Val
            100                 105                 110
Ser Asn Gly Thr Val Lys Lys Glu Ser Ser Asn Lys Glu Gly Ala Arg
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415

SUBSTITUTE SHEET (RULE 26)

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                115                 120                 125
Met Trp Ile Asn Asp Met Lys Met Arg Ser Phe Ser Pro Thr Met Lys
    130                 135                 140
Val Pro Val Val Lys Glu Asp Asp Glu Pro Glu Glu Glu Asp Glu Glu
145                 150                 155                 160
Glu Met Gly His Ala Glu Thr Tyr Ala Glu Tyr Met Pro Ile Lys Leu
                165                 170                 175
Lys Ile Gly Leu Arg His Pro Asp Ala Val Val Glu Thr Ser Ser Leu
            180                 185                 190
Ser Ser Val Thr Pro Pro Asp Val Trp Tyr Lys Thr Ser Ile Ser Glu
        195                 200                 205
Glu Thr Ile Asp Asn Gly Trp Leu Ser Ala Leu Gln Leu Glu Ala Ile
    210                 215                 220
Thr Tyr Ala Ala Gln Gln His Glu Thr Phe Leu Pro Asn Gly Asp Arg
225                 230                 235                 240
Ala Gly Phe Leu Ile Gly Asp Gly Ala Gly Val Gly Lys Gly Arg Thr
                245                 250                 255
Ile Ala Gly Ile Ile Tyr Glu Asn Tyr Leu Leu Ser Arg Lys Arg Ala
            260                 265                 270
Leu Trp Phe Ser Val Ser Asn Asp Leu Lys Tyr Asp Ala Glu Arg Asp
        275                 280                 285
Leu Arg Asp Ile Gly Ala Lys Asn Ile Leu Val His Ser Leu Asn Lys
    290                 295                 300
Phe Lys Tyr Gly Lys Ile Ser Ser Lys His Asn Gly Ser Val Lys Lys
305                 310                 315                 320
Gly Val Ile Phe Ala Thr Tyr Ser Ser Leu Ile Gly Glu Ser Gln Ser
                325                 330                 335
Gly Gly Lys Tyr Lys Thr Arg Leu Lys Gln Leu Leu His Trp Cys Gly
            340                 345                 350
Asp Asp Phe Asp Gly Val Ile Val Phe Asp Glu Cys His Lys Ala Lys
        355                 360                 365
Asn Leu Cys Pro Val Gly Ser Ser Lys Pro Thr Lys Thr Gly Leu Ala
    370                 375                 380
Val Leu Glu Leu Gln Asn Lys Leu Pro Lys Ala Arg Val Val Tyr Ala
385                 390                 395                 400
Ser Ala Thr Gly Ala Ser Glu Pro Arg Asn Met Ala Tyr Met Asn Arg
                405                 410                 415
Leu Gly Ile Trp Gly Glu Gly Thr Pro Phe Arg Glu Phe Ser Asp Phe
            420                 425                 430
Ile Gln Ala Val Glu Arg Arg Gly Val Gly Ala Met Glu Ile Val Ala
        435                 440                 445
Met Asp Met Lys Leu Arg Gly Met Tyr Ile Ala Arg Gln Leu Ser Phe
    450                 455                 460
Thr Gly Val Thr Phe Lys Ile Glu Glu Val Leu Leu Ser Gln Ser Tyr
465                 470                 475                 480
Val Lys Met Tyr Asn Lys Ala Val Lys Leu Trp Val Ile Ala Arg Glu
                485                 490                 495
Arg Phe Gln Gln Ala Ala Asp Leu Ile Asp Ala Glu Gln Arg Met Lys
            500                 505                 510
Lys Ser Met Trp Gly Gln Phe Trp Ser Ala His Gln Arg Phe Phe Lys
        515                 520                 525
Tyr Leu Cys Ile Ala Ser Lys Val Lys Arg Val Val Gln Leu Ala Arg
    530                 535                 540
Glu Glu Ile Lys Asn Gly Lys Cys Val Val Ile Gly Leu Gln Ser Thr
545                 550                 555                 560
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416

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

<210> 187
<211> 595
<212> PRT
<213> Homo sapien

<400> 187
Glu Ser Pro Arg His Arg Gly Glu Gly Gly Gly Glu Trp Gly Pro Gly
1 5 10 15
Val Pro Arg Glu Arg Arg Glu Ser Ala Gly Glu Trp Gly Ala Asp Thr
20 25 30
Pro Lys Glu Gly Gly Glu Ser Ala Gly Glu Trp Gly Ala Glu Val Pro
35 40 45
Arg Gly Arg Gly Glu Gly Ala Gly Glu Trp Gly Pro Asp Thr Pro Lys
50 55 60
Glu Arg Gly Gln Gly Val Arg Glu Trp Gly Pro Glu Ile Pro Gln Glu
65 70 75 80
His Gly Glu Ala Thr Arg Asp Trp Ala Leu Glu Ser Pro Arg Ala Leu
85 90 95
Gly Glu Asp Ala Arg Glu Leu Gly Ser Ser Pro His Asp Arg Gly Ala
100 105 110
Ser Pro Arg Asp Leu Ser Gly Glu Ser Pro Cys Thr Gln Arg Ser Gly
115 120 125
Leu Leu Pro Glu Arg Arg Gly Asp Ser Pro Trp Pro Pro Trp Pro Ser
130 135 140
Pro Gln Glu Arg Asp Ala Gly Thr Arg Asp Arg Glu Glu Ser Pro Arg
145 150 155 160
Asp Trp Gly Gly Ala Glu Ser Pro Arg Gly Trp Glu Ala Gly Pro Arg
165 170 175
Glu Trp Gly Pro Ser Pro Ser Gly His Gly Asp Gly Pro Arg Arg Arg
180 185 190
Pro Arg Lys Arg Arg Gly Arg Lys Gly Arg Met Gly Arg Gln His Glu
195 200 205
Ala Ala Ala Thr Ala Ala Thr Ala Ala Thr Ala Thr Gly Gly Thr Ala
210 215 220

450
420
417

Glu Glu Ala Gly Ala Ser Ala Pro Glu Ser Gln Ala Gly Gly Gly Pro
225 230 235 240
Arg Gly Arg Ala Arg Gly Pro Arg Gln Gln Gly Arg Arg Arg His Gly
245 250 255
Thr Gln Arg Arg Arg Gly Pro Pro Gln Ala Arg Glu Glu Gly Pro Arg
260 265 270
Asp Ala Thr Thr Ile Leu Gly Leu Gly Thr Pro Ser Gly Glu Gln Arg
275 280 285
Ala Asp Gln Ser Gln Ala Leu Pro Ala Leu Ala Gly Ala Ala Ala Ala
290 295 300
His Ala His Ala Ile Pro Gly Ala Gly Pro Ala Ala Ala Pro Val Gly
305 310 315 320
Gly Arg Gly Arg Arg Gly Gly Trp Arg Gly Gly Arg Arg Gly Gly Ser
325 330 335
Ala Gly Ala Gly Gly Gly Gly Arg Gly Gly Arg Gly Arg Gly Arg Gly
340 345 350
Gly Gly Arg Gly Gly Gly Gly Ala Gly Arg Gly Gly Gly Ala Ala Gly
355 360 365
Pro Arg Glu Gly Ala Ser Ser Pro Gly Ala Arg Arg Gly Glu Gln Arg
370 375 380
Arg Arg Gly Arg Gly Pro Pro Ala Ala Gly Ala Ala Gln Val Ser Ala
385 390 395 400
Arg Gly Arg Arg Ala Arg Gly Gln Arg Ala Gly Glu Glu Ala Gln Asp
405 410 415
Gly Leu Leu Pro Arg Gly Arg Asp Arg Leu Pro Leu Arg Pro Gly Asp
420 425 430
Ala Asn Gln Arg Ala Glu Arg Pro Gly Pro Pro Arg Gly Gly His Gly
435 440 445
Pro Val Asn Ala Ser Ser Ala Pro Asp Thr Ser Pro Pro Arg His Pro
450 455 460
Arg Arg Trp Val Ser Gln Gln Arg Gln Arg Leu Trp Arg Gln Phe Arg
465 470 475 480
Val Gly Gly Gly Phe Pro Pro Pro Pro Pro Ser Arg Pro Pro Ala Val
485 490 495
Leu Leu Pro Leu Leu Arg Leu Ala Cys Ala Gly Asp Pro Gly Ala Thr
500 505 510
Arg Pro Gly Pro Arg Arg Pro Ala Arg Arg Pro Arg Gly Glu Leu Ile
515 520 525
Pro Arg Arg Pro Asp Pro Ala Ala Pro Ser Glu Glu Gly Leu Arg Met
530 535 540
Glu Ser Ser Val Asp Asp Gly Ala Thr Ala Thr Thr Ala Asp Ala Ala
545 550 555 560
Ser Gly Glu Ala Pro Glu Ala Gly Pro Ser Pro Ser His Ser Pro Thr
565 570 575
Met Cys Gln Thr Gly Gly Pro Gly Pro Pro Pro Pro Gln Pro Pro Arg
580 585 590
Trp Leu Pro
595

<210> 188
<211> 376
<212> PRT
<213> Homo sapien

<400> 188

Glu Met Arg Lys Phe Asp Val Pro Ser Met Glu Ser Thr Leu Asn Gln
1 5 10 15
Pro Ala Met Leu Glu Thr Leu Tyr Ser Asp Pro His Tyr Arg Ala His
20 25 30
Phe Pro Asn Pro Arg Pro Asp Thr Asn Lys Asp Val Tyr Lys Val Leu
35 40 45
Pro Glu Ser Lys Lys Ala Pro Gly Ser Gly Ala Val Phe Glu Arg Asn
50 55 60
Gly Pro His Ala Ser Ser Ser Gly Val Leu Pro Leu Gly Leu Gln Pro
65 70 75 80
Ala Pro Gly Leu Ser Lys Ser Leu Ser Ser Gln Val Trp Gln Pro Ser
85 90 95
Pro Asp Pro Trp His Pro Gly Glu Gln Ser Cys Glu Leu Ser Thr Cys
100 105 110
Arg Gln Gln Leu Glu Leu Ile Arg Leu Gln Met Glu Gln Met Gln Leu
115 120 125
Gln Asn Gly Ala Met Cys His His Pro Ala Ala Phe Ala Pro Leu Leu
130 135 140
Pro Thr Leu Glu Pro Ala Gln Trp Leu Ser Ile Leu Asn Ser Asn Glu
145 150 155 160
His Leu Leu Lys Glu Lys Glu Leu Leu Ile Asp Lys Gln Arg Lys His
165 170 175
Ile Ser Gln Leu Glu Gln Lys Val Arg Glu Ser Glu Leu Gln Val His
180 185 190
Ser Ala Leu Leu Gly Arg Pro Ala Pro Phe Gly Asp Val Cys Leu Leu
195 200 205
Arg Leu Gln Glu Leu Gln Arg Glu Asn Thr Phe Leu Arg Ala Gln Phe
210 215 220
Ala Gln Lys Thr Glu Ala Leu Ser Lys Glu Lys Met Glu Leu Glu Lys
225 230 235 240
Lys Leu Ser Ala Ser Glu Val Glu Ile Gln Leu Ile Arg Glu Ser Leu
245 250 255
Lys Val Thr Leu Gln Lys His Ser Glu Glu Gly Lys Lys Gln Glu Glu
260 265 270
Arg Val Lys Gly Arg Asp Lys His Ile Asn Asn Leu Lys Lys Lys Cys
275 280 285
Gln Lys Glu Ser Glu Gln Asn Arg Glu Lys Gln Gln Arg Ile Glu Thr
290 295 300
Leu Glu Arg Tyr Leu Ala Asp Leu Pro Thr Leu Glu Asp His Gln Lys
305 310 315 320
Gln Thr Glu Gln Leu Lys Asp Ala Glu Leu Lys Asn Thr Glu Leu Gln
325 330 335
Glu Arg Val Ala Glu Leu Glu Thr Leu Leu Glu Asp Thr Gln Ala Thr
340 345 350
Cys Arg Glu Lys Glu Val Gln Leu Glu Ser Leu Arg Gln Arg Glu Ala
355 360 365
Asp Leu Ser Ser Ala Arg His Arg
370 375

<210> 189
<211> 160
<212> PRT
<213> Homo sapien

<400> 189

152
422
419

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

<210> 190
<211> 146
<212> PRT
<213> Homo sapien

<400> 190
Met Asp Pro Arg Ala Ser Leu Leu Leu Leu Gly Asn Val Tyr Ile His
1 5 10 15
Pro Thr Ala Lys Val Ala Pro Ser Ala Val Leu Gly Pro Asn Val Ser
20 25 30
Ile Gly Lys Gly Val Thr Val Gly Glu Gly Val Arg Leu Arg Glu Ser
35 40 45
Ile Val Leu His Gly Ala Thr Leu Gln Glu His Thr Cys Val Leu His
50 55 60
Ser Ile Val Gly Trp Gly Ser Thr Val Gly Arg Trp Ala Arg Val Glu
65 70 75 80
Gly Thr Pro Ser Asp Pro Asn Pro Asn Asp Pro Arg Ala Arg Met Asp
85 90 95
Ser Glu Ser Leu Phe Lys Asp Gly Lys Leu Leu Pro Ala Ile Thr Ile
100 105 110
Leu Gly Cys Arg Val Arg Ile Pro Ala Glu Val Leu Ile Leu Asn Ser
115 120 125
Ile Val Leu Pro His Lys Glu Leu Ser Arg Ser Phe Thr Asn Gln Ile
130 135 140
Ile Leu
145

<210> 191
<211> 704
<212> PRT
<213> Homo sapien

<400> 191
Glu Gly Gly Cys Ala Ala Gly Arg Gly Arg Glu Leu Glu Pro Glu Leu

```
 1               5                  10                  15
Glu Pro Gly Pro Gly Pro Gly Ser Ala Leu Glu Pro Gly Glu Glu Phe
            20                  25                  30
Glu Ile Val Asp Arg Ser Gln Leu Pro Gly Pro Gly Asp Leu Arg Ser
        35                  40                  45
Ala Thr Arg Pro Arg Ala Ala Glu Gly Trp Ser Ala Pro Ile Leu Thr
    50                  55                  60
Leu Ala Arg Arg Ala Thr Gly Asn Leu Ser Ala Ser Cys Gly Ser Ala
65                  70                  75                  80
Leu Arg Ala Ala Ala Gly Leu Gly Gly Gly Asp Ser Gly Asp Gly Thr
                85                  90                  95
Ala Arg Ala Ala Ser Lys Cys Gln Met Met Glu Glu Arg Ala Asn Leu
            100                 105                 110
Met His Met Met Lys Leu Ser Ile Lys Val Leu Leu Gln Ser Ala Leu
        115                 120                 125
Ser Leu Gly Arg Ser Leu Asp Ala Asp His Ala Pro Leu Gln Gln Phe
    130                 135                 140
Phe Val Val Met Glu His Cys Leu Lys His Gly Leu Lys Val Lys Lys
145                 150                 155                 160
Ser Phe Ile Gly Gln Asn Lys Ser Phe Phe Gly Pro Leu Glu Leu Val
                165                 170                 175
Glu Lys Leu Cys Pro Glu Ala Ser Asp Ile Ala Thr Ser Val Arg Asn
            180                 185                 190
Leu Pro Glu Leu Lys Thr Ala Val Gly Arg Gly Arg Ala Trp Leu Tyr
        195                 200                 205
Leu Ala Leu Met Gln Lys Lys Leu Ala Asp Tyr Leu Lys Val Leu Ile
    210                 215                 220
Asp Asn Lys His Leu Leu Ser Glu Phe Tyr Glu Pro Glu Ala Leu Met
225                 230                 235                 240
Met Glu Glu Glu Gly Met Val Ile Val Gly Leu Leu Val Gly Leu Asn
                245                 250                 255
Val Leu Asp Ala Asn Leu Cys Leu Lys Gly Glu Asp Leu Asp Ser Gln
            260                 265                 270
Val Gly Val Ile Asp Phe Ser Leu Tyr Leu Lys Asp Val Gln Asp Leu
        275                 280                 285
Asp Gly Gly Lys Glu His Glu Arg Ile Thr Asp Val Leu Asp Gln Lys
    290                 295                 300
Asn Tyr Val Glu Glu Leu Asn Arg His Leu Ser Cys Thr Val Gly Asp
305                 310                 315                 320
Leu Gln Thr Lys Ile Asp Gly Leu Glu Lys Thr Asn Ser Lys Leu Gln
                325                 330                 335
Glu Glu Leu Ser Ala Ala Thr Asp Arg Ile Cys Ser Leu Gln Glu Glu
            340                 345                 350
Gln Gln Gln Leu Arg Glu Gln Asn Glu Leu Ile Arg Glu Arg Ser Glu
        355                 360                 365
Lys Ser Val Glu Ile Thr Lys Gln Asp Thr Lys Val Glu Leu Glu Thr
    370                 375                 380
Tyr Lys Gln Thr Arg Gln Gly Leu Asp Glu Met Tyr Ser Asp Val Trp
385                 390                 395                 400
Lys Gln Leu Lys Glu Glu Lys Lys Val Arg Leu Glu Leu Glu Lys Glu
                405                 410                 415
Leu Glu Leu Gln Ile Gly Met Lys Thr Glu Met Glu Ile Ala Met Lys
            420                 425                 430
Leu Leu Glu Lys Asp Thr His Glu Lys Gln Asp Thr Leu Val Ala Leu
        435                 440                 445
```

Arg Gln Gln Leu Glu Glu Val Lys Ala Ile Asn Leu Gln Met Phe His
450 455 460
Lys Ala Gln Asn Ala Glu Ser Ser Leu Gln Gln Lys Asn Glu Ala Ile
465 470 475 480
Thr Ser Phe Glu Gly Lys Thr Asn Gln Val Met Ser Ser Met Lys Gln
485 490 495
Met Glu Glu Arg Leu Gln His Ser Glu Arg Ala Arg Gln Gly Ala Glu
500 505 510
Glu Arg Ser His Lys Leu Gln Gln Glu Leu Gly Gly Arg Ile Gly Ala
515 520 525
Leu Gln Leu Gln Leu Ser Gln Leu His Glu Gln Cys Ser Ser Leu Glu
530 535 540
Lys Glu Leu Lys Ser Glu Lys Glu Gln Arg Gln Ala Leu Gln Arg Glu
545 550 555 560
Leu Gln His Glu Lys Asp Thr Ser Ser Leu Leu Arg Met Glu Leu Gln
565 570 575
Gln Val Glu Gly Leu Lys Lys Glu Leu Arg Glu Leu Gln Asp Glu Lys
580 585 590
Ala Glu Leu Gln Lys Ile Cys Glu Glu Gln Glu Gln Ala Leu Gln Glu
595 600 605
Met Gly Leu His Leu Ser Gln Ser Lys Leu Lys Met Glu Asp Ile Lys
610 615 620
Glu Val Asn Gln Ala Leu Lys Gly His Ala Trp Leu Lys Asp Asp Glu
625 630 635 640
Ala Thr His Cys Arg Gln Cys Glu Lys Glu Phe Ser Ile Ser Arg Arg
645 650 655
Lys His His Cys Arg Asn Cys Gly His Ile Phe Cys Asn Thr Cys Ser
660 665 670
Ser Asn Glu Leu Ala Leu Pro Ser Tyr Pro Lys Pro Val Arg Val Cys
675 680 685
Asp Ser Cys His Thr Leu Leu Leu Gln Arg Cys Ser Ser Thr Ala Ser
690 695 700

<210> 192
<211> 331
<212> PRT
<213> Homo sapien

<400> 192
Arg Ala Gly Ala Ser Ala Met Ala Leu Arg Lys Glu Leu Leu Lys Ser
1 5 10 15
Ile Trp Tyr Ala Phe Thr Ala Leu Asp Val Glu Lys Ser Gly Lys Val
20 25 30
Ser Lys Ser Gln Leu Lys Val Leu Ser His Asn Leu Tyr Thr Val Leu
35 40 45
His Ile Pro His Asp Pro Val Ala Leu Glu Glu His Phe Arg Asp Asp
50 55 60
Asp Asp Gly Pro Val Ser Ser Gln Gly Tyr Met Pro Tyr Leu Asn Lys
65 70 75 80
Tyr Ile Leu Asp Lys Val Glu Glu Gly Ala Phe Val Lys Glu His Phe
85 90 95
Asp Glu Leu Cys Trp Thr Leu Thr Ala Lys Lys Asn Tyr Arg Ala Asp
100 105 110
Ser Asn Gly Asn Ser Met Leu Ser Asn Gln Asp Ala Phe Arg Leu Trp
115 120 125

Cys Leu Phe Asn Phe Leu Ser Glu Asp Lys Tyr Pro Leu Ile Met Val
130 135 140
Pro Asp Glu Val Glu Tyr Leu Leu Lys Lys Val Leu Ser Ser Met Ser
145 150 155 160
Leu Glu Val Ser Leu Gly Glu Leu Glu Glu Leu Leu Ala Gln Glu Ala
165 170 175
Gln Val Ala Gln Thr Thr Gly Gly Leu Ser Val Trp Gln Phe Leu Glu
180 185 190
Leu Phe Asn Ser Gly Arg Cys Leu Arg Gly Val Gly Arg Asp Thr Leu
195 200 205
Ser Met Ala Ile His Glu Val Tyr Gln Glu Leu Ile Gln Asp Val Leu
210 215 220
Lys Gln Gly Tyr Leu Trp Lys Arg Gly His Leu Arg Arg Asn Trp Ala
225 230 235 240
Glu Arg Trp Phe Gln Leu Gln Pro Ser Cys Leu Cys Tyr Phe Gly Ser
245 250 255
Glu Glu Cys Lys Glu Lys Arg Gly Ile Ile Pro Leu Asp Ala His Cys
260 265 270
Cys Val Glu Val Leu Pro Asp Arg Asp Gly Lys Arg Cys Met Phe Cys
275 280 285
Val Lys Thr Ala Thr Arg Thr Tyr Glu Met Ser Ala Ser Asp Thr Arg
290 295 300
Gln Arg Gln Glu Trp Thr Ala Ala Ile Gln Met Ala Ile Arg Leu Gln
305 310 315 320
Ala Glu Gly Lys Thr Ser Leu His Lys Asp Leu
325 330

<210> 193
<211> 475
<212> PRT
<213> Homo sapien

<400> 193
Lys Asn Ser Pro Leu Leu Ser Val Ser Ser Gln Thr Ile Thr Lys Glu
1 5 10 15
Asn Asn Arg Asn Val His Leu Glu His Ser Glu Gln Asn Pro Gly Ser
20 25 30
Ser Ala Gly Asp Thr Ser Ala Ala His Gln Val Val Leu Gly Glu Asn
35 40 45
Leu Ile Ala Thr Ala Leu Cys Leu Ser Gly Ser Gly Ser Gln Ser Asp
50 55 60
Leu Lys Asp Val Ala Ser Thr Ala Gly Glu Glu Gly Asp Thr Ser Leu
65 70 75 80
Arg Glu Ser Leu His Pro Val Thr Arg Ser Leu Lys Ala Gly Cys His
85 90 95
Thr Lys Gln Leu Ala Ser Arg Asn Cys Ser Glu Glu Lys Ser Pro Gln
100 105 110
Thr Ser Ile Leu Lys Glu Gly Asn Arg Asp Thr Ser Leu Asp Phe Arg
115 120 125
Pro Val Val Ser Pro Ala Asn Gly Val Glu Gly Val Arg Val Asp Gln
130 135 140
Asp Asp Asp Gln Asp Ser Ser Ser Leu Lys Leu Ser Gln Asn Ile Ala
145 150 155 160
Val Gln Thr Asp Phe Lys Thr Ala Asp Ser Glu Val Asn Thr Asp Gln
165 170 175

156
426
423

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

<210> 194
<211> 241
<212> PRT
<213> Homo sapien

<400> 194
Met Ser Gly Glu Ser Ala Arg Ser Leu Gly Lys Gly Ser Ala Pro Pro
1 5 10 15
Gly Pro Val Pro Glu Gly Ser Ile Arg Ile Tyr Ser Met Arg Phe Cys
20 25 30
Pro Phe Ala Glu Arg Thr Arg Leu Val Leu Lys Ala Lys Gly Ile Arg
35 40 45
His Glu Val Ile Asn Ile Asn Leu Lys Asn Lys Pro Glu Trp Phe Phe
50 55 60
Lys Lys Asn Pro Phe Gly Leu Val Pro Val Leu Glu Asn Ser Gln Gly
65 70 75 80

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

<210> 195
<211> 138
<212> PRT
<213> Homo sapien

<400> 195

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

<210> 196
<211> 102
<212> PRT
<213> Homo sapien

<400> 196

```
Met Ser Lys Arg Lys Ala Pro Gln Glu Thr Leu Asn Gly Gly Ile Thr
```

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

<210> 197
<211> 138
<212> PRT
<213> Homo sapien

<400> 197

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

<210> 198
<211> 100
<212> PRT
<213> Homo sapien

<400> 198

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

459
426

426

Pro Ala Phe Gly Val Ala Ser Pro Pro Pro Leu Thr Asp Thr Pro Asp
85 90 95
Thr Thr Ala Asn
100

<210> 199
<211> 127
<212> PRT
<213> Homo sapien

<400> 199
Met Val Lys Glu Thr Thr Tyr Tyr Asp Val Leu Gly Val Lys Pro Asn
1 5 10 15
Ala Thr Gln Glu Glu Leu Lys Lys Ala Tyr Arg Lys Leu Ala Leu Lys
20 25 30
Tyr His Pro Asp Lys Asn Pro Asn Glu Gly Glu Lys Phe Lys Gln Ile
35 40 45
Ser Gln Ala Tyr Glu Val Leu Ser Asp Ala Lys Lys Arg Glu Leu Tyr
50 55 60
Asp Lys Gly Gly Glu Gln Ala Ile Lys Glu Gly Gly Ala Gly Gly Gly
65 70 75 80
Phe Gly Ser Pro Met Asp Ile Phe Asp Met Phe Phe Gly Gly Gly Gly
85 90 95
Arg Met Gln Arg Glu Arg Arg Gly Lys Asn Val Val His Gln Leu Ser
100 105 110
Val Thr Leu Glu Asp Leu Tyr Asn Gly Ala Thr Arg Lys Leu Ala
115 120 125

<210> 200
<211> 90
<212> PRT
<213> Homo sapien

<400> 200
Met Ala Cys Pro Leu Asp Gln Ala Ile Gly Leu Leu Val Ala Ile Phe
1 5 10 15
His Lys Tyr Ser Gly Arg Glu Gly Asp Lys His Thr Leu Ser Lys Lys
20 25 30
Glu Leu Lys Glu Leu Ile Gln Lys Glu Leu Thr Ile Gly Ser Lys Leu
35 40 45
Gln Asp Ala Glu Ile Ala Arg Leu Met Glu Asp Leu Asp Arg Asn Lys
50 55 60
Asp Gln Glu Val Asn Phe Gln Glu Tyr Val Thr Phe Leu Gly Ala Leu
65 70 75 80
Ala Leu Ile Tyr Asn Glu Ala Leu Lys Gly
85 90

<210> 201
<211> 120
<212> PRT
<213> Homo sapien

<400> 201
Met Glu Thr Pro Ser Gln Arg Arg Ala Thr Arg Ser Gly Ala Gln Ala
1 5 10 15

166
430
427

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

<210> 202
<211> 177
<212> PRT
<213> Homo sapien

<400> 202
Met Ala Ala Gly Val Glu Ala Ala Ala Glu Val Ala Ala Thr Glu Ile
1 5 10 15
Lys Met Glu Glu Glu Ser Gly Ala Pro Gly Val Pro Ser Gly Asn Gly
20 25 30
Ala Pro Gly Pro Lys Gly Glu Gly Glu Arg Pro Ala Gln Asn Glu Lys
35 40 45
Arg Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr
50 55 60
Ala Asn Pro Thr Lys Arg Tyr Arg Ala Phe Ile Thr Asn Ile Pro Phe
65 70 75 80
Asp Val Lys Trp Gln Ser Leu Lys Asp Leu Val Lys Glu Lys Val Gly
85 90 95
Glu Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg
100 105 110
Gly Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala
115 120 125
Ala Glu Val Leu Asn Lys His Ser Leu Ser Gly Arg Pro Leu Lys Val
130 135 140
Lys Glu Asp Pro Asp Gly Glu His Ala Arg Arg Ala Met Gln Lys Ala
145 150 155 160
Gly Arg Leu Gly Ser Thr Val Phe Val Ala Asn Leu Asp Tyr Lys Val
165 170 175
Gly

<210> 203
<211> 164
<212> PRT
<213> Homo sapien

<400> 203
Met Arg Leu Ala Val Gly Ala Leu Leu Val Cys Ala Val Leu Gly Leu
1 5 10 15
Cys Leu Ala Val Pro Asp Lys Thr Val Arg Trp Cys Ala Val Ser Glu

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


      <210> 204
      <211> 241
      <212> PRT
      <213> Homo sapien

      <400> 204
Met Ser Gly Glu Ser Ala Arg Ser Leu Gly Lys Gly Ser Ala Pro Pro
 1               5                  10                  15
Gly Pro Val Pro Glu Gly Ser Ile Arg Ile Tyr Ser Met Arg Phe Cys
            20                  25                  30
Pro Phe Ala Glu Arg Thr Arg Leu Val Leu Lys Ala Lys Gly Ile Arg
        35                  40                  45
His Glu Val Ile Asn Ile Asn Leu Lys Asn Lys Pro Glu Trp Phe Phe
    50                  55                  60
Lys Lys Asn Pro Phe Gly Leu Val Pro Val Leu Glu Asn Ser Gln Gly
65                  70                  75                  80
Gln Leu Ile Tyr Glu Ser Ala Ile Thr Cys Glu Tyr Leu Asp Glu Ala
                85                  90                  95
Tyr Pro Gly Lys Lys Leu Leu Pro Asp Asp Pro Tyr Glu Lys Ala Cys
            100                 105                 110
Gln Lys Met Ile Leu Glu Leu Phe Ser Lys Val Pro Ser Leu Val Gly
        115                 120                 125
Ser Phe Ile Arg Ser Gln Asn Lys Glu Asp Tyr Asp Gly Leu Lys Glu
    130                 135                 140
Glu Phe Arg Lys Glu Phe Thr Lys Leu Glu Glu Val Leu Thr Asn Lys
145                 150                 155                 160
Lys Thr Thr Phe Phe Gly Gly Asn Ser Ile Ser Met Ile Asp Tyr Leu
                165                 170                 175
Ile Trp Pro Trp Phe Glu Arg Leu Glu Ala Met Lys Leu Asn Glu Cys
            180                 185                 190
Val Asp His Thr Pro Lys Leu Lys Leu Trp Met Ala Ala Met Lys Glu
        195                 200                 205
Asp Pro Thr Val Ser Ala Leu Leu Thr Ser Glu Lys Asp Trp Gln Gly
    210                 215                 220
Phe Leu Glu Leu Tyr Leu Gln Asn Ser Pro Glu Ala Cys Asp Tyr Gly
```

182
485
429

225 230 235 240
Leu

<210> 205
<211> 160
<212> PRT
<213> Homo sapien

<400> 205
Met Gln Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu
1 5 10 15
Val Glu Pro Ser Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp
20 25 30
Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys
35 40 45
Gln Leu Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu
50 55 60
Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe
65 70 75 80
Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val Glu Pro Ser
85 90 95
Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp Lys Glu Gly Ile
100 105 110
Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu Glu Asp
115 120 125
Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu Ser Thr Leu His
130 135 140
Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe Val Lys Thr Leu
145 150 155 160

<210> 206
<211> 197
<212> PRT
<213> Homo sapien

<400> 206
Thr Ser Pro Ser Glu Ala Cys Ala Pro Leu Leu Ile Ser Leu Ser Thr
1 5 10 15
Leu Ile Tyr Asn Gly Ala Leu Pro Cys Gln Cys Asn Pro Gln Gly Ser
20 25 30
Leu Ser Ser Glu Cys Asn Pro His Gly Gly Gln Cys Leu Cys Lys Pro
35 40 45
Gly Val Val Gly Arg Arg Cys Asp Leu Cys Ala Pro Gly Tyr Tyr Gly
50 55 60
Phe Gly Pro Thr Gly Cys Gln Gly Ala Cys Leu Gly Cys Arg Asp His
65 70 75 80
Thr Gly Gly Glu His Cys Glu Arg Cys Ile Ala Gly Phe His Gly Asp
85 90 95
Pro Arg Leu Pro Tyr Gly Gly Gln Cys Arg Pro Cys Pro Cys Pro Glu
100 105 110
Gly Pro Gly Ser Gln Arg His Phe Ala Thr Ser Cys His Gln Asp Glu
115 120 125
Tyr Ser Gln Gln Ile Val Cys His Cys Arg Ala Gly Tyr Thr Gly Leu
130 135 140

163
463
430

Arg Cys Glu Ala Cys Ala Pro Gly His Phe Gly Asp Pro Ser Arg Pro
145 150 155 160
Gly Gly Arg Cys Gln Leu Cys Glu Cys Ser Gly Asn Ile Asp Pro Met
165 170 175
Asp Pro Asp Ala Cys Asp Pro His Thr Gly Gln Cys Leu Arg Cys Leu
180 185 190
His His Thr Glu Gly
195

<210> 207
<211> 175
<212> PRT
<213> Homo sapien

<400> 207
Ile Ile Arg Gln Gln Gly Leu Ala Ser Tyr Asp Tyr Val Arg Arg Arg
1 5 10 15
Leu Thr Ala Glu Asp Leu Phe Glu Ala Arg Ile Ile Ser Leu Glu Thr
20 25 30
Tyr Asn Leu Leu Arg Glu Gly Thr Arg Ser Leu Arg Glu Ala Leu Glu
35 40 45
Ala Glu Ser Ala Trp Cys Tyr Leu Tyr Gly Thr Gly Ser Val Ala Gly
50 55 60
Val Tyr Leu Pro Gly Ser Arg Gln Thr Leu Ser Ile Tyr Gln Ala Leu
65 70 75 80
Lys Lys Gly Leu Leu Ser Ala Glu Val Ala Arg Leu Leu Leu Glu Ala
85 90 95
Gln Ala Ala Thr Gly Phe Leu Leu Asp Pro Val Lys Gly Glu Arg Leu
100 105 110
Thr Val Asp Glu Ala Val Arg Lys Gly Leu Val Gly Pro Glu Leu His
115 120 125
Asp Arg Leu Leu Ser Ala Glu Arg Ala Val Thr Gly Tyr Arg Asp Pro
130 135 140
Tyr Thr Glu Gln Thr Ile Ser Leu Phe Gln Ala Met Lys Lys Glu Leu
145 150 155 160
Ile Pro Thr Glu Glu Ala Leu Arg Leu Trp Met Pro Ser Trp Pro
165 170 175

<210> 208
<211> 177
<212> PRT
<213> Homo sapien

<400> 208
Met Ala Ala Gly Val Glu Ala Ala Ala Glu Val Ala Ala Thr Glu Ile
1 5 10 15
Lys Met Glu Glu Glu Ser Gly Ala Pro Gly Val Pro Ser Gly Asn Gly
20 25 30
Ala Pro Gly Pro Lys Gly Glu Gly Glu Arg Pro Ala Gln Asn Glu Lys
35 40 45
Arg Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr
50 55 60
Ala Asn Pro Thr Lys Arg Tyr Arg Ala Phe Ile Thr Asn Ile Pro Phe
65 70 75 80
Asp Val Lys Trp Gln Ser Leu Lys Asp Leu Val Lys Glu Lys Val Gly

434
431

```
                    85                  90                  95
Glu Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg
                100                 105                 110
Gly Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala
            115                 120                 125
Ala Glu Val Leu Asn Lys His Ser Leu Ser Gly Arg Pro Leu Lys Val
        130                 135                 140
Lys Glu Asp Pro Asp Gly Glu His Ala Arg Arg Ala Met Gln Lys Val
145                 150                 155                 160
Met Ala Thr Thr Gly Gly Met Gly Met Gly Pro Gly Gly Pro Gly Met
                165                 170                 175
Ile
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<210> 209
<211> 196
<212> PRT
<213> Homo sapien

<400> 209
Asp Leu Gln Asp Met Phe Ile Val His Thr Ile Glu Glu Ile Glu Gly
 1   5   10   15
Leu Ile Ser Ala His Asp Gln Phe Lys Ser Thr Leu Pro Asp Ala Asp
            20   25   30
Arg Glu Arg Glu Ala Ile Leu Ala Ile His Lys Glu Ala Gln Arg Ile
        35   40   45
Ala Glu Ser Asn His Ile Lys Leu Ser Gly Ser Asn Pro Tyr Thr Thr
    50   55   60
Val Thr Pro Gln Ile Ile Asn Ser Lys Trp Glu Lys Val Gln Gln Leu
65   70   75   80
Val Pro Lys Arg Asp His Ala Leu Leu Glu Glu Gln Ser Lys Gln Gln
                85   90   95
Ser Asn Glu His Leu Arg Arg Gln Phe Ala Ser Gln Ala Asn Val Val
            100   105   110
Gly Pro Trp Ile Gln Thr Lys Met Glu Glu Ile Gly Arg Ile Ser Ile
        115   120   125
Glu Met Asn Gly Thr Leu Glu Asp Gln Leu Ser His Leu Lys Gln Tyr
    130   135   140
Glu Arg Ser Ile Val Asp Tyr Lys Pro Asn Leu Asp Leu Leu Glu Gln
145   150   155   160
Gln His Gln Leu Ile Gln Glu Ala Leu Ile Phe Asp Asn Lys His Thr
                165   170   175
Asn Tyr Thr Met Glu His Ile Arg Val Gly Trp Glu Gln Leu Leu Thr
            180   185   190
Thr Ile Ala Arg
        195

<210> 210
<211> 156
<212> PRT
<213> Homo sapien

<400> 210
Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly Lys Glu
 1   5   10   15
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105
435
432

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

<210> 211
<211> 92
<212> PRT
<213> *Homo sapien*

<400> 211
Met Glu Ser Pro Ser Ala Pro Pro His Arg Trp Cys Ile Pro Trp Gln
1 5 10 15
Arg Leu Leu Leu Thr Ala Ser Leu Leu Thr Phe Trp Asn Pro Pro Thr
20 25 30
Thr Ala Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly
35 40 45
Lys Glu Val Leu Leu Leu Val His Asn Leu Pro Gln His Leu Phe Gly
50 55 60
Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Arg Gln Ile Ile
65 70 75 80
Gly Tyr Val Ile Gly Thr Gln Gln Ala Thr Pro Gly
85 90

<210> 212
<211> 142
<212> PRT
<213> Homo sapien

<400> 212
Glu Lys Gln Lys Asn Lys Glu Phe Ser Gln Thr Leu Glu Asn Glu Lys
1 5 10 15
Asn Thr Leu Leu Ser Gln Ile Ser Thr Lys Asp Gly Glu Leu Lys Met
20 25 30
Leu Gln Glu Glu Val Thr Lys Met Asn Leu Leu Asn Gln Gln Ile Gln
35 40 45
Glu Glu Leu Ser Arg Val Thr Lys Leu Lys Glu Thr Ala Glu Glu Glu
50 55 60
Lys Asp Asp Leu Glu Glu Arg Leu Met Asn Gln Leu Ala Glu Leu Asn
65 70 75 80
Gly Ser Ile Gly Asn Tyr Cys Gln Asp Val Thr Asp Ala Gln Ile Lys

466
436
433

SUBSTITUTE SHEET (RULE 26)

85 90 95
Asn Glu Leu Leu Glu Ser Glu Met Lys Asn Leu Lys Lys Cys Val Ser
100 105 110
Glu Leu Glu Glu Glu Lys Gln Gln Leu Val Lys Glu Lys Thr Lys Val
115 120 125
Glu Ser Glu Ile Arg Lys Glu Tyr Leu Glu Lys Ile Gln Gly
130 135 140

<210> 213
<211> 142
<212> PRT
<213> Homo sapien

<400> 213
Gly Gly Tyr Gly Gly Gly Tyr Gly Gly Val Leu Thr Ala Ser Asp Gly
1 5 10 15
Leu Leu Ala Gly Asn Glu Lys Leu Thr Met Gln Asn Leu Asn Asp Arg
20 25 30
Leu Ala Ser Tyr Leu Asp Lys Val Arg Ala Leu Glu Ala Ala Asn Gly
35 40 45
Glu Leu Glu Val Lys Ile Arg Asp Trp Tyr Gln Lys Gln Gly Pro Gly
50 55 60
Pro Ser Arg Asp Tyr Ser His Tyr Tyr Thr Thr Ile Gln Asp Leu Arg
65 70 75 80
Asp Lys Ile Leu Gly Ala Thr Ile Glu Asn Ser Arg Ile Val Leu Gln
85 90 95
Ile Asp Asn Ala Arg Leu Ala Ala Asp Asp Phe Arg Thr Lys Phe Glu
100 105 110
Thr Glu Gln Ala Leu Arg Met Ser Val Glu Ala Asp Ile Asn Gly Leu
115 120 125
Arg Arg Val Leu Asp Glu Leu Thr Leu Ala Arg Thr Asp Leu
130 135 140

<210> 214
<211> 129
<212> PRT
<213> Homo sapien

<400> 214
Val Met Arg Val Asp Phe Asn Val Pro Met Lys Asn Asn Gln Ile Thr
1 5 10 15
Asn Asn Gln Arg Ile Lys Ala Ala Val Pro Ser Ile Lys Phe Cys Leu
20 25 30
Asp Asn Gly Ala Lys Ser Val Val Leu Met Ser His Leu Gly Arg Pro
35 40 45
Asp Gly Val Pro Met Pro Asp Lys Tyr Ser Leu Glu Pro Val Ala Val
50 55 60
Glu Leu Arg Ser Leu Leu Gly Lys Asp Val Leu Phe Leu Lys Asp Cys
65 70 75 80
Val Gly Pro Glu Val Glu Lys Ala Cys Ala Asn Pro Ala Ala Gly Ser
85 90 95
Val Ile Leu Leu Glu Asn Leu Arg Phe His Val Glu Glu Glu Gly Lys
100 105 110
Gly Lys Asp Ala Ser Gly Asn Lys Val Lys Ala Glu Pro Ala Lys Ile
115 120 125

169
455
434

Glu

<210> 215
<211> 148
<212> PRT
<213> Homo sapien

<400> 215

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Met Ala Thr Leu Lys Glu Lys Leu Ile Ala Pro Val Ala Glu Glu Glu
 1               5                  10                  15
Ala Thr Val Pro Asn Asn Lys Ile Thr Val Val Gly Val Gly Gln Val
            20                  25                  30
Gly Met Ala Cys Ala Ile Ser Ile Leu Gly Lys Ser Leu Ala Asp Glu
        35                  40                  45
Leu Ala Leu Val Asp Val Leu Glu Asp Lys Leu Lys Gly Glu Met Met
    50                  55                  60
Asp Leu Gln His Gly Ser Leu Phe Leu Gln Thr Pro Lys Ile Val Ala
65                  70                  75                  80
Asp Lys Asp Tyr Ser Val Thr Ala Asn Ser Lys Ile Val Val Val Thr
                85                  90                  95
Ala Gly Val Arg Gln Gln Glu Gly Glu Ser Arg Leu Asn Leu Val Gln
            100                 105                 110
Arg Asn Val Asn Val Phe Lys Phe Ile Ile Pro Gln Ile Val Lys Tyr
        115                 120                 125
Ser Pro Asp Cys Ile Ile Ile Val Val Ser Asn Pro Val Asp Ile Leu
    130                 135                 140
Thr Tyr Val Thr
145
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<210> 216
<211> 527
<212> PRT
<213> Homo sapien

<400> 216

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

166
458
435

145 150 155 160
Glu Thr Gly Gly Ala Pro Arg Ala Pro Gly Ala Gly Arg Leu Asp Leu
165 170 175
Gly Ser Gly Gly Arg Ala Pro Val Gly Thr Gly Thr Ala Pro Gly Gly
180 185 190
Gly Pro Gly Ser Gly Val Asp Ala Lys Ala Gly Trp Val Asp Asn Thr
195 200 205
Arg Pro Gln Pro Pro Pro Pro Pro Leu Pro Pro Pro Pro Glu Ala Gln
210 215 220
Pro Arg Arg Leu Glu Pro Ala Pro Pro Arg Ala Arg Pro Glu Val Ala
225 230 235 240
Pro Glu Gly Glu Pro Gly Ala Pro Asp Ser Arg Ala Gly Gly Asp Thr
245 250 255
Ala Leu Ser Gly Asp Gly Asp Pro Pro Lys Pro Glu Arg Lys Gly Pro
260 265 270
Glu Met Pro Arg Leu Phe Leu Asp Leu Gly Pro Pro Gln Gly Asn Ser
275 280 285
Glu Gln Ile Lys Ala Arg Leu Ser Arg Leu Ser Leu Ala Leu Pro Pro
290 295 300
Leu Thr Leu Thr Pro Phe Pro Gly Pro Gly Pro Arg Arg Pro Pro Trp
305 310 315 320
Glu Gly Ala Asp Ala Gly Ala Ala Gly Gly Glu Ala Gly Gly Ala Gly
325 330 335
Ala Pro Gly Pro Ala Glu Glu Asp Gly Glu Asp Glu Asp Glu Asp Glu
340 345 350
Glu Glu Asp Glu Glu Ala Ala Ala Pro Gly Ala Ala Ala Gly Pro Arg
355 360 365
Gly Pro Gly Arg Ala Arg Ala Ala Pro Val Pro Val Val Val Ser Ser
370 375 380
Ala Asp Ala Asp Ala Ala Arg Pro Leu Arg Gly Leu Leu Lys Ser Pro
385 390 395 400
Arg Gly Ala Asp Glu Pro Glu Asp Ser Glu Leu Glu Arg Lys Arg Lys
405 410 415
Met Val Ser Phe His Gly Asp Val Thr Val Tyr Leu Phe Asp Gln Glu
420 425 430
Thr Pro Thr Asn Glu Leu Ser Val Gln Ala Pro Pro Glu Gly Asp Thr
435 440 445
Asp Pro Ser Thr Pro Pro Ala Pro Pro Thr Pro Pro His Pro Ala Thr
450 455 460
Pro Gly Asp Gly Phe Pro Ser Asn Asp Ser Gly Phe Gly Gly Ser Phe
465 470 475 480
Glu Trp Ala Glu Asp Phe Pro Leu Leu Pro Pro Pro Gly Pro Pro Leu
485 490 495
Cys Phe Ser Arg Phe Ser Val Ser Pro Ala Leu Glu Thr Pro Gly Pro
500 505 510
Pro Ala Arg Ala Pro Asp Ala Arg Pro Ala Gly Pro Val Glu Asn
515 520 525

<210> 217
<211> 466
<212> DNA
<213> Homo sapien

<400> 217
gaatggtgcc tgtcctgctg tctctgctgc tgcttctggg tcctgctgtc ccccaggaga

169
459
436

accaagatgg tcgttactct ctgacctata tctacactgg gctgtccaag catgttgaag 12(
acgtccccgc gtttcaggcc cttggctcac tcaatgacct ccagttcttt agatacaaca 18(
gtaaagacag gaagtctcag cccatgggac tctggagaca ggtggaagga atggaggatt 24(
ggaagcagga cagccaactt cagaaggcca gggaggacat ctttatggag accctgaaag 30·
acatcgtgga gtattacaac gacagtaacg ggtctcacgt attgcaggga aggtttggtt 36
gtgagatcga gaataacaga agcagcggag cattctggaa atattactat gatggaaagg 42
actacattga attcaacaaa gaaatcccag cctgggtccc cttcga 46·

<210> 218
<211> 381
<212> DNA
<213> Homo sapien

<400> 218
gagtttcctt cgcaagttca tgtggggtac cttcccaggc tgcctggctg accagctggt 6
tttaaagcgc cggggtaacc agttggagat ctgtgccgtg gtcctgaggc agttgtctcc 12
acacaagtac tacttcctcg tgggctacag tgaaactttg ctgtcctact tttacaaatg 18
tcctgtgcga ctccacctcc aaactgtgcc ctcaaaggtt gtgtataagt acctctagaa 24
caatcccctt ttttccatca agctgtagcc tgcagagaat ggaaacgtgg gaaaggaatg 3(
gtatgtgggg gaaatgcatc ccctcagagg actgaggcat agtctctcat ctgctattga 36
ataaagacct tctatcttgt a 3E

<210> 219
<211> 1293
<212> DNA
<213> Homo sapien

<400> 219
gaggggaggc gcatggcggg gatggcgctg gcgcgggcct ggaagcagat gtcctggttc (
tactaccagt acctgctggt cacggcgctc tacatgctgg agccctggga gcggacggtg 1:
ttcaattcca tgctggtttc cattgtgggg atggcactat acacaggata cgtcttcatg 1f
ccccagcaca tcatggcgat attgcactac tttgaaatcg tacaatgacc aagatgcgac 2·
caggatcaga ggttccttgg ggaagaccca ccctacgaag ttggaatgag accatcagat 3(
gtgataagaa actcttctag atgtcaacat aaccaacctt ataaagacta aaattcatga 3(
gtagaacagg aaaatcatcc tgactcatgt gttgtgttct ttatttttaa ttttcaaaga 4.
ggctcttgta tagcagtttt tgtctatttt aacattgtag tcatttgtac tttgatatca 4·
gtattttctt aacctttgtg actgtttcaa tattaccccc gtgaaagctt ttcttaatgt 5·
aactttgagt acattttaat tgccttctat ttttaaaact caaaatcatt agttgggctt 6
tactgttctt gctattgtat ggcatataca tctgcctgga tatatttcta ctcttgacca 6·
aagttttgta aagaacaata taagatttcg ggtaggggta tggggaggga agatatttta 7
ttgagaacta cttaacaaaa gatttatctg taagcttgaa ctcaggagta cagttttagc 7
tatctagact ctaacagctt ttgctttaaa attattaaag tgtttcttaa tgaaaaagaa 8
aagatcttgc taaagttaaa ataaggaaca tttcaccttt taaatattta attcttatgt 9
ggacttattt ccagaaaact ttggtgataa ttcttgagac aaaaggtggt taagtagcat 9
tattatgtaa tgcttatata ccatagagtt tttaatagaa gagaaatcca tttcctccga 10
gggtcactat taacaatgta cttccttaaa tttagtttaa tgattgtaat gggtgctgca 10
tttgcacatt gcattaagtt atgatgagac gaattgttgt taaaaattat agcaaaaaga 11
aatgtaaact tggttaaaat cctttcactc tttgtattgt ttttttaag gtttttattc 12
cttaaatgta aaatgactac ctaatttttt gatgtaaata cattaaattc aaagagaaaa 12
aaaatcaaaa aaaaaaaaaa aaaaaaactc gag 12

<210> 220
<211> 983
<212> DNA
<213> Homo sapien

<400> 220
caggttattc tgatcctgcc gcctgtcttc cctgtaagag tggagcctcg aggtgtacct 60
taaagtgacc ggaatgttag agatgcaatt tgcagagctg gggcaaggaa gggctccttg 120
tcactgtagt tactttcctt gcagtggcca aatgcccaat aagaaggaat acatgaccac 180
tgctgtgggg agtcagcagg tgcgtgatgc agctggccac actccatcca cggccatgac 240
ataaaacaga caagaagtaa ggctggactg taacacctca aggcctgctc cagtgaccca 300
ctttcttcag agaggctcta ccacacacac aaccaccttc caaatttaca ctcagatcac 360
tacaccatgt ctcccaagtt aaaacatgta tccacctaga ctttaaatgt gctttgtaac 420
tgttgatggc actgtacaga gggccaaagt atttcccatc agatagcatt tttctgaacc 480
catgcctctt gggacgagat cacaggactt gacccatcat caaataggac caggtgacct 540
acagagacat cacaatgatg gcttcctaca gtcaagtcca tttccaataa tgctctcatc 600
taagagaacc catgaacctt atttgaatcc tggttcaaac aaaaacctta aattatttat 660
gagacaatta taaacttgat agattttgat gtgtgaaggt atttatgaat atttttagtc 720
agtgatggta tactgttaag gaaaaggttc atattttagg gacaaaggct gaaacattta 780
tggacagagt gatatgatat ctgggatttg ttttaggatg aagtgggagg gaggaaatga 840
atggaaatag tgttgaaaca gtattggcca cgagtcagct attgtgtgct aagacgctcc 900
tcacaccagt ctactctgta tgtgtttgaa tatctctgta ataaacttaa caaggaaaaa 960
aaaaaaaaaa aaaaaaactc gag 983

<210> 221
<211> 373
<212> DNA
<213> Homo sapien

<400> 221
cattttatgg gttaattttt tattaaatag caataagata cttttataac tcaataaaat 60
tattcaatga tacattcgga aaataaatgt ataaaatatg aaaaagtact aaaaagcatt 120
tttcagtact tttaggtaag attaatccaa ctaaacacta gcatatgtta tacagtaata 180
ataaggggaa aatacaataa tgttgagaaa gcaaactcaa agcatagatc aatgaaaaaa 240
ttgagaaatg gacataaatg atttagtatt tttaaagaga gtgaaaaatc attattttat 300
gcttttgtgt agcgttagat gaattaaata acatatgcac atatagcttt gcgatacaaa 360
tttccagacc ata 373

<210> 222
<211> 544
<212> DNA
<213> Homo sapien

<400> 222
cagagatgct gctgctacaa aggatcggtg taagcagtta acccaggaaa tgatgacaga
gaaagaaaga agcaatgtgg ttataacaag gatgaaagat cgaattggaa cattagaaaa 1
ggaacataat gtatttcaaa acaaaataca tgtcagttat caagagactc aacagatgca 1
gatgaagttt cagcaagttc gtgagcagat ggaggcagag atagctcact tgaagcagga 2
aaatggtata ctgagagatg cagtcagcaa cactacaaat caactggaaa gcaagcagtc 3
tgcagaacta aataaactac gccaggatta tgctaggttg gtgaatgagc tgactgagaa 3
aacaggaaag ctacagcaag aggaagtcca aaagaagaat gctgagcaag cagctactca 4
gttgaaggtt caactacaag aagctgagag aaggtgggaa gaagttcaga gctacatcag 4
gaagagaaca gcggaacatg aggcagcaca gctagattta cagagtaaat ttgtggccaa 5
agaa 5

<210> 223
<211> 316
<212> DNA
<213> Homo sapien

<400> 223

gaggcaaggg atatgcttta gtgcctatta tagttaattc ttcaactcca aagtctaaaa 6
cagttgaatc tgctgaagga aaatctgaag aagtaaatga aacattagtt atacccactg 12
aggaagcaga aatggaagaa agtggacgaa gtgcaactcc tgttaactgt gaacagcctg 18
atatcttggt ttcttctaca ccaataaatg aaggacagac tgtgttagac aaggtggctg 24
agcagtgtga acctgctgaa agtcagccag aagcacttct gagaggaaga tgtttgcaag 30
gtaactctaa cagttg 31

<210> 224
<211> 1583
<212> DNA
<213> Homo sapien

<400> 224

cagaccacgt ctgccctcgc cgctctagcc ctgcgcccca gccccggccgc ggcacctccg 6
cctcgccgcc gctaggtcgg ccggctccgc ccggctgccg cctaggatga atatcatgga 12
cttcaacgtg aagaagctgg cggccgacgc aggcaccttc ctcagtcgcg ccgtgcagtt 18
cacagaagaa aagcttggcc aggctgagaa gacagaattg gatgctcact tagagaacct 24
ccttagcaaa gctgaatgta ccaaaatatg gacagaaaaa ataatgaaac aaactgaagt 30
gttattgcag ccaaatccaa atgccaggat agaagaattt gtttatgaga aactggatag 36
aaaagctcca agtcgtataa acaacccaga acttttggga caatatatga ttgatgcagg 42
gactgagttt ggcccaggaa cagcttatgg taatgcccct attaaatgtg gagaaaccca 48
aaaaagaatt ggaacagcag acagagaact gattcaaacg tcagccttaa attttcttac 54
tcctttaaga aactttatag aaggagatta caaaacaatt gctaaagaaa ggaaactatt 60
gcaaaataag agactggatt tggatgctgc aaaaacgaga ctaaaaaagg caaaagctgc 66
agaaactaga aattcatctg aacaggaatt aagaataact caaagtgaat ttgatcgtca 72
agcagagatt accagacttc tgctagaggg aatcagcagt acacatgccc atcaccttcg 78
ctgtctgaat gactttgtag aagcccagat gacttactat gcacagtgtt accagtatat 84
gttggacctc cagaaacaac tgggaagttt tccatccaat tatcttagta acaacaatca 90
gacttctgtg acacctgtac catcagtttt accaaatgcg attggttctt ctgccatggc 96
ttcaacaagt ggcctagtaa tcacctctcc ttccaacctc agtgaccttа aggagtgtag 102
tggcagcaga aaggccaggg ttctctatga ttatgatgca gcaaacagta ctgaattatc 108
acttctggca gatgaggtga tcactgtgtt cagtgttgtt ggaatggatt cagactggct 114
aatgggggaa aggggaaacc agaagggcaa ggtgccaatt acctacttag aactgctcaa 120
ttaagtaggt ggactatgga aaggttgccc atcatgactt tgtatttata tacaattaac 126
tctaaataaa gcaggttaag tatcttccat gttaatgtgt taagagactg aaaataccag 132
ccatcagaaa ctggcctttt tgccaataaa gttgcatggt aaatatttca ttacagaatt 138
tatgttagag ctttcatgcc aagaatgttt tcttacaaaa ttctcttttt attgaggttt 144
cactaataag cagcttctac ttttgagcct caacttaaag cagaactgtt ttttactgga 150
tttttcatta acagcaagct tttttttta tgtaaaataa atctattgtg aattgaaaaa 156
aaaaaaaaaa aaaaaaactc gag 159

<210> 225
<211> 491
<212> DNA
<213> Homo sapien

<400> 225

gaacaacatc atcttgaatc actagataga ctcttgacgg aaagcaaagg ggaaatgaaa
aaggaaaata tgaagaaaga tgaagcttta aaagcattac agaaccaagt atctgaagaa 1
acaatcaagg ttaggcaact agattcagca ttggaaattt gtaaggaaga acttgtcttg 1
catttgaatc aattggaagg aaataaggaa aagtttgaaa aacagttaaa gaagaaatct 2
gaagaggtat attgtttaca gaaagagcta aagataaaaa atcacagtct tcaagagact 3
tctgagcaaa acgttattct acagcatact cttcagcaac agcagcaaat gttacaacaa 3

Confidential

gagacaatta gaaatggaga gctagaagat actcaaacta aacttgaaaa acaggtgtca 42
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PATE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Steven G. Reed, Michael J. Lodes and Roadoh Mohamath
Filed	:	April 2, 1999
For	:	COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE
		Docket No. : 210121.475
		Date : April 2, 1999

Box Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION

Sir:

I, Lawrence Teague, in accordance with 37 C.F.R. § 1.821(f) do her declare that, to the best of my knowledge, the content of the paper entitled "Seque Listing" and the computer readable copy contained within the floppy disk are the same.

I declare further that all statements made herein of my own knowledge true and that all statements made on information and belief are believed to be true and fur that these statements are made with the knowledge that willful false statements and the so made are punishable by fine or imprisonment, or both, under Section 1001 of Title I the United States Code and that such willful false statements may jeopardize the validit the application or any patent issuing thereon.

Dated this 2nd day of April, 1999.

Lawrence Teague
Legal Assistant

6300 Columbia Center
Seattle, WA 98104-7092
(206) 622-4900
FAX (206) 682-6031

TRADUCCIÓN OFICIAL No.2000/095 de un documento escrito en inglés, el cual para su identificación se sella con el sello del traductor al tiempo con la presente. Esta traducción ha sido preparada por Hilda Aguilera de Piedrahita traductora e intérprete oficial debidamente reconocida por el Ministerio de Relaciones Exteriores y autorizada por el Ministerio de Justicia y del Derecho, por resolución número 323 de 1980.

(Se traduce el certificado de la Oficina de Patentes y Marcas de los Estados Unidos de América, correspondiente a la solicitud 09/285/323 y el capítulo reivindicatorio, escritos en inglés.)

ESTADOS UNIDOS DE AMÉRICA

A TODOS A QUIENES ESTOS PRESENTES LLEGAREN:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS

Abril 12, 2000

POR EL PRESENTE CERTIFICO QUE ADJUNTA SE ENCUENTRA UNA COPIA FIEL DE LOS ARCHIVOS DE LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE AMÉRICA DE AQUELLOS PAPELES DE LA SOLICITUD DE PATENTE IDENTIFICADA ABAJO Y QUE CUMPLIERON CON

TRADUCCION OFICIAL No. 2000/095
HILDA AGUILERA DE PIEDRAHITA
INTERPRETE OFICIAL
Res. No. 323 1980 MIN. DE JUSTICIA

LOS REQUISITOS PARA QUE SE LES OTORGARA UNA FECHA DE SOLICITUD BAJO EL CÓDIGO DE COMERCIO DE LOS ESTADOS UNIDOS DE AMÉRICA TÍTULO 35 SECCIÓN 111.

NUMERO DE SOLICITUD: ***09/285,323***

FECHA DE PRESENTACIÓN: ***Abril 02, 1999***

Por autoridad del

COMISARIO DE PATENTES Y MARCAS

(Firmado.) H. PHILLIPS

Funcionario que Certifica

(SELLO DE OBLEA DE LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE AMÉRICA)

(Nota: al margen aparece un sello a tinta en todas las páginas: 09285323.040299)

Reivindicaciones

1. Un polinucleótido aislado que incluye una secuencia nucleótida seleccionada del grupo consistente de:

(a) Las secuencias presentadas en los NO SEQ ID: 218-222 y 224-226;

(b) Los complementos de las presentadas en los NO SEQ ID: 218-222 y 224-226; y

(c) Variantes de las secuencias de (a) y (b).

2. Un polipéptido aislado que incluye una porción inmunogéncia de una proteína de tumor pulmonar o una variante de ella, donde dicha proteína incluye una secuencia de aminoácidos que está codificada por un polinucleótido de la reivindicación 1.

3. Un vector de expresión que incluye un polinucleótido de la reivindicación 1.

4. Una célula anfitriona transformada con el vector de expresión de la reivindicación 3.

5. La célula anfitriona de la reivindicación 4 donde la célula anfitriona se selecciona del grupo consistente de *E. Coli*, levadura y líneas de células de mamíferos.

6. Una composición farmacéutica que incluye el polipéptido de la reivindicación 2 y un portador fisiológicamente aceptable.

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7. Una vacuna que incluye el polipéptido de la reivindicación 2 y un mejorador de respuesta inmune.

8. La vacuna de la reivindicación 7, donde el mejorador de respuesta inmune es un adyuvante.

9. Una vacuna que incluye el polinucleótido de la reivindicación 1 y un mejorador de respuesta inmune.

10. La vacuna de la reivindicación 9 donde el mejorador de respuesta inmune es un adyuvante.

11. Una composición farmacéutica para el tratamiento de cáncer de pulmón que incluye un polipéptido y un portador fisiológicamente aceptable, el polipéptido incluye una porción inmunogénica de una proteína de pulmón o una variante de la misma, donde dicha proteína incluye una secuencia de aminoácidos codificada por un polinucleótido que incluye una secuencia seleccionada del grupo que consiste de:

(a) Las secuencias presentadas en los NO SEQ ID: 217, 223 y 227-237;

(b) Las secuencias complementarias a las secuencias de NO SEQ ID: 217, 223 y 227-237;y

(c) Variantes de las secuencias de (a) y (b).

12. Una vacuna para el tratamiento de cáncer de pulmón que incluye un polipéptido y un mejorador de respuesta inmune, dicho polipéptido incluye una porción inmunogénica de una proteína de pulmón o una variante de la misma, donde dicha proteína incluye una secuencia de aminoácidos codificada por un polinucleótido que incluye una secuencia seleccionada del grupo que consiste de:

(a) Las secuencias presentadas en los NO SEQ ID: 217, 223 y 227-237;

(b) Las secuencias complementarias a las secuencias de NO SEQ ID: 217, 223 y 227-237; y

(c) Variantes de las secuencias de (a) y (b).

13. Una vacuna para el tratamiento de cáncer de pulmón que incluye un polinucleótido y un mejorador de respuesta inmune, el polinucleótido incluye una secuencia seleccionada del grupo que consiste de:

(a) Las secuencias presentadas en los NO SEQ ID: 217, 223 y 227-237;

(b) Las secuencias complementarias a las secuencias de NO SEQ ID: 217, 223 y 227-237; y

(c) Variantes de las secuencias de (a) y (b).

14. Un método para inhibir el desarrollo de cáncer de pulmón en un paciente, que incluye la administración al paciente, de una cantidad efectiva de la composición farmacéutica de las reivindicaciones 6 o 11.

15. Un método para inhibir el desarrollo de cáncer de pulmón en un paciente, que incluye la administración al paciente de una cantidad efectiva de la vacuna de cualesquiera de las reivindicaciones 7, 9, 12 o 13.

16. Una proteína de fusión que incluye por lo menos un polipéptido de acuerdo con la reivindicación 2.

17. Una proteína de fusión que incluye por lo menos dos polipéptidos de acuerdo con la reivindicación 2.

18. Una proteína de fusión que incluye un polipéptido de acuerdo con la reivindicación 2 y un antígeno conocido de tumor de pulmón.

19. Una composición farmacéutica que incluye una proteína de fusión de acuerdo con cualesquiera de las reivindicaciones 16-18 y un portador fisiológicamente aceptable.

20. Una vacuna que incluye una proteína de fusión de acuerdo con cualesquiera de las reivindicaciones 16-18 y un mejorador de respuesta inmune.

21. La vacuna de la reivindicación 20 donde el mejorador de respuesta inmune es un adyuvante.

22. Un método para inhibir el desarrollo de cáncer de pulmón en un paciente, que incluye la administración al paciente de una cantidad efectiva de la composición farmacéutica de la reivindicación 19.

23. Un método para inhibir el desarrollo de cáncer de pulmón en un paciente, que incluye la administración al paciente, de una cantidad efectiva de la vacuna de la reivindicación 20.

24. Un método para detectar cáncer de pulmón en un paciente, que incluye:

(a) poner en contacto una muestra biológica obtenida de un paciente con un agente ligante el cual es capaz de ligarse a un polipéptido, el polipéptido incluye una porción inmunogénica de una proteína de tumor pulmonar o una variante del mismo, donde dicha proteína incluye una secuencia de aminoácidos que es codificada por un polinucleótido que incluye una secuencia nucleótida seleccionada del grupo que consiste de secuencias presentadas en los NO SEQ ID: 217-237, los complementos de dichas secuencias y variantes de las mismas; y

(b) detectar en la muestra un polipéptido que se liga al agente ligante, y así detectar de cáncer de pulmón en el paciente.

25. El método de la reivindicación 24 donde el agente ligante es un anticuerpo monoclonal.

26. El método de la reivindicación 25 donde el agente ligante es un anticuerpo policlonal.

27. Un método para supervisar la progresión de cáncer de pulmón en un paciente, que incluye:

(a) poner en contacto una muestra biológica obtenida de un paciente con un agente ligante que es capaz de ligarse a un polipéptido, dicho polipéptido incluye una porción inmunogénica de una proteína de tumor pulmonar o una variante de la misma, donde dicha proteína incluye una secuencia de aminoácidos que es codificada por un polinucleótido que incluye una secuencia nucleótida seleccionada del grupo que consiste de secuencias presentadas en los NO SEQ ID: 217-237, los complementos de dichas secuencias y variantes de las mismas;

(b) determinar en la muestra una cantidad de polipéptido que se liga al agente ligante;

(c) repetir las etapas (a) y (b); y

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(d) comparar la cantidad de polipéptido detectado en las etapas (b) y (c) para supervisar la progresión de cáncer de pulmón en el paciente.

28. Un anticuerpo monoclonal que se liga a un polipéptido que incluye una porción inmunogénica de una proteína de tumor de pulmón o una variante de la misma, donde dicha proteína incluye una secuencia de aminoácidos codificada por un polinucleótido que incluye una secuencia nucleótida seleccionada del grupo que consiste de:

(a) Las secuencias presentadas en los NO SEQ ID: 218-222 y 224-226;

(b) Las secuencias de nucleótido complementarias presentadas en los NO SEQ ID: 218-222 y 224-226; y

(c) Variantes de las secuencias de (a) y (b).

29. Un método para inhibir el desarrollo de cáncer de pulmón en un paciente, que incluye la administración al paciente una cantidad terapéuticamente efectiva de un anticuerpo monoclonal de acuerdo con la reivindicación 28.

30. El método de la reivindicación 29 donde el anticuerpo monoclonal es conjugado con un agente terapéutico.

31. Un método para detectar cáncer de pulmón en un paciente, que incluye:

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(a) obtener una muestra biológica del paciente;

(b) poner en contacto la muestra con por lo menos dos oligonucleótidos primarios en una reacción de polimerasa en cadena, donde por lo menos uno de los oligonucleótidos es específico para un polinucleótido que codifica un polipéptido que incluye una porción inmunogénica de una proteína de tumor pulmonar o una variante del mismo, dicha proteína incluye una secuencia de aminoácidos que es codificada por un polinucleótido que incluye una secuencia nucleótida seleccionada del grupo que consiste de secuencias presentadas en los NO SEQ ID: 217-237, los complementos de dichas secuencias y variantes de las mismas; y

(c) detectar en la muestra una secuencia DNA que se amplíe en la presencia de los oligonucleótidos primarios, y así detectar cáncer de pulmón en el paciente.

32. El método de la reivindicación 31, donde por lo menos uno de los oligonucleótidos primarios incluye por lo menos aproximadamente 10 nucleótidos contiguos de un polinucleótido que incluye una secuencia seleccionada de los NO SEQ ID: 217-237.

33. Un conjunto de diagnóstico, que incluye:

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(a) uno o más anticuerpos monoclonales de acuerdo con la reivindicación 28; y

(b) un agente de detección.

34. El conjunto de la reivindicación 33, donde los anticuerpos monoclonales son inmovilizados sobre un soporte sólido.

35. El conjunto de la reivindicación 34, donde el soporte sólido incluye nitrocelulosa, látex o un material plástico.

36. El conjunto de la reivindicación 33, donde el agente de detección incluye un grupo reportero conjugado con un agente ligante.

37. El conjunto de la reivindicación 36 donde el agente ligante es seleccionado del grupo que consiste de anti-inmunoglobulina, Proteína G, Proteína A o lectinas.

38. El conjunto de la reivindicación 36, donde el grupo reportero es seleccionado del grupo que consiste de radioisótopos, grupos fluorescentes, grupos luminiscentes, enzimas, biotina y partículas de tinte.

39. Un conjunto de diagnóstico que incluye por lo menos dos oligonucleótidos primarios, por lo menos uno de los oligonucleótidos primarios es específico para un polinucleótido que codifica un polipéptido que incluye una porción inmunogénica de una proteína de tumor pulmonar o una

variante del mismo, dicha proteína incluye una secuencia de aminoácidos que es codificada por un polinucleótido que incluye una secuencia nucleótida seleccionada del grupo que consiste de secuencias presentadas en los NO SEQ ID: 217-237, los complementos de dichas secuencias y variantes de las mismas.

40. El conjunto de diagnóstico de la reivindicación 39 donde por lo menos uno de los oligonucleótidos primarios incluye por lo menos aproximadamente 10 nucleótidos contiguos de un polinucleótido que tiene una secuencia nucleótida seleccionada del grupo que consiste de secuencias presentadas en los NO SEQ ID: 217-237, los complementos de dichas secuencias y variantes de las mismas.

41. Un método para detectar cáncer de pulmón en un paciente, que incluye:

(a) obtener una muestra biológica del paciente;

(b) poner en contacto la muestra con un oligonucleótido detector específico para un polinucleótido que codifica un polipéptido que incluye una porción inmunogénica de una proteína de tumor pulmonar o una variante del mismo, dicha proteína incluye una secuencia de aminoácidos que es codificada por un polinucleótido que incluye una secuencia nucleótida seleccionada del grupo que consiste de secuencias presentadas en los NO SEQ ID: 217-237,

los complementos de dichas secuencias y variantes de las mismas; y

(c) detectar en la muestra una secuencia DNA que se hibridiza al oligonucleótido detector, así detectar cáncer de pulmón en el paciente.

42. El método de la reivindicación 41 donde el oligonucleótido detector incluye por lo menos aproximadamente 15 nucleótidos contiguos de un polinucleótido que tiene una secuencia nucleótida seleccionada del grupo que consiste de secuencias presentadas en los NO SEQ ID: 217-237, los complementos de dichas secuencias y variantes de las mismas.

43. Un conjunto de diagnóstico que incluye en oligonucleótido detector específico para un polinucleótido que codifica un polipéptido que incluye una porción inmunogénica de una proteína de tumor pulmonar o una variante del mismo, dicha proteína incluye una secuencia de aminoácidos que es codificada por un polinucleótido que incluye una secuencia nucleótida seleccionada del grupo que consiste de secuencias presentadas en los NO SEQ ID: 217-237, los complementos de dichas secuencias y variantes de las mismas.

44. El conjunto de diagnóstico de la reivindicación 43, donde el oligonucleótido detector incluye por lo menos aproximadamente 15 nucleótidos contiguos de un polinucleótido que tiene una secuencia

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nucleótida seleccionada del grupo que consiste de secuencias presentadas en los NO SEQ ID: 217-237, los complementos de dichas secuencias y variantes de las mismas.

45. Un método para tratar cáncer de pulmón en un paciente, que incluye las etapas de:

(a) obtener células de sangre periféricas del paciente;

(b) incubar las células en presencia de por lo menos un polipéptido de la reivindicación 2, tal como células T proliferadas; y

(c) administrar las células T proliferadas al paciente.

46. Un método para tratar cáncer de pulmón en un paciente, que incluye las etapas de:

(a) obtener células de sangre periféricas del paciente;

(b) incubar las células en presencia de por lo menos un polinucleótido de la reivindicación 1, tal como células T proliferadas; y

(c) administrar las células T proliferadas al paciente.

47. El método de cualesquiera de las reivindicaciones 45 y 46 donde la etapa de incubación de las células T se repite una o más veces.

PRODUCCIÓN OFICIAL
MESA ASISTENCIA DE PRESENTA

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48. El método de cualesquiera de las reivindicaciones 45 y 46 donde la etapa (a) además incluye la separación de las células T de las células de sangre periféricas, y las células incubadas en la etapa (b) son células T.

49. El método de cualesquiera de las reivindicaciones 45 y 46 donde la etapa (a) además incluye la separación de las células CD4+ o CD8+ de las células de sangre periféricas, y las células proliferadas en la etapa (b) son células T CD4+ o CD8+.

50. El método de cualesquiera de las reivindicaciones 45 y 46 donde la etapa (b) además incluye la clonación de una o más células T que se proliferan en presencia del polipéptido.

51. Una composición para el tratamiento de cáncer de pulmón en un paciente que incluye células T proliferadas en presencia de un polipéptido de la reivindicación 2, en combinación con un portador farmacéuticamente aceptable.

52. Una composición para el tratamiento de cáncer de pulmón en un paciente que incluye células T proliferadas en presencia de un polinucleótido de la reivindicación 1, en combinación con un portador farmacéuticamente aceptable.

53. Un método para tratar cáncer de pulmón en un paciente, que incluye las etapas de:

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(a) incubar células que presentan antígeno en presencia de por lo menos un polipéptido de la reivindicación 2; y

(b) administrar al paciente las células que presentan antígeno incubadas.

54. Un método para tratar cáncer de pulmón en un paciente, que incluye las etapas de:

(a) incubar células que presentan antígeno en presencia de por lo menos un polinucleótido de la reivindicación 1; y

(b) administrar al paciente las células que presentan antígeno incubadas.

55. El método de las reivindicaciones 53 y 54 donde las células que presentan antígeno son seleccionadas del grupo que consiste de células dendríticas y células macrófagas.

56. Una composición para el tratamiento de cáncer de pulmón en un paciente que incluye células que presentan antígeno incubadas en presencia de un polipéptido de la reivindicación 2, en combinación con un portador farmacéuticamente aceptable.

57. Una composición para el tratamiento de cáncer de pulmón en un paciente que incluye células que presentan antígeno incubadas en presencia de un

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polinucleótido de la reivindicación 1, en combinación con un portador farmacéuticamente aceptable.

ES TRADUCCIÓN FIEL Y COMPLETA de la cual se deja copia en los archivos de esta oficina para su confrontación y a la cual me remito.

Santafé de Bogotá, 6 de Junio del 2000.

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PA 333384

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

April 12, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: ***09/370,838***
FILING DATE: ***August 09, 1999***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

L. Edelen

L. EDELEN
Certifying Officer

TRADUCCION OFICIAL No. 2000/094
BILDA AGUILERA DE PIEDMARITA
INTERPRETE OFICIAL
DES No. 223 DEL MIN OF JUSTICIA

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PTO/SB/05 (2/98)

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR § 1.53(b))

Attorney Docket No.	210121.47SC1
First Inventor or Application Identifier	Steven G. Reed
Title	COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE
Express Mail Label No.	EM001237414US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Box Patent Application, Assistant Commissioner for Patents, Washington, D.C. 20231

1. [ ] General Authorization Form & Fee Transmittal (Submit an original and a duplicate for fee processing)
2. [X] Specification [Total Pages] 76 (preferred arrangement set forth below)
   - Descriptive Title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings (If filed)
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
3. [ ] Drawing(s) (35 USC 113) [Total Sheets]
4. Oath or Declaration [Total Pages]
   a. [ ] Newly executed (original or copy)
   b. [ ] Copy from a prior application (37 CFR 1.63(d)) (for continuation/divisional with Box 17 completed)
      i. [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b)
5. [ ] Incorporation By Reference (useable if box 4b is checked) The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered to be part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. [ ] Microfiche Computer Program (Appendix)
7. Nucleotide and Amino Acid Sequence Submission (If applicable, all necessary)
   a. [X] Computer-Readable Copy
   b. [X] Paper Copy (identical to computer copy)
   c. [X] Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. [ ] Assignment Papers (cover sheet & document(s))
9. [ ] 37 CFR 3.73(b) Statement (when there is an assignee) [ ] Power of Attorney
10. [ ] English Translation Document (If applicable)
11. [ ] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copies of IDS Citations
12. [ ] Preliminary Amendment
13. [X] Return Receipt Postcard
14. [ ] Small Entity Statement(s) [ ] Statement filed in prior application, Status still proper and desired
15. [ ] Certified Copy of Priority Document(s) (If foreign priority is claimed)
16. [X] Other: Certificate of Express Mail

17. If a CONTINUING APPLICATION, check appropriate box and supply the requisite information below and in a preliminary amendment:
    [ ] Continuation [ ] Divisional [X] Continuation-in-Part (CIP) of prior Application No.: 09/285,373
    Prior application information: Examiner _____ Group / Art Unit _____
    [ ] Claims the benefit of Provisional Application No. _____

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(206) 622-4900 phone
(206) 682-6031 fax

Respectfully submitted,

TYPED or PRINTED NAME David J. Maki REGISTRATION NO. 31,392

SIGNATURE _____ Date August 9, 1999

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COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE

REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Patent Application No. 09/285,323, filed April 2, 1999.

TECHNICAL FIELD

The present invention relates generally to compositions and methods for the treatment of lung cancer. The invention is more specifically related to nucleotide sequences that are preferentially expressed in lung tumor tissue, together with polypeptides encoded by such nucleotide sequences. The inventive nucleotide sequences and polypeptides may be used in vaccines and pharmaceutical compositions for the treatment of lung cancer.

BACKGROUND OF THE INVENTION

Lung cancer is the primary cause of cancer death among both men and women in the U.S., with an estimated 172,000 new cases being reported in 1994. The five-year survival rate among all lung cancer patients, regardless of the stage of disease at diagnosis, is only 13%. This contrasts with a five-year survival rate of 46% among cases detected while the disease is still localized. However, only 16% of lung cancers are discovered before the disease has spread.

Early detection is difficult since clinical symptoms are often not seen until the disease has reached an advanced stage. Currently, diagnosis is aided by the use of chest x-rays, analysis of the type of cells contained in sputum and fiberoptic examination of the bronchial passages. Treatment regimens are determined by the type and stage of the cancer, and include surgery, radiation therapy and/or chemotherapy. In spite of considerable research into therapies for the disease, lung cancer remains difficult to treat.

Accordingly, there remains a need in the art for improved vaccines, treatment methods and diagnostic techniques for lung cancer.

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SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compounds and methods for the therapy and diagnosis of cancer, such as lung cancer. In one aspect, the present invention provides polypeptides comprising at least a portion of a lung tumor protein, or a variant thereof .. Certain portions and other variants are immunogenic, such that the ability of the variant to react with antigen-specific antisera is not substantially diminished. Within certain embodiments, the polypeptide comprises a sequence that is encoded by a polynucleotide sequence selected from the group consisting of: (a) sequences recited in SEQ ID NOS: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282 and 285; (b) variants of a sequence recited in SEQ ID NOS: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282 and 285; and (c) complements of a sequence of (a) or (b).

The present invention further provides polynucleotides that encode a polypeptide as described above, or a portion thereof (such as a portion encoding at least 15 contiguous amino acid residues of a lung tumor protein), expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, vaccines are provided. Such vaccines comprise a polypeptide or polynucleotide as described above and a non-specific immune response enhancer.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a lung tumor protein; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, vaccines are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a non-specific

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immune response enhancer.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

Within related aspects, pharmaceutical compositions comprising a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a physiologically acceptable carrier are provided.

Vaccines are further provided, within other aspects, that comprise a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a non-specific immune response enhancer.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition or vaccine as recited above.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a lung tumor protein, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a lung tumor protein, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polynucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

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The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating $CD4^+$ and/or $CD8^+$ T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of a lung tumor protein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody. The cancer may be lung cancer.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a

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predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

SEQUENCE IDENTIFIERS

SEQ ID NO: 1 is the determined cDNA sequence for L363C1.cons

SEQ ID NO: 2 is the determined cDNA sequence for L263C2.cons

SEQ ID NO: 3 is the determined cDNA sequence for L263C2c

SEQ ID NO: 4 is the determined cDNA sequence for L263C1.cons

SEQ ID NO: 5 is the determined cDNA sequence for L263C1b

SEQ ID NO: 6 is the determined cDNA sequence for L164C2.cons

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SEQ ID NO: 8 is the determined cDNA sequence for L366C1a

SEQ ID NO: 9 is the determined cDNA sequence for L260C1.cons

SEQ ID NO: 10 is the determined cDNA sequence for L163C1c

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SEQ ID NO: 12 is the determined cDNA sequence for L255C1.cons

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SEQ ID NO: 14 is the determined cDNA sequence for L355C1.cons

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SEQ ID NO: 21 is the determined cDNA sequence for LT86-5

SEQ ID NO: 22 is the determined cDNA sequence for LT86-6

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SEQ ID NO: 24 is the determined cDNA sequence for LT86-8

SEQ ID NO: 25 is the determined cDNA sequence for LT86-9

SEQ ID NO: 26 is the determined cDNA sequence for LT86-10

SEQ ID NO: 27 is the determined cDNA sequence for LT86-11

SEQ ID NO: 28 is the determined cDNA sequence for LT86-12

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SEQ ID NO: 30 is the determined cDNA sequence for LT86-14

SEQ ID NO: 31 is the determined cDNA sequence for LT86-15

SEQ ID NO: 32 is the predicted amino acid sequence for LT86-1

SEQ ID NO: 33 is the predicted amino acid sequence for LT86-2

SEQ ID NO: 34 is the predicted amino acid sequence for LT86-3

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SEQ ID NO: 36 is the predicted amino acid sequence for LT86-5

SEQ ID NO: 37 is the predicted amino acid sequence for LT86-6

SEQ ID NO: 38 is the predicted amino acid sequence for LT86-7

SEQ ID NO: 39 is the predicted amino acid sequence for LT86-8

SEQ ID NO: 40 is the predicted amino acid sequence for LT86-9

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SEQ ID NO: 45 is the predicted amino acid sequence for LT86-14

SEQ ID NO: 46 is the predicted amino acid sequence for LT86-15

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SEQ ID NO: 48 is a primer

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SEQ ID NO: 52 is the determined 5' cDNA sequence for L86S-25

SEQ ID NO: 53 is the determined 5' cDNA sequence for L86S-36

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SEQ ID NO: 56 is the predicted amino acid sequence for L86S-3

SEQ ID NO: 57 is the predicted amino acid sequence for L86S-12

SEQ ID NO: 58 is the predicted amino acid sequence for L86S-16

SEQ ID NO: 59 is the predicted amino acid sequence for L86S-25

SEQ ID NO: 60 is the predicted amino acid sequence for L86S-36

SEQ ID NO: 61 is the predicted amino acid sequence for L86S-40

SEQ ID NO: 62 is the predicted amino acid sequence for L86S-46

SEQ ID NO: 63 is the determined 5' cDNA sequence for L86S-30

SEQ ID NO: 64 is the determined 5' cDNA sequence for L86S-41

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SEQ ID NO: 65 is the predicted amino acid sequence from the 5' end of LT86-9

SEQ ID NO: 66 is the determined extended cDNA sequence for LT86-4

SEQ ID NO: 67 is the predicted extended amino acid sequence for LT86-4

SEQ ID NO: 68 is the determined 5' cDNA sequence for LT86-20

SEQ ID NO: 69 is the determined 3' cDNA sequence for LT86-21

SEQ ID NO: 70 is the determined 5' cDNA sequence for LT86-22

SEQ ID NO: 71 is the determined 5' cDNA sequence for LT86-26

SEQ ID NO: 72 is the determined 5' cDNA sequence for LT86-27

SEQ ID NO: 73 is the predicted amino acid sequence for LT86-20

SEQ ID NO: 74 is the predicted amino acid sequence for LT86-21

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SEQ ID NO: 77 is the predicted amino acid sequence for LT86-27

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SEQ ID NO: 81 is the predicted extended amino acid sequence for L86S-12

SEQ ID NO: 82 is the predicted extended amino acid sequence for L86S-36

SEQ ID NO: 83 is the predicted extended amino acid sequence for L86S-46

SEQ ID NO: 84 is the determined 5'cDNA sequence for L86S-6

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SEQ ID NO: 86 is the determined 5'cDNA sequence for L86S-14

SEQ ID NO: 87 is the determined 5'cDNA sequence for L86S-29

SEQ ID NO: 88 is the determined 5'cDNA sequence for L86S-34

SEQ ID NO: 89 is the determined 5'cDNA sequence for L86S-39

SEQ ID NO: 90 is the determined 5'cDNA sequence for L86S-47

SEQ ID NO: 91 is the determined 5'cDNA sequence for L86S-49

SEQ ID NO: 92 is the determined 5'cDNA sequence for L86S-51

SEQ ID NO: 93 is the predicted amino acid sequence for L86S-6

SEQ ID NO: 94 is the predicted amino acid sequence for L86S-11

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SEQ ID NO: 95 is the predicted amino acid sequence for L86S-14

SEQ ID NO: 96 is the predicted amino acid sequence for L86S-29

SEQ ID NO: 97 is the predicted amino acid sequence for L86S-34

SEQ ID NO: 98 is the predicted amino acid sequence for L86S-39

SEQ ID NO: 99 is the predicted amino acid sequence for L86S-47

SEQ ID NO: 100 is the predicted amino acid sequence for L86S-49

SEQ ID NO: 101 is the predicted amino acid sequence for L86S-51

SEQ ID NO: 102 is the determined DNA sequence for SLT-T1

SEQ ID NO: 103 is the determined 5' cDNA sequence for SLT-T2

SEQ ID NO: 104 is the determined 5' cDNA sequence for SLT-T3

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SEQ ID NO: 106 is the determined 5' cDNA sequence for SLT-T7

SEQ ID NO: 107 is the determined 5' cDNA sequence for SLT-T9

SEQ ID NO: 108 is the determined 5' cDNA sequence for SLT-T10

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SEQ ID NO: 112 is the predicted amino acid sequence for SLT-T2

SEQ ID NO: 113 is the predicted amino acid sequence for SLT-T3

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SEQ ID NO: 115 is the predicted amino acid sequence for SLT-T12

SEQ ID NO: 116 is the determined 5' cDNA sequence for SALT-T3

SEQ ID NO: 117 is the determined 5' cDNA sequence for SALT-T4

SEQ ID NO: 118 is the determined 5' cDNA sequence for SALT-T7

SEQ ID NO: 119 is the determined 5' cDNA sequence for SALT-T8

SEQ ID NO: 120 is the determined 5' cDNA sequence for SALT-T9

SEQ ID NO: 121 is the predicted amino acid sequence for SALT-T3

SEQ ID NO: 122 is the predicted amino acid sequence for SALT-T4

SEQ ID NO: 123 is the predicted amino acid sequence for SALT-T7

SEQ ID NO: 124 is the predicted amino acid sequence for SALT-T8

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SEQ ID NO: 125 is the predicted amino acid sequence for SALT-T9

SEQ ID NO: 126 is the determined cDNA sequence for PSLT-1

SEQ ID NO: 127 is the determined cDNA sequence for PSLT-2

SEQ ID NO: 128 is the determined cDNA sequence for PSLT-7

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SEQ ID NO: 133 is the determined cDNA sequence for PSLT-40

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SEQ ID NO: 140 is the determined cDNA sequence for PSLT-011

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SEQ ID NO: 144 is the determined cDNA sequence for PSLT-37

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SEQ ID NO: 147 is the determined cDNA sequence for PSLT-012

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SEQ ID NO: 151 is the determined 5' cDNA sequence for SAL-25

SEQ ID NO: 152 is the determined 5' cDNA sequence for SAL-33

SEQ ID NO: 153 is the determined 5' cDNA sequence for SAL-50

SEQ ID NO: 154 is the determined 5' cDNA sequence for SAL-57

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SEQ ID NO: 155 is the determined 5' cDNA sequence for SAL-66

SEQ ID NO: 156 is the determined 5' cDNA sequence for SAL-82

SEQ ID NO: 157 is the determined 5' cDNA sequence for SAL-99

SEQ ID NO: 158 is the determined 5' cDNA sequence for SAL-104

SEQ ID NO: 159 is the determined 5' cDNA sequence for SAL-109

SEQ ID NO: 160 is the determined 5' cDNA sequence for SAL-5

SEQ ID NO: 161 is the determined 5' cDNA sequence for SAL-8

SEQ ID NO: 162 is the determined 5' cDNA sequence for SAL-12

SEQ ID NO: 163 is the determined 5' cDNA sequence for SAL-14

SEQ ID NO: 164 is the determined 5' cDNA sequence for SAL-16

SEQ ID NO: 165 is the determined 5' cDNA sequence for SAL-23

SEQ ID NO: 166 is the determined 5' cDNA sequence for SAL-26

SEQ ID NO: 167 is the determined 5' cDNA sequence for SAL-29

SEQ ID NO: 168 is the determined 5' cDNA sequence for SAL-32

SEQ ID NO: 169 is the determined 5' cDNA sequence for SAL-39

SEQ ID NO: 170 is the determined 5' cDNA sequence for SAL-42

SEQ ID NO: 171 is the determined 5' cDNA sequence for SAL-43

SEQ ID NO: 172 is the determined 5' cDNA sequence for SAL-44

SEQ ID NO: 173 is the determined 5' cDNA sequence for SAL-48

SEQ ID NO: 174 is the determined 5' cDNA sequence for SAL-68

SEQ ID NO: 175 is the determined 5' cDNA sequence for SAL-72

SEQ ID NO: 176 is the determined 5' cDNA sequence for SAL-77

SEQ ID NO: 177 is the determined 5' cDNA sequence for SAL-86

SEQ ID NO: 178 is the determined 5' cDNA sequence for SAL-88

SEQ ID NO: 179 is the determined 5' cDNA sequence for SAL-93

SEQ ID NO: 180 is the determined 5' cDNA sequence for SAL-100

SEQ ID NO: 181 is the determined 5' cDNA sequence for SAL-105

SEQ ID NO: 182 is the predicted amino acid sequence for SAL-3

SEQ ID NO: 183 is the predicted amino acid sequence for SAL-24

SEQ ID NO: 184 is a first predicted amino acid sequence for SAL-25

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SEQ ID NO: 185 is a second predicted amino acid sequence for SAL-25

SEQ ID NO: 186 is the predicted amino acid sequence for SAL-33

SEQ ID NO: 187 is a first predicted amino acid sequence for SAL-50

SEQ ID NO: 188 is the predicted amino acid sequence for SAL-57

SEQ ID NO: 189 is a first predicted amino acid sequence for SAL-66

SEQ ID NO: 190 is a second predicted amino acid sequence for SAL-66

SEQ ID NO: 191 is the predicted amino acid sequence for SAL-82

SEQ ID NO: 192 is the predicted amino acid sequence for SAL-99

SEQ ID NO: 193 is the predicted amino acid sequence for SAL-104

SEQ ID NO: 194 is the predicted amino acid sequence for SAL-5

SEQ ID NO: 195 is the predicted amino acid sequence for SAL-8

SEQ ID NO: 196 is the predicted amino acid sequence for SAL-12

SEQ ID NO: 197 is the predicted amino acid sequence for SAL-14

SEQ ID NO: 198 is the predicted amino acid sequence for SAL-16

SEQ ID NO: 199 is the predicted amino acid sequence for SAL-23

SEQ ID NO: 200 is the predicted amino acid sequence for SAL-26

SEQ ID NO: 201 is the predicted amino acid sequence for SAL-29

SEQ ID NO: 202 is the predicted amino acid sequence for SAL-32

SEQ ID NO: 203 is the predicted amino acid sequence for SAL-39

SEQ ID NO: 204 is the predicted amino acid sequence for SAL-42

SEQ ID NO: 205 is the predicted amino acid sequence for SAL-43

SEQ ID NO: 206 is the predicted amino acid sequence for SAL-44

SEQ ID NO: 207 is the predicted amino acid sequence for SAL-48

SEQ ID NO: 208 is the predicted amino acid sequence for SAL-68

SEQ ID NO: 209 is the predicted amino acid sequence for SAL-72

SEQ ID NO: 210 is the predicted amino acid sequence for SAL-77

SEQ ID NO: 211 is the predicted amino acid sequence for SAL-86

SEQ ID NO: 212 is the predicted amino acid sequence for SAL-88

SEQ ID NO: 213 is the predicted amino acid sequence for SAL-93

SEQ ID NO: 214 is the predicted amino acid sequence for SAL-100

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SEQ ID NO: 215 is the predicted amino acid sequence for SAL-105

SEQ ID NO: 216 is a second predicted amino acid sequence for SAL-50

SEQ ID NO: 217 is the determined cDNA sequence for SSLT-4

SEQ ID NO: 218 is the determined cDNA sequence for SSLT-9

SEQ ID NO: 219 is the determined cDNA sequence for SSLT-10

SEQ ID NO: 220 is the determined cDNA sequence for SSLT-12

SEQ ID NO: 221 is the determined cDNA sequence for SSLT-19

SEQ ID NO: 222 is the determined cDNA sequence for SSLT-31

SEQ ID NO: 223 is the determined cDNA sequence for SSLT-38

SEQ ID NO: 224 is the determined cDNA sequence for LT4690-2

SEQ ID NO: 225 is the determined cDNA sequence for LT4690-3

SEQ ID NO: 226 is the determined cDNA sequence for LT4690-22

SEQ ID NO: 227 is the determined cDNA sequence for LT4690-24

SEQ ID NO: 228 is the determined cDNA sequence for LT4690-37

SEQ ID NO: 229 is the determined cDNA sequence for LT4690-39

SEQ ID NO: 230 is the determined cDNA sequence for LT4690-40

SEQ ID NO: 231 is the determined cDNA sequence for LT4690-41

SEQ ID NO: 232 is the determined cDNA sequence for LT4690-49

SEQ ID NO: 233 is the determined 3' cDNA sequence for LT4690-55

SEQ ID NO: 234 is the determined 5' cDNA sequence for LT4690-55

SEQ ID NO: 235 is the determined cDNA sequence for LT4690-59

SEQ ID NO: 236 is the determined cDNA sequence for LT4690-63

SEQ ID NO: 237 is the determined cDNA sequence for LT4690-71

SEQ ID NO: 238 is the determined cDNA sequence for 2LT-3

SEQ ID NO: 239 is the determined cDNA sequence for 2LT-6

SEQ ID NO: 240 is the determined cDNA sequence for 2LT-22

SEQ ID NO: 241 is the determined cDNA sequence for 2LT-25

SEQ ID NO: 242 is the determined cDNA sequence for 2LT-26

SEQ ID NO: 243 is the determined cDNA sequence for 2LT-31

SEQ ID NO: 244 is the determined cDNA sequence for 2LT-36

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SEQ ID NO: 245 is the determined cDNA sequence for 2LT-42

SEQ ID NO: 246 is the determined cDNA sequence for 2LT-44

SEQ ID NO: 247 is the determined cDNA sequence for 2LT-54

SEQ ID NO: 248 is the determined cDNA sequence for 2LT-55

SEQ ID NO: 249 is the determined cDNA sequence for 2LT-57

SEQ ID NO: 250 is the determined cDNA sequence for 2LT-58

SEQ ID NO: 251 is the determined cDNA sequence for 2LT-59

SEQ ID NO: 252 is the determined cDNA sequence for 2LT-62

SEQ ID NO: 253 is the determined cDNA sequence for 2LT-63

SEQ ID NO: 254 is the determined cDNA sequence for 2LT-65

SEQ ID NO: 255 is the determined cDNA sequence for 2LT-66

SEQ ID NO: 256 is the determined cDNA sequence for 2LT-70

SEQ ID NO: 257 is the determined cDNA sequence for 2LT-73

SEQ ID NO: 258 is the determined cDNA sequence for 2LT-74

SEQ ID NO: 259 is the determined cDNA sequence for 2LT-76

SEQ ID NO: 260 is the determined cDNA sequence for 2LT-77

SEQ ID NO: 261 is the determined cDNA sequence for 2LT-78

SEQ ID NO: 262 is the determined cDNA sequence for 2LT-80

SEQ ID NO: 263 is the determined cDNA sequence for 2LT-85

SEQ ID NO: 264 is the determined cDNA sequence for 2LT-87

SEQ ID NO: 265 is the determined cDNA sequence for 2LT-89

SEQ ID NO: 266 is the determined cDNA sequence for 2LT-94

SEQ ID NO: 267 is the determined cDNA sequence for 2LT-95

SEQ ID NO: 268 is the determined cDNA sequence for 2LT-98

SEQ ID NO: 269 is the determined cDNA sequence for 2LT-100

SEQ ID NO: 270 is the determined cDNA sequence for 2LT-103

SEQ ID NO: 271 is the determined cDNA sequence for 2LT-105

SEQ ID NO: 272 is the determined cDNA sequence for 2LT-107

SEQ ID NO: 273 is the determined cDNA sequence for 2LT-108

SEQ ID NO: 274 is the determined cDNA sequence for 2LT-109

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SEQ ID NO: 275 is the determined cDNA sequence for 2LT-118

SEQ ID NO: 276 is the determined cDNA sequence for 2LT-120

SEQ ID NO: 277 is the determined cDNA sequence for 2LT-121

SEQ ID NO: 278 is the determined cDNA sequence for 2LT-122

SEQ ID NO: 279 is the determined cDNA sequence for 2LT-124

SEQ ID NO: 280 is the determined cDNA sequence for 2LT-126

SEQ ID NO: 281 is the determined cDNA sequence for 2LT-127

SEQ ID NO: 282 is the determined cDNA sequence for 2LT-128

SEQ ID NO: 283 is the determined cDNA sequence for 2LT-129

SEQ ID NO: 284 is the determined cDNA sequence for 2LT-133

SEQ ID NO: 285 is the determined cDNA sequence for 2LT-137

SEQ ID NO: 286 is the determined cDNA sequence for LT4690-71

SEQ ID NO: 287 is the determined cDNA sequence for LT4690-82

SEQ ID NO: 288 is the determined full-length cDNA sequence for SSLT-74

SEQ ID NO: 289 is the determined cDNA sequence for SSLT-78

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DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the therapy and diagnosis of cancer, such as lung cancer. The compositions described herein may include lung tumor polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (*e.g.*, T cells). Polypeptides of the present invention generally comprise at least a portion (such as an immunogenic portion) of a lung tumor protein or a variant thereof. A "lung tumor protein" is a protein that is expressed in lung tumor cells at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in a normal tissue, as determined using a representative assay provided herein. Certain lung tumor proteins are tumor proteins that react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera of a patient afflicted with lung cancer. Polynucleotides of the subject invention generally comprise a DNA or RNA sequence that encodes all or a portion of such a polypeptide, or that is complementary to such a sequence. Antibodies are

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generally immune system proteins, or antigen-binding fragments thereof, that are capable of binding to a polypeptide as described above. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B-cells that express a polypeptide as described above. T cells that may be employed within such compositions are generally T cells that are specific for a polypeptide as described above.

The present invention is based on the discovery of human lung tumor proteins. Sequences of polynucleotides encoding specific tumor proteins are provided in SEQ ID NOS: 1-31, 49-55, 63,64, 66, 68-72, 78-80, 84-92 and 217-289.

LUNG TUMOR PROTEIN POLYNUCLEOTIDES

Any polynucleotide that encodes a lung tumor protein or a portion or other variant thereof as described herein is encompassed by the present invention. Preferred polynucleotides comprise at least 15 consecutive nucleotides, preferably at least 30 consecutive nucleotides and more preferably at least 45 consecutive nucleotides, that encode a portion of a lung tumor protein. More preferably, a polynucleotide encodes an immunogenic portion of a lung tumor protein. Polynucleotides complementary to any such sequences are also encompassed by the present invention. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a lung tumor protein or a portion thereof) or may comprise a variant of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native tumor protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most

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preferably at least about 90% identity to a polynucleotide sequence that encodes a native lung tumor protein or a portion thereof.

Two polynucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS 5*:151-153; Myers, E.W. and Muller W. (1988) *CABIOS 4*:11-17; Robinson, E.D. (1971) *Comb. Theor 11*:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol. 4*:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy -- the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA 80*:726-730.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (i.e. gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is

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calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (i.e. the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Variants may also, or alternatively, be substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are capable of hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding a native lung tumor protein (or a complementary sequence). Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Polynucleotides may be prepared using any of a variety of techniques. For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least five fold greater in a lung tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad.*

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Sci. USA 94:2150-2155, 1997). Alternatively, polypeptides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as lung tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion may be used to isolate a full length gene from a suitable library (*e.g.*, a lung tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (*e.g.*, by nick-translation or end-labeling with ^{32}P) using well known techniques. A bacterial or bacteriophage library is then screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences are then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for

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example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (*see* Triglia et al., *Nucl. Acids Res. 16*:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., *PCR Methods Applic. 1*:111-19, 1991) and walking PCR (Parker et al., *Nucl. Acids. Res. 19*:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (*e.g.*, NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence.

Certain nucleic acid sequences of cDNA molecules encoding portions of lung tumor proteins are provided in SEQ ID NO: 1-31, 49-55, 63,64, 66, 68-72, 78-80, 84-92 and 217-289. The isolation of these sequences is described in detail below.

Polynucleotide variants may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical

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synthesis. Modifications in a polynucleotide sequence may also be introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis (*see* Adelman et al., *DNA 2*:183, 1983). Alternatively, RNA molecules may be generated by *in vitro* or *in vivo* transcription of DNA sequences encoding a lung tumor protein, or portion thereof, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Certain portions may be used to prepare an encoded polypeptide, as described herein. In addition, or alternatively, a portion may be administered to a patient such that the encoded polypeptide is generated *in vivo* (*e.g.*, by transfecting antigen-presenting cells, such as dendritic cells, with a cDNA construct encoding a lung tumor polypeptide, and administering the transfected cells to the patient).

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A portion of a sequence complementary to a coding sequence (*i.e.*, an antisense polynucleotide) may also be used as a probe or to modulate gene expression. cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells of tissues to facilitate the production of antisense RNA. An antisense polynucleotide may be used, as described herein, to inhibit expression of a tumor protein. Antisense technology can be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (*see* Gee et al., *In* Huber and Carr, *Molecular and Immunologic Approaches*, Futura Publishing Co. (Mt. Kisco, NY; 1994)). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (*e.g.*, promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes.

A portion of a coding sequence, or of a complementary sequence, may also be designed as a probe or primer to detect gene expression. Probes may be labeled with a variety of reporter groups, such as radionuclides and enzymes, and are preferably at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and still more preferably at least 30 nucleotides in length. Primers, as noted above, are preferably 22-30 nucleotides in length.

Any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at

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the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl-, methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In general, a vector will contain an origin of replication functional in at least one organism, convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Such formulations are particularly useful for therapeutic purposes, as described below. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (*e.g.*, avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also be accomplished using an antibody, by methods known to those of ordinary skill in the art.

Other formulations for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*,

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an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

LUNG TUMOR POLYPEPTIDES

Within the context of the present invention, polypeptides may comprise at least an immunogenic portion of a lung tumor protein or a variant thereof, as described herein. As noted above, a "lung tumor protein" is a protein that is expressed by lung tumor cells. Proteins that are lung tumor proteins also react detectably within an immunoassay (such as an ELISA) with antisera from a patient with lung cancer. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of a protein that is recognized (*i.e.*, specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of a lung tumor protein or a variant thereof. Certain preferred immunogenic portions include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other preferred immunogenic portions may contain a small N- and/or C-terminal deletion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (*i.e.*, they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well known techniques. An immunogenic portion of a native lung tumor protein is a portion that reacts with such antisera and/or T-cells at a level that is not substantially less than the reactivity of the full length

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polypeptide (*e.g.*, in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ^{125}I-labeled Protein A.

As noted above, a composition may comprise a variant of a native lung tumor protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native lung tumor protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with antigen-specific antisera may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antigen-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity (determined as described above) to the identified polypeptides.

Preferably, a variant contains conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For

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example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

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As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (*e.g.*, poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to

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further purify a recombinant polypeptide.

Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. *See* Merrifield, *J. Am. Chem. Soc.* *85*:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused protein, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and the

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second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene 40*:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA 83*:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

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The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (*see*, for example, Stoute et al. *New Engl. J. Med., 336*:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (*e.g.*, the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D

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fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in *E. coli* (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10*:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

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In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

BINDING AGENTS

The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to a lung tumor protein. As used herein, an

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antibody, or antigen-binding fragment thereof, is said to "specifically bind" to a lung tumor protein if it reacts at a detectable level (within, for example, an ELISA) with a lung tumor protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a complex is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10^3 L/mol. The binding constant may be determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as lung cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a lung tumor protein will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (*e.g.*, blood, sera, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of

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monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (*e.g.*, mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate

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host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988) and digested by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ^{90}Y, ^{123}I, ^{125}I, ^{131}I, ^{186}Re, ^{188}Re, ^{211}At, and ^{212}Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and

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thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*,

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U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

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T CELLS

Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for a lung tumor protein. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the ISOLEX™ system, available from Nexell Therapeutics Inc., Irvine, CA (see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a lung tumor polypeptide, polynucleotide encoding a lung tumor polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, a lung tumor polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a lung tumor polypeptide if the T cells kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T

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cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., *Cancer Res.* *54*:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (*e.g.*, by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a lung tumor polypeptide (100 ng/ml - 100 μg/ml, preferably 200 ng/ml - 25 μg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (*e.g.*, TNF or IFN-γ) is indicative of T cell activation (*see* Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a lung tumor polypeptide, polynucleotide or polypeptide-expressing APC may be $CD4^+$ and/or $CD8^+$. Lung tumor protein-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from either a patient or a related, or unrelated, donor and are administered to the patient following stimulation and expansion.

For therapeutic purposes, $CD4^+$ or $CD8^+$ T cells that proliferate in response to a lung tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a lung tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a lung tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of a lung tumor protein can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

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PHARMACEUTICAL COMPOSITIONS AND VACCINES

Within certain aspects, polypeptides, polynucleotides, T cells and/or binding agents disclosed herein may be incorporated into pharmaceutical compositions or immunogenic compositions (*i.e.*, vaccines). Pharmaceutical compositions comprise one or more such compounds and a physiologically acceptable carrier. Vaccines may comprise one or more such compounds and a non-specific immune response enhancer. A non-specific immune response enhancer may be any substance that enhances an immune response to an exogenous antigen. Examples of non-specific immune response enhancers include adjuvants, biodegradable microspheres (*e.g.*, polylactic galactide) and liposomes (into which the compound is incorporated; *see e.g.*, Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and vaccines within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound, within the composition or vaccine.

A pharmaceutical composition or vaccine may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems 15*:143-198, 1998, and references cited therein. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope. In a preferred embodiment, the DNA may be introduced using a viral expression system (*e.g.*, vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et

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al., *Proc. Natl. Acad. Sci. USA 86*:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci. 569*:86-103, 1989; Flexner et al., *Vaccine 8*:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques 6*:616-627, 1988; Rosenfeld et al., *Science 252*:431-434, 1991; Kolls et al., *Proc. Natl. Acad. Sci. USA 91*:215-219, 1994; Kass-Eisler et al., *Proc. Natl. Acad. Sci. USA 90*:11498-11502, 1993; Guzman et al., *Circulation 88*:2838-2848, 1993; and Guzman et al., *Cir. Res. 73*:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., *Science 259*:1745-1749, 1993 and reviewed by Cohen, *Science 259*:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

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While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (*e.g.*, polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Such compositions may also comprise buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione, adjuvants (*e.g.*, aluminum hydroxide) and/or preservatives. Alternatively, compositions of the present invention may be formulated as a

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lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of non-specific immune response enhancers may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bortadella pertussis* or *Mycobacterium tuberculosis* derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

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Within the vaccines provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (*e.g.*, IFN-γ, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (*e.g.*, IL-4, IL-5, IL-6, IL-10 and TNF-β) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, *Ann. Rev. Immunol.* 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Ribi ImmunoChem Research Inc. (Hamilton, MT) (*see* US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which

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the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555. Another preferred adjuvant is a saponin, preferably QS21, which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprises an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210. Any vaccine provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient.

The compositions described herein may be administered as part of a sustained release formulation (*i.e.*, a formulation such as a capsule or sponge that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and vaccines to facilitate production of an antigen-specific immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell

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response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med. 50*:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*) and based on the lack of differentiation markers of B cells (CD19 and CD20), T cells (CD3), monocytes (CD14) and natural killer cells (CD56), as determined using standard assays. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (*see* Zitvogel et al., *Nature Med. 4*:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFα, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high

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capacity for antigen uptake and processing, which correlates with the high expression of Fcγ receptor, mannose receptor and DEC-205 marker. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (*e.g.*, CD54 and CD11) and costimulatory molecules (*e.g.*, CD40, CD80 and CD86).

APCs may generally be transfected with a polynucleotide encoding a lung tumor protein (or portion or other variant thereof) such that the lung tumor polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place *ex vivo*, and a composition or vaccine comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs *in vivo*. *In vivo* and *ex vivo* transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., *Immunology and cell Biology 75*:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the lung tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (*e.g.*, vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (*e.g.*, a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

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CANCER THERAPY

In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as lung cancer. Within such methods, pharmaceutical compositions and vaccines are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and vaccines may be used to prevent the development of a cancer or to treat a patient afflicted

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with a cancer. A cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides disclosed herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as $CD8^+$ cytotoxic T lymphocytes and $CD4^+$ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well

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known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (*see*, for example, Cheever et al., *Immunological Reviews 157*:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

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Routes and frequency of administration of the therapeutic compositions disclosed herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (*i.e.*, untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells *in vitro*. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 100 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size

of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a lung tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

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METHODS FOR DETECTING CANCER

In general, a cancer may be detected in a patient based on the presence of one or more lung tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as lung cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a lung tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. *See*, *e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of

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the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length lung tumor proteins and portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 μg, and preferably about 100 ng to about 1 μg, is sufficient to immobilize an adequate amount

of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see*, *e.g.*, Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with lung cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30

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minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

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To determine the presence or absence of a cancer, such as lung cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the

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value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1μg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use lung tumor polypeptides to

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detect antibodies that bind to such polypeptides in a biological sample. The detection of such lung tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a lung tumor protein in a biological sample. Within certain methods, a biological sample comprising $CD4^+$ and/or $CD8^+$ T cells isolated from a patient is incubated with a lung tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated *in vitro* for 2-9 days (typically 4 days) at 37°C with polypeptide (*e.g.*, 5 - 25 μg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of lung tumor polypeptide to serve as a control. For $CD4^+$ T cells, activation is preferably detected by evaluating proliferation of the T cells. For $CD8^+$ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a lung tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a lung tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the lung tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a lung tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably

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at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a lung tumor protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes will hybridize to a polynucleotide encoding a polypeptide disclosed herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence recited in SEQ ID NOS: 1-31, 49-55, 63,64, 66, 68-72, 78-80, 84-92 and 217-289. Techniques for both PCR based assays and hybridization assays are well known in the art (*see*, for example, Mullis et al., *Cold Spring Harbor Symp. Quant. Biol.*, *51*:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989).

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One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the disclosed compositions may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with

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time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple lung tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

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DIAGNOSTIC KITS

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a lung tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a lung tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a lung tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the

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detection of a polynucleotide encoding a lung tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1

PREPARATION OF LUNG TUMOR-SPECIFIC cDNA SEQUENCES USING DIFFERENTIAL DISPLAY RT-PCR

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This example illustrates the preparation of cDNA molecules encoding lung tumor-specific polypeptides using a differential display screen.

Tissue samples were prepared from lung tumor and normal tissue of a patient with lung cancer that was confirmed by pathology after removal of samples from the patient. Normal RNA and tumor RNA was extracted from the samples and mRNA was isolated and converted into cDNA using a $(dT)_{12}AG$ (SEQ ID NO: 47) anchored 3' primer. Differential display PCR was then executed using a randomly chosen primer (SEQ ID NO: 48). Amplification conditions were standard buffer containing 1.5 mM $MgCl_2$, 20 pmol of primer, 500 pmol dNTP and 1 unit of Taq DNA polymerase (Perkin-Elmer, Branchburg, NJ). Forty cycles of amplification were performed using 94 °C denaturation for 30 seconds, 42 °C annealing for 1 minute and 72 °C extension for 30 seconds. Bands that were repeatedly observed to be specific to the RNA fingerprint pattern of the tumor were cut out of a silver stained gel, subcloned into the pGEM-T vector (Promega, Madison, WI) and sequenced. The isolated 3' sequences are provided in SEQ ID NO: 1-16.

Comparison of these sequences to those in the public databases using the BLASTN program, revealed no significant homologies to the sequences provided in SEQ ID NO: 1-11. To the best of the inventors' knowledge, none of the isolated DNA sequences have previously been shown to be expressed at a greater level in human lung tumor tissue than in normal lung tissue.

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Example 2

USE OF PATIENT SERA TO IDENTIFY DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by expression screening of lung tumor samples with autologous patient sera.

A human lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a late SCID mouse passaged human squamous epithelial lung carcinoma and poly A+ RNA was isolated using the Message Maker kit (Gibco BRL, Gaithersburg, MD). The resulting library was screened using *E. coli*-absorbed autologous patient serum, as described in Sambrook et al., (*Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989), with the secondary antibody being goat anti-human IgG-A-M (H + L) conjugated with alkaline phosphatase, developed with NBT/BCIP (Gibco BRL). Positive plaques expressing immunoreactive antigens were purified. Phagemid from the plaques was rescued and the nucleotide sequences of the clones was determined.

Fifteen clones were isolated, referred to hereinafter as LT86-1 – LT86-15. The isolated cDNA sequences for LT86-1 – LT86-8 and LT86-10 - LT86-15 are provided in SEQ ID NO: 17-24 and 26-31, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 32-39 and 41-46, respectively. The determined cDNA sequence for LT86-9 is provided in SEQ ID NO: 25, with the corresponding predicted amino acid sequences from the 3' and 5' ends being provided in SEQ ID NO: 40 and 65, respectively. These sequences were compared to those in the gene bank as described above. Clones LT86-3, LT86-6 – LT86-9, LT86-11 – LT86-13 and LT86-15 (SEQ ID NO: 19, 22-25, 27-29 and 31, respectively) were found to show some homology to previously identified expressed sequence tags (ESTs), with clones LT86-6, LT86-8, LT86-11, LT86-12 and LT86-15 appearing to be similar or identical to each other. Clone LT86-3 was found to show some homology with a human transcription repressor. Clones LT86-6, 8, 9, 11, 12 and 15 were

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found to show some homology to a yeast RNA Pol II transcription regulation mediator. Clone LT86-13 was found to show some homology with a *C. elegans* leucine aminopeptidase. Clone LT86-9 appears to contain two inserts, with the 5' sequence showing homology to the previously identified antisense sequence of interferon alpha-induced P27, and the 3' sequence being similar to LT86-6. Clone LT86-14 (SEQ ID NO: 30) was found to show some homology to the trithorax gene and has an "RGD" cell attachment sequence and a beta-Lactamase A site which functions in hydrolysis of penicillin. Clones LT86-1, LT86-2, LT86-4, LT86-5 and LT86-10 (SEQ ID NOS: 17, 18, 20, 21 and 26, respectively) were found to show homology to previously identified genes. A subsequently determined extended cDNA sequence for LT86-4 is provided in SEQ ID NO: 66, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 67.

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Subsequent studies led to the isolation of five additional clones, referred to as LT86-20, LT86-21, LT86-22, LT86-26 and LT86-27. The determined 5' cDNA sequences for LT86-20, LT86-22, LT86-26 and LT86-27 are provided in SEQ ID NO: 68 and 70-72, respectively, with the determined 3' cDNA sequences for LT86-21 being provided in SEQ ID NO: 69. The corresponding predicted amino acid sequences for LT86-20, LT86-21, LT86-22, LT86-26 and LT86-27 are provided in SEQ ID NO: 73-77, respectively. LT86-22 and LT86-27 were found to be highly similar to each other. Comparison of these sequences to those in the gene bank as described above, revealed no significant homologies to LT86-22 and LT86-27. LT86-20, LT86-21 and LT86-26 were found to show homology to previously identified genes.

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Example 3

USE OF MOUSE ANTISERA TO IDENTIFY DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by screening of lung tumor cDNA libraries with mouse anti-tumor sera.

A directional cDNA lung tumor expression library was prepared as described above in Example 2. Sera was obtained from SCID mice containing late passaged human squamous cell and adenocarcinoma tumors. These sera were pooled and injected into normal mice to produce anti-lung tumor serum. Approximately 200,000 PFUs were screened from the unamplified library using this antiserum. Using a goat anti-mouse IgG-A-M (H+L) alkaline phosphatase second antibody developed with NBT/BCIP (BRL Labs.), approximately 40 positive plaques were identified. Phage was purified and phagemid excised for 9 clones with inserts in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined cDNA sequences for 7 of the isolated clones (hereinafter referred to as L86S-3, L86S-12, L86S-16, L86S-25, L86S-36, L86S-40 and L86S-46) are provided in SEQ ID NO: 49-55, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 56-62, respectively. The 5' cDNA sequences for the remaining 2 clones (hereinafter referred to as L86S-30 and L86S-41) are provided in SEQ ID NO: 63 and 64. L86S-36 and L86S-46 were subsequently determined to represent the same gene. Comparison of these sequences with those in the public database as described above, revealed no significant homologies to clones L86S-30, L86S-36 and L86S-46 (SEQ ID NO: 63, 53 and 55, respectively). L86S-16 (SEQ ID NO: 51) was found to show some homology to an EST previously identified in fetal lung and germ cell tumor. The remaining clones were found to show at least some degree of homology to previously identified human genes. Subsequently determined extended cDNA sequences for L86S-12, L86S-36 and L86S-46 are provided in SEQ ID NO: 78-80, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 81-83.

Subsequent studies led to the determination of 5' cDNA sequences for an additional nine clones, referred to as L86S-6, L86S-11, L86S-14, L86S-29, L86S-34, L86S-

39, L86S-47, L86S-49 and L86S-51 (SEQ ID NO: 84-92, respectively). The corresponding predicted amino acid sequences are provided in SEQ ID NO: 93-101, respectively. L86S-30, L86S-39 and L86S-47 were found to be similar to each other. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to L86S-14. L86S-29 was found to show some homology to a previously identified EST. L86S-6, L86S-11, L86S-34, L86S-39, L86S-47, L86S-49 and L86S-51 were found to show some homology to previously identified genes.

In further studies, a directional cDNA library was constructed using a Stratagene kit with a Lambda Zap Express vector. Total RNA for the library was isolated from two primary squamous lung tumors and poly A+ RNA was isolated using an oligo dT column. Antiserum was developed in normal mice using a pool of sera from three SCID mice implanted with human squamous lung carcinomas. Approximately 700,000 PFUs were screened from the unamplified library with *E. coli* absorbed mouse anti-SCID tumor serum. Positive plaques were identified as described above. Phage was purified and phagemid excised for 180 clones with inserts in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined cDNA sequences for 23 of the isolated clones are provided in SEQ ID NO: 126-148. Comparison of these sequences with those in the public database as described above revealed no significant homologies to the sequences of SEQ ID NO: 139 and 143-148. The sequences of SEQ ID NO: 126-138 and 140-142 were found to show homology to previously identified human polynucleotide sequences.

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Example 4

USE OF MOUSE ANTISERA TO SCREEN LUNG TUMOR LIBRARIES PREPARED FROM SCID MICE

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by screening of lung tumor cDNA libraries prepared from SCID mice with mouse anti-tumor sera.

A directional cDNA lung tumor expression library was prepared using a Stratagene kit with a Lambda Zap Express vector. Total RNA for the library was taken from a late passaged lung adenocarcinoma grown in SCID mice. Poly A+ RNA was isolated using a Message Maker Kit (Gibco BRL). Sera was obtained from two SCID mice implanted with lung adenocarcinomas. These sera were pooled and injected into normal mice to produce anti-lung tumor serum. Approximately 700,000 PFUs were screened from the unamplified library with *E. coli*-absorbed mouse anti-SCID tumor serum. Positive plaques were identified with a goat anti-mouse IgG-A-M (H+L) alkaline phosphatase second antibody developed with NBT/BCIP (Gibco BRL). Phage was purified and phagemid excised for 100 clones with insert in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined 5' cDNA sequences for 33 of the isolated clones are provided in SEQ ID NO: 149-181. The corresponding predicted amino acid sequences for SEQ ID NO: 149, 150, 152-154, 156-158 and 160-181 are provided in SEQ ID NO: 182, 183, 186, 188-193 and 194-215, respectively. The clone of SEQ ID NO: 151 (referred to as SAL-25) was found to contain two open reading frames (ORFs). The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 184 and 185. The clone of SEQ ID NO: 153 (referred to as SAL-50) was found to contain two open reading frames encoding the predicted amino acid sequences of SEQ ID NO: 187 and 216. Similarly, the clone of SEQ ID NO: 155 (referred to as SAL-66) was found to contain two open reading frames encoding the predicted amino acid sequences of SEQ ID NO: 189 and 190. Comparison of the isolated sequences with those in the public database revealed no significant homologies to the sequences of SEQ ID NO: 151, 153 and 154. The sequences of SEQ ID NO: 149, 152, 156, 157 and 158 were found to show some homology to previously isolated expressed sequence

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tags (ESTs). The sequences of SEQ ID NO: 150, 155 and 159-181 were found to show homology to sequences previously identified in humans.

Using the procedures described above, two directional cDNA libraries (referred to as LT46-90 and LT86-21) were prepared from two late passaged lung squamous carcinomas grown in SCID mice and screened with sera obtained from SCID mice implanted with human squamous lung carcinomas. The determined cDNA sequences for the isolated clones are provided in SEQ ID NO: 217-237 and 286-289. SEQ ID NO: 286 was found to be a longer sequence of LT4690-71 (SEQ ID NO: 237). Comparison of these sequences with those in the public databases revealed no known homologies to the sequences of SEQ ID NO: 219, 220, 225, 226, 287 and 288. The sequences of SEQ ID NO: 218, 221, 222 and 224 were found to show some homology to previously identified sequences of unknown function. The sequence of SEQ ID NO: 236 was found to show homology to a known mouse mRNA sequence. The sequences of SEQ ID NO: 217, 223, 227-237, 286 and 289 showed some homology to known human DNA and/or RNA sequences.

In further studies using the techniques described above, one of the cDNA libraries described above (LT86-21) was screened with *E. coli*-absorbed mouse anti-SCID tumor serum. This serum was obtained from normal mice immunized with a pool of 3 sera taken from SCID mice implanted with human squamous lung carcinomas. The determined cDNA sequences for the isolated clones are provided in SEQ ID NO: 238-285. Comparison of these sequences with those in the public databases revealed no significant homologies to the sequences of SEQ ID NO: 253, 260, 277 and 285. The sequences of SEQ ID NO: 249, 250, 256, 266, 276 and 282 were found to show some homology to previously isolated expressed sequence tags (ESTs). The sequences of SEQ ID NO: 238-248, 251, 252, 254, 255, 257-259, 261-263, 265, 267-275, 278-281, 283 and 284 were found to show some homology to previously identified DNA or RNA sequences.

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Example 5

DETERMINATION OF TISSUE SPECIFICITY OF LUNG TUMOR POLYPEPTIDES

Using gene specific primers, mRNA expression levels for representative lung tumor polypeptides were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent. First strand synthesis was carried out using 2 μg of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42 °C for one hour. The cDNA was then amplified by PCR with gene-specific primers. To ensure the semi-quantitative nature of the RT-PCR, β-actin was used as an internal control for each of the tissues examined. 1 μl of 1:30 dilution of cDNA was employed to enable the linear range amplification of the β-actin template and was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the β-actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in five different types of tumor tissue (lung squamous tumor from 3 patients, lung adenocarcinoma, prostate tumor colon tumor and lung tumor), and different normal tissues, including lung from four patients, prostate, brain, kidney, liver, ovary, skeletal muscle, skin, small intestine, myocardium, retina and testes. L86S-46 was found to be expressed at high levels in lung squamous tumor, colon tumor and prostate tumor, and was undetectable in the other tissues examined. L86S-5 was found to be expressed in the lung tumor samples and in 2 out of 4 normal lung samples, but not in the other normal or tumor tissues tested. L86S-16 was found to be expressed in all tissues except normal liver and normal stomach. Using real-time PCR, L86S-46 was found to be over-expressed in lung squamous tissue and normal tonsil, with expression being low or undetectable in all other tissues examined.

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Example 6

ISOLATION OF DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

DNA sequences encoding antigens potentially involved in squamous cell lung tumor formation were isolated as follows.

A lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a pool of two human squamous epithelial lung carcinomas and poly A+ RNA was isolated using oligo-dT cellulose (Gibco BRL, Gaithersburg, MD). Phagemid were rescued at random and the cDNA sequences of isolated clones were determined.

The determined cDNA sequence for the clone SLT-T1 is provided in SEQ ID NO: 102, with the determined 5' cDNA sequences for the clones SLT-T2, SLT-T3, SLT-T5, SLT-T7, SLT-T9, SLT-T10, SLT-T11 and SLT-T12 being provided in SEQ ID NO: 103-110, respectively. The corresponding predicted amino acid sequence for SLT-T1, SLT-T2, SLT-T3, SLT-T10 and SLT-T12 are provided in SEQ ID NO: 111-115, respectively. Comparison of the sequences for SLT-T2, SLT-T3, SLT-T5, SLT-T7, SLT-T9 and SLT-T11 with those in the public databases as described above, revealed no significant homologies. The sequences for SLT-T10 and SLT-T12 were found to show some homology to sequences previously identified in humans.

The sequence of SLT-T1 was determined to show some homology to a PAC clone of unknown protein function. The cDNA sequence of SLT-T1 (SEQ ID NO: 102) was found to contain a mutator (MUTT) domain. Such domains are known to function in removal of damaged guanine from DNA that can cause A to G transversions (see, for example, el-Deiry, W.S., 1997 *Curr. Opin. Oncol. 9*:79-87; Okamoto, K. et al. 1996 *Int. J. Cancer 65*:437-41; Wu, C. et al. 1995 *Biochem. Biophys. Res. Commun. 214*:1239-45; Porter, D.W. et al. 1996 *Chem. Res. Toxicol. 9*:1375-81). SLT-T1 may thus be of use in the treatment, by gene therapy, of lung cancers caused by, or associated with, a disruption in DNA repair.

In further studies, DNA sequences encoding antigens potentially involved in adenocarcinoma lung tumor formation were isolated as follows. A human lung tumor

directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a late SCID mouse passaged human adenocarcinoma and poly A+ RNA was isolated using the Message Maker kit (Gibco BRL, Gaithersburg, MD). Phagemid were rescued at random and the cDNA sequences of isolated clones were determined.

The determined 5' cDNA sequences for five isolated clones (referred to as SALT-T3, SALT-T4, SALT-T7, SALT-T8, and SALT-T9) are provided in SEQ ID NO: 116-120, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 121-125. SALT-T3 was found to show 98% identity to the previously identified human transducin-like enhancer protein TLE2. SALT-T4 appears to be the human homologue of the mouse H beta 58 gene. SALT-T7 was found to have 97% identity to human 3-mercaptopyruvate sulfurtransferase and SALT-T8 was found to show homology to human interferon-inducible protein 1-8U. SALT-T9 shows approximately 90% identity to human mucin MUC 5B.

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Example 7

SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

Example 8

ISOLATION AND CHARACTERIZATION OF DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS BY T-CELL EXPRESSION CLONING

Lung tumor antigens may also be identified by T cell expression cloning. One source of tumor specific T cells is from surgically excised tumors from human patients.

A non-small cell lung carcinoma was minced and enzymatically digested for several hours to release tumor cells and infiltrating lymphocytes (tumor infiltrating T cells, or TILs). The cells were washed in HBSS buffer and passed over a Ficoll (100%/75%/HBSS) discontinuous gradient to separate tumor cells and lymphocytes from non-viable cells. Two bands were harvested from the interfaces; the upper band at the 75%/HBSS interface contained predominantly tumor cells, while the lower band at the 100%/75%/HBSS interface contained a majority of lymphocytes. The TILs were expanded in culture, either in 24-well

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plates with culture media supplemented with 10 ng/ml IL-7 and 100 U/ml IL-2, or alternatively, 24-well plates that have been pre-coated with the anti-CD3 monoclonal antibody OKT3. The resulting TIL cultures were analyzed by FACS to confirm that a high percentage were CD8+ T cells (>90% of gated population) with only a small percentage of CD4+ cells.

In addition, non-small cell lung carcinoma cells were expanded in culture using standard techniques to establish a tumor cell line, which was later confirmed to be a lung carcinoma cell line by immunohistochemical analysis. This tumor cell line was transduced with a retroviral vector to express human CD80, and characterized by FACS analysis to confirm high expression levels of CD80, and class I and II MHC molecules.

The specificity of the TIL lines to lung tumor was confirmed by INF-γ and/or TNF-α cytokine release assays. TIL cells from day 21 cultures were co-cultured with either autologous or allogeneic tumor cells, EBV-immortalized LCL, or control cell lines Daudi and K562, and the culture supernatant monitored by ELISA for the presence of cytokines. The TIL specifically recognized autologous tumor but not allogeneic tumor. In addition, there was no recognition of EBV-immortalized LCL or the control cell lines, indicating that the TIL lines are tumor specific and are potentially recognizing a tumor antigen presented by autologous MHC molecules.

The characterized tumor-specific TIL lines were expanded to suitable numbers for T cell expression cloning using soluble anti-CD3 antibody in culture with irradiated EBV transformed LCLs and PBL feeder cells in the presence of 20 U/ml IL-2. Clones from the expanded TIL lines were generated by standard limiting dilution techniques. Specifically, TIL cells were seeded at 0.5 cells/well in a 96-well U bottom plate and stimulated with CD-80-transduced autologous tumor cells, EBV transformed LCL, and PBL feeder cells in the presence of 50 U/ml IL-2. These clones were further analyzed for tumor specificity by ^{51}Cr microcytotoxicity and IFN-γ bioassays. The MHC restriction element recognized by the TIL clones may be determined by antibody blocking studies.

CTL lines or clones prepared as described above may be employed to identify tumor specific antigens. For example, autologous fibroblasts or LCL from a patient may be transfected or transduced with polynucleotide fragments derived from a lung tumor cDNA

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library to generate target cells expressing tumor polypeptides. The target cells expressing tumor polypeptides in the context of MHC will be recognized by the CTL line or clone, resulting in T-cell activation which can be monitored by cytokine detection assays. The tumor gene being expressed by the target cell and recognized by the tumor-specific CTL may then be isolated.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

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Claims

1. An isolated polypeptide comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NOS: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282 and 285;

(b) sequences that hybridize to a sequence of SEQ ID NO218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282 and 285 under moderately stringent conditions; and

(c) a complement of a sequence of (a) or (b).

2. An isolated polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOS: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282 and 285 or a complement of any of the foregoing polynucleotide sequences.

3. An isolated polynucleotide encoding at least 15 amino acid residues of a lung tumor protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOS: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282 and 285 or a complement of any of the foregoing sequences.

4. An isolated polynucleotide encoding a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOS: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282 and 285 or a complement of any of the foregoing sequences.

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5. An isolated polynucleotide comprising a sequence recited in any one of SEQ ID NOS: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282 and 285.

6. An isolated polynucleotide comprising a sequence that hybridizes to a sequence recited in any one of SEQ ID NOS: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282 and 285 under moderately stringent conditions.

7. An isolated polynucleotide complementary to a polynucleotide according to any one of claims 3-6.

8. An expression vector comprising a polynucleotide according to any one of claims 3-6.

9. A host cell transformed or transfected with an expression vector according to claim 8.

10. An expression vector comprising a polynucleotide according claim 7.

11. A host cell transformed or transfected with an expression vector according to claim 10.

12. A pharmaceutical composition comprising a polypeptide according to claim 1, in combination with a physiologically acceptable carrier.

13. A vaccine comprising a polypeptide according to claim 1, in combination with a non-specific immune response enhancer.

14. A vaccine according to claim 13, wherein the non-specific immune response enhancer is an adjuvant.

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15. A vaccine according to claim 13, wherein the non-specific immune response enhancer induces a predominantly Type 1 response.

16. A pharmaceutical composition comprising a polynucleotide according to claim 3, in combination with a physiologically acceptable carrier.

17. A vaccine comprising a polynucleotide according to claim 3, in combination with a non-specific immune response enhancer.

18. A vaccine according to claim 17, wherein the non-specific immune response enhancer is an adjuvant.

19. A vaccine according to claim 17, wherein the non-specific immune response enhancer induces a predominantly Type I response.

20. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a lung tumor protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOS: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282 and 285 or a complement of any of the foregoing polynucleotide sequences.

21. A pharmaceutical composition comprising an antibody or fragment thereof according to claim 17, in combination with a physiologically acceptable carrier.

22. A pharmaceutical composition comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a pharmaceutically acceptable carrier or excipient.

23. A pharmaceutical composition according to claim 22, wherein the antigen presenting cell is a dendritic cell or a macrophage.

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24. A vaccine comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a non-specific immune response enhancer.

25. A vaccine according to claim 24, wherein the non-specific immune response enhancer is an adjuvant.

26. A vaccine according to claim 24, wherein the non-specific immune response enhancer induces a predominantly Type I response.

27. A vaccine according to claim 24, wherein the antigen-presenting cell is a dendritic cell.

28. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a polypeptide according to claim 1, and thereby inhibiting the development of a cancer in the patient.

29. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a polynucleotide according to claim 3, and thereby inhibiting the development of a cancer in the patient.

30. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antibody or antigen-binding fragment thereof according to claim 20, and thereby inhibiting the development of a cancer in the patient.

31. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antigen-presenting cell that expresses a polypeptide according to claim 1, and thereby inhibiting the development of a cancer in the patient.

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32. A method according to claim 31, wherein the antigen-presenting cell is a dendritic cell.

33. A method according to any one of claims 28-31, wherein the cancer is lung cancer.

34. A fusion protein comprising at least one polypeptide according to claim 1.

35. A fusion protein according to claim 34, wherein the fusion protein comprises an expression enhancer that increases expression of the fusion protein in a host cell transfected with a polynucleotide encoding the fusion protein.

36. A fusion protein according to claim 34, wherein the fusion protein comprises a T helper epitope that is not present within the polypeptide of claim 1.

37. A fusion protein according to claim 34, wherein the fusion protein comprises an affinity tag.

38. An isolated polynucleotide encoding a fusion protein according to claim 34.

39. A pharmaceutical composition comprising a fusion protein according to claim 31, in combination with a physiologically acceptable carrier.

40. A vaccine comprising a fusion protein according to claim 34, in combination with a non-specific immune response enhancer.

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41. A vaccine according to claim 40, wherein the non-specific immune response enhancer is an adjuvant.

42. A vaccine according to claim 40, wherein the non-specific immune response enhancer induces a predominantly Type I response.

43. A pharmaceutical composition comprising a polynucleotide according to claim 39, in combination with a physiologically acceptable carrier.

44. A vaccine comprising a polynucleotide according to claim 39, in combination with a non-specific immune response enhancer.

45. A vaccine according to claim 44, wherein the non-specific immune response enhancer is an adjuvant.

46. A vaccine according to claim 44, wherein the non-specific immune response enhancer induces a predominantly Type I response.

47. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 39 or claim 43.

48. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a vaccine according to claim 40 or claim 44.

49. A method for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

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(i) polynucleotides recited in any one of SEQ ID NOS: 217-289; and

(ii) complements of the foregoing polynucleotides;

wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the antigen from the sample.

50. A method according to claim 49, wherein the biological sample is blood or a fraction thereof.

51. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated according to the method of claim 49.

52. A method for stimulating and/or expanding T cells specific for a lung tumor protein, comprising contacting T cells with one or more of:

(i) a polypeptide according to claim 1;

(ii) a polynucleotide encoding such a polypeptide; and/or

(iii) an antigen presenting cell that expresses such a polypeptide;

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

53. An isolated T cell population, comprising T cells prepared according to the method of claim 52.

54. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population according to claim 53.

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55. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating $CD4^+$ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:

(i) a polypeptide according to claim 1;

(ii) a polynucleotide encoding such a polypeptide; or

(iii) an antigen-presenting cell that expresses such a polypeptide;

such that T cells proliferate; and

(b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.

56. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating $CD4^+$ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:

(i) a polypeptide according to claim 1;

(ii) a polynucleotide encoding such a polypeptide; or

(iii) an antigen-presenting cell that expresses such a polypeptide;

such that T cells proliferate;

(b) cloning at least one proliferated cell; and

(c) administering to the patient an effective amount of the cloned T cells, and thereby inhibiting the development of a cancer in the patient.

57. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with a binding agent that binds to a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

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(i) polynucleotides recited in any one of SEQ ID NOS: 217-289; and

(ii) complements of the foregoing polynucleotides;

(b) detecting in the sample an amount of polypeptide that binds to the binding agent; and

(c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

58. A method according to claim 57, wherein the binding agent is an antibody.

59. A method according to claim 58, wherein the antibody is a monoclonal antibody.

60. A method according to claim 57, wherein the cancer is lung cancer.

61. A method for monitoring the progression of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOS: 217-289 or a complement of any of the foregoing polynucleotides;

(b) detecting in the sample an amount of polypeptide that binds to the binding agent;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polypeptide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

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62. A method according to claim 61, wherein the binding agent is an antibody.

63. A method according to claim 62, wherein the antibody is a monoclonal antibody.

64. A method according to claim 61, wherein the cancer is a lung cancer.

65. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOS: 217-289 or a complement of any of the foregoing polynucleotides;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and

(c) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

66. A method according to claim 65, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

67. A method according to claim 65, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.

68. A method for monitoring the progression of a cancer in a patient,

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comprising the steps of:

(a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOS: 217-289 or a complement of any of the foregoing polynucleotides;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

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69. A method according to claim 68, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

70. A method according to claim 68, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.

71. A diagnostic kit, comprising:

(a) one or more antibodies according to claim 20; and

(b) a detection reagent comprising a reporter group.

72. A kit according to claim 71, wherein the antibodies are immobilized on a solid support.

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73. A kit according to claim 72, wherein the solid support comprises nitrocellulose, latex or a plastic material.

74. A kit according to claim 71, wherein the detection reagent comprises an anti-immunoglobulin, protein G, protein A or lectin.

75. A kit according to claim 71, wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.

76. An oligonucleotide comprising 10 to 40 nucleotides that hybridizes under moderately stringent conditions to a polynucleotide that encodes a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOS: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282 and 285 or a complement of any of the foregoing polynucleotides.

77. A oligonucleotide according to claim 76, wherein the oligonucleotide comprises 10-40 nucleotides recited in any one of SEQ ID NOS: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282 and 285.

78. A diagnostic kit, comprising:

(a) an oligonucleotide according to claim 76; and

(b) a diagnostic reagent for use in a polymerase chain reaction or hybridization assay.

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COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE

Abstract of the Disclosure

Compositions and methods for the therapy and diagnosis of cancer, such as lung cancer, are disclosed. Compositions may comprise one or more lung tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a lung tumor protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as lung cancer. Diagnostic methods based on detecting a lung tumor protein, or mRNA encoding such a protein, in a sample are also provided.

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Steven G. Reed, Michael J. Lodes, Roadoh Mohamath and Heather Secrist
Filed	:	August 9, 1999
For	:	COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE
	Docket No.	: 210121.475C1
	Date	. August 9, 1999

Box Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION

Sir:

I, Lawrence Teague, in accordance with 37 C.F.R. § 1.821(f) do hereby declare that, to the best of my knowledge, the content of the paper entitled "Sequence Listing" and the computer readable copy contained within the floppy disk are the same.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated this 9th day of August, 1999.

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Legal Assistant

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Seattle, WA 98104-7092
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09370838.080999

SEQUENCE LISTING

<110> Reed, Steven G.
Lodes, Michael J.
Mohamath, Roadoh
Secrist, Heather

<120> COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE

<130> 210121.475C1

<140> US
<141> 1999-08-09

<150> US 09/285,323
<151> 1999-04-02

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09370838 .080 99

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<212> DNA
<213> Homo sapien

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tccggaanct tggtttccc 679

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<211> 369
<212> DNA
<213> Homo sapien

<220>
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<223> n = A,T,C or G

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<212> DNA
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278
546
543

09370838.080 99

tgaacactac actcggaatc aggaagccct gcctggcgcc tctgtcacct gtctaggggc 240
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<210> 8
<211> 280
<212> DNA
<213> Homo sapien

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<222> (1)...(280)
<223> n = A,T,C or G

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accgcccccna ttaagaatta gagcaagcag tgaggtgaag ccttgtcctt gcttttaaca 180
tagaaagtga tccaaattca ccaaacttga cttnnggttt tgcagtgtgg cctcctgatt 240
ctagacnctg gcgaaacatt tgatgggcaa aaaaaaaaaa 280

<210> 9
<211> 449
<212> DNA
<213> Homo sapien

<220>
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<222> (1)...(449)
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ggtacgggag gaaacactgg gctnacccag atnctggact tgagtcttgc ctctgctgct 300
tgctgcacag cttctgtcat ggtgctaaac ctgtgacctg cctcacaggc ttagagcatg 360
cccgtagaag tactctnaac taaratgctt tccacaaatg agatggtttc atgaaaactt 420
caaatagagg gcctgggcaa aaaaaaaaa 449

<210> 10
<211> 538
<212> DNA
<213> Homo sapien

<220>
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<210> 11
<211> 543
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(543)
<223> n = A,T,C or G

<400> 11
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tcaggcatct gggacttgat gtgggtntgg gatttgaaat cagagcacct nggtctctat 180
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ctaagaggna attctgaact catcccccnna tgacctctcc cgaatnagaa tatctctggc 480
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aaa 543

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<211> 329
<212> DNA
<213> Homo sapien

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ggcaagacca taggtggggt gctgggaatc ctcggggccg gctggcaccc actcctggtg 180
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gagccacaga gtcaaataaa aatcaatttt gagagaccac agcacctgct gctttgatcg 300
tgatgttcaa ggcaagttgc aagtcatcg 329

<210> 13
<211> 314
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(314)
<223> n = A,T,C or G

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atcccaagtc atcg 314

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<211> 691
<212> DNA
<213> Homo sapien

<220>
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<223> n = A,T,C or G

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<213> Homo sapien

<220>
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<223> n = A,T,C or G

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<211> 522
<212> DNA
<213> Homo sapien

<220>
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<222> (1)...(522)
<223> n = A,T,C or G

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214
549
546

<400> 16
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<211> 317
<212> DNA
<213> Homo sapien

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<210> 18
<211> 392
<212> DNA
<213> Homo sapien

<400> 18
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<213> Homo sapien

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<210> 20
<211> 488
<212> DNA
<213> Homo sapien

<400> 20
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<210> 21
<211> 391
<212> DNA
<213> Homo sapien

284
557
548

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<400> 21
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<211> 1320
<212> DNA
<213> Homo sapien

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<210> 23
<211> 633
<212> DNA
<213> Homo sapien

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549

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<210> 24
<211> 1328
<212> DNA
<213> Homo sapien

<400> 24

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<210> 25
<211> 1758
<212> DNA
<213> Homo sapien

<400> 25

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<210> 26
<211> 493
<212> DNA
<213> Homo sapien

<400> 26
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<210> 27
<211> 1331
<212> DNA
<213> Homo sapien

<400> 27
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<210> 28
<211> 1333
<212> DNA
<213> Homo sapien

<400> 28
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<210> 29
<211> 813
<212> DNA
<213> Homo sapien

<400> 29
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264
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551

265
553
552

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<210> 30
<211> 1316
<212> DNA
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<400> 30

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<210> 31
<211> 1355
<212> DNA
<213> Homo sapien

<400> 31

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<210> 32
<211> 80
<212> PRT
<213> Homo sapien

<400> 32
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Val Leu Lys Tyr Tyr Lys Val Asp Glu Asn Gly Lys Ile Ser Cys Leu
35 40 45
Arg Arg Glu Cys Pro Ser Asp Glu Cys Gly Ala Gly Val Phe Met Ala
50 55 60
Ser His Phe Asp Arg His Tyr Cys Gly Lys Cys Cys Leu Thr His Cys
65 70 75 80

<210> 33
<211> 130
<212> PRT
<213> Homo sapien

<400> 33
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Leu Asp Ala Gln Glu His Val Lys Asn Pro Tyr Lys Gly Lys Lys Leu
20 25 30
Lys Lys His Pro Asp Phe Pro Lys Lys Pro Leu Thr Pro Tyr Phe Arg
35 40 45
Phe Phe Met Glu Lys Arg Ala Lys Tyr Ala Lys Leu His Pro Gln Met
50 55 60
Ser Asn Leu Asp Leu Thr Lys Ile Leu Ser Lys Lys Tyr Lys Glu Leu
65 70 75 80
Pro Glu Lys Lys Lys Met Lys Tyr Val Pro Asp Phe Gln Arg Arg Glu
85 90 95
Thr Gly Val Arg Ala Lys Pro Gly Pro Ile Gln Gly Gly Ser Pro Pro
100 105 110
Pro Tyr Pro Glu Cys Gln Glu Ser Asp Ile Pro Glu Lys Pro Gln Asp
115 120 125
Pro Pro
130

<210> 34
<211> 506
<212> PRT
<213> Homo sapien

<400> 34
Asn Ser Glu Lys Glu Ile Pro Val Leu Asn Glu Leu Pro Val Pro Met
1 5 10 15

```
Val Ala Arg Tyr Ile Arg Ile Asn Pro Gln Ser Trp Phe Asp Asn Gly
            20                  25                  30
Ser Ile Cys Met Arg Met Glu Ile Leu Gly Cys Pro Leu Pro Asp Pro
        35                  40                  45
Asn Asn Tyr Tyr His Arg Arg Asn Glu Met Thr Thr Thr Asp Asp Leu
    50                  55                  60
Asp Phe Lys His His Asn Tyr Lys Glu Met Arg Gln Leu Met Lys Val
65                  70                  75                  80
Val Asn Glu Met Cys Pro Asn Ile Thr Arg Ile Tyr Asn Ile Gly Lys
                85                  90                  95
Ser His Gln Gly Leu Lys Leu Tyr Ala Val Glu Ile Ser Asp His Pro
            100                 105                 110
Gly Glu His Glu Val Gly Glu Pro Glu Phe His Tyr Ile Ala Gly Ala
        115                 120                 125
His Gly Asn Glu Val Leu Gly Arg Glu Leu Leu Leu Leu Leu Leu His
    130                 135                 140
Phe Leu Cys Gln Glu Tyr Ser Ala Gln Asn Ala Arg Ile Val Arg Leu
145                 150                 155                 160
Val Glu Glu Thr Arg Ile His Ile Leu Pro Ser Leu Asn Pro Asp Gly
                165                 170                 175
Tyr Glu Lys Ala Tyr Glu Gly Gly Ser Glu Leu Gly Gly Trp Ser Leu
            180                 185                 190
Gly Arg Trp Thr His Asp Gly Ile Asp Ile Asn Asn Asn Phe Pro Asp
        195                 200                 205
Leu Asn Ser Leu Leu Trp Glu Ala Glu Asp Gln Gln Asn Ala Pro Arg
    210                 215                 220
Lys Val Pro Asn His Tyr Ile Ala Ile Pro Glu Trp Phe Leu Ser Glu
225                 230                 235                 240
Asn Ala Thr Val Ala Thr Glu Thr Arg Ala Val Ile Ala Trp Met Glu
                245                 250                 255
Lys Ile Pro Phe Val Leu Gly Gly Asn Leu Gln Gly Gly Glu Leu Val
            260                 265                 270
Val Ala Tyr Pro Tyr Asp Met Val Arg Ser Leu Trp Lys Thr Gln Glu
        275                 280                 285
His Thr Pro Thr Pro Asp Asp His Val Phe Arg Trp Leu Ala Tyr Ser
    290                 295                 300
Tyr Ala Ser Thr His Arg Leu Met Thr Asp Ala Arg Arg Arg Val Cys
305                 310                 315                 320
His Thr Glu Asp Phe Gln Lys Glu Glu Gly Thr Val Asn Gly Ala Ser
                325                 330                 335
Trp His Thr Val Ala Gly Ser Leu Asn Asp Phe Ser Tyr Leu His Thr
            340                 345                 350
Asn Cys Phe Glu Leu Ser Ile Tyr Val Gly Cys Asp Lys Tyr Pro His
        355                 360                 365
Glu Ser Glu Leu Pro Glu Glu Trp Glu Asn Asn Arg Glu Ser Leu Ile
    370                 375                 380
Val Phe Met Glu Gln Val His Arg Gly Ile Lys Gly Ile Val Arg Asp
385                 390                 395                 400
Leu Gln Gly Lys Gly Ile Ser Asn Ala Val Ile Ser Val Glu Gly Val
                405                 410                 415
Asn His Asp Ile Arg Thr Ala Ser Asp Gly Asp Tyr Trp Arg Leu Leu
            420                 425                 430
Asn Pro Gly Glu Tyr Val Val Thr Ala Lys Ala Glu Gly Phe Ile Thr
        435                 440                 445
Ser Thr Lys Asn Cys Met Val Gly Tyr Asp Met Gly Ala Thr Arg Cys
```

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```
    450                 455                 460
Asp Phe Thr Leu Thr Lys Thr Asn Leu Ala Arg Ile Arg Glu Ile Met
465                 470                 475                 480
Glu Thr Phe Gly Lys Gln Pro Val Ser Leu Pro Ser Arg Arg Leu Lys
                485                 490                 495
Leu Arg Gly Arg Lys Arg Arg Gln Arg Gly
            500                 505
```

<210> 35
<211> 96
<212> PRT
<213> Homo sapien

<400> 35

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

<210> 36
<211> 129
<212> PRT
<213> Homo sapien

<400> 36

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

<210> 37
<211> 238
<212> PRT

289
589
556

6 6080'08238 09

<213> Homo sapien

<400> 37

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

<210> 38
<211> 202
<212> PRT
<213> Homo sapien

<400> 38

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

290
560
557

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```
        115                 120                 125
Met Lys Lys Tyr Ser Pro Ser Asp Pro Ala Phe Ala Tyr Ala Gln Leu
    130                 135                 140
Thr His Asp Glu Leu Ile Gln Leu Val Leu Lys Gln Lys Glu Thr Ile
145                 150                 155                 160
Ser Lys Lys Glu Phe Gln Val Arg Glu Leu Glu Asp Tyr Ile Asp Asn
                165                 170                 175
Leu Leu Val Arg Val Met Glu Glu Thr Pro Asn Ile Leu Arg Ile Pro
            180                 185                 190
Thr Gln Val Gly Lys Lys Ala Gly Lys Met
        195                 200
```

<210> 39
<211> 243
<212> PRT
<213> Homo sapien

<400> 39

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

<210> 40
<211> 245
<212> PRT
<213> Homo sapien

291
561
558

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<400> 40
Ala Ala Val Asp Ile Arg Asp Asn Leu Leu Gly Ile Ser Trp Val Asp
1 5 10 15
Ser Ser Trp Ile Pro Ile Leu Asn Ser Gly Ser Val Leu Asp Tyr Phe
20 25 30
Ser Glu Arg Ser Asn Pro Phe Tyr Asp Arg Thr Cys Asn Asn Glu Val
35 40 45
Val Lys Met Gln Arg Leu Thr Leu Glu His Leu Asn Gln Met Val Gly
50 55 60
Ile Glu Tyr Ile Leu Leu His Ala Gln Glu Pro Ile Leu Phe Ile Ile
65 70 75 80
Arg Lys Gln Gln Arg Gln Ser Pro Ala Gln Val Ile Pro Leu Ala Asp
85 90 95
Tyr Tyr Ile Ile Ala Gly Val Ile Tyr Gln Ala Pro Asp Leu Gly Ser
100 105 110
Val Ile Asn Ser Arg Val Leu Thr Ala Val His Gly Ile Gln Ser Ala
115 120 125
Phe Asp Glu Ala Met Ser Tyr Cys Arg Tyr His Pro Ser Lys Gly Tyr
130 135 140
Trp Trp His Phe Lys Asp His Glu Glu Gln Asp Lys Val Arg Pro Lys
145 150 155 160
Ala Lys Arg Lys Glu Glu Pro Ser Ser Ile Phe Gln Arg Gln Arg Val
165 170 175
Asp Ala Leu Leu Leu Asp Leu Arg Gln Lys Phe Pro Pro Lys Phe Val
180 185 190
Gln Leu Lys Pro Gly Glu Lys Pro Val Pro Val Asp Gln Thr Lys Lys
195 200 205
Glu Ala Glu Pro Ile Pro Glu Thr Val Lys Pro Glu Glu Lys Glu Thr
210 215 220
Thr Lys Asn Val Gln Gln Thr Val Ser Ala Lys Gly Pro Pro Glu Lys
225 230 235 240
Arg Met Arg Leu Gln
245

<210> 41
<211> 163
<212> PRT
<213> Homo sapien

<400> 41
Gly Glu Arg Gln Gly Leu Val Ala Arg Ala Arg Leu Ser Leu Arg Pro
1 5 10 15
Ser Ile Pro Glu Leu Ser Glu Arg Thr Ser Arg Pro Cys Arg Ala Ser
20 25 30
Pro Ala Ser Leu Pro Ser Gln His Thr Ser Ser Pro Ala Gln Ala Arg
35 40 45
Val Arg Asn Leu Ala Gln Ser Thr Phe Pro Leu Ala Ala Gln Glu Thr
50 55 60
Pro Gly Arg Ala Pro Ala His Ala Pro Leu Ser Ser Phe Val Pro Gly
65 70 75 80
Val Gly Gly Arg Ser Pro Ala Ser Val Gly Ile Ser Ala Pro Gly Gly
85 90 95
Gly Pro Ser Gly Ala Ala Ala Lys Ile Pro Leu Glu Leu Thr Gln Ser
100 105 110

290
562
559

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Arg Val Gln Lys Ile Trp Val Pro Val Asp His Arg Pro Ser Leu Pro
115 120 125
Arg Ser Cys Gly Pro Lys Leu Thr Asn Ser Pro Ala Val Phe Val Met
130 135 140
Val Gly Leu Pro Arg Pro Gly Gln Asp Leu Leu Leu His Glu Ser Leu
145 150 155 160
Leu Ala Ala

<210> 42
<211> 243
<212> PRT
<213> Homo sapien

<400> 42
Val Asp Ile Arg Asp Asn Leu Leu Gly Ile Ser Trp Val Asp Ser Ser
1 5 10 15
Trp Ile Pro Ile Leu Asn Ser Gly Ser Val Leu Asp Tyr Phe Ser Glu
20 25 30
Arg Ser Asn Pro Phe Tyr Asp Arg Thr Cys Asn Asn Glu Val Val Lys
35 40 45
Met Gln Arg Leu Thr Leu Glu His Leu Asn Gln Met Val Gly Ile Glu
50 55 60
Tyr Ile Leu Leu His Ala Gln Glu Pro Ile Leu Phe Ile Ile Arg Lys
65 70 75 80
Gln Gln Arg Gln Ser Pro Ala Gln Val Ile Pro Leu Ala Asp Tyr Tyr
85 90 95
Ile Ile Ala Gly Val Ile Tyr Gln Ala Pro Asp Leu Gly Ser Val Ile
100 105 110
Asn Ser Arg Val Leu Thr Ala Val His Gly Ile Gln Ser Ala Phe Asp
115 120 125
Glu Ala Met Ser Tyr Cys Arg Tyr His Pro Ser Lys Gly Tyr Trp Trp
130 135 140
His Phe Lys Asp His Glu Glu Gln Asp Lys Val Arg Pro Lys Ala Lys
145 150 155 160
Arg Lys Glu Glu Pro Ser Ser Ile Phe Gln Arg Gln Arg Val Asp Ala
165 170 175
Leu Leu Leu Asp Leu Arg Gln Lys Phe Pro Pro Lys Phe Val Gln Leu
180 185 190
Lys Pro Gly Glu Lys Pro Val Pro Val Asp Gln Thr Lys Lys Glu Ala
195 200 205
Glu Pro Ile Pro Glu Thr Val Lys Pro Glu Glu Lys Glu Thr Thr Lys
210 215 220
Asn Val Gln Gln Thr Val Ser Ala Lys Gly Pro Pro Glu Lys Arg Met
225 230 235 240
Arg Leu Gln

<210> 43
<211> 244
<212> PRT
<213> Homo sapien

<400> 43
Ala Val Asp Ile Arg Asp Asn Leu Leu Gly Ile Ser Trp Val Asp Ser

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

<210> 44
<211> 109
<212> PRT
<213> Homo sapien

<400> 44

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

<210> 45
<211> 324

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<212> PRT
<213> Homo sapien

<400> 45

```
Arg Arg Pro Val Met Ala Gln Glu Thr Ala Pro Pro Cys Gly Pro Val
 1               5                  10                  15
Ser Arg Gly Asp Ser Pro Ile Ile Glu Lys Met Glu Lys Arg Thr Cys
            20                  25                  30
Ala Leu Cys Pro Glu Gly His Glu Trp Ser Gln Ile Tyr Phe Ser Pro
        35                  40                  45
Ser Gly Asn Ile Val Ala His Glu Asn Cys Leu Leu Tyr Ser Ser Gly
    50                  55                  60
Leu Val Glu Cys Glu Thr Leu Asp Leu Arg Asn Thr Ile Arg Asn Phe
65                  70                  75                  80
Asp Val Lys Ser Val Lys Lys Glu Ile Trp Arg Gly Arg Arg Leu Lys
                85                  90                  95
Cys Ser Phe Cys Asn Lys Gly Gly Ala Thr Val Gly Cys Asp Leu Trp
            100                 105                 110
Phe Cys Lys Lys Ser Tyr His Tyr Val Cys Ala Lys Lys Asp Gln Ala
        115                 120                 125
Ile Leu Gln Val Asp Gly Asn His Gly Thr Tyr Lys Leu Phe Cys Pro
    130                 135                 140
Glu His Ser Pro Glu Gln Glu Glu Ala Thr Glu Ser Ala Asp Asp Pro
145                 150                 155                 160
Ser Met Lys Lys Lys Arg Gly Lys Asn Lys Arg Leu Ser Ser Gly Pro
                165                 170                 175
Pro Ala Gln Pro Lys Thr Met Lys Cys Ser Asn Ala Lys Arg His Met
            180                 185                 190
Thr Glu Glu Pro His Gly His Thr Asp Ala Ala Val Lys Ser Pro Phe
        195                 200                 205
Leu Lys Lys Cys Gln Glu Ala Gly Leu Leu Thr Glu Leu Phe Glu His
    210                 215                 220
Ile Leu Glu Asn Met Asp Ser Val His Gly Arg Leu Val Asp Glu Thr
225                 230                 235                 240
Ala Ser Glu Ser Asp Tyr Glu Gly Ile Glu Thr Leu Leu Phe Asp Cys
                245                 250                 255
Gly Leu Phe Lys Asp Thr Leu Arg Lys Phe Gln Glu Val Ile Lys Ser
            260                 265                 270
Lys Ala Cys Glu Trp Glu Glu Arg Gln Arg Gln Met Lys Gln Gln Leu
        275                 280                 285
Glu Ala Leu Ala Asp Leu Gln Gln Ser Leu Cys Ser Phe Gln Glu Asn
    290                 295                 300
Gly Asp Leu Asp Cys Ser Ser Ser Thr Ser Gly Ser Leu Leu Pro Pro
305                 310                 315                 320
Glu Asp His Gln
```

<210> 46
<211> 264
<212> PRT
<213> Homo sapien

<400> 46

```
Ala Val Asp Ile Arg Asp Asn Leu Leu Gly Ile Ser Trp Val Asp Ser
 1               5                  10                  15
```

295
565
562

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

<210> 47
<211> 14
<212> DNA
<213> Homo sapien

<400> 47
ttttttttt ttag 14

<210> 48
<211> 10
<212> DNA
<213> Homo sapien

<400> 48
cttcaacctc 10

<210> 49
<211> 496
<212> DNA
<213> Homo sapien

<400> 49
gcaccatgta ccgagcactt cggctcctcg cgcgctcgcg tcccctcgtg cgggctccag 60
ccgcagcctt agcttcggct cccggcttgg gtggcgcggc cgtgccctcg ttttggcctc 120

cgaacgcggc tcgaatggca agccaaaatt ccttccggat agaatatgat acctttggtg 180
aactaaaggt gccaaatgat aagtattatg gcgcccagac cgtgagatct acgatgaact 240
ttaagattgg aggtgtgaca gaacgcatgc caacccccagt tattaaagct tttggcatct 300
tgaagcgagc ggccgctgaa gtaaaccagg attatggtct tgatccaaag attgctaatg 360
caataatgaa ggcagcagat gaggtagctg aaggtaaatt aaatgatcat tttcctctcg 420
tggtatggca gactggatca ggaactcaga caaatatgaa tgtaaatgaa gtcattagcc 480
aatagagcaa ttgaaa 496

<210> 50
<211> 499
<212> DNA
<213> Homo sapien

<400> 50
agaaaaagtc tatgtttgca gaaatacaga tccaagacaa agacaggatg ggcactgctg 60
gaaaagttat taaatgcaaa gcagctgtgc tttgggagca gaagcaaccc ttctccattg 120
aggaaataga agttgcccca ccaaagacta aagaagttcg cattaagatt ttggccacag 180
gaatctgtcg cacagatgac catgtgataa aaggaacaat ggtgtccaag tttccagtga 240
ttgtgggaca tgaggcaact gggattgtag agagcattgg agaaggagtg actacagtga 300
aaccaggtga caaagtcatc cctctctttc tgccacaatg tagagaatgc aatgcttgtc 360
gcaacccaga tggcaacctt tgcattagga gcgatattac tggtcgtgga gtactggctg 420
atggcaccac cagatttaca tgcaagggcg aaccagtcca ccacttcatg aacaccagta 480
catttaccga gtacacagt 499

<210> 51
<211> 887
<212> DNA
<213> Homo sapien

<400> 51
gagtctgagc agaaaggaaa agcagccttg gcagccacgt tagaggaata caaagccaca 60
gtggccagtg accagataga gatgaatcgc ctgaaggctc agctggagaa tgaaaagcag 120
aaagtggcag agctgtattc tatccataac tctggagaca aatctgatat tcaggacctc 180
ctggagagtg tcaggctgga caaagaaaaa gcagagactt tggctagtag cttgcaggaa 240
gatctggctc atacccgaaa tgatgccaat cgattacagg atgccattgc taaggtagag 300
gatgaatacc gagccttcca agaagaagct aagaaacaaa ttgaagattt gaatatgacg 360
ttagaaaaat taagatcaga cctggatgaa aaagaaacag aaaggagtga catgaaagaa 420
accatctttg aacttgaaga tgaagtagaa caacatcgtg ctgtgaaact tcatgacaac 480
ctcattattt ctgatctaga gaatacagtt aaaaaactcc aggaccaaaa gcacgacatg 540
gaaagagaaa taaagacact ccacagaaga cttcgggaag aatctgcgga atggcggcag 600
tttcaggctg atctccagac tgcagtagtc attgcaaatg acattaaatc tgaagcccaa 660
gaggagattg gtgatctaaa gcgccggtta catgaggctc aagaaaaaaa tgagaaactc 720
acaaaagaat tggaggaaat aaagtcacgc aagcaagagg aggagcgagg cgggtataca 780
attacatgaa tgccgttgag agagatttgg cagccttaag gcagggaatg ggactgagta 840
gaaggtcctc gacttcctca gagccaactc ctacagtaaa aaccctc 887

<210> 52
<211> 491
<212> DNA
<213> Homo sapien

<400> 52
ggcacgagct tttccaaaaa tcatgctgct cctttctcta aagttcttac attttataga 60
aaggaacctt tcactcttga ggcctactac agctctcctc aggatttgcc ctatccagat 120
cctgctatag ctcagttttc agttcagaaa gtcactcctc agtctgatgg ctccagttca 180

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aaagtgaaag tcaaagttcg agtaaatgtc catggcattt tcagtgtgtc cagtgcatct 240
ttagtggagg ttcacaagtc tgaggaaaat gaggagccaa tggaaacaga tcagaatgca 300
aaggaggaag agaagatgca agtggaccag gaggaaccac atgttgaaga gcaacagcag 360
cagacaccag gcagaaaata aggcagagtc tgaagaaatg gagacctctc aagctggatc 420
caaggataaa aagatggacc aaccacccca agccaagaag gcaaaagtga agaccagtac 480
tgtggacctg g 491

<210> 53
<211> 787
<212> DNA
<213> Homo sapien

<400> 53
aagcagttga gtaggcagaa aaaagaacct cttcattaag gattaaaatg tataggccag 60
cacgtgtaac ttcgacttca agatttctga atccatatgt agtatgtttc attgtcgtcg 120
caggggtagt gatcctggca gtcaccatag ctctacttgt ttacttttta gcttttgatc 180
aaaaatctta cttttatagg agcagttttc aactcctaaa tgttgaatat aatagtcagt 240
taaattcacc agctacacag gaatacagga ctttgagtgg aagaattgaa tctctgatta 300
ctaaaacatt caaagaatca aatttaagaa atcagttcat cagagctcat gttgccaaac 360
tgaggcaaga tggtagtggt gtgagagcgg atgttgtcat gaaatttcaa ttcactagaa 420
ataacaatgg agcatcaatg aaaagcagaa ttgagtctgt tttacgacaa atgctgaata 480
actctggaaa cctggaaata aacccttcaa ctgagataac atcacttact gaccaggctg 540
cagcaaattg gcttattaat gaatgtgggg ccggtccaga cctaataaca ttgtctgagc 600
agagaatcct tggaggcact gaggctgagg agggaagctg gccgtggcaa gtcagtctgc 660
ggctcaataa tgcccaccac tgtggaggca gcctgatcaa taacatgtgg atcctgacag 720
cagctcactg cttcagaagc aactctaatc ctcgtgactg gattgccacg tctggtattt 780
ccacaac 787

<210> 54
<211> 386
<212> DNA
<213> Homo sapien

<400> 54
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gagccaatgg aaacagatca gaatgcaaag gaggaagaga agatgcaagt ggaccaggag 120
gaaccacatg ttgaagagca acagcagcag acaccagcag aaaataaggc agagtctgaa 180
gaaatggaga cctctcaagc tggatccaag gataaaaaga tggaccaacc accccaagcc 240
aagaaggcaa aagtgaagac cagtactgtg gacctgccaa tcgagaatca gctattatgg 300
cagatagaca gagagatgct caacttgtac attgaaaatg agggtaagat gatcatgcag 360
gataaactgg agaaggagcg gaatga 386

<210> 55
<211> 1462
<212> DNA
<213> Homo sapien

<400> 55
aagcagttga gtaggcagaa aaaagaacct cttcattaag gattaaaatg tataggccag 60
cacgtgtaac ttcgacttca agatttctga atccatatgt agtatgtttc attgtcgtcg 120
caggggtagt gatcctggca gtcaccatag ctctacttgt ttacttttta gcttttgatc 180
aaaaatctta cttttatagg agcagttttc aactcctaaa tgttgaatat aatagtcagt 240
taaattcacc agctacacag gaatacagga ctttgagtgg aagaattgaa tctctgatta 300
ctaaaacatt caaagaatca aatttaagaa atcagttcat cagagctcat gttgccaaac 360
tgaggcaaga tggtagtggt gtgagagcgg atgttgtcat gaaatttcaa ttcactagaa 420

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28
565

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ataacaatgg agcatcaatg aaaagcagaa ttgagtctgt tttacgacaa atgctgaata 480
actctggaaa cctggaaata aacccttcaa ctgagataac atcacttact gaccaggctg 540
cagcaaattg gcttattaat gaatgtgggg ccggtccaga cctaataaca ttgtctgagc 600
agagaatcct tggaggcact gaggctgagg agggaagctg gccgtggcaa gtcagtctgc 660
ggctcaataa tgcccaccac tgtggaggca gcctgatcaa taacatgtgg atcctgacag 720
cagctcactg cttcagaagc aactctaatc ctcgtgactg gattgccacg tctggtattt 780
ccacaacatt tcctaaacta agaatgagag taagaaatat tttaattcat aacaattata 840
aatctgcaac tcatgaaaat gacattgcac ttgtgagact tgagaacagt gtcaccttta 900
ccaaagatat ccatagtgtg tgtctcccag ctgctaccca gaatattcca cctggctcta 960
ctgcttatgt aacaggatgg ggcgctcaag aatatgctgg ccacacagtt ccagagctaa 1020
ggcaaggaca ggtcagaata ataagtaatg atgtatgtaa tgcaccacat agttataatg 1080
gagccatctt gtctggaatg ctgtgtgctg gagtacctca aggtggagtg gacgcatgtc 1140
agggtgactc tggtggccca ctagtacaag aagactcacg gcggctttgg tttattgtgg 1200
ggatagtaag ctggggagat cagtgtggcc tgccggataa gccaggagtg tatactcgag 1260
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ctgttgcaaa gtctgtatgc aggtgtgcct gtcttaaatt ccaaagcttt acatttcaac 1380
tgaaaaagaa actagaaatg tcctaattta acatcttgtt acataaatat ggtttaacaa 1440
aaaaaaaaaa aaaaaactcg ag 1462

<210> 56
<211> 159
<212> PRT
<213> Homo sapien

<400> 56
Thr Met Tyr Arg Ala Leu Arg Leu Leu Ala Arg Ser Arg Pro Leu Val
1 5 10 15
Arg Ala Pro Ala Ala Ala Leu Ala Ser Ala Pro Gly Leu Gly Gly Ala
20 25 30
Ala Val Pro Ser Phe Trp Pro Pro Asn Ala Ala Arg Met Ala Ser Gln
35 40 45
Asn Ser Phe Arg Ile Glu Tyr Asp Thr Phe Gly Glu Leu Lys Val Pro
50 55 60
Asn Asp Lys Tyr Tyr Gly Ala Gln Thr Val Arg Ser Thr Met Asn Phe
65 70 75 80
Lys Ile Gly Gly Val Thr Glu Arg Met Pro Thr Pro Val Ile Lys Ala
85 90 95
Phe Gly Ile Leu Lys Arg Ala Ala Ala Glu Val Asn Gln Asp Tyr Gly
100 105 110
Leu Asp Pro Lys Ile Ala Asn Ala Ile Met Lys Ala Ala Asp Glu Val
115 120 125
Ala Glu Gly Lys Leu Asn Asp His Phe Pro Leu Val Val Trp Gln Thr
130 135 140
Gly Ser Gly Thr Gln Thr Asn Met Asn Val Asn Glu Val Ile Ser
145 150 155

<210> 57
<211> 165
<212> PRT
<213> Homo sapien

<400> 57
Lys Lys Ser Met Phe Ala Glu Ile Gln Ile Gln Asp Lys Asp Arg Met
1 5 10 15
Gly Thr Ala Gly Lys Val Ile Lys Cys Lys Ala Ala Val Leu Trp Glu

299
Seq
566

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

      <210> 58
      <211> 259
      <212> PRT
      <213> Homo sapien

      <400> 58
Glu Ser Glu Gln Lys Gly Lys Ala Ala Leu Ala Ala Thr Leu Glu Glu
 1               5                  10                  15
Tyr Lys Ala Thr Val Ala Ser Asp Gln Ile Glu Met Asn Arg Leu Lys
            20                  25                  30
Ala Gln Leu Glu Asn Glu Lys Gln Lys Val Ala Glu Leu Tyr Ser Ile
        35                  40                  45
His Asn Ser Gly Asp Lys Ser Asp Ile Gln Asp Leu Leu Glu Ser Val
    50                  55                  60
Arg Leu Asp Lys Glu Lys Ala Glu Thr Leu Ala Ser Ser Leu Gln Glu
65                  70                  75                  80
Asp Leu Ala His Thr Arg Asn Asp Ala Asn Arg Leu Gln Asp Ala Ile
                85                  90                  95
Ala Lys Val Glu Asp Glu Tyr Arg Ala Phe Gln Glu Glu Ala Lys Lys
            100                 105                 110
Gln Ile Glu Asp Leu Asn Met Thr Leu Glu Lys Leu Arg Ser Asp Leu
        115                 120                 125
Asp Glu Lys Glu Thr Glu Arg Ser Asp Met Lys Glu Thr Ile Phe Glu
    130                 135                 140
Leu Glu Asp Glu Val Glu Gln His Arg Ala Val Lys Leu His Asp Asn
145                 150                 155                 160
Leu Ile Ile Ser Asp Leu Glu Asn Thr Val Lys Lys Leu Gln Asp Gln
                165                 170                 175
Lys His Asp Met Glu Arg Glu Ile Lys Thr Leu His Arg Arg Leu Arg
            180                 185                 190
Glu Glu Ser Ala Glu Trp Arg Gln Phe Gln Ala Asp Leu Gln Thr Ala
        195                 200                 205
Val Val Ile Ala Asn Asp Ile Lys Ser Glu Ala Gln Glu Glu Ile Gly
    210                 215                 220
Asp Leu Lys Arg Arg Leu His Glu Ala Gln Glu Lys Asn Glu Lys Leu
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350
5/30
567

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225 230 235 240
Thr Lys Glu Leu Glu Glu Ile Lys Ser Arg Lys Gln Glu Glu Glu Arg
245 250 255
Gly Gly Tyr

<210> 59
<211> 125
<212> PRT
<213> Homo sapien

<400> 59
Gly Thr Ser Phe Ser Lys Asn His Ala Ala Pro Phe Ser Lys Val Leu
1 5 10 15
Thr Phe Tyr Arg Lys Glu Pro Phe Thr Leu Glu Ala Tyr Tyr Ser Ser
20 25 30
Pro Gln Asp Leu Pro Tyr Pro Asp Pro Ala Ile Ala Gln Phe Ser Val
35 40 45
Gln Lys Val Thr Pro Gln Ser Asp Gly Ser Ser Ser Lys Val Lys Val
50 55 60
Lys Val Arg Val Asn Val His Gly Ile Phe Ser Val Ser Ser Ala Ser
65 70 75 80
Leu Val Glu Val His Lys Ser Glu Glu Asn Glu Glu Pro Met Glu Thr
85 90 95
Asp Gln Asn Ala Lys Glu Glu Glu Lys Met Gln Val Asp Gln Glu Glu
100 105 110
Pro His Val Glu Glu Gln Gln Gln Gln Thr Pro Gly Arg
115 120 125

<210> 60
<211> 246
<212> PRT
<213> Homo sapien

<400> 60
Met Tyr Arg Pro Ala Arg Val Thr Ser Thr Ser Arg Phe Leu Asn Pro
1 5 10 15
Tyr Val Val Cys Phe Ile Val Val Ala Gly Val Val Ile Leu Ala Val
20 25 30
Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
35 40 45
Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
50 55 60
Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65 70 75 80
Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
85 90 95
Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
100 105 110
Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
115 120 125
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
130 135 140
Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145 150 155 160

304
SX
568

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Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
                165                 170                 175
Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
            180                 185                 190
Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
        195                 200                 205
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
    210                 215                 220
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225                 230                 235                 240
Thr Ser Gly Ile Ser Thr
                245
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<210> 61
<211> 128
<212> PRT
<213> Homo sapien

<400> 61

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Gly Ile Phe Ser Val Ser Ser Ala Ser Leu Val Glu Val His Lys Ser
 1               5                  10                  15
Glu Glu Asn Glu Glu Pro Met Glu Thr Asp Gln Asn Ala Lys Glu Glu
            20                  25                  30
Glu Lys Met Gln Val Asp Gln Glu Glu Pro His Val Glu Glu Gln Gln
        35                  40                  45
Gln Gln Thr Pro Ala Glu Asn Lys Ala Glu Ser Glu Glu Met Glu Thr
    50                  55                  60
Ser Gln Ala Gly Ser Lys Asp Lys Lys Met Asp Gln Pro Pro Gln Ala
65                  70                  75                  80
Lys Lys Ala Lys Val Lys Thr Ser Thr Val Asp Leu Pro Ile Glu Asn
                85                  90                  95
Gln Leu Leu Trp Gln Ile Asp Arg Glu Met Leu Asn Leu Tyr Ile Glu
            100                 105                 110
Asn Glu Gly Lys Met Ile Met Gln Asp Lys Leu Glu Lys Glu Arg Asn
        115                 120                 125
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<210> 62
<211> 418
<212> PRT
<213> Homo sapien

<400> 62

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Met Tyr Arg Pro Ala Arg Val Thr Ser Thr Ser Arg Phe Leu Asn Pro
 1               5                  10                  15
Tyr Val Val Cys Phe Ile Val Val Ala Gly Val Val Ile Leu Ala Val
            20                  25                  30
Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
        35                  40                  45
Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
    50                  55                  60
Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65                  70                  75                  80
Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
                85                  90                  95
Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
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302
572
569

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            100                 105                 110
Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
        115                 120                 125
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
    130                 135                 140
Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145                 150                 155                 160
Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
                165                 170                 175
Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
            180                 185                 190
Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
        195                 200                 205
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
    210                 215                 220
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225                 230                 235                 240
Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
                245                 250                 255
Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
            260                 265                 270
Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
        275                 280                 285
His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
    290                 295                 300
Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
305                 310                 315                 320
Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
                325                 330                 335
Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
            340                 345                 350
Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
        355                 360                 365
Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
    370                 375                 380
Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
385                 390                 395                 400
Val Tyr Thr Arg Val Thr Ala Tyr Ile Asp Trp Ile Arg Gln Gln Thr
                405                 410                 415
Gly Ile
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<210> 63
<211> 776
<212> DNA
<213> Homo sapien

<400> 63

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cacagatggt gatagaggaa tccatcttgc agtcagataa agccctcact gatagagaga      60
aggcagtagc agtggatcgg gccaagaagg aggcagctga gaaggaacag gaacttttaa     120
aacagaaatt acaggagcag ccagcaacag atggaggctc aagataagag tcgcaaggaa     180
aactagccaa ctgaaggaga agctgcagat ggagagagaa cacctactga gagagcagat     240
tatgatgttg gagcacacgc agaaggtcca aaatgattgg cttcatgaag gatttaagaa     300
gaagtatgag gagatgaatg cagagataag tcaatttaaa cgtatgattg atactacaaa     360
aaatgatgat actccctgga ttgcacgaac cttggacaac cttgccgatg agctaactgc     420
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303
573
570

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aatattgtct gctcctgcta aattaattgg tcatggtgtc aaaggtgtga gctcactctt 480
taaaaagcat aagctccect tttaaggata ttatagattg tacatatatg ctttggacta 540
tttttgatct gtatgttttt cattttcatt cagcaagttt ttttttttt tcagagtctt 600
actctgttgc ccaggctgga gtacagtggt gcaatctcag ctcactgcaa cctctgcctc 660
ctgggttcaa gagattcacc tgcctcagcc ccctagtagc tgggattata ggtgtacacc 720
accacaccca gctaattttt gtatttttag tagagatggg gtttcactat gttggc 776

<210> 64
<211> 160
<212> DNA
<213> Homo sapien

<400> 64
gcagcgctct cggttgcagt acccactgga aggacttagg cgctcgcgtg gacaccgcaa 60
gcccctcagt agcctcggcc caagaggcct gctttccact cgctagcccc gccgggggtc 120
cgtgtcctgt ctcggtggcc ggacccgggc ccgagcccga 160

<210> 65
<211> 72
<212> PRT
<213> Homo sapien

<400> 65
Leu Ser Ala Met Gly Phe Thr Ala Ala Gly Ile Ala Ser Ser Ser Ile
1 5 10 15
Ala Ala Lys Met Met Ser Ala Ala Ala Ile Ala Asn Gly Gly Gly Val
20 25 30
Ala Ser Gly Ser Leu Val Ala Thr Leu Gln Ser Leu Gly Ala Thr Gly
35 40 45
Leu Ser Gly Leu Thr Lys Phe Ile Leu Gly Ser Ile Gly Ser Ala Ile
50 55 60
Ala Ala Val Ile Ala Arg Phe Tyr
65 70

<210> 66
<211> 2581
<212> DNA
<213> Homo sapien

<400> 66
ctttcaaccc gcgctcgccg gctccagccc cgcgcgcccc cacccccttgc cctccccggcg 60
gctccgcagg gtgaggtggc tttgaccccg ggttgcccgg ccagcacgac cgaggaggtg 120
gctggacagc tggaggatga acggagaagc cgactgcccc acagacctgg aaatggccgc 180
ccccaaaggc caagaccgtt ggtcccagga agacatgctg actttgctgg aatgcatgaa 240
gaacaaccct ccatccaatg acagctccaa gttcaaaacc accgaatcac acatggactg 300
ggaaaaagta gcatttaaag acttttctgg agacatgtgc aagctcaaat gggtggagat 360
ttctaatgag gtgaggaagt tccgtacatt gacagaattg atcctcgatg ctcaggaaca 420
tgttaaaaat ccttacaaag gcaaaaaact caagaaacac ccagacttcc caaagaagcc 480
cctgacccct tatttccgct tcttcatgga gaagcgggcc aagtatgcga aactccaccc 540
tgagatgagc aacctggacc taaccaagat tctgtccaag aaatacaagg agcttccgga 600
gaagaagaag atgaaatata ttcaggactt ccagagagag aaacaggagt tcgagcgaaa 660
cctggcccga ttcagggagg atcaccccga cctaatccag aatgccaaga aatcggacat 720
cccagagaag cccaaaaccc cccagcagct gtggtacacc cacgagaaga aggtgtatct 780
caaagtgcgg ccagatgcca ctacgaagga ggtgaaggac tccctgggga agcagtggtc 840
tcagctctcg gacaaaaaga ggctgaaatg gattcataag gccctggagc agcggaagga 900

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gtacgaggag atcatgagag actatatcca gaagcaccca gagctgaaca tcagtgagga     960
gggtatcacc aagtccaccc tcaccaaggc cgaacgccag ctcaaggaca agtttgacgg    1020
gcgacccacc aagccacctc cgaacagcta ctcgctgtac tgcgcagagc tcatggccaa    1080
catgaaggac gtgcccagca cagagcgcat ggtgctgtgc agccagcagt ggaagctgct    1140
gtcccagaag gagaaggacg cctatcacaa gaagtgtgat cagaaaaaga aagattacga    1200
ggtggagctg ctccgtttcc tcgagagcct gcctgaggag gagcagcagc gggtcttggg    1260
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agcccaggaa gggggcaagg gcggctccga gaagcccaag cggcccgtgt cggccatgtt    1380
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cgaggaacgg ggcaagctgc ccgagtcccc caaaagagct gaggagatct ggcaacagag    1620
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ggaaatgacc tggaataaca tggaaaagaa ggagaaactg atgtggatta agaaggcagc    1740
cgaagaccaa aagcgatatg agagagagct gagtgagatg cgggcacctc cagctgctac    1800
aaattcttcc aagaagatga aattccaggg agaacccaag aagcctccca tgaacggtta    1860
ccagaagttc tcccaggagc tgctgtccaa tggggagctg aaccacctgc cgctgaagga    1920
gcgcatggtg gagatcggca gtcgctggca gcgcatctcc cagagccaga aggagcacta    1980
caaaaagctg gccgaggagc agcaaaagca gtacaaggtg cacctggacc tctgggttaa    2040
gagcctgtct ccccaggacc gtgcagcata taaagagtac atctccaata aacgtaagag    2100
catgaccaag ctgcgaggcc caaaccccaa atccagccgg actactctgc agtccaagtc    2160
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agatgatgag aatggggact cctctgaaga tggcggcgac tcctctgagt ccagcagcga    2280
ggacgaggagc gaggatgggg atgagaatga agaggatgac gaggacgaag acgacgacga    2340
ggatgacgat gaggatgaag ataatgagtc cgagggcagc agctccagct cctcctcctt    2400
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g                                                                     2581
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<210> 67
<211> 764
<212> PRT
<213> Homo sapien

<400> 67

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Lys Gly Gln Asp Arg Trp Ser Gln Glu Asp Met Leu Thr Leu Leu Glu
            20                  25                  30
Cys Met Lys Asn Asn Leu Pro Ser Asn Asp Ser Ser Lys Phe Lys Thr
        35                  40                  45
Thr Glu Ser His Met Asp Trp Glu Lys Val Ala Phe Lys Asp Phe Ser
    50                  55                  60
Gly Asp Met Cys Lys Leu Lys Trp Val Glu Ile Ser Asn Glu Val Arg
65                  70                  75                  80
Lys Phe Arg Thr Leu Thr Glu Leu Ile Leu Asp Ala Gln Glu His Val
                85                  90                  95
Lys Asn Pro Tyr Lys Gly Lys Lys Leu Lys Lys His Pro Asp Phe Pro
            100                 105                 110
Lys Lys Pro Leu Thr Pro Tyr Phe Arg Phe Phe Met Glu Lys Arg Ala
        115                 120                 125
Lys Tyr Ala Lys Leu His Pro Glu Met Ser Asn Leu Asp Leu Thr Lys
    130                 135                 140
Ile Leu Ser Lys Lys Tyr Lys Glu Leu Pro Glu Lys Lys Lys Met Lys
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```
145                 150                 155                 160
Tyr Ile Gln Asp Phe Gln Arg Glu Lys Gln Glu Phe Glu Arg Asn Leu
                165                 170                 175
Ala Arg Phe Arg Glu Asp His Pro Asp Leu Ile Gln Asn Ala Lys Lys
            180                 185                 190
Ser Asp Ile Pro Glu Lys Pro Lys Thr Pro Gln Gln Leu Trp Tyr Thr
        195                 200                 205
His Glu Lys Lys Val Tyr Leu Lys Val Arg Pro Asp Ala Thr Thr Lys
    210                 215                 220
Glu Val Lys Asp Ser Leu Gly Lys Gln Trp Ser Gln Leu Ser Asp Lys
225                 230                 235                 240
Lys Arg Leu Lys Trp Ile His Lys Ala Leu Glu Gln Arg Lys Glu Tyr
            245                 250                 255
Glu Glu Ile Met Arg Asp Tyr Ile Gln Lys His Pro Glu Leu Asn Ile
            260                 265                 270
Ser Glu Glu Gly Ile Thr Lys Ser Thr Leu Thr Lys Ala Glu Arg Gln
        275                 280                 285
Leu Lys Asp Lys Phe Asp Gly Arg Pro Thr Lys Pro Pro Pro Asn Ser
    290                 295                 300
Tyr Ser Leu Tyr Cys Ala Glu Leu Met Ala Asn Met Lys Asp Val Pro
305                 310                 315                 320
Ser Thr Glu Arg Met Val Leu Cys Ser Gln Gln Trp Lys Leu Leu Ser
                325                 330                 335
Gln Lys Glu Lys Asp Ala Tyr His Lys Lys Cys Asp Gln Lys Lys Lys
            340                 345                 350
Asp Tyr Glu Val Glu Leu Leu Arg Phe Leu Glu Ser Leu Pro Glu Glu
        355                 360                 365
Glu Gln Gln Arg Val Leu Gly Glu Glu Lys Met Leu Asn Ile Asn Lys
    370                 375                 380
Lys Gln Ala Thr Ser Pro Ala Ser Lys Lys Pro Ala Gln Glu Gly Gly
385                 390                 395                 400
Lys Gly Gly Ser Glu Lys Pro Lys Arg Pro Val Ser Ala Met Phe Ile
                405                 410                 415
Phe Ser Glu Glu Lys Arg Arg Gln Leu Gln Glu Glu Arg Pro Glu Leu
            420                 425                 430
Ser Glu Ser Glu Leu Thr Arg Leu Leu Ala Arg Met Trp Asn Asp Leu
        435                 440                 445
Ser Glu Lys Lys Lys Ala Lys Tyr Lys Ala Arg Glu Ala Ala Leu Lys
    450                 455                 460
Ala Gln Ser Glu Arg Lys Pro Gly Gly Glu Arg Glu Glu Arg Gly Lys
465                 470                 475                 480
Leu Pro Glu Ser Pro Lys Arg Ala Glu Glu Ile Trp Gln Gln Ser Val
                485                 490                 495
Ile Gly Asp Tyr Leu Ala Arg Phe Lys Asn Asp Arg Val Lys Ala Leu
            500                 505                 510
Lys Ala Met Glu Met Thr Trp Asn Asn Met Glu Lys Lys Glu Lys Leu
        515                 520                 525
Met Trp Ile Lys Lys Ala Ala Glu Asp Gln Lys Arg Tyr Glu Arg Glu
    530                 535                 540
Leu Ser Glu Met Arg Ala Pro Pro Ala Ala Thr Asn Ser Ser Lys Lys
545                 550                 555                 560
Met Lys Phe Gln Gly Glu Pro Lys Lys Pro Pro Met Asn Gly Tyr Gln
                565                 570                 575
Lys Phe Ser Gln Glu Leu Leu Ser Asn Gly Glu Leu Asn His Leu Pro
            580                 585                 590
```

Leu Lys Glu Arg Met Val Glu Ile Gly Ser Arg Trp Gln Arg Ile Ser
595 600 605
Gln Ser Gln Lys Glu His Tyr Lys Lys Leu Ala Glu Glu Gln Gln Lys
610 615 620
Gln Tyr Lys Val His Leu Asp Leu Trp Val Lys Ser Leu Ser Pro Gln
625 630 635 640
Asp Arg Ala Ala Tyr Lys Glu Tyr Ile Ser Asn Lys Arg Lys Ser Met
645 650 655
Thr Lys Leu Arg Gly Pro Asn Pro Lys Ser Ser Arg Thr Thr Leu Gln
660 665 670
Ser Lys Ser Glu Ser Glu Glu Asp Asp Glu Glu Asp Glu Asp Asp Glu
675 680 685
Asp Glu Asp Glu Glu Glu Glu Asp Asp Glu Asn Gly Asp Ser Ser Glu
690 695 700
Asp Gly Gly Asp Ser Ser Glu Ser Ser Ser Glu Asp Glu Ser Glu Asp
705 710 715 720
Gly Asp Glu Asn Glu Glu Asp Asp Glu Asp Glu Asp Asp Asp Glu Asp
725 730 735
Asp Asp Glu Asp Glu Asp Asn Glu Ser Glu Gly Ser Ser Ser Ser Ser
740 745 750
Ser Ser Leu Gly Asp Ser Ser Asp Phe Asp Ser Asn
755 760

<210> 68
<211> 434
<212> DNA
<213> Homo sapien

<400> 68
ctaagatgct ggatgctgaa gacatcgtcg gaactgcccg gccagatgag aaagccatta 60
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ccaatcgcat ctgcaaagtg ttggcggtca atcaagagaa cgagcagctt atggaagact 180
atgagaagct ggccagtgat ctgttggagt ggatccgccg caccatccca tggctggaga 240
atcgggtgcc tgagaacacc atgcatgcca tgcagcagaa gctggaggac ttccgagact 300
atagacgcct gcacaagccg cccaaggtgc aggagaagtg ccagctggag atcaacttta 360
acacgctgca gaccaaactg cggctcagca accggcctgc cttcatgccc tccgagggca 420
ggatggtctc ggat 434

<210> 69
<211> 244
<212> DNA
<213> Homo sapien

<400> 69
aggcagcatg ctcgttgaga gtcatcacca ctccctaatc tcaagtacgc agggacacaa 60
acactgcgga aggccgcagg gtcctctgcc taggaaaacc agagaccttt gttcacttgt 120
ttatgtgctg accttccctc cactattgtc ctgtgaccct gccaaatccc cctttgtgag 180
aaacacccaa gaatgatcaa taaaaaataa attaatttag gaaaaaaaaa aaaaaaaact 240
cgag 244

<210> 70
<211> 437
<212> DNA
<213> Homo sapien

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509
592
574

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<400> 70

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ccaggcagtg ggaccccgcg agctgcacgt ccctgggcac ggacaagtgt gaggcactgt 180
tggggctgtg ccagggtgcgg ggtgggctgc ccccttctc agaaccttcc agcctggtgc 240
cgtggccccc aggccggagt cttcctaagg ctgtgaggcc acccctgtcc tggcctccgt 300
tctcgcagca gcagaccttg cccgtgatga gcggggaggc ccttggctgg ctgggccagg 360
ctggttccct ggccatgggg gctgcacctc tgggggagcc agccaaggag gaccccatgc 420
tggcgcagga agccggg 437

<210> 71
<211> 271 .
<212> DNA
<213> Homo sapien

<400> 71

gcgcagagtt ctgtcgtcca ccatcgagtg aggaagagag cattggttcc cctgagatag 60
aagagatggc tctcttcagt gcccagtctc catacattaa cccgatcatc ccctttactg 120
gaccaatcca aggagggctg caggagggac ttcaggtgac cctccagggg actaccgaga 180
gttttgcaca aaagtttgtg gtgaactttt cagaacagct tcaatggaga tgacttggcc 240
ttccacttca accccggtta tgaggaagga g 271

<210> 72
<211> 290
<212> DNA
<213> Homo sapien

<400> 72

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ctggtgccct ctcctgctgc gaggactcgg cccagggctc gggcccgccc aaggccccta 120
cggtggccga gggtcccagc tcctgccttc ggcggaacgt gatcagcgag agggagcgca 180
ggaagcggat gtcgttgagc tgtgagcgtc tgcgggccct gctgccccag ttcgatggcc 240
ggcgggagga catggcctcg gtcctggaga tgtctgttgc aattcctgcg 290

<210> 73
<211> 144
<212> PRT
<213> Homo sapien

<400> 73

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

```
        115                 120                 125
Ser Asn Arg Pro Ala Phe Met Pro Ser Glu Gly Arg Met Val Ser Asp
    130                 135                 140

      <210> 74
      <211> 64
      <212> PRT
      <213> Homo sapien

      <400> 74
Gly Ser Met Leu Val Glu Ser His His His Ser Leu Ile Ser Ser Thr
 1               5                  10                  15
Gln Gly His Lys His Cys Gly Arg Pro Gln Gly Pro Leu Pro Arg Lys
            20                  25                  30
Thr Arg Asp Leu Cys Ser Leu Val Tyr Val Leu Thr Phe Pro Pro Leu
        35                  40                  45
Leu Ser Cys Asp Pro Ala Lys Ser Pro Phe Val Arg Asn Thr Gln Glu
    50                  55                  60

      <210> 75
      <211> 145
      <212> PRT
      <213> Homo sapien

      <400> 75
Gly Thr Gly Ala Ser Ser Gly Thr Arg Thr Pro Asp Val Lys Ala Phe
 1               5                  10                  15
Leu Glu Ser Pro Trp Ser Leu Asp Pro Ala Ser Ala Ser Pro Glu Pro
            20                  25                  30
Val Pro His Ile Leu Ala Ser Ser Arg Gln Trp Asp Pro Ala Ser Cys
        35                  40                  45
Thr Ser Leu Gly Thr Asp Lys Cys Glu Ala Leu Leu Gly Leu Cys Gln
    50                  55                  60
Val Arg Gly Gly Leu Pro Pro Phe Ser Glu Pro Ser Ser Leu Val Pro
65                  70                  75                  80
Trp Pro Pro Gly Arg Ser Leu Pro Lys Ala Val Arg Pro Pro Leu Ser
                85                  90                  95
Trp Pro Pro Phe Ser Gln Gln Gln Thr Leu Pro Val Met Ser Gly Glu
            100                 105                 110
Ala Leu Gly Trp Leu Gly Gln Ala Gly Ser Leu Ala Met Gly Ala Ala
        115                 120                 125
Pro Leu Gly Glu Pro Ala Lys Glu Asp Pro Met Leu Ala Gln Glu Ala
    130                 135                 140
Gly
145

      <210> 76
      <211> 69
      <212> PRT
      <213> Homo sapien

      <400> 76
Ala Glu Phe Cys Arg Pro Pro Ser Ser Glu Glu Glu Ser Ile Gly Ser
 1               5                  10                  15
Pro Glu Ile Glu Glu Met Ala Leu Phe Ser Ala Gln Ser Pro Tyr Ile
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            20                  25                  30
Asn Pro Ile Ile Pro Phe Thr Gly Pro Ile Gln Gly Gly Leu Gln Glu
        35                  40                  45
Gly Leu Gln Val Thr Leu Gln Gly Thr Thr Glu Ser Phe Ala Gln Lys
    50                  55                  60
Phe Val Val Asn Phe
65
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<210> 77
<211> 96
<212> PRT
<213> Homo sapien

<400> 77

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

<210> 78
<211> 2076
<212> DNA
<213> Homo sapien

<400> 78

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gaaaagttat taaatgcaaa gcagctgtgc tttgggagca gaagcaaccc ttctccattg     120
aggaaataga agttgcccca ccaaagacta aagaagttcg cattaagatt ttggccacag     180
gaatctgtcg cacagatgac catgtgataa aaggaacaat ggtgtccaag tttccagtga     240
ttgtgggaca tgaggcaact gggattgtag agagcattgg agaaggagtg actacagtga     300
aaccaggtga caaagtcatc cctctctttc tgccacaatg tagagaatgc aatgcttgtc     360
gcaacccaga tggcaacctt tgcattagga gcgatattac tggtcgtgga gtactggctg     420
atggcaccac cagatttaca tgcaagggca aaccagtcca ccacttcatg aacaccagta     480
catttaccga gtacacagtg gtggatgaat cttctgttgc taagattgat gatgcagctc     540
ctcctgagaa agtctgttta attggctgtg ggttttccac tggatatggc gctgctgtta     600
aaactggcaa ggtcaaacct ggttccactt gcgtcgtctt tggcctgaga ggagttggcc     660
tgtcagtcat catgggctgt aagtcagctg gtgcatctag gatcattggg attgacctca     720
acaaagacaa atttgagaag gccatggctg taggtgccac tgagtgtatc agtcccaagg     780
actctaccaa acccatcagt gaggtgctgt cagaaatgac aggcaacaac gtgggataca     840
cctttgaagt tattgggcat cttgaaacca tgattgatgc cctggcatcc tgccacatga     900
actatgggac cagcgtggtt gtaggagttc ctccatcagc caagatgctc acctatgacc     960
cgatgttgct cttcactgga cgcacatgga agggatgtgt ctttggaggt ttgaaaagca    1020
gagatgatgt cccaaaacta gtgactgagt tcctggcaaa gaaatttgac ctggaccagt    1080
tgataactca tgtcttacca tttaaaaaaa tcagtgaagg atttgagctg ctcaattcag    1140
gacaaagcat tcgaacggtc ctgacgtttt gagatccaaa gtggcaggag gtctgtgttg    1200
tcatggtgaa ctggagtttc tcttgtgaga gttcccctcat ctgaaatcat gtatctgtct    1260
cacaaataca agcataagta gaagatttgt tgaagacata gaacccttat aaagaattat    1320
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taacctttat aaacatttaa agtcttgtga gcacctggga attagtataa taacaatgtt 1380
aatatttttg atttacattt tgtaaggcta taattgtatc ttttaagaaa acatacactt 1440
ggatttctat gttgaaatgg agatttttaa gagttttaac cagctgctgc agatatatat 1500
ctcaaaacag atatagcgta taaagatata gtaaatgcat ctcctagagt aatattcact 1560
taacacattg aaactattat tttttagatt tgaatataaa tgtatttttt aaacacttgt 1620
tatgagttaa cttggattac attttgaaat cagttcattc catgatgcat attactggat 1680
tagattaaga aagacagaaa agattaaggg acgggcacat ttttcaacga ttaagaatca 1740
tcattacata acttggtgaa actgaaaaag tatatcatat gggtacacaa ggctatttgc 1800
cagcatatat taatatttta gaaaatattc cttttgtaat actgaatata aacatagagc 1860
tagaatcata ttatcatact tatcataatg ttcaatttga tacagtagaa ttgcaagtcc 1920
ttaagtcccc attcactgtg cttagtagtg actccattta ataaaaagtg tttttagttt 1980
ttaacaacta cactgatgta tttatatata tttataacat gttaaaaatt tttaaggaaa 2040
ttaaaaatta tataaaaaaa aaaaaaaaaa ctcgag 2076

<210> 79
<211> 2790
<212> DNA
<213> Homo sapien

<400> 79
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cacgtgtaac ttcgacttca agatttctga atccatatgt agtatgtttc attgtcgtcg 120
caggggtagt gatcctggca gtcaccatag ctctacttgt ttacttttta gcttttgatc 180
aaaaatctta cttttatagg agcagttttc aactcctaaa tgttgaatat aatagtcagt 240
taaattcacc agctacacag gaatacagga ctttgagtgg aagaattgaa tctctgatta 300
ctaaaacatt caaagaatca aatttaagaa atcagttcat cagagctcat gttgccaaac 360
tgaggcaaga tggtagtggt gtgagagcgg atgttgtcat gaaatttcaa ttcactagaa 420
atnacaatgg agcatcaatg aaaagcagaa ttgagtctgt tttacgacaa atgctgaata 480
actctggaaa cctggaaata aacccttcaa ctgagataac atcacttact gaccaggctg 540
cagcaaattg gcttattaat gaatgtgggg ccggtccaga cctaataaca ttgtctgagc 600
agagaatcct tggaggcact gaggctgagg agggaagctg gccgtggcaa gtcagtctgc 660
ggctcaataa tgcccaccac tgtggaggca gcctgatcaa taacatgtgg atcctgacag 720
cagctcactg cttcagaagc aactctaatc ctcgtgactg gattgccacg tctggtattt 780
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ccaaagatat ccatagtgtg tgtctcccag ctgctaccca gaatattcca cctggctcta 960
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caatatctta tacttagtat gagtcctaaa attaaaaatg tgaaactgtt gtactatacg 1860
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tcagctattt aaggcaaaag ctaaaatagt tcactcctca actgagaccc aaagaattat 1980
agatattttt catgatgacc catgaaaaat atcactcatc tacataaagg agagactata 2040
tctattttat agagaagcta agaaatatac ctacacaaac ttgtcaggtg ctttacaact 2100

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34
58
578

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acatagtact ttttaacaac aaaataataa ttttaagaat gaaaaattta atcatcggga 2160
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gtcaaacgct aaatctaagt aatgaattga aagtttaaag agggggaaga gttggtttgc 2280
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<210> 80
<211> 1460
<212> DNA
<213> Homo sapien

<400> 80
ctcaaagcag ttgagtaggc agaaaaaaga acctcttcat taaggattaa aatgtatagg 60
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gtcgcagggg tagtgatcct ggcagtcacc atagctctac ttgtttactt tttagctttt 180
gatcaaaaat cttactttta taggagcagt tttcaactcc taaatgttga atataatagt 240
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attactaaaa cattcaaaga atcaaattta agaaatcagt tcatcagagc tcatgttgcc 360
aaactgaggc aagatggtag tggtgtgaga gcggatgttg tcatgaaatt tcaattcact 420
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aataactctg gaaacctgga aataaaccct tcaactgaga taacatcact tactgaccag 540
gctgcagcaa attggcttat taatgaatgt ggggccggtc cagacctaat aacattgtct 600
gagcagagaa tccttggagg cactgaggct gaggagggaa gctggccgtg gcaagtcagt 660
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caactgaaaa agaaactaga aatgtcctaa tttaacatct tgttacataa atatggttta 1440
acaaaaaaaa aaaaaaaaaa 1460

<210> 81
<211> 386
<212> PRT
<213> Homo sapien

<400> 81
Met Phe Ala Glu Ile Gln Ile Gln Asp Lys Asp Arg Met Gly Thr Ala
1 5 10 15
Gly Lys Val Ile Lys Cys Lys Ala Ala Val Leu Trp Glu Gln Lys Gln
20 25 30

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582
579

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Pro Phe Ser Ile Glu Glu Ile Glu Val Ala Pro Pro Lys Thr Lys Glu
        35                  40                  45
Val Arg Ile Lys Ile Leu Ala Thr Gly Ile Cys Arg Thr Asp Asp His
    50                  55                  60
Val Ile Lys Gly Thr Met Val Ser Lys Phe Pro Val Ile Val Gly His
65                  70                  75                  80
Glu Ala Thr Gly Ile Val Glu Ser Ile Gly Glu Gly Val Thr Thr Val
                85                  90                  95
Lys Pro Gly Asp Lys Val Ile Pro Leu Phe Leu Pro Gln Cys Arg Glu
            100                 105                 110
Cys Asn Ala Cys Arg Asn Pro Asp Gly Asn Leu Cys Ile Arg Ser Asp
        115                 120                 125
Ile Thr Gly Arg Gly Val Leu Ala Asp Gly Thr Thr Arg Phe Thr Cys
    130                 135                 140
Lys Gly Lys Pro Val His His Phe Met Asn Thr Ser Thr Phe Thr Glu
145                 150                 155                 160
Tyr Thr Val Val Asp Glu Ser Ser Val Ala Lys Ile Asp Asp Ala Ala
                165                 170                 175
Pro Pro Glu Lys Val Cys Leu Ile Gly Cys Gly Phe Ser Thr Gly Tyr
            180                 185                 190
Gly Ala Ala Val Lys Thr Gly Lys Val Lys Pro Gly Ser Thr Cys Val
        195                 200                 205
Val Phe Gly Leu Arg Gly Val Gly Leu Ser Val Ile Met Gly Cys Lys
    210                 215                 220
Ser Ala Gly Ala Ser Arg Ile Ile Gly Ile Asp Leu Asn Lys Asp Lys
225                 230                 235                 240
Phe Glu Lys Ala Met Ala Val Gly Ala Thr Glu Cys Ile Ser Pro Lys
                245                 250                 255
Asp Ser Thr Lys Pro Ile Ser Glu Val Leu Ser Glu Met Thr Gly Asn
            260                 265                 270
Asn Val Gly Tyr Thr Phe Glu Val Ile Gly His Leu Glu Thr Met Ile
        275                 280                 285
Asp Ala Leu Ala Ser Cys His Met Asn Tyr Gly Thr Ser Val Val Val
    290                 295                 300
Gly Val Pro Pro Ser Ala Lys Met Leu Thr Tyr Asp Pro Met Leu Leu
305                 310                 315                 320
Phe Thr Gly Arg Thr Trp Lys Gly Cys Val Phe Gly Gly Leu Lys Ser
                325                 330                 335
Arg Asp Asp Val Pro Lys Leu Val Thr Glu Phe Leu Ala Lys Lys Phe
            340                 345                 350
Asp Leu Asp Gln Leu Ile Thr His Val Leu Pro Phe Lys Lys Ile Ser
        355                 360                 365
Glu Gly Phe Glu Leu Leu Asn Ser Gly Gln Ser Ile Arg Thr Val Leu
    370                 375                 380
Thr Phe
385
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<210> 82
<211> 418
<212> PRT
<213> Homo sapien

<400> 82

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Met Tyr Arg Pro Ala Arg Val Thr Ser Thr Ser Arg Phe Leu Asn Pro
 1               5                  10                  15
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213
583
580

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Tyr Val Val Cys Phe Ile Val Val Ala Gly Val Val Ile Leu Ala Val
            20                  25                  30
Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
        35                  40                  45
Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
    50                  55                  60
Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65                  70                  75                  80
Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
                85                  90                  95
Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
            100                 105                 110
Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
        115                 120                 125
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
    130                 135                 140
Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145                 150                 155                 160
Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
                165                 170                 175
Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
            180                 185                 190
Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
        195                 200                 205
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
    210                 215                 220
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225                 230                 235                 240
Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
                245                 250                 255
Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
            260                 265                 270
Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
        275                 280                 285
His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
    290                 295                 300
Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
305                 310                 315                 320
Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
                325                 330                 335
Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
            340                 345                 350
Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
        355                 360                 365
Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
    370                 375                 380
Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
385                 390                 395                 400
Val Tyr Thr Arg Val Thr Ala Tyr Leu Asp Trp Ile Arg Gln Gln Thr
                405                 410                 415
Gly Ile
```

<210> 83
<211> 418

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<212> PRT
<213> Homo sapien

<400> 83

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 1               5                  10                  15
Tyr Val Val Cys Phe Ile Val Val Ala Gly Val Val Ile Leu Ala Val
            20                  25                  30
Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
        35                  40                  45
Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
    50                  55                  60
Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65                  70                  75                  80
Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
                85                  90                  95
Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
            100                 105                 110
Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
        115                 120                 125
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
    130                 135                 140
Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145                 150                 155                 160
Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
                165                 170                 175
Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
            180                 185                 190
Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
        195                 200                 205
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
    210                 215                 220
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225                 230                 235                 240
Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
                245                 250                 255
Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
            260                 265                 270
Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
        275                 280                 285
His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
    290                 295                 300
Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
305                 310                 315                 320
Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
                325                 330                 335
Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
            340                 345                 350
Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
        355                 360                 365
Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
    370                 375                 380
Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
385                 390                 395                 400
Val Tyr Thr Arg Val Thr Ala Tyr Leu Asp Trp Ile Arg Gln Gln Thr
```

405 410 415

Gly Ile

<210> 84
<211> 489
<212> DNA
<213> Homo sapien

<400> 84

aaaagggtaa gcttgatgat taccaggaac gaatgaacaa aggggaaagg cttaatcaag 60
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aattacagag gagtttcatg gcactaagtc aagatattca gaaaacaata aagaagacag 180
cacgtcggga gcagcttatg agagaagaag ctgaacagaa acgtttaaaa actgtacttg 240
agctacagta tgttttggac aaattgggag atgatgaagt gcggactgac ctgaaacaag 300
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agctagtaga ccctgaacgg gacatgagct tgaggttgaa tgaacagtat gaacatgcct 420
ccattcacct gtgggacctg ctggaaggga aggaaaaacc tgtatgtgga accacctata 480
aagttctaa 489

<210> 85
<211> 304
<212> DNA
<213> Homo sapien

<400> 85

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agctggagaa ggagaagagc gagatgaaga tggagatcga tgacctcgct tgtaacatgg 180
aggtcatctc caaatctaag ggaaaccttg agaagatgtg ccgcacactg gaggaccaag 240
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agag 304

<210> 86
<211> 296
<212> DNA
<213> Homo sapien

<400> 86

gaaaatcctt cctttgaatg ggaatctcca agcagttgaa ttgggcgaaa aaagaacctc 60
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tccatatgtt gtatgtttcc ttgtcctccc aggggttgtg atcctggcag tccccatagc 180
tctacttgtt tacttttag cttttgatca aaaatcttac ttttattgga gcaatttttcc 240
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<210> 87
<211> 904
<212> DNA
<213> Homo sapien

<400> 87

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tatctgatcg ttctaaaaaa gagttgtccc cggttttaac cagtgaagtt catagtgttc 180
gtgcaggacg gcatcttgct accaaattga atattttagt acagcaacat tttgacttgg 240

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cttcaactac tattacaaat attccaatga aggaagaaca gcatgctaac acatctgcca 300
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attcgcatct aggtggcggc agtcgagaag gctcgtttaa agaaacaata acattaaagt 420
ggtgtacacc aaggacaaat aacattgaat tacactattg tactggagct tatcggattt 480
cacctgtaga tgtaaatagt agaccttcct cctgccttac taatttttct ctaaatggtc 540
gttctgtttt attggaacaa ccacgaaagt caggttctaa agtcattagt catatgctta 600
gtagccatgg aggagagatt tttttgcacg tccttagcag ttctcgatcc attctagaag 660
atccaccttc aattagtgaa ggatgtggag gaagagttac agactaccgg attacagatt 720
ttggtgaatt tatgagggga aaacagatta actccttttc tacaccccag atataaaatc 780
gatggaagtc ttgaggtccc tttggaaccg agccaaaaga tcagttaaaa aaacataccc 840
gttactggcc tatgatttca aaaacccacc atttttaaca tgcaagcggt agttccgtta 900
acca 904

<210> 88
<211> 387
<212> DNA
<213> Homo sapien

<400> 88
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ccgctgcgat tcagaagatg ttggatgaca ataaccatct tattcagtgt ataatggact 180
ctcagaataa aggaaagacc tcagagtgtt ctcagtatca gcagatgttg cacacaaact 240
tggtatacct tgctacaata gcagattcta atcaaaatat gcagtctctt ttaccagcac 300
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ctccacgctc tcacaacatg ccttcaa 387

<210> 89
<211> 481
<212> DNA
<213> Homo sapien

<400> 89
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tgaaccagca agctatacag attcttgaaa agatttctca gccagtggtg gtggtggcca 180
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a 481

<210> 90
<211> 491
<212> DNA
<213> Homo sapien

<400> 90
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taggactgta ccgtacaggg aaatcctact tgatgaacca tctggcagga cagaatcatg 240
gcttccctct gggctccacg gtgcagtctg aaaccaaggg catctggatg tggtgcgtgc 300
cccacccatc caagccaaac cacaccctgg tccttctgga caccgaaggt ctgggcgatg 360

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tggaaaaggg tgaccctaag aatgactcct ggatctttgc cctggctgtg ctcctgtgca 420
gcacctttgt ctacaacagc atgagcacca tcaaccacca agccctggag cagctgcatt 480
atgtgacgga c 491

<210> 91
<211> 488
<212> DNA
<213> Homo sapien

<400> 91
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ctgcttttaa ctctggtaaa gtggatattg ttgccatcaa tgacccttc attgacctca 180
actacatggt ttacatgttc caatatgatt ccacccatgg caaattccat ggcaccgtcg 240
aggctgagaa cgggaagctt gtcatcaatg gaaatcccat caccatcttc caggagcgag 300
atcctccaa aatcaagtgg ggcgatgctg gcgctgagta cgtcgtggag tccactggcg 360
tcttcaccac catggagaag gctggggctc atttgcaggg gggagccaaa agggtcatca 420
tctctgcccc tctgctgatg ccccatgttc gtcatgggtg tgaaccatga gaagtatgac 480
acagcctc 488

<210> 92
<211> 384
<212> DNA
<213> Homo sapien

<400> 92
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acatggttta catgttccaa tatgattcca cccatggcaa attccatggc accgtcgagg 240
ctgagaacgg gaagcttgtc atcaatggaa atcccatcac catcttccag gagcgagatc 300
cctccaaaat caagtggggc gatactggcg ctgagtacgt cgtggagtcc actggcgtct 360
tcaccaccat ggagaaggct gggg 384

<210> 93
<211> 162
<212> PRT
<213> Homo sapien

<400> 93
Lys Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg
1 5 10 15
Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr
20 25 30
Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu
35 40 45
Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln
50 55 60
Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu
65 70 75 80
Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp
85 90 95
Leu Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu
100 105 110Ser Leu Leu Asp Glu
Phe Tyr Lys Leu Val Asp Pro Glu Arg Asp Met

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346
588
585

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```
        115                 120                 125
Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp
    130                 135                 140
Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys Gly Thr Thr Tyr Lys
145                 150                 155                 160
Val Leu
```

<210> 94
<211> 100
<212> PRT
<213> Homo sapien

<400> 94

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Asp Leu Glu Glu Ala Thr Leu Gln His Glu Ala Thr Ala Ala Thr Leu
 1               5                  10                  15
Arg Lys Lys His Ala Asp Ser Val Ala Glu Leu Gly Glu Gln Ile Asp
            20                  25                  30
Asn Leu Gln Arg Val Lys Gln Lys Leu Glu Lys Glu Lys Ser Glu Met
        35                  40                  45
Lys Met Glu Ile Asp Asp Leu Ala Cys Asn Met Glu Val Ile Ser Lys
    50                  55                  60
Ser Lys Gly Asn Leu Glu Lys Met Cys Arg Thr Leu Glu Asp Gln Val
65                  70                  75                  80
Ser Glu Leu Lys Thr Gln Glu Glu Glu Gln Gln Arg Leu Ile Asn Glu
                85                  90                  95
Leu Thr Ala Gln
            100
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<210> 95
<211> 99
<212> PRT
<213> Homo sapien

<400> 95

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

<210> 96
<211> 257
<212> PRT
<213> Homo sapien

3149
589
586

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<400> 96
Val Gln Glu Thr Ile His Glu His Asn Lys Leu Ala Ala Asn Ser Asp
1 5 10 15
His Leu Met Gln Ile Gln Lys Cys Glu Leu Val Leu Ile His Thr Tyr
20 25 30
Pro Val Gly Glu Asp Ser Leu Val Ser Asp Arg Ser Lys Lys Glu Leu
35 40 45
Ser Pro Val Leu Thr Ser Glu Val His Ser Val Arg Ala Gly Arg His
50 55 60
Leu Ala Thr Lys Leu Asn Ile Leu Val Gln Gln His Phe Asp Leu Ala
65 70 75 80
Ser Thr Thr Ile Thr Asn Ile Pro Met Lys Glu Glu Gln His Ala Asn
85 90 95
Thr Ser Ala Asn Tyr Asp Val Glu Leu Leu His His Lys Asp Ala His
100 105 110
Val Asp Phe Leu Lys Ser Gly Asp Ser His Leu Gly Gly Gly Ser Arg
115 120 125
Glu Gly Ser Phe Lys Glu Thr Ile Thr Leu Lys Trp Cys Thr Pro Arg
130 135 140
Thr Asn Asn Ile Glu Leu His Tyr Cys Thr Gly Ala Tyr Arg Ile Ser
145 150 155 160
Pro Val Asp Val Asn Ser Arg Pro Ser Ser Cys Leu Thr Asn Phe Leu
165 170 175
Leu Asn Gly Arg Ser Val Leu Leu Glu Gln Pro Arg Lys Ser Gly Ser
180 185 190
Lys Val Ile Ser His Met Leu Ser Ser His Gly Gly Glu Ile Phe Leu
195 200 205
His Val Leu Ser Ser Ser Arg Ser Ile Leu Glu Asp Pro Pro Ser Ile
210 215 220
Ser Glu Gly Cys Gly Gly Arg Val Thr Asp Tyr Arg Ile Thr Asp Phe
225 230 235 240
Gly Glu Phe Met Arg Gly Lys Gln Ile Asn Ser Phe Ser Thr Pro Gln
245 250 255
Ile

<210> 97
<211> 128
<212> PRT
<213> Homo sapien

<400> 97
Ser Leu Pro Gln Phe Ala Val His Pro Glu Arg Ser Gly Leu Ala Asp
1 5 10 15
Ser Gly Asp Gly Gly Asn Met Ser Val Ala Phe Ala Ala Pro Arg Gln
20 25 30
Arg Gly Lys Gly Glu Ile Thr Pro Ala Ala Ile Gln Lys Met Leu Asp
35 40 45
Asp Asn Asn His Leu Ile Gln Cys Ile Met Asp Ser Gln Asn Lys Gly
50 55 60
Lys Thr Ser Glu Cys Ser Gln Tyr Gln Gln Met Leu His Thr Asn Leu
65 70 75 80
Val Tyr Leu Ala Thr Ile Ala Asp Ser Asn Gln Asn Met Gln Ser Leu
85 90 95
Leu Pro Ala Pro Pro Thr Gln Asn Met Pro Met Gly Pro Gly Gly Met

590
587

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```
            100                 105                 110
Asn Gln Ser Gly Pro Pro Pro Pro Pro Arg Ser His Asn Met Pro Ser
        115                 120                 125

      <210> 98
      <211> 159
      <212> PRT
      <213> Homo sapien

      <400> 98
Phe Leu Asp Leu Arg Cys Tyr Arg Ala Gly Ser Ser Arg Leu Ala Val
 1               5                  10                  15
Ala Met Glu Ser Gly Pro Lys Met Leu Ala Pro Val Cys Leu Val Glu
            20                  25                  30
Asn Asn Asn Glu Gln Leu Leu Val Asn Gln Gln Ala Ile Gln Ile Leu
        35                  40                  45
Glu Lys Ile Ser Gln Pro Val Val Val Val Ala Ile Val Gly Leu Tyr
    50                  55                  60
Arg Thr Gly Lys Ser Tyr Leu Met Asn His Leu Ala Gly Gln Asn His
65                  70                  75                  80
Gly Phe Pro Leu Gly Ser Thr Val Gln Ser Glu Thr Lys Gly Ile Trp
                85                  90                  95
Met Trp Cys Val Pro His Pro Ser Lys Pro Asn His Thr Leu Val Leu
            100                 105                 110
Leu Asp Thr Glu Gly Leu Gly Asp Val Glu Lys Gly Asp Pro Lys Asn
        115                 120                 125
Asp Ser Trp Ile Phe Ala Leu Ala Val Leu Leu Cys Ser Thr Phe Val
    130                 135                 140
Tyr Asn Ser Met Ser Thr Ile Asn His Gln Ala Leu Glu Gln Leu
145                 150                 155

      <210> 99
      <211> 147
      <212> PRT
      <213> Homo sapien

      <400> 99
Met Glu Ser Gly Pro Lys Met Leu Ala Pro Val Cys Leu Val Glu Asn
 1               5                  10                  15
Asn Asn Glu Gln Leu Leu Val Asn Gln Gln Ala Ile Gln Ile Leu Glu
            20                  25                  30
Lys Ile Ser Gln Pro Val Val Val Val Ala Ile Val Gly Leu Tyr Arg
        35                  40                  45
Thr Gly Lys Ser Tyr Leu Met Asn His Leu Ala Gly Gln Asn His Gly
    50                  55                  60
Phe Pro Leu Gly Ser Thr Val Gln Ser Glu Thr Lys Gly Ile Trp Met
65                  70                  75                  80
Trp Cys Val Pro His Pro Ser Lys Pro Asn His Thr Leu Val Leu Leu
                85                  90                  95
Asp Thr Glu Gly Leu Gly Asp Val Glu Lys Gly Asp Pro Lys Asn Asp
            100                 105                 110
Ser Trp Ile Phe Ala Leu Ala Val Leu Leu Cys Ser Thr Phe Val Tyr
        115                 120                 125
Asn Ser Met Ser Thr Ile Asn His Gln Ala Leu Glu Gln Leu His Tyr
    130                 135                 140
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324
591
588

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Val Thr Asp
145

<210> 100
<211> 124
<212> PRT
<213> Homo sapien

<400> 100
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20 25 30
Ile Asn Asp Pro Phe Ile Asp Leu Asn Tyr Met Val Tyr Met Phe Gln
35 40 45
Tyr Asp Ser Thr His Gly Lys Phe His Gly Thr Val Glu Ala Glu Asn
50 55 60
Gly Lys Leu Val Ile Asn Gly Asn Pro Ile Thr Ile Phe Gln Glu Arg
65 70 75 80
Asp Pro Ser Lys Ile Lys Trp Gly Asp Ala Gly Ala Glu Tyr Val Val
85 90 95
Glu Ser Thr Gly Val Phe Thr Thr Met Glu Lys Ala Gly Ala His Leu
100 105 110
Gln Gly Gly Ala Lys Arg Val Ile Ile Ser Ala Pro
115 120

<210> 101
<211> 127
<212> PRT
<213> Homo sapien

<400> 101
Gln Ser Ala Ala Ser Ser Phe Ala Ser Pro Ala Glu Pro His Arg Ser
1 5 10 15
Asp Thr Met Gly Lys Val Lys Val Gly Val Asn Gly Phe Gly Arg Ile
20 25 30
Gly Arg Leu Val Thr Arg Ala Ala Phe Asn Ser Gly Lys Val Asp Ile
35 40 45
Val Ala Ile Asn Asp Pro Phe Ile Asp Leu Asn Tyr Met Val Tyr Met
50 55 60
Phe Gln Tyr Asp Ser Thr His Gly Lys Phe His Gly Thr Val Glu Ala
65 70 75 80
Glu Asn Gly Lys Leu Val Ile Asn Gly Asn Pro Ile Thr Ile Phe Gln
85 90 95
Glu Arg Asp Pro Ser Lys Ile Lys Trp Gly Asp Thr Gly Ala Glu Tyr
100 105 110
Val Val Glu Ser Thr Gly Val Phe Thr Thr Met Glu Lys Ala Gly
115 120 125

<210> 102
<211> 1225
<212> DNA
<213> Homo sapien

<400> 102

322
592
589

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<210> 103
<211> 741
<212> DNA
<213> Homo sapien

<400> 103
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atcctcgatg aagcacataa aataaaaacc tcatctacta agtcagcaat atgtgctcgt 180
gctattcctg caagtaatcg cctcctcctc acaggaaccc caatccagaa taatttacaa 240
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<210> 104
<211> 321
<212> DNA
<213> Homo sapien

<400> 104
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aagaagaagc acgagctgaa gattactcag cagggcacgg acccgcttgt tctcgccgtc 180
cagagcaagg aacaggccga gcagtggctg aaggtgatca aagaagccta cagtggttgt 240
agtggccccg tggattcaga gtgtcctcct ccaccaagct ccccggtgca caaggcagaa 300
ctggagaaga aactgtcttc a 321

323
593
590

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<210> 105
<211> 389
<212> DNA
<213> Homo sapien

<400> 105
cagcactggc cacactataa aattcaggtt cagaaaaaca gggtaagtca cagacagcaa 60
cgcttccagc atttatttte tttgcaccca tgggcaattt gagaaaattt acctttagaa 120
cgaactctgt taaaggtaca gacagtacaa tacttttttat tcagaaggtt tctgcataaa 180
ggtgatagtc ttttgactta atatattatt gtctcctgcc ttgtgtttct ggaatgaatg 240
aaggtcatta tttagaagat aatctgggtt gtatttgtgt cgtcagattg aattttcatt 300
gcacatgcta cttaatgtct ttaccaaata ataacaaagg gaaagaaaac caaatataga 360
tgtataataa ggaaaagctg gcctataga 389

<210> 106
<211> 446
<212> DNA
<213> Homo sapien

<400> 106
gccacatttg ccctggtcat agtttaaaca ccaggtcctg tgtcacatct ttttggtgcc 60
acaagtatca ctccattgtt cagagagtaa tgtattagtt ctgcccaatt cattcttcac 120
ttttatttct tccatttcat tagcatttat atcagctcaa gaagttaagg ttagaaaatt 180
ttccacttca aattttcagt acagaaatgt gctgtgatgt ttgacaagac tatttcatag 240
taagtgagtt aatgtttatt ggcctctgct ctcctctgtg tcagacctag gaagcctgag 300
gattacttag ttgttctgtc tctgggtcca caggcagaat ttggcccatc caaagactgg 360
ccaagtgcca aaaaaaggcc tgattaggcc ctgaaattca gtgaaattct gcctgaagaa 420
acctcttatt gaatttgaaa accata 446

<210> 107
<211> 467
<212> DNA
<213> Homo sapien

<400> 107
ccgccgctgc cgtcgccttc ctgggattgg agtctcgagc tttcttcgtt cgttcgccgg 60
cgggttcgcg cccttctcgc gcctcggggc tgcgaggctg gggaaggggt tggaggggcc 120
tgttgatcgc cgcgtttaag ttgcgctcgg ggcggccatg tcggccggcg aggtcgagcg 180
cctagtgtcg gagctgagcg gcgggaccgg aggggatgag gaggaagagt ggctctatgg 240
cgatgaagat gaagttgaaa ggccagaaga agaaaatgcc agtgctaatc ctccatctgg 300
aattgaagat gaaactgctg aaaatggtgt accaaaaccg aaagtgactg agaccgaaga 360
tgatagtgat agtgacagcg atgatgatga agatgatgtg catgtcacta taggagacat 420
taaaacggga gcaccacagt atgggagtta tggtacagca cctgtaa 467

<210> 108
<211> 491
<212> DNA
<213> Homo sapien

<400> 108
gaaagataca acttccccaa cccaaacccg tttgtggagg acgacatgga taagaatgaa 60
atcgcctctg ttgcgtaccg ttaccgcagg tggaagcttg gagatgatat tgaccttatt 120
gtccgttgtg agcacgatgg cgtcatgact ggagccaacg gggaagtgtc cttcatcaac 180
atcaagacac tcaatgagtg ggattccagg cactgtaatg gcgttgactg gcgtcagaag 240
ctggactctc agcgaggggc tgtcattgcc acggagctga agaacaacag ctacaagttg 300

324
594
591

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gcccggtgga cctgctgtgc tttgctggct ggatctgagt acctcaagct tggttatgtg 360
tctcggtacc acgtgaaaga ctcctcacgc cacgtcatcc taggcaccca gcagttcaag 420
cctaatgagt ttgccagcca gatcaacctg agcgtggaga atgcctgagg cattttacgc 480
tgcgtcattg a 491

<210> 109
<211> 489
<212> DNA
<213> Homo sapien

<400> 109
ctcagatagt actgaaccct ttatcaacta tgtttttca gtctgacaac caaggcggct 60
actaagtgac taaggggcag gtagtataca gtgtggataa gcaggacaaa ggggtgattc 120
acatcccagg caggacagag caggagatca tgagatttca tcactcagga tggcttgtga 180
tttatttttat tttattcttt tttttttttg agatggagtc tcactcttgc ccaggctgga 240
gtgcagtggt gcgatcttgg ctcactgcaa cctctgcctc ctgggttcaa gcagttctcc 300
tgcctcagcc tcccaagtag ctgggattac aggcgtccgc caccatgccc agccaatttt 360
tgtacttttta gtagagatgg ggtttcacca tgttggccag gctggtctcg aactcctgac 420
ctcaggtgat ccactcgcct cggcctccca aagtgctggg attataggca tgcgccacca 480
tgcccgggc 489

<210> 110
<211> 391
<212> DNA
<213> Homo sapien

<400> 110
gcggagtccg ctggctgacc cgagcgctgg tctccgccgg gaaccctggg gcatggagag 60
gtctgagtac ctcggccgcg gcgcacgctg catcgcggag ccaggctgcc gctgtcccag 120
tggagttcca ggagcaccac ctgagtgagg tgcagaatat ggcatctgag gagaagctgg 180
agcaggtgct gagttccatg aaggagaaca aagtggccat cattggaaag attcataccc 240
cgatggagta taaggggggag ctagcctcct atgatatgcg gctgaggcgt aagttggact 300
tatttgccaa cgtaatccat gtgaagtcac ttcctgggta tatgactcgg cacaacaatc 360
tagacctggt gatcattcga gagcagacag a 391

<210> 111
<211> 172
<212> PRT
<213> Homo sapien

<400> 111
Met Met Lys Leu Lys Ser Asn Gln Thr Arg Thr Tyr Asp Gly Asp Gly
1 5 10 15
Tyr Lys Lys Arg Ala Ala Cys Leu Cys Phe Arg Ser Glu Ser Glu Glu
20 25 30
Glu Val Leu Leu Val Ser Ser Ser Arg His Pro Asp Arg Trp Ile Val
35 40 45
Pro Gly Gly Gly Met Glu Pro Glu Glu Glu Pro Ser Val Ala Ala Val
50 55 60
Arg Glu Val Cys Glu Glu Ala Gly Val Lys Gly Thr Leu Gly Arg Leu
65 70 75 80
Val Gly Ile Phe Glu Asn Gln Glu Arg Lys His Arg Thr Tyr Val Tyr
85 90 95
Val Leu Ile Val Thr Glu Val Leu Glu Asp Trp Glu Asp Ser Val Asn
100 105 110

330
593
592

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Ile Gly Arg Lys Arg Glu Trp Phe Lys Ile Glu Asp Ala Ile Lys Val
115 120 125
Leu Gln Tyr His Lys Pro Val Gln Ala Ser Tyr Phe Glu Thr Leu Arg
130 135 140
Gln Gly Tyr Ser Ala Asn Asn Gly Thr Pro Val Val Ala Thr Thr Tyr
145 150 155 160
Ser Val Ser Ala Gln Ser Ser Met Ser Gly Ile Arg
165 170

<210> 112
<211> 247
<212> PRT
<213> Homo sapien

<400> 112
Arg Asn Leu Asn Arg Ile Gln Gln Arg Asn Gly Val Ile Ile Thr Thr
1 5 10 15
Tyr Gln Met Leu Ile Asn Asn Trp Gln Gln Leu Ser Ser Phe Arg Gly
20 25 30
Gln Glu Phe Val Trp Asp Tyr Val Ile Leu Asp Glu Ala His Lys Ile
35 40 45
Lys Thr Ser Ser Thr Lys Ser Ala Ile Cys Ala Arg Ala Ile Pro Ala
50 55 60
Ser Asn Arg Leu Leu Leu Thr Gly Thr Pro Ile Gln Asn Asn Leu Gln
65 70 75 80
Glu Leu Trp Ser Leu Phe Asp Phe Ala Cys Gln Gly Ser Leu Leu Gly
85 90 95
Thr Leu Lys Thr Phe Lys Met Glu Tyr Glu Asn Pro Ile Thr Arg Ala
100 105 110
Arg Glu Lys Asp Ala Thr Pro Gly Glu Lys Ala Leu Gly Phe Lys Ile
115 120 125
Ser Glu Asn Leu Met Ala Ile Ile Lys Pro Tyr Phe Leu Arg Arg Thr
130 135 140
Lys Glu Asp Val Gln Lys Lys Lys Ser Ser Asn Pro Glu Ala Arg Leu
145 150 155 160
Asn Glu Lys Asn Pro Asp Val Asp Ala Ile Cys Glu Met Pro Ser Leu
165 170 175
Ser Arg Arg Asn Asp Leu Ile Ile Trp Ile Arg Leu Val Pro Leu Gln
180 185 190
Glu Glu Ile Tyr Arg Lys Phe Val Ser Leu Asp His Ile Lys Glu Leu
195 200 205
Leu Met Glu Thr Arg Ser Pro Leu Ala Glu Leu Gly Val Leu Lys Lys
210 215 220
Leu Cys Asp His Pro Arg Leu Leu Ser Ala Arg Ala Cys Cys Leu Leu
225 230 235 240
Asn Leu Gly Thr Phe Ser Ala
245

<210> 113
<211> 107
<212> PRT
<213> Homo sapien

<400> 113
Leu Leu Cys Val Ile Lys Asp Thr Lys Leu Leu Cys Tyr Lys Ser Ser

326
548
543

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

      <210> 114
      <211> 155
      <212> PRT
      <213> Homo sapien

      <400> 114
Glu Arg Tyr Asn Phe Pro Asn Pro Asn Pro Phe Val Glu Asp Asp Met
 1               5                  10                  15
Asp Lys Asn Glu Ile Ala Ser Val Ala Tyr Arg Tyr Arg Arg Trp Lys
            20                  25                  30
Leu Gly Asp Asp Ile Asp Leu Ile Val Arg Cys Glu His Asp Gly Val
        35                  40                  45
Met Thr Gly Ala Asn Gly Glu Val Ser Phe Ile Asn Ile Lys Thr Leu
    50                  55                  60
Asn Glu Trp Asp Ser Arg His Cys Asn Gly Val Asp Trp Arg Gln Lys
65                  70                  75                  80
Leu Asp Ser Gln Arg Gly Ala Val Ile Ala Thr Glu Leu Lys Asn Asn
                85                  90                  95
Ser Tyr Lys Leu Ala Arg Trp Thr Cys Cys Ala Leu Leu Ala Gly Ser
            100                 105                 110
Glu Tyr Leu Lys Leu Gly Tyr Val Ser Arg Tyr His Val Lys Asp Ser
        115                 120                 125
Ser Arg His Val Ile Leu Gly Thr Gln Gln Phe Lys Pro Asn Glu Phe
    130                 135                 140
Ala Ser Gln Ile Asn Leu Ser Val Glu Asn Ala
145                 150                 155

      <210> 115
      <211> 129
      <212> PRT
      <213> Homo sapien

      <400> 115
Gly Val Arg Trp Leu Thr Arg Ala Leu Val Ser Ala Gly Asn Pro Gly
 1               5                  10                  15
Ala Trp Arg Gly Leu Ser Thr Ser Ala Ala Ala His Ala Ala Ser Arg
            20                  25                  30
Ser Gln Ala Ala Ala Val Pro Val Glu Phe Gln Glu His His Leu Ser
        35                  40                  45
Glu Val Gln Asn Met Ala Ser Glu Glu Lys Leu Glu Gln Val Leu Ser
    50                  55                  60
```

Ser Met Lys Glu Asn Lys Val Ala Ile Ile Gly Lys Ile His Thr Pro
65 70 75 80
Met Glu Tyr Lys Gly Glu Leu Ala Ser Tyr Asp Met Arg Leu Arg Arg
85 90 95
Lys Leu Asp Leu Phe Ala Asn Val Ile His Val Lys Ser Leu Pro Gly
100 105 110
Tyr Met Thr Arg His Asn Asn Leu Asp Leu Val Ile Ile Arg Glu Gln
115 120 125
Thr

<210> 116
<211> 550
<212> DNA
<213> Homo sapien

<400> 116
gaattcggca ccagcctcag agccccccag cccggctacc acccccctgcg gaaaggtacc 60
catctgcatt cctgcccgtc gggacctggt ggacagtcca gcctccttgg cctctagcct 120
tggctcaccg ctgcctagag ccaaggagct catcctgaat gaccttcccg ccagcactcc 180
tgcctccaaa tcctgtgact cctccccgcc ccaggacgct tccacccccа ggcccagctc 240
ggccagtcac ctctgccagc ttgctgccaa gccagcacct tccacggaca gcgtcgccct 300
gaggagcccc ctgactctgt ccagtcccct caccacgtcc ttcagcctgg gctcccacag 360
cactctcaac ggagacctct ccgtgcccag ctcctacgtc agcctccacc tgtccccccа 420
ggtcagcagc tctgtggtgt acggacgctc ccccgtgatg gcatttgagt ctcatcccca 480
tctccgaggg tcatccgtct cttcctccct acccagcatc cctgggggaa agccggccta 540
ctccttccac 550

<210> 117
<211> 154
<212> DNA
<213> Homo sapien

<400> 117
ttctgaggga aagccgagtg gagtgggcga cccggcggcg gtgacaatga gttttcttgg 60
aggcttttt ggtcccattt gtgagattga tgttgccctt aatgatgggg aaaccaggaa 120
aatggcagaa atgaaaactg aggatggcaa agta 154

<210> 118
<211> 449
<212> DNA
<213> Homo sapien

<400> 118
gaattcggca ccagggcccg cagcccgagt gtcgccgcca tggcttcgcc gcagctctgc 60
cgcgcgctgg tgtcggcgca atgggtggcg gaggcgctgc gggccccgcg cgctgggcag 120
cctctgcagc tgctggacgc ctcctggtac ctgccgaagc tggggcgcga cgcgcgacgc 180
gagttcgagg agcgccacat cccgggcgcc gctttcttcg acatcgacca gtgcagcgac 240
cgcacctcgc cctacgacca catgctgccc ggggccgagc atttcgcgga gtacgcaggc 300
cgcctgggcg tgggcgcggc cacccacgtc gtgatctacg acgccagcga ccagggcctc 360
tactccgccc cgcgcgtctg gtggatgttc cgcgccttcg gccaccacgc cgtgtcactg 420
cttgatggcg gcctccgcca ctggctgcg 449

<210> 119
<211> 642

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321
598
595

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<212> DNA
<213> Homo sapien

<400> 119
gaattcggca cgagcagtaa cccgaccgcc gctggtcttc gctggacacc atgaatcaca 60
ctgtccaaac cttcttctct cctgtcaaca gtggccagcc ccccaactat gagatgctca 120
aggaggagca cgaggtggct gtgctggggg cgccccacaa ccctgctccc ccgacgtcca 180
ccgtgatcca catccgcagc gagacctccg tgcccgacca tgtcgtctgg tccctgttca 240
acaccctctt catgaacccc tgctgcctgg gcttcatagc attcgcctac tccgtgaagt 300
ctagggacag gaagatggtt ggcgacgtga ccggggccca ggcctatgcc tccaccgcca 360
agtgcctgaa catctgggcc ctgattctgg gcatcctcat gaccattctg ctcatcgtca 420
tcccagtgct gatcttccag gcctatggat agatcaggag gcatcactga ggccaggagc 480
tctgcccatg acctgtatcc cacgtactcc aacttccatt cctcgccctg ccccccggagc 540
cgagtcctgt atcagccctt tatcctcaca cgcttttcta caatggcatt caataaagtg 600
cacgtgtttc tggtgaaaaa aaaaaaaaaa aaaaaactcg ag 642

<210> 120
<211> 603
<212> DNA
<213> Homo sapien

<400> 120
gaattcggca cgagccacaa cagccactac gactgcatcc actggatcca cggccacccc 60
gtcctccacc ccgggaacag ctcccccctcc caaagtgctg accagcccgg ccaccacacc 120
catgtccacc atgtccacaa tccacacctc ctctactcca gagaccaccc acacctccac 180
agtgctgacc accacagcca ccatgacaag ggccaccaat tccacggcca cacccctcctc 240
cactctgggg acgacccgga tcctcactga gctgaccaca acagccacta caactgcagc 300
cactggatcc acggccaccc tgtcctccac cccagggacc acctggatcc tcacagagcc 360
gagcactata gccaccgtga tggtgcccac cggttccacg gccaccgcct cctccactct 420
gggaacagct cacaccccca aagtggtgac caccatggcc actatgccca cagccactgc 480
ctccacggtt cccagctcgt ccaccgtggg gaccacccgc acccctgcag tgctccccag 540
cagcctgcca accttcagcg tgtccactgt gtcctcctca gtcctcacca ccctgagacc 600
cac 603

<210> 121
<211> 178
<212> PRT
<213> Homo sapien

<400> 121
Ser Glu Pro Pro Ser Pro Ala Thr Thr Pro Cys Gly Lys Val Pro Ile
1 5 10 15
Cys Ile Pro Ala Arg Arg Asp Leu Val Asp Ser Pro Ala Ser Leu Ala
20 25 30
Ser Ser Leu Gly Ser Pro Leu Pro Arg Ala Lys Glu Leu Ile Leu Asn
35 40 45
Asp Leu Pro Ala Ser Thr Pro Ala Ser Lys Ser Cys Asp Ser Ser Pro
50 55 60
Pro Gln Asp Ala Ser Thr Pro Arg Pro Ser Ser Ala Ser His Leu Cys
65 70 75 80
Gln Leu Ala Ala Lys Pro Ala Pro Ser Thr Asp Ser Val Ala Leu Arg
85 90 95
Ser Pro Leu Thr Leu Ser Ser Pro Phe Thr Thr Ser Phe Ser Leu Gly
100 105 110
Ser His Ser Thr Leu Asn Gly Asp Leu Ser Val Pro Ser Ser Tyr Val

596

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```
        115                 120                 125
Ser Leu His Leu Ser Pro Gln Val Ser Ser Ser Val Val Tyr Gly Arg
    130                 135                 140
Ser Pro Val Met Ala Phe Glu Ser His Pro His Leu Arg Gly Ser Ser
145                 150                 155                 160
Val Ser Ser Ser Leu Pro Ser Ile Pro Gly Gly Lys Pro Ala Tyr Ser
                165                 170                 175
Phe His
```

<210> 122
<211> 36
<212> PRT
<213> Homo sapien

<400> 122

```
Met Ser Phe Leu Gly Gly Phe Phe Gly Pro Ile Cys Glu Ile Asp Val
 1               5                  10                  15
Ala Leu Asn Asp Gly Glu Thr Arg Lys Met Ala Glu Met Lys Thr Glu
            20                  25                  30
Asp Gly Lys Val
        35
```

<210> 123
<211> 136
<212> PRT
<213> Homo sapien

<400> 123

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

<210> 124
<211> 133
<212> PRT
<213> Homo sapien

<400> 124

```
Met Asn His Thr Val Gln Thr Phe Phe Ser Pro Val Asn Ser Gly Gln
```

330
508
597

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

      <210> 125
      <211> 195
      <212> PRT
      <213> Homo sapien

      <400> 125
Thr Thr Ala Thr Thr Thr Ala Ser Thr Gly Ser Thr Ala Thr Pro Ser
 1               5                  10                  15
Ser Thr Pro Gly Thr Ala Pro Pro Pro Lys Val Leu Thr Ser Pro Ala
            20                  25                  30
Thr Thr Pro Met Ser Thr Met Ser Thr Ile His Thr Ser Ser Thr Pro
        35                  40                  45
Glu Thr Thr His Thr Ser Thr Val Leu Thr Thr Thr Ala Thr Met Thr
    50                  55                  60
Arg Ala Thr Asn Ser Thr Ala Thr Pro Ser Ser Thr Leu Gly Thr Thr
65                  70                  75                  80
Arg Ile Leu Thr Glu Leu Thr Thr Thr Ala Thr Thr Thr Ala Ala Thr
                85                  90                  95
Gly Ser Thr Ala Thr Leu Ser Ser Thr Pro Gly Thr Thr Trp Ile Leu
            100                 105                 110
Thr Glu Pro Ser Thr Ile Ala Thr Val Met Val Pro Thr Gly Ser Thr
        115                 120                 125
Ala Thr Ala Ser Ser Thr Leu Gly Thr Ala His Thr Pro Lys Val Val
    130                 135                 140
Thr Thr Met Ala Thr Met Pro Thr Ala Thr Ala Ser Thr Val Pro Ser
145                 150                 155                 160
Ser Ser Thr Val Gly Thr Thr Arg Thr Pro Ala Val Leu Pro Ser Ser
                165                 170                 175
Leu Pro Thr Phe Ser Val Ser Thr Val Ser Ser Ser Val Leu Thr Thr
            180                 185                 190
Leu Arg Pro
        195

      <210> 126
      <211> 509
      <212> DNA
      <213> Homo sapien
```

337
501
598

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<400> 126
gaattcggca cgagccaagt acccccctgag gaatctgcag cctgcatctg agtacaccgt 60
atccctcgtg gccataaagg gcaaccaaga gagccccaaa gccactggag tctttaccac 120
actgcagcct gggagctcta ttccacctta caacaccgag gtgactgaga ccaccattgt 180
gatcacatgg acgcctgctc caagaattgg ttttaagctg ggtgtacgac caagccaggg 240
aggagaggca ccacgagaag tgacttcaga ctcaggaagc atcgttgtgt ccggcttgac 300
tccaggagta gaatacgtct acaccatcca agtcctgaga gatggacagg aaagagatgc 360
gccaattgta aacaaagtgg tgacaccatt gtctccacca acaaacttgc atctggaggc 420
aaaccctgac actggagtgc tcacagtctc ctggagagga gcaccacccc agacattact 480
gggtatagaa ttaccacaac ccctacaaa 509

<210> 127
<211> 500
<212> DNA
<213> Homo sapien

<400> 127
gaattcggca cgagccactg atgtccgggg agtcagccag gagcttgggg aagggaagcg 60
cgccccgggg gccggtcccg gagggctcga tccgcatcta cagcatgagg ttctgcccgt 120
ttgctgagag gacgcgtcta gtcctgaagg ccaagggaat caggcatgaa gtcatcaata 180
tcaacctgaa aaataagcct gagtggttct ttaagaaaaa tccctttggt ctggtgccag 240
ttctggaaaa cagtcagggt cagctgatct acgagtctgc catcacctgt gagtacctgg 300
atgaagcata cccagggaag aagctgttgc cggatgaccc ctatgagaaa gcttgccaga 360
agatgatctt agagttgttt tctaaggtgc catccttggt aggaagcttt attagaagcc 420
aaaataaaga agactatgct ggcctaaaag aagaatttcg taaagaattt accaagctag 480
aggaggttct gactaataag 500

<210> 128
<211> 500
<212> DNA
<213> Homo sapien

<400> 128
agctttcctc tgctgccgct cggtcacgct tgtgcccgaa ggaggaaaca gtgacagacc 60
tggagactgc agttctctat ccttcacaca gctctttcac catgcctgga tcacttcctt 120
tgaatgcaga agcttgctgg ccaaaagatg tgggaattgt tgcccttgag atctattttc 180
cttctcaata tgttgatcaa gcagagttgg aaaaatatga tggtgtagat gctggaaagt 240
ataccattgg cttgggccag gccaagatgg gcttctgcac agatagagaa gatattaact 300
ctctttgcat gactgtggtt cagaatctta tggagagaaa taacctttcc tatgattgca 360
ttgggcggct ggaagttgga acagagacaa tcatcgacaa atcaaagtct gtgaagacta 420
atttgatgca gctgtttgaa gagtctggga atacagatat agaaggaatc gacacaacta 480
atgcatgcta tggaggcaca 500

<210> 129
<211> 497
<212> DNA
<213> Homo sapien

<400> 129
gaattcggca cgagcagagg tctccagagc cttctctctc ctgtgcaaaa tggcaactct 60
taaggaaaaa ctcattgcac cagttgcgga agaagaggca acagttccaa acaataagat 120
cactgtagtg ggtgttggac aagttggtat ggcgtgtgct atcagcattc tgggaaagtc 180
tctggctgat gaacttgctc ttgtggatgt tttggaagat aagcttaaag gagaaatgat 240
ggatctgcag catgggagct tatttcttca gacacctaaa attgtggcag ataaagatta 300

ttctgtgacc gccaattcta agattgtagt ggtaactgca ggagtccgtc agcaagaagg 360
ggagagtcgg ctcaatctgg tgcagagaaa tgttaatgtc ttcaaattca ttattcctca 420
gatcgtcaag tacagtcctg attgcatcat aattgtggtt tccaacccag tggacattct 480
tacgtatgtt acctgga 497

<210> 130
<211> 383
<212> DNA
<213> Homo sapien

<400> 130
gaattcggca cgagggccgc ggctgccgac tgggtcccct gccgctgtcg ccaccatggc 60
tccgcaccgc cccgcgcccg cgctgctttg cgcgctgtcc ctggcgctgt gcgcgctgtc 120
gctgcccgtc cgcgcggcca ctgcgtcgcg gggggcgtcc caggcggggg cgccccaggg 180
gcgggtgccc gaggcgcggc ccaacagcat ggtggtggaa caccccgagt tcctcaaggc 240
agggaaggag cctggcctgc agatctggcg tgtggagaaa gttcgatctg gtggccccgtg 300
cccaccaacc tttatggaga cttcttcacg ggcgacgcct acgtcatcct gaagacagtg 360
cagcttaaga acggaaaatc ttg 383

<210> 131
<211> 509
<212> DNA
<213> Homo sapien

<400> 131
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<210> 132
<211> 357
<212> DNA
<213> Homo sapien

<400> 132
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gacgatttgt cttctccctg gacacctctg tcagcacggc atatctgcag atcagca 357

<210> 133
<211> 468
<212> DNA
<213> Homo sapien

<400> 133
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352
592
599

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acgcctacga cggcaaggat tacatcgccc tgaacgagga cctgcgct 468

<210> 134
<211> 214
<212> DNA
<213> Homo sapien

<400> 134
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ccttccggag cgggggcagt cgtagcttca gcaccgcctc tgccatcacc ccgtctgtct 180
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<210> 135
<211> 355
<212> DNA
<213> Homo sapien

<400> 135
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aagaagcgga cggagctgtt cattgccgcc gagggcattc acacgggcca gtttgtgtat 300
tgcggcaaga aggcccagct caacattggc aatgtgctcc ctgtgggcac catgc 355

<210> 136
<211> 242
<212> DNA
<213> Homo sapien

<400> 136
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<210> 137
<211> 424
<212> DNA
<213> Homo sapien

<400> 137
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gccaggagca agccgagagc cagccggccg gcgcactccg actccgagca gtctctgtcc 120
ttcgacccga gccccgcgcc ctttccggga cccctgcccc gcgggcagcg ctgccaacct 180
gccggccatg gagaccccgt cccagcggcg cgccacccgc agcggggcgc aggccagctc 240
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337/69/601

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ggcc 424

<210> 138
<211> 448
<212> DNA
<213> Homo sapien

<400> 138
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tcaaaacatt gcgctactgt gcaggttg 448

<210> 139
<211> 510
<212> DNA
<213> Homo sapien

<400> 139
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ggacttcttc atcgacctgc ggctacccta 510

<210> 140
<211> 360
<212> DNA
<213> Homo sapien

<400> 140
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<210> 141
<211> 483
<212> DNA
<213> Homo sapien

<400> 141
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345
505
602

09370838 - 08009999

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<210> 142
<211> 500
<212> DNA
<213> Homo sapien

<400> 142
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<210> 143
<211> 400
<212> DNA
<213> Homo sapien

<400> 143
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gtttgcacaa catttgcatc tacttgggac aaagcaagaa 400

<210> 144
<211> 243
<212> DNA
<213> Homo sapien

<400> 144
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ctg 243

<210> 145
<211> 450
<212> DNA
<213> Homo sapien

356
606
603

6660080 08037E38

<400> 145
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<210> 146
<211> 451
<212> DNA
<213> Homo sapien

<400> 146
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aaccgtgaga acgcgtccag caaccacgac c 451

<210> 147
<211> 400
<212> DNA
<213> Homo sapien

<400> 147
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<210> 148
<211> 503
<212> DNA
<213> Homo sapien

<400> 148
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337
597
604

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<210> 149
<211> 1061
<212> DNA
<213> Homo sapien

<400> 149
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<211> 781
<212> DNA
<213> Homo sapien

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<211> 3275
<212> DNA
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337
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606

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<211> 2179
<212> DNA
<213> Homo sapien

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gggtgccagc agttgcctgg gtggaggagg cggtggccgt ggatccggtg ggcaccgtca 2100

2114
5/4
611

09370838.0800999

cgggagtact tcta 2114

<210> 159
<211> 278
<212> DNA
<213> Homo sapien

<400> 159
gaattcggca caggtaactt tgcctggggt atttaaaaaa aaaaaaaaaa aaaaaaaaag 60
tcaaatatct gagtactaat ttcctgaaaa gtatgttccg atagatgaac agatcattaa 120
tgcagaatga gaatcactcc taaaataggt aatggtaaaa attaaattga caattacctc 180
tctctatgca gaaggaaata tcacctatat gacatcatca tcatctattg atacttgctg 240
gcagtgctaa taatggtttt aatgccaatt tgtaagaa 278

<210> 160
<211> 848
<212> DNA
<213> Homo sapien

<400> 160
gaattcggca cgagccccag aggagctcgg cctgcgctgc gccacgatgt ccggggagtc 60
agccaggagc ttggggaagg gaagcgcgcc cccggggccg gtcccggagg gctcgatccg 120
catctacagc atgaggttct gcccgtttgc tgagaggacg cgtctagtcc tgaaggccaa 180
gggaatcagg catgaagtca tcaatatcaa cctgaaaaat aagcctgagt ggttctttaa 240
gaaaaatccc tttggtctgg tgccagttct ggaaaacagt cagggtcagc tgatctacga 300
gtctgccatc acctgtgagt acctggatga agcataccca gggaagaagc tgttgccgga 360
tgacccctat gagaaagctt gccagaagat gatcttagag ttgttttcta aggtgccatc 420
cttggtagga agctttatta gaagccaaaa taaagaagac tatgctggcc taaaagaaga 480
atttcgtaaa gaatttacca agctagagga ggttctgact aataagaaga cgaccttctt 540
tggtggcaat tctatctcta tgattgatta cctcatctgg ccctggtttg aacggctgga 600
agcaatgaag ttaaatgagt gtgtagacca cactccaaaa ctgaaactgt ggatggcagc 660
catgaaggaa gatcccacag tctcagccct gcttactagt gagaaagact ggcaaggttt 720
cctagagctc tacttacaga acagccctga ggcctgtgac tatgggctct gaaggggggca 780
ggagtcagca ataaagctat gtctgatatt ttccttcact aaaaaaaaaa aaaaaaaaaa 840
aactcgag 848

<210> 161
<211> 432
<212> DNA
<213> Homo sapien

<400> 161
gaattcggca cgagggcaga ccaagatcct ggaggaggac ctggaacaga tcaagctgtc 60
cttgagagag cgaggccggg agctgaccac tcagaggcag ctgatgcagg aacgggcaga 120
ggaagggaag ggcccaagta aagcacagcg cgggagccta gagcacatga agctgatcct 180
gcgtgataag gagaaggagg tggaatgtca gcaggagcat atccatgaac tccaggagct 240
caaagaccag ctggagcagc agctccaggg cctgcacagg aaggtaggtg agaccagcct 300
cctcctgtcc cagcgagagc aggaaatagt ggtcctgcag cagcaactgc aggaagccag 360
ggaacaaggg gagctgaagg agcagtcact tcagagtcaa ctggatgagg cccagagagc 420
cctagcccag ag 432

<210> 162
<211> 433
<212> DNA
<213> Homo sapien

545
6/5
612

6660080 '08080990

<400> 162

gattcggcac gagccggagc tgggttgctc ctgctcccgt ctccaagtcc tggtacctcc 60
ttcaagctgg gagagggctc tagtccctgg ttctgaacac tctggggttc tcgggtgcag 120
gccgccatga gcaaacggaa ggcgccgcag gagactctca acgggggaat caccgacatg 180
ctcacagaac tcgcaaactt tgagaagaac gtgagccaag ctatccacaa gtacaatgct 240
tacagaaaag cagcatctgt tatagcaaaa tacccacaca aaataaagag tggagctgaa 300
gctaagaaat tgcctggagt aggaacaaaa attgctgaaa agattgatga gtttttagca 360
actggaaaat tacgtaaact ggaaaagatt cggcaggatg atacgagttc atccatcaat 420
ttcctgactc gag 433

<210> 163
<211> 432
<212> DNA
<213> Homo sapien

<400> 163

gaattcggca ccagatgagg ccaacgaggt gacggacagc gcgtacatgg gctccgagag 60
cacctacagt gagtgtgaga ccttcacgga cgaggacacc agcaccctgg tgcaccctga 120
gctgcaacct gaaggggacg cagacagtgc cggcggctcg gccgtgccct ctgagtgcct 180
ggacgccatg gaggagcccg accatggtgc cctgctgctg ctcccaggca ggcctcaccc 240
ccatggccag tctgtcatca cggtgatcgg gggcgaggag cactttgagg actacggtga 300
aggcagtgag gcggagctgt ccccagagac cctatgcaac gggcagctgg gctgcagtga 360
ccccgctttc ctcacgccca gtccgacaaa gcggctctcc agcaagaagg tggcaaggta 420
cctgcaccag tc 432

<210> 164
<211> 395
<212> DNA
<213> Homo sapien

<400> 164

gacacttgaa tcatgggtga cgttaaaaat tttctgtatg cctggtgtgg caaaaggaag 60
atgaccccat cctatgaaat tagagcagtg gggaacaaaa acaggcagaa attcatgtgt 120
gaggttcagg tggaaggtta taattacact ggcatgggaa attccaccaa taaaaaagat 180
gcacaaagca atgctgccag agactttgtt aactatttgg ttcgaataaa tgaaataaag 240
agtgaagaag ttccagcttt tggggtagca tctccgcccc cacttactga tactcctgac 300
actacagcaa atgctgaagg catcttgttg acatcgaata tgactttgat aataaatacc 360
ggttcctgaa aaaaaaaaaa aaaaaaaaac tcgag 395

<210> 165
<211> 503
<212> DNA
<213> Homo sapien

<400> 165

gaattcggca ccaggaacgc tcggtgagag gcggaggagc ggtaactacc ccggttgcgc 60
acagctcggc gctccttccc gctcccctcac acaccggcct cagcccgcac cggcagtaga 120
agatggtgaa agaaacaact tactacgatg ttttgggggt caaacccaat gctactcagg 180
aagaattgaa aaaggcttat aggaaactgg ccttgaagta ccatcctgat aagaacccaa 240
atgaaggaga gaagtttaaa cagatttctc aagcttacga agttctctct gatgcaaaga 300
aaagggaatt atatgacaaa ggaggagaac aggcaattaa agagggtgga gcaggtggcg 360
gttttggctc ccccatggac atctttgata tgtttttgg aggaggagga aggatgcaga 420
gagaaaggag aggtaaaaat gttgtacatc agctctcagt aaccctagaa gacttatata 480
atggtgcaac aagaaaactg gct 503

4/8
5/8
613

09370838.0860930

<210> 166
<211> 893
<212> DNA
<213> Homo sapien

<400> 166
gaattcggca cgagaggaac ttctcttgac gagaagagag accaaggagg ccaagcaggg 60
gctgggccag aggtgccaac atggggaaac tgaggctcgg ctcggaaggg tgagagtgag 120
actacatctc aaaaaaaaaa aaaaaaaaaa aaaagaaaga aaagaaaaga aaaaagaaag 180
aacggaagta gttgtaggta gtggtatggt ggtatgagtc tgttttctgt tacttataac 240
aacaacaaca acaaaaaacg ctgaaactgg gtaatttata aagaaaagga aaaaaagcag 300
aaaaaaatca ggaagaagag aaaggaaaag aagacaaata aatgaaattt atgtattaca 360
gttctgaagg ctgagacatc ccaggtcaag ggtccacact tggcgagggc tttcttgctg 420
gtggagactc tttgtggagt cctgggacag tgcagaagga tcacgcctcc ctaccgctcc 480
aagcccagcc ctcagccatg gcatgccccc tggatcaggc cattggcctc ctcgtggcca 540
tcttccacaa gtactccggc agggagggtg acaagcacac cctgagcaag aaggagctga 600
aggagctgat ccagaaggag ctcaccattg gctcgaagct gcaggatgct gaaattgcaa 660
ggctgatgga agacttggac cggaacaagg accaggaggt gaacttccag gagtatgtca 720
ccttcctggg ggccttggct ttgatctaca atgaagccct caagggctga aaataaatag 780
ggaagatgga gacaccctct gggggtcctc tctgagtcaa atccagtggt gggtaattgt 840
acaataaatt ttttttggtc aaatttaaaa aaaaaaaaaa aaaaaaactc gag 893

<210> 167
<211> 549
<212> DNA
<213> Homo sapien

<400> 167
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gccaggagca agccgagagc cagccggccg gcgcactccg actccgagca gtctctgtcc 120
ttcgacccga gccccgcgcc ctttccggga cccctgcccc gcgggcagcg ctgccaacct 180
gccggccatg gagaccccgt cccagcggcg cgccacccgc agcggggcgc aggccagctc 240
cactccgctg tcgcccaccc gcatcacccg gctgcaggag aaggaggacc tgcaggagct 300
caatgatcgc ttggcggtct acatcgaccg tgtgcgctcg ctggaaacgg agaacgcagg 360
gctgcgcctt cgcatcaccg agtctgaaga ggtggtcagc cgcgaggtgt ccggcatcaa 420
ggccgcctac gaggccgagc tcggggatgc ccgcaagacc cttgactcag tagccaagga 480
gcgcgcccgc ctgcagctgg agctgagcaa agtgcgtgaa gagtttaagg agctgaaagc 540
gcgcaatac 549

<210> 168
<211> 547
<212> DNA
<213> Homo sapien

<400> 168
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tcaaaatgga ggaagagagc ggcgcgcccg gcgtgccgag cggcaacggg gctccgggcc 120
ctaagggtga aggagaacga cctgctcaga atgagaagag gaaggagaaa aacataaaaa 180
gaggaggcaa tcgctttgag ccatatgcca atccaactaa aagatacaga gccttcatta 240
caaacatacc ttttgatgtg aaatggcagt cacttaaaga cctggttaaa gaaaaagttg 300
gtgaggtaac atacgtggag ctcttaatgg acgctgaagg aaagtcaagg ggatgtgctg 360
ttgttgaatt caagatggaa gagagcatga aaaaagctgc ggaagtccta aacaagcata 420
gtctgagcgg aagaccactg aaagtcaaag aagatcctga tggtgaacat gccaggagag 480
caatgcaaaa ggctggaaga cttggaagca cagtatttgt agcaaatctg gattataaag 540

ttggctg 547

<210> 169
<211> 547
<212> DNA
<213> Homo sapien

<400> 169
gaattcggca ccaggagtcc gactgtgctc gctgctcagc gccgcacccg gaagatgagg 60
ctcgccgtgg gagccctgct ggtctgcgcc gtcctggggc tgtgtctggc tgtccctgat 120
aaaactgtga gatggtgtgc agtgtcggag catgaggcca ctaagtgcca gagtttccgc 180
gaccatatga aaagcgtcat tccatccgat ggtcccagtg ttgcttgtgt gaagaaagcc 240
tcctaccttg attgcatcag ggccattgcg gcaaacgaag cggatgctgt gacactggat 300
gcaggtttgg tgtatgatgc ttacctggct cccaataacc tgaagcctgt ggtggcagag 360
ttctatgggt caaaagagga tccacagact ttctattatg ctgttgctgt ggtgaagaag 420
gatagtggct tccagatgaa ccagcttcga ggcaagaagt cctgccacac gggtctaggc 480
aggtccgctg ggtggaacat ccccataggc ttactttact gtgacttacc tgagccacgt 540
aaacctc 547

<210> 170
<211> 838
<212> DNA
<213> Homo sapien

<400> 170
gaattcggca ccagaggagc tcggcctgcg ctgcgccacg atgtccgggg agtcagccag 60
gagcttgggg aagggaagcg cgccccggg gccggtcccg gagggctcga tccgcatcta 120
cagcatgagg ttctgcccgt ttgctgagag gacgcgtcta gtcctgaagg ccaagggaat 180
caggcatgaa gtcatcaata tcaacctgaa aaataagcct gagtggttct ttaagaaaaa 240
tccctttggt ctggtgccag ttctggaaaa cagtcagggt cagctgatct acgagtctgc 300
catcacctgt gagtacctgg atgaagcata cccagggaag aagctgttgc cggatgaccc 360
ctatgagaaa gcttgccaga agatgatctt agagttgttt tctaaggtgc catccttggt 420
aggaagcttt attgaagcc aaaataaaga agactatgat ggcctaaaag aagaatttcg 480
taaagaattt accaagctag aggaggttct gactaataag aagacgacct tctttggtgg 540
caattctatc tctatgattg attacctcat ctggccctgg tttgaacggc tggaagcaat 600
gaagttaaat gagtgtgtag accacactcc aaaactgaaa ctgtggatgg cagccatgaa 660
ggaagatccc acagtctcag ccctgcttac tagtgagaaa gactggcaag gtttcctaga 720
gctctactta cagaacagcc ctgaggcctg tgactatggg ctctgaaggg ggcaggagtc 780
agcaataaag ctatgtctga tattttcctt cactaaaaaa aaaaaaaaaa aactcgag 838

<210> 171
<211> 547
<212> DNA
<213> Homo sapien

<400> 171
gaattcggca ccagcgggat ttgggtcgca gttcttgttt gtggattgct gtgatcgtca 60
cttgacaatg cagatcttcg tgaagactct gactggtaag accatcaccc tcgaggttga 120
gcccagtgac accatcgaga atgtcaaggc aaagatccaa gataaggaag gcatccctcc 180
tgaccagcag aggctgatct ttgctggaaa acagctggaa gatgggcgca ccctgtctga 240
ctacaacatc cagaaagagt ccaccctgca cctggtgctc cgtctcaggg gtgggatgca 300
aatcttcgtg aagacactca ctggcaagac catcaccctt gaggtcgagc ccagtgacac 360
catcgagaac gtcaaagcaa agatccagga caaggaaggc attcctcctg accagcagag 420
gttgatcttt gccggaaagc agctggaaga tgggcgcacc ctgtctgact acaacatcca 480
gaaagagtct accctgcacc tggtgctccg tctcagaggt gggatgcaga tcttcgtgaa 540

09370838.0809999

347
5/2
614

378
5/8
615

gaccctg 547

<210> 172
<211> 608
<212> DNA
<213> Homo sapien

<400> 172
gaattcggca ccagagactt ctcccctctga ggcctgcgca cccctcctca tcagcctgtc 60
caccctcatc tacaatggtg ccctgccatg tcagtgcaac cctcaaggtt cactgagttc 120
tgagtgcaac cctcatggtg gtcagtgcct gtgcaagcct ggagtggttg ggcgccgctg 180
tgacctctgt gcccctggct actatggctt tggccccaca ggctgtcaag gcgcttgcct 240
gggctgccgt gatcacacag ggggtgagca ctgtgaaagg tgcattgctg gtttccacgg 300
ggacccacgg ctgccatatg ggggccagtg ccggccctgt ccctgtcctg aaggccctgg 360
gagccaacgg cactttgcta cttcttgcca ccaggatgaa tattcccagc agattgtgtg 420
ccactgccgg gcaggctata cggggctgcg atgtgaagct tgtgcccctg ggcactttgg 480
ggacccatca aggccaggtg gccggtgcca actgtgtgag tgcagtggga acattgaccc 540
aatggatcct gatgcctgtg acccccacac ggggcaatgc ctgcgctgtt tacaccacac 600
agagggtc 608

<210> 173
<211> 543
<212> DNA
<213> Homo sapien

<400> 173
gaattcggca ccagagatca tccgccagca gggtctggcc tcctacgact acgtgcgccg 60
ccgcctcacg gctgaggacc tgttcgaggc tcggatcatc tctctcgaga cctacaacct 120
gctccgggag ggcaccagga gcctccgtga ggctctcgag gcggagtccg cctggtgcta 180
cctctatggc acgggctccg tggctggtgt ctacctgccc ggttccaggc agacactgag 240
catctaccag gctctcaaga aagggctgct gagtgccgag gtggcccgcc tgctgctgga 300
ggcacaggca gccacaggct tcctgctgga cccggtgaag ggggaacggc tgactgtgga 360
tgaagctgtg cggaagggcc tcgtggggcc cgaactgcac gaccgcctgc tctcggctga 420
gcgggcggtc accggctacc gtgacccctа caccgagcag accatctcgc tcttccaggc 480
catgaagaag gaactgatcc ctactgagga ggccctgcgg ctgtggatgc ccagctggcc 540
acc 543

<210> 174
<211> 548
<212> DNA
<213> Homo sapien

<400> 174
gaattcggca cgagaaatgg cggcaggggt cgaagcggcg gcggaggtgg cggcgacgga 60
gatcaaaatg gaggaagaga gcggcgcgcc cggcgtgccg agcggcaacg gggctccggg 120
ccctaagggt gaaggagaac gacctgctca gaatgagaag aggaaggaga aaaacataaa 180
aagaggaggc aatcgctttg agccatatgc caatccaact aaaagataca gagccttcat 240
tacaaacata ccttttgatg tgaaatggca gtcacttaaa gacctggtta aagaaaaagt 300
tggtgaggta acatacgtgg agctcttaat ggacgctgaa ggaaagtcaa ggggatgtgc 360
tgttgttgaa ttcaagatgg aagagagcat gaaaaaagct gcggaagtcc taaacaagca 420
tagtctgagc ggaagaccac tgaaagtcaa agaagatcct gatggtgaac atgccaggag 480
agcaatgcaa aaggtgatgg ctacgactgg tgggatgggt atgggaccag gtggcccagg 540
aatgatta 548

<210> 175

09708838 - 08099

349
6/9
616

09270838 · 88080 · 5660

<211> 604
<212> DNA
<213> Homo sapien

<400> 175
gaattcggca ccagaggacc tccaggacat gttcatcgtc cataccatcg aggagattga 60
gggcctgatc tcagcccatg accagttcaa gtccaccctg ccggacgccg atagggagcg 120
cgaggccatc ctggccatcc acaaggaggc ccagaggatc gctgagagca accacatcaa 180
gctgtcgggc agcaacccct acaccaccgt caccccgcaa atcatcaact ccaagtggga 240
gaaggtgcag cagctggtgc caaaacggga ccatgccctc ctggaggagc agagcaagca 300
gcagtccaac gagcacctgc gccgccagtt cgccagccag gccaatgttg tggggccctg 360
gatccagacc aagatggagg agatcgggcg catctccatt gagatgaacg ggaccctgga 420
ggaccagctg agccacctga agcagtatga acgcagcatc gtggactaca agcccaacct 480
ggacctgctg gagcagcagc accagcttat ccaggaggcc ctcatcttcg acaacaagca 540
caccaactat accatggagc acatccgcgt gggctgggag cagctgctca ccaccattgc 600
ccgg 604

<210> 176
<211> 486
<212> DNA
<213> Homo sapien

<400> 176
gaattcggca ccagccaagc tcactattga atccacgccg ttcaatgtcg cagaggggaa 60
ggaggttctt ctactcgccc acaacctgcc ccagaatcgt attggttaca gctggtacaa 120
aggcgaaaga gtggatggca acagtctaat tgtaggatat gtaataggaa ctcaacaagc 180
taccccaggg cccgcataca gtggtcgaga gacaatatac cccaatgcat ccctgctgat 240
ccagaacgtc acccagaatg acacaggatt ctatacccta caagtcataa agtcagatct 300
tgtgaatgaa gaagcaaccg gacagttcca tgtatacccg gagctgccca agccctccat 360
ctccagcaac aactccaacc ccgtggagga caaggatgct gtggccttca cctgtgaacc 420
tgaggttcag aacacaacct acctgtggtg ggtaaatggt cagagcctcc cggtcagtcc 480
caaggc 486

<210> 177
<211> 387
<212> DNA
<213> Homo sapien

<400> 177
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gaactcaagc tcttctccac agaggaggac agagcagaca gcagagacca tggagtctcc 120
ctcggccccc ccccacagat ggtgcatccc ctggcagagg ctcctgctca cagcctcact 180
tctaaccttc tggaacccgc ccaccactgc caagctcact attgaatcca cgccgttcaa 240
tgtcgcagag gggaaggagg tgcttctact tgtccacaat ctgccccagc atcttttgg 300
ctacagctgg tacaaaggtg aaagagtgga tggcaaccgt caaattatag gatatgtaat 360
aggaactcaa caagctaccc cagggcc 387

<210> 178
<211> 440
<212> DNA
<213> Homo sapien

<400> 178
gaattcggca cgaggagaag cagaaaaaca aggaatttag ccagacttta gaaaatgaga 60
aaaatacctt actgagtcag atatcaacaa aggatggtga actaaaaatg cttcaggagg 120

aagtaaccaa aatgaacctg ttaaatcagc aaatccaaga agaactctct agagttacca 180
aactaaagga gacagcagaa gaagagaaag atgatttgga agagaggctt atgaatcaat 240
tagcagaact taatggaagc attgggaatt actgtcagga tgttacagat gcccaaataa 300
aaaatgagct attggaatct gaaatgaaga accttaaaaa gtgtgtgagt gaattggaag 360
aagaaaagca gcagttagtc aaggaaaaaa ctaaggtgga atcagaaata cgaaaggaat 420
atttggagaa aatacaaggt 440

<210> 179
<211> 443
<212> DNA
<213> Homo sapien

<400> 179
gaattcggca ccagcggggg gctacggcgg cggctacggc ggcgtcctga ccgcgtccga 60
cgggctgctg gcgggcaacg agaagctaac catgcagaac ctcaacgacc gcctggcctc 120
ctacctggac aaggtgcgcg ccctggaggc ggccaacggc gagctagagg tgaagatccg 180
cgactggtac cagaagcagg ggcctgggcc ctcccgcgac tacagccact actacacgac 240
catccaggac ctgcgggaca agattcttgg tgccaccatt gagaactcca ggattgtcct 300
gcagatcgac aacgcccgtc tggctgcaga tgacttccga accaagtttg agacggaaca 360
ggctctgcgc atgagcgtgg aggccgacat caacggcctg cgcagggtgc tggatgagct 420
gaccctggcc aggaccgacc tgg 443

<210> 180
<211> 403
<212> DNA
<213> Homo sapien

<400> 180
gaattcggca cgaggttatg agagtcgact tcaatgttcc tatgaagaac aaccagataa 60
caaacaacca gaggattaag gctgctgtcc caagcatcaa attctgcttg gacaatggag 120
ccaagtcggt agtccttatg agccacctag gccggcctga tggtgtgccc atgcctgaca 180
agtactcctt agagccagtt gctgtagaac tcagatctct gctgggcaag gatgttctgt 240
tcttgaagga ctgtgtaggc ccagaagtgg agaaagcctg tgccaaccca gctgctgggt 300
ctgtcatcct gctggagaac ctccgctttc atgtggagga agaagggaag ggaaaagatg 360
cttctgggaa caaggttaaa gccgagccag ccaaaatagg agc 403

<210> 181
<211> 493
<212> DNA
<213> Homo sapien

<400> 181
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taaggaaaaa ctcattgcac cagttgcgga agaagaggca acagttccaa acaataagat 120
cactgtagtg ggtgttggac aagttggtat ggcgtgtgct atcagcattc tgggaaagtc 180
tctggctgat gaacttgctc ttgtggatgt tttggaagat aagcttaaag gagaaatgat 240
ggatctgcag catgggagct tatttcttca gacacctaaa attgtggcag ataaagatta 300
ttctgtgacc gccaattcta agattgtagt ggtaactgca ggagtccgtc agcaagaagg 360
ggagagtcgg ctcaatctgg tgcagagaaa tgttaatgtc ttcaaattca ttattcctca 420
gatcgtcaag tacagtcctg attgcatcat aattgtggtt tccaacccag tggacattct 480
tacgtatgtt acc 493

<210> 182
<211> 209
<212> PRT

09370838.080999

3E7
62T
618

09370838 - 08099

<213> Homo sapien

<400> 182

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Ala Phe Ser Ser Asn Pro Lys Val Gln Val Glu Ala Ile Glu Gly Gly
 1               5                  10                  15
Ala Leu Gln Lys Leu Leu Val Ile Leu Ala Thr Glu Gln Pro Leu Thr
            20                  25                  30
Ala Lys Lys Lys Val Leu Phe Ala Leu Cys Ser Leu Leu Arg His Phe
        35                  40                  45
Pro Tyr Ala Gln Arg Gln Phe Leu Lys Leu Gly Gly Leu Gln Val Leu
    50                  55                  60
Arg Thr Leu Val Gln Glu Lys Gly Thr Glu Val Leu Ala Val Arg Val
65                  70                  75                  80
Val Thr Leu Leu Tyr Asp Leu Val Thr Glu Lys Met Phe Ala Glu Glu
                85                  90                  95
Glu Ala Glu Leu Thr Gln Glu Met Ser Pro Glu Lys Leu Gln Gln Tyr
            100                 105                 110
Arg Gln Val His Leu Leu Pro Gly Leu Trp Glu Gln Gly Trp Cys Glu
        115                 120                 125
Ile Thr Ala His Leu Leu Ala Leu Pro Glu His Asp Ala Arg Glu Lys
    130                 135                 140
Val Leu Gln Thr Leu Gly Val Leu Leu Thr Thr Cys Arg Asp Arg Tyr
145                 150                 155                 160
Arg Gln Asp Pro Gln Leu Gly Arg Thr Leu Ala Ser Leu Gln Ala Glu
                165                 170                 175
Tyr Gln Val Leu Ala Ser Leu Glu Leu Gln Asp Gly Glu Asp Glu Gly
            180                 185                 190
Tyr Phe Gln Glu Leu Leu Gly Ser Val Asn Ser Leu Leu Lys Glu Leu
        195                 200                 205
Arg
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<210> 183
<211> 255
<212> PRT
<213> Homo sapien

<400> 183

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 1               5                  10                  15
Lys Met Glu Glu Glu Ser Gly Ala Pro Cys Val Pro Ser Gly Asn Gly
            20                  25                  30
Ala Pro Gly Pro Lys Gly Glu Glu Arg Pro Thr Gln Asn Glu Lys Arg
        35                  40                  45
Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr Ser
    50                  55                  60
Asn Pro Thr Lys Arg Tyr Arg Ala Phe Ile Thr Asn Ile Pro Phe Asp
65                  70                  75                  80
Val Lys Trp Gln Ser Leu Lys Asp Leu Val Lys Glu Lys Val Gly Glu
                85                  90                  95
Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg Gly
            100                 105                 110
Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala Ala
        115                 120                 125
Glu Val Leu Asn Lys His Ser Leu Ser Gly Arg Pro Leu Lys Val Lys
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522
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    130                 135                 140
Glu Asp Pro Asp Gly Glu His Ala Arg Arg Ala Met Gln Lys Ala Gly
145                 150                 155                 160
Arg Leu Gly Ser Thr Val Phe Val Ala Asn Leu Asp Tyr Lys Val Gly
                165                 170                 175
Trp Lys Lys Leu Lys Glu Val Phe Ser Met Ala Gly Val Val Val Arg
            180                 185                 190
Ala Asp Ile Leu Glu Asp Lys Asp Gly Lys Ser Arg Gly Ile Gly Ile
        195                 200                 205
Val Thr Phe Glu Gln Ser Ile Glu Ala Val Gln Ala Ile Ser Met Phe
    210                 215                 220
Asn Gly Gln Leu Leu Phe Asp Arg Pro Met His Val Lys Met Asp Glu
225                 230                 235                 240
Arg Ala Leu Pro Lys Gly Asp Phe Phe Pro Pro Glu Arg His Ser
                245                 250                 255

      <210> 184
      <211> 188
      <212> PRT
      <213> Homo sapien

      <400> 184
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 1               5                  10                  15
Gln Val Val Leu Phe Glu Glu Ala Ser Trp Thr Cys Thr Pro Ala Cys
            20                  25                  30
Gly Asp Glu Pro Arg Thr Val Ile Leu Leu Ser Ser Met Leu Ala Asp
        35                  40                  45
His Arg Leu Lys Leu Glu Asp Tyr Lys Asp Arg Leu Lys Ser Gly Glu
    50                  55                  60
His Leu Asn Pro Asp Gln Leu Glu Ala Val Glu Lys Tyr Glu Glu Val
65                  70                  75                  80
Leu His Asn Leu Glu Phe Ala Lys Glu Leu Gln Lys Thr Phe Ser Gly
                85                  90                  95
Leu Ser Leu Asp Leu Leu Lys Ala Gln Lys Lys Ala Gln Arg Arg Glu
            100                 105                 110
His Met Leu Lys Leu Glu Ala Glu Lys Lys Lys Leu Arg Thr Ile Leu
        115                 120                 125
Gln Val Gln Tyr Val Leu Gln Asn Leu Thr Gln Glu His Val Gln Lys
    130                 135                 140
Asp Phe Lys Gly Gly Leu Asn Gly Ala Val Tyr Leu Pro Ser Lys Glu
145                 150                 155                 160
Leu Asp Tyr Leu Ile Lys Phe Ser Lys Leu Thr Cys Pro Glu Arg Asn
                165                 170                 175
Glu Ser Leu Arg Gln Thr Leu Glu Gly Ser Thr Val
            180                 185

      <210> 185
      <211> 746
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      <400> 185
Asp Lys His Leu Lys Asp Leu Leu Ser Lys Leu Leu Asn Ser Gly Tyr
 1               5                  10                  15
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Phe Glu Ser Ile Pro Val Pro Lys Asn Ala Lys Glu Lys Glu Val Pro
            20                  25                  30
Leu Glu Glu Glu Met Leu Ile Gln Ser Glu Lys Lys Thr Gln Leu Ser
        35                  40                  45
Lys Thr Glu Ser Val Lys Glu Ser Glu Ser Leu Met Glu Phe Ala Gln
    50                  55                  60
Pro Glu Ile Gln Pro Gln Glu Phe Leu Asn Arg Arg Tyr Met Thr Glu
65                  70                  75                  80
Val Asp Tyr Ser Asn Lys Gln Gly Glu Glu Gln Pro Trp Glu Ala Asp
                85                  90                  95
Tyr Ala Arg Lys Pro Asn Leu Pro Lys Arg Trp Asp Met Leu Thr Glu
            100                 105                 110
Pro Asp Gly Gln Glu Lys Lys Gln Glu Ser Phe Lys Ser Trp Glu Ala
        115                 120                 125
Ser Gly Lys His Gln Glu Val Ser Lys Pro Ala Val Ser Leu Glu Gln
    130                 135                 140
Arg Lys Gln Asp Thr Ser Lys Leu Arg Ser Thr Leu Pro Glu Glu Gln
145                 150                 155                 160
Lys Lys Gln Glu Ile Ser Lys Ser Lys Pro Ser Pro Ser Gln Trp Lys
                165                 170                 175
Gln Asp Thr Pro Lys Ser Lys Ala Gly Tyr Val Gln Glu Glu Gln Lys
            180                 185                 190
Lys Gln Glu Thr Pro Lys Leu Trp Pro Val Gln Leu Gln Lys Glu Gln
        195                 200                 205
Asp Pro Lys Lys Gln Thr Pro Lys Ser Trp Thr Pro Ser Met Gln Ser
    210                 215                 220
Glu Gln Asn Thr Thr Lys Ser Trp Thr Thr Pro Met Cys Glu Glu Gln
225                 230                 235                 240
Asp Ser Lys Gln Pro Glu Thr Pro Lys Ser Trp Glu Asn Asn Val Glu
                245                 250                 255
Ser Gln Lys His Ser Leu Thr Ser Gln Ser Gln Ile Ser Pro Lys Ser
            260                 265                 270
Trp Gly Val Ala Thr Ala Ser Leu Ile Pro Asn Asp Gln Leu Leu Pro
        275                 280                 285
Arg Lys Leu Asn Thr Glu Pro Lys Asp Val Pro Lys Pro Val His Gln
    290                 295                 300
Pro Val Gly Ser Ser Ser Thr Leu Pro Lys Asp Pro Val Leu Arg Lys
305                 310                 315                 320
Glu Lys Leu Gln Asp Leu Met Thr Gln Ile Gln Gly Thr Cys Asn Phe
                325                 330                 335
Met Gln Glu Ser Val Leu Asp Phe Asp Lys Pro Ser Ser Ala Ile Pro
            340                 345                 350
Thr Ser Gln Pro Pro Ser Ala Thr Pro Gly Ser Pro Val Ala Ser Lys
        355                 360                 365
Glu Gln Asn Leu Ser Ser Gln Ser Asp Phe Leu Gln Glu Pro Leu Gln
    370                 375                 380
Val Phe Asn Val Asn Ala Pro Leu Pro Pro Arg Lys Glu Gln Glu Ile
385                 390                 395                 400
Lys Glu Ser Pro Tyr Ser Pro Gly Tyr Asn Gln Ser Phe Thr Thr Ala
                405                 410                 415
Ser Thr Gln Thr Pro Pro Gln Cys Gln Leu Pro Ser Ile His Val Glu
            420                 425                 430
Gln Thr Val His Ser Gln Glu Thr Ala Ala Asn Tyr His Pro Asp Gly
        435                 440                 445
Thr Ile Gln Val Ser Asn Gly Ser Leu Ala Phe Tyr Pro Ala Gln Thr
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(Se traduce el certificado de la Oficina de Patentes y Marcas de los Estados Unidos de América, correspondiente a la solicitud 09/370/838 y el capítulo reivindicatorio, escritos en inglés.)

ESTADOS UNIDOS DE AMÉRICA

A TODOS A QUIENES ESTOS PRESENTES LLEGAREN:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS

Abril 12, 2000

POR EL PRESENTE CERTIFICO QUE ADJUNTA SE ENCUENTRA UNA COPIA FIEL DE LOS ARCHIVOS DE LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE AMÉRICA DE AQUELLOS PAPELES DE LA SOLICITUD DE PATENTE IDENTIFICADA ABAJO Y QUE CUMPLIERON CON LOS REQUISITOS PARA QUE SE LES OTORGARA UNA FECHA DE SOLICITUD BAJO EL CÓDIGO DE COMERCIO DE LOS ESTADOS UNIDOS DE AMÉRICA

TRADUCCION OFICIAL POR
HILDA AGUILERA DE PIEDRAHITA
INTERPRETE OFICIAL
RES. No 323 DEL MIN. OF JUSTICE

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TÍTULO 35 SECCIÓN 111.

NUMERO DE SOLICITUD: ***09/370,838***

FECHA DE PRESENTACIÓN: ***Agosto 09, 1999***

Por autoridad del

COMISARIO DE PATENTES Y MARCAS

(Firmado.) **L. EDELEN**

Funcionario que Certifica

(SELLO DE OBLEA DE LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE AMÉRICA)

(Nota: al margen aparece un sello a tinta en todas las páginas: 09370838.080999)

Reivindicaciones

1. Un polipéptido aislado que incluye por lo menos una porción inmunogénica de una proteína de tumor pulmonar, o una variante de ella, donde la proteína de tumor incluye una secuencia de aminoácidos que está codificada por una secuencia polinucleótida seleccionada del grupo consistente de:

   (a) Las secuencias presentadas en los NOS SEQ ID 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282 y 285;

   (b) Las secuencias presentadas en los NOS SEQ ID 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282 y 285; bajo condiciones

moderadamente severas; y

(c) Un complemento de la secuencia (a) o (b).

2. Un polipéptido aislado de acuerdo con la reivindicación 1, donde el polipéptido incluye una secuencia de aminoácidos codificada por una secuencia polinucleótida presentada en cualesquiera de los NOS SEQ ID 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282 y 285 o un complemento de cualesquiera de las anteriores secuencias polinucleótidas.

3. Un polinucleótido aislado que codifica por lo menos 15 residuos aminoácidos de proteína de tumor pulmonar, o una variante de ellos que difiere en una o más sustituciones, supresiones, adiciones, y/o inserciones tales que la habilidad de la variante para reaccionar con antisera antígeno específico no se disminuye sustancialmente, donde la proteína de tumor incluye una secuencia de aminoácidos que está codificada por un polinucleótido que incluye la secuencia presentada en cualesquiera de los NOS SEQ ID 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282 y 285 o un complemento de cualesquiera de las secuencias anteriores.

4. Un polinucleótido aislado que codifica una proteína de tumor pulmonar, o una variante de él, donde la proteína de tumor incluye una secuencia de aminoácidos que está codificada por un polinucleótido que incluye la secuencia presentada en cualesquiera de los NOS SEQ ID 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282 y 285 o un complemento de

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cualesquiera de las secuencias anteriores.

5. Un polinucleótido aislado que incluye una secuencia presentada en cualesquiera de los NOS SEQ ID 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282 y 285.

6. Un polinucleótido aislado que incluye una secuencia que hibridiza a una secuencia presentada en cualesquiera de los NOS SEQ ID 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282 y 285 bajo condiciones moderadamente severas.

7. Un polinucleótido aislado complementario a un polinucleótido de acuerdo con cualesquiera de las reivindicaciones 3-6.

8. Un vector de expresión que incluye un polinucleótido de acuerdo con cualesquiera de las reivindicaciones 3-6.

9. Una célula anfitriona transformada o transfectada con un vector de expresión de acuerdo con la reivindicación 8.

10. Un vector de expresión que incluye un polinucleótido de acuerdo con la reivindicación 7.

11. Una célula anfitriona transformada o transfectada con un vector de expresión de acuerdo con la reivindicación 10.

12. Una composición farmacéutica que incluye un polipéptido de acuerdo con la

reivindicación 1, en combinación con un portador fisiológicamente aceptable.

13. Una vacuna que incluye un polipéptido de acuerdo con la reivindicación 1, en combinación con un mejorador de respuesta no específica inmune.

14. Una vacuna de acuerdo con la reivindicación 13, donde el mejorador de respuesta no específica inmune es un adyuvante.

15. Una vacuna de acuerdo con la reivindicación 13 donde el mejorador de respuesta no específica inmune induce una respuesta predominantemente Tipo I.

16. Una composición farmacéutica que incluye un polinucleótido de acuerdo con la reivindicación 3, en combinación con un portador fisiológicamente aceptable.

17. Una vacuna que incluye un polinucleótido de acuerdo con la reivindicación 3, en combinación con un mejorador de respuesta no específica inmune.

18. Una vacuna de acuerdo con la reivindicación 17, donde el mejorador de respuesta no específica inmune es un adyuvante.

19. Una vacuna de acuerdo con la reivindicación 17, donde el mejorador de respuesta no específica inmune induce una respuesta predominantemente de Tipo I.

20. Un anticuerpo aislado o un antígeno ligante del mismo, que específicamente

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se liga a la proteína de tumor pulmonar que incluye una secuencia de aminoácidos que está codificada por una secuencia polinucleótida presentada en los NOS SEQ ID 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282 y 285 o un complemento de cualesquiera de las secuencias polinucleótidas anteriores.

21. Una composición farmacéutica que incluye un anticuerpo o un fragmento del mismo de acuerdo con la reivindicación 17, en combinación con un portador fisiológicamente aceptable.

22. Una composición farmacéutica que incluye una célula que presenta antígeno que expresa un polipéptido de acuerdo con la reivindicación 1, en combinación con un portador o excipiente farmacéuticamente aceptable.

23. Una composición farmacéutica de acuerdo con la reivindicación 22, donde la célula que presenta antígeno es una célula dendrítica o macrófaga.

24. Una vacuna que incluye una célula que presenta antígeno que expresa el polipéptido de acuerdo con la reivindicación 1, en combinación con el mejorador de respuesta no específica inmune.

25. Una vacuna de acuerdo con la reivindicación 24 donde mejorador de respuesta no específica inmune es un adyuvante.

26. Una vacuna de acuerdo con la reivindicación 24, donde el mejorador de respuesta no específica inmune induce una respuesta predominantemente

de Tipo I.

27. Una vacuna de acuerdo con la reivindicación 24 donde la célula que presenta antígeno es una célula dendrítica.

28. Un método para inhibir el desarrollo de cáncer en un paciente, que incluye la administración al paciente, de una cantidad efectiva del polipéptido de acuerdo con la reivindicación 1, y así inhibir el desarrollo de un cáncer en el paciente.

29. Un método para inhibir el desarrollo de cáncer en un paciente, que incluye la administración al paciente, de una cantidad efectiva del polinucleótido de acuerdo con la reivindicación 3, y así inhibir el desarrollo de un cáncer en el paciente.

30. Un método para inhibir el desarrollo de cáncer en un paciente, que incluye la administración al paciente, de una cantidad efectiva de un anticuerpo o del fragmento ligante de antígeno del mismo, de acuerdo con la reivindicación 20, y así inhibir el desarrollo de un cáncer en el paciente.

31. Un método para inhibir el desarrollo de cáncer en un paciente, que incluye la administración al paciente, de una cantidad efectiva de una célula que presenta antígeno que expresa un polipéptido de acuerdo con la reivindicación 1, y así inhibir el desarrollo de un cáncer en el paciente.

32. Un método de acuerdo con la reivindicación 31, donde la célula que

presenta antígeno es una célula dendrítica.

33. Un método de acuerdo con las reivindicaciones 28-31, donde el cáncer es cáncer de pulmón.

34. Una proteína de fusión que incluye por lo menos un polipéptido de acuerdo con la reivindicación 1.

35. Una proteína de fusión de acuerdo con la reivindicación 34, donde la proteína de fusión incluye una expresión mejoradora, que aumenta la expresión de la proteína de fusión en una célula anfitriona transfectada con un polinucleótido codificando la proteína de fusión.

36. Una proteína de fusión de acuerdo con la reivindicación 34, donde la proteína de fusión incluye un ayudador T epitope que no está presente dentro del polipéptido de la reivindicación 1.

37. Una proteína de fusión de acuerdo con la reivindicación 34, donde la proteína de fusión incluye una etiqueta de afinidad.

38. Un polinucleótido aislado que codifica la proteína de fusión de acuerdo con la reivindicación 34.

39. Una composición farmacéutica que incluye una proteína de fusión de acuerdo con la reivindicación 31, en combinación con un portador fisiológicamente aceptable.

40. Una vacuna que incluye una proteína de fusión de acuerdo con la reivindicación 34, en combinación con un mejorador de respuesta no específica inmune.

41. Una vacuna de acuerdo con la reivindicación 40, donde el mejorador de respuesta no específica inmune es un adyuvante.

42. Una vacuna de acuerdo con la reivindicación 40, donde el mejorador de respuesta no específica inmune induce una respuesta predominantemente de Tipo I.

43. Una composición farmacéutica que incluye un polinucleótido de acuerdo con la reivindicación 39, en combinación con un portador fisiológicamente aceptable.

44. Una vacuna que incluye un polinucleótido de acuerdo con la reivindicación 39, en combinación con un mejorador de respuesta no específica inmune.

45. Una vacuna de acuerdo con la reivindicación 44, donde el mejorador de respuesta no específica inmune es un adyuvante.

46. Una vacuna de acuerdo con la reivindicación 44, donde el mejorador de respuesta no específica inmune induce una respuesta predominantemente de Tipo I.

47. Un método para inhibir el desarrollo de cáncer en un paciente, que incluye la

administración al paciente, de una cantidad efectiva de una composición farmacéutica de acuerdo con la reivindicación 39 o la reivindicación 43.

48. Un método para inhibir el desarrollo de cáncer en un paciente, que incluye la administración al paciente, de una cantidad efectiva de una vacuna de acuerdo con la reivindicación 40 o la reivindicación 44.

49. Un método para remover células de tumor de una muestra biológica, que incluye poner en contacto una muestra biológica con células T que reaccionan específicamente con una proteína de tumor pulmonar, donde la proteína de tumor incluye una secuencia de aminoácidos que es codificada por una secuencia de polinucleótido seleccionada del grupo consistente de:

(i) polinucleótidos presentados en cualesquiera de NOS SEQ ID: 217-289 y

(ii) complementos de los anteriores polinucleótidos;

donde la etapa de contacto se lleva a cabo bajo condiciones y por un tiempo suficiente para permitir la remoción de las células que expresan el antígeno de la muestra.

50. Un método de acuerdo con la reivindicación 49, donde la muestra biológica es sangre o una fracción de la misma.

51. Un método para inhibir el desarrollo de cáncer en un paciente, que incluye la

administración al paciente, de una muestra biológica tratada de acuerdo con el método de la reivindicación 49.

52. Un método para estimular y/o expandir las células T específicas para una proteína de tumor pulmonar, que incluye poner en contacto células T con uno o más de:

(i) un polipéptido de acuerdo con la reivindicación 1;

(ii) un polinucleótido codificando tal polipéptido; y/o

(iii) un antígeno presente en la célula que se expresa tal polipéptido;

bajo condiciones y por un tiempo suficiente para permitir la estimulación y/o expansión de las células T.

53. Una población de células T aisladas, que incluyen células T preparadas de acuerdo con el método de la reivindicación 52.

54. Un método para inhibir el desarrollo de cáncer en un paciente, que incluye la administración al paciente una cantidad efectiva de una población de células T de acuerdo con la reivindicación 53.

55. Un método para inhibir el desarrollo de cáncer en un paciente, que incluye las etapas de:

(a) incubar células T $CD4^+$ y /o $CD8^+$ aisladas de un paciente con por lo menos un componente seleccionado del grupo consistente de:

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(i) un polipéptido de acuerdo con la reivindicación 1;

(ii) un polinucleótido codificando tal polipéptido; o

(iii) una célula que presenta antígeno que expresa tal polipéptido;

tal que las células T proliferan; y

(b) administrar al paciente una cantidad efectiva células T proliferadas, y así inhibir el desarrollo de cáncer en un paciente.

56. Un método para inhibir el desarrollo de cáncer en un paciente, que incluye las etapas de:

(a) incubar células T $CD4^+$ y /o $CD8^+$ aisladas de un paciente con por lo menos un componente seleccionado del grupo consistente de:

(i) un polipéptido de acuerdo con la reivindicación 1;

(ii) un polinucleótido codificando tal polipéptido; o

(iii) una célula que presenta antígeno que expresa tal polipéptido;

tal que las células T proliferan; y

(b) clonar por lo menos una célula proliferada; y

(c) administrar al paciente una cantidad efectiva células T clonadas, y así inhibir el desarrollo de cáncer en un paciente.

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57. Un método para determinar la presencia o ausencia de cáncer en un paciente, que incluye las etapas de:

(a) poner en contacto una muestra biológica obtenida de un paciente con un agente ligante que se liga a una proteína de tumor pulmonar, donde la proteína de tumor incluye una secuencia de aminoácidos que es codificada por una secuencia de polinucleótido seleccionado del grupo que consiste de:

(i) polinucleótidos presentados en cualesquiera de NOS SEQ ID: 217-289 y

(ii) complementos de los anteriores polinucleótidos;

(b) detectar en la muestra una cantidad de polipéptido que se liga al agente ligante; y

(c) comparar la cantidad de polipéptido a un valor de corte predeterminado, y así determinar la presencia o ausencia de cáncer en el paciente.

58. Un método de acuerdo con la reivindicación 57, donde el agente ligante es un anticuerpo.

59. Un método de acuerdo con la reivindicación 58, donde el anticuerpo es un anticuerpo monoclonal.

60. Un método de acuerdo a la reivindicación 57, donde el cáncer es cáncer de

pulmón.

61. Un método para monitorear la progresión de cáncer en un paciente, que incluye las etapas de:

(a) poner en contacto una muestra biológica obtenida de un paciente a un primer instante en el tiempo con un agente ligante que se liga a una proteína de tumor pulmonar, donde la proteína de tumor incluye una secuencia de aminoácidos que es codificada por una secuencia de polinucleótido presentada en cualesquiera de NOS SEQ ID: 217-289 o un complemento de cualesquiera de los anteriores polinucleótidos;

(b) detectar en la muestra una cantidad de polipéptido que se liga al agente ligante;

(c) repetir las etapas (a) y (b) usando una muestra biológica obtenida del paciente a un punto subsiguiente en el tiempo; y

(d) comparar la cantidad de polipéptido detectado en la etapa (c) con la cantidad detectada en la etapa (b) y desde allí supervisar la progresión del cáncer en el paciente.

62. Un método de acuerdo con la reivindicación 61, donde el agente ligante es un anticuerpo.

63. Un método de acuerdo con la reivindicación 62, donde el anticuerpo es un

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anticuerpo monoclonal.

64. Un método de acuerdo con la reivindicación 61, donde el cáncer es cáncer de pulmón.

65. Un método para determinar la presencia o ausencia de un cáncer en un paciente, que incluye las etapas de:

(a) poner en contacto una muestra biológica obtenida de un paciente con un oligonucleótido que hibridiza a un polinucleótido que codifica una proteína de tumor pulmonar, donde la proteína de tumor incluye una secuencia de aminoácidos que es codificada por una secuencia de polinucleótido presentada en cualesquiera de NOS SEQ ID: 217-289 o un complemento de cualesquiera de los anteriores polinucleótidos;

(b) detectar en la muestra una cantidad de polinucleótido que hibridiza al oligonucleótido; y

(c) comparar la cantidad de polinucleótido que hibridiza al oligonucleótido a un valor predeterminado de corte, y desde allí determinar la presencia o ausencia de cáncer en un paciente.

66. Un método de acuerdo con la reivindicación 65, donde la cantidad de polinucleótido que hibridiza al oligonucleótido es determinada usando una reacción en cadena de polimerasa.

67. Un método de acuerdo con la reivindicación 65, donde la cantidad de polinucleótido que hibridiza al oligonucleótido es determinada usando un ensayo de hibridización.

68. Un método para supervisar la progresión de cáncer en un paciente, que incluye las etapas de :

(a) poner en contacto una muestra biológica obtenida de un paciente con un oligonucleótido que hibridiza a un polinucleótido que codifica una proteína de tumor pulmonar, donde la proteína de tumor incluye una secuencia de aminoácidos que es codificada por una secuencia de polinucleótido presentada en cualesquiera de NOS SEQ ID: 217-289 o un complemento de cualesquiera de los anteriores polinucleótidos;

(b) detectar en la muestra una cantidad de polinucleótido que hibridiza al oligonucleótido; y

(c) repetir las etapas (a) y (b) usando una muestra biológica obtenida del paciente a un punto subsecuente en tiempo; y

(d) comparar la cantidad de polinucleótido detectado en la etapa (c) con la cantidad detectada en la etapa (b) y desde allí monitorear la progresión del cáncer en el paciente.

69. Un método de acuerdo con la reivindicación 68, donde la cantidad de polinucleótido que hibridiza al oligonucleótido es determinada usando una

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NILDA ARCILLER DE PADILLA

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reacción en cadena de polimerasa.

70. Un método de acuerdo con la reivindicación 68, donde la cantidad de polinucleótido que hibridiza al oligonucleótido es determinada usando un ensayo de hibridización.

71. Un conjunto de diagnóstico, que incluye:

(a) uno o más anticuerpos de acuerdo con la reivindicación 20; y

(b) un agente de detección que incluye un grupo reportero.

72. Un conjunto de acuerdo con la reivindicación 71, donde los anticuerpos son inmovilizados en un soporte sólido.

73. Un conjunto de acuerdo con la reivindicación 72, donde el soporte sólido incluye nitrocelulosa, látex o un material plástico.

74. Un conjunto de acuerdo con la reivindicación 71, donde el agente de detección incluye un anti-inmunoglobulina, proteína G, proteína A o lectina.

75. Un conjunto de acuerdo con la reivindicación 71, donde el grupo reportero es seleccionado del grupo que consiste de radioisótopos, grupos fluorescentes, grupos luminiscentes, enzimas, biotina y partículas de tinte.

76. Un oligonucleótido que incluye de 10 a 40 nucleótidos que hibridiza bajo condiciones moderadamente severas a un polinucleótido que codifica una proteína de tumor pulmonar, donde la proteína de tumor incluye una

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secuencia de aminoácidos que es codificada por una secuencia de polinucleótido presentada en cualesquiera de los NOS SEQ ID 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282 y 285 o un complemento de cualesquiera de las anteriores secuencias polinucleótidas.

77. Un oligonucleótido de acuerdo con la reivindicación 76, donde el oligonucleótido incluye de 10 a 40 nucleótidos presentada en cualesquiera de los NOS SEQ ID 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282 y 285. .

78. Un conjunto de diagnóstico, que incluye:

(a) un oligonucleótido de acuerdo con la reivindicación 76; y

(b) un agente de diagnóstico para ser usado en una reacción de polimerasa en cadena o un ensayo de hibridización.

ES TRADUCCIÓN FIEL Y COMPLETA de la cual se deja copia en los archivos de esta oficina para su confrontación y a la cual me remito.

Santafé de Bogotá, 6 de Junio del 2000.

2000/094

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```
    450                 455                 460
Asn Val Phe Pro Arg Pro Thr Gln Pro Phe Val Asn Ser Arg Gly Ser
465                 470                 475                 480
Val Arg Gly Cys Thr Arg Gly Gly Arg Leu Ile Thr Asn Ser Tyr Arg
                485                 490                 495
Ser Pro Gly Gly Tyr Lys Gly Phe Asp Thr Tyr Arg Gly Leu Pro Ser
            500                 505                 510
Ile Ser Asn Gly Asn Tyr Ser Gln Leu Gln Phe Gln Ala Arg Glu Tyr
        515                 520                 525
Ser Gly Ala Pro Tyr Ser Gln Arg Asp Asn Phe Gln Gln Cys Tyr Lys
    530                 535                 540
Arg Gly Gly Thr Ser Gly Gly Pro Arg Ala Asn Ser Arg Ala Gly Trp
545                 550                 555                 560
Ser Asp Ser Ser Gln Val Ser Ser Pro Glu Arg Asp Asn Glu Thr Phe
                565                 570                 575
Asn Ser Gly Asp Ser Gly Gln Gly Asp Ser Arg Ser Met Thr Pro Val
            580                 585                 590
Asp Val Pro Val Thr Asn Pro Ala Ala Thr Ile Leu Pro Val His Val
        595                 600                 605
Tyr Pro Leu Pro Gln Gln Met Arg Val Ala Phe Ser Ala Ala Arg Thr
    610                 615                 620
Ser Asn Leu Ala Pro Gly Thr Leu Asp Gln Pro Ile Val Phe Asp Leu
625                 630                 635                 640
Leu Leu Asn Asn Leu Gly Glu Thr Phe Asp Leu Gln Leu Gly Arg Phe
                645                 650                 655
Asn Cys Pro Val Asn Gly Thr Tyr Val Phe Ile Phe His Met Leu Lys
            660                 665                 670
Leu Ala Val Asn Val Pro Leu Tyr Val Asn Leu Met Lys Asn Glu Glu
        675                 680                 685
Val Leu Val Ser Ala Tyr Ala Asn Asp Gly Ala Pro Asp His Glu Thr
    690                 695                 700
Ala Ser Asn His Ala Ile Leu Gln Leu Phe Gln Gly Asp Gln Ile Trp
705                 710                 715                 720
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Thr Phe Ser Gly Tyr Leu Leu Tyr Gln Asp
            740                 745

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      <211> 705
      <212> PRT
      <213> Homo sapien

      <400> 186
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Asn Gln Ile Asn His Leu Pro Pro Leu Gly Ser Thr Ile Val Met Thr
            20                  25                  30
Lys Thr Pro Pro Val Thr Thr Asn Arg Gln Thr Ile Thr Leu Thr Lys
        35                  40                  45
Phe Ile Gln Thr Thr Ala Ser Thr Arg Pro Ser Val Ser Ala Pro Thr
    50                  55                  60
Val Arg Asn Ala Met Thr Ser Ala Pro Ser Lys Asp Gln Val Gln Leu
65                  70                  75                  80
Lys Asp Leu Leu Lys Asn Asn Ser Leu Asn Glu Leu Met Lys Leu Lys
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                85                  90                  95
Pro Pro Ala Asn Ile Ala Gln Pro Val Ala Thr Ala Ala Thr Asp Val
            100                 105                 110
Ser Asn Gly Thr Val Lys Lys Glu Ser Ser Asn Lys Glu Gly Ala Arg
        115                 120                 125
Met Trp Ile Asn Asp Met Lys Met Arg Ser Phe Ser Pro Thr Met Lys
    130                 135                 140
Val Pro Val Val Lys Glu Asp Asp Glu Pro Glu Glu Glu Asp Glu Glu
145                 150                 155                 160
Glu Met Gly His Ala Glu Thr Tyr Ala Glu Tyr Met Pro Ile Lys Leu
                165                 170                 175
Lys Ile Gly Leu Arg His Pro Asp Ala Val Val Glu Thr Ser Ser Leu
            180                 185                 190
Ser Ser Val Thr Pro Pro Asp Val Trp Tyr Lys Thr Ser Ile Ser Glu
        195                 200                 205
Glu Thr Ile Asp Asn Gly Trp Leu Ser Ala Leu Gln Leu Glu Ala Ile
    210                 215                 220
Thr Tyr Ala Ala Gln Gln His Glu Thr Phe Leu Pro Asn Gly Asp Arg
225                 230                 235                 240
Ala Gly Phe Leu Ile Gly Asp Gly Ala Gly Val Gly Lys Gly Arg Thr
                245                 250                 255
Ile Ala Gly Ile Ile Tyr Glu Asn Tyr Leu Leu Ser Arg Lys Arg Ala
            260                 265                 270
Leu Trp Phe Ser Val Ser Asn Asp Leu Lys Tyr Asp Ala Glu Arg Asp
        275                 280                 285
Leu Arg Asp Ile Gly Ala Lys Asn Ile Leu Val His Ser Leu Asn Lys
    290                 295                 300
Phe Lys Tyr Gly Lys Ile Ser Ser Lys His Asn Gly Ser Val Lys Lys
305                 310                 315                 320
Gly Val Ile Phe Ala Thr Tyr Ser Ser Leu Ile Gly Glu Ser Gln Ser
                325                 330                 335
Gly Gly Lys Tyr Lys Thr Arg Leu Lys Gln Leu Leu His Trp Cys Gly
            340                 345                 350
Asp Asp Phe Asp Gly Val Ile Val Phe Asp Glu Cys His Lys Ala Lys
        355                 360                 365
Asn Leu Cys Pro Val Gly Ser Ser Lys Pro Thr Lys Thr Gly Leu Ala
    370                 375                 380
Val Leu Glu Leu Gln Asn Lys Leu Pro Lys Ala Arg Val Val Tyr Ala
385                 390                 395                 400
Ser Ala Thr Gly Ala Ser Glu Pro Arg Asn Met Ala Tyr Met Asn Arg
                405                 410                 415
Leu Gly Ile Trp Gly Glu Gly Thr Pro Phe Arg Glu Phe Ser Asp Phe
            420                 425                 430
Ile Gln Ala Val Glu Arg Arg Gly Val Gly Ala Met Glu Ile Val Ala
        435                 440                 445
Met Asp Met Lys Leu Arg Gly Met Tyr Ile Ala Arg Gln Leu Ser Phe
    450                 455                 460
Thr Gly Val Thr Phe Lys Ile Glu Glu Val Leu Leu Ser Gln Ser Tyr
465                 470                 475                 480
Val Lys Met Tyr Asn Lys Ala Val Lys Leu Trp Val Ile Ala Arg Glu
                485                 490                 495
Arg Phe Gln Gln Ala Ala Asp Leu Ile Asp Ala Glu Gln Arg Met Lys
            500                 505                 510
Lys Ser Met Trp Gly Gln Phe Trp Ser Ala His Gln Arg Phe Phe Lys
        515                 520                 525
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641

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

<210> 187
<211> 595
<212> PRT
<213> Homo sapien

<400> 187
Glu Ser Pro Arg His Arg Gly Glu Gly Gly Gly Glu Trp Gly Pro Gly
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Val Pro Arg Glu Arg Arg Glu Ser Ala Gly Glu Trp Gly Ala Asp Thr
20 25 30
Pro Lys Glu Gly Gly Glu Ser Ala Gly Glu Trp Gly Ala Glu Val Pro
35 40 45
Arg Gly Arg Gly Glu Gly Ala Gly Glu Trp Gly Pro Asp Thr Pro Lys
50 55 60
Glu Arg Gly Gln Gly Val Arg Glu Trp Gly Pro Glu Ile Pro Gln Glu
65 70 75 80
His Gly Glu Ala Thr Arg Asp Trp Ala Leu Glu Ser Pro Arg Ala Leu
85 90 95
Gly Glu Asp Ala Arg Glu Leu Gly Ser Ser Pro His Asp Arg Gly Ala
100 105 110
Ser Pro Arg Asp Leu Ser Gly Glu Ser Pro Cys Thr Gln Arg Ser Gly
115 120 125
Leu Leu Pro Glu Arg Arg Gly Asp Ser Pro Trp Pro Pro Trp Pro Ser
130 135 140
Pro Gln Glu Arg Asp Ala Gly Thr Arg Asp Arg Glu Glu Ser Pro Arg
145 150 155 160
Asp Trp Gly Gly Ala Glu Ser Pro Arg Gly Trp Glu Ala Gly Pro Arg
165 170 175
Glu Trp Gly Pro Ser Pro Ser Gly His Gly Asp Gly Pro Arg Arg Arg
180 185 190

357
SEQ
642

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Pro Arg Lys Arg Arg Gly Arg Lys Gly Arg Met Gly Arg Gln His Glu
        195                 200                 205
Ala Ala Ala Thr Ala Ala Thr Ala Ala Thr Ala Thr Gly Gly Thr Ala
    210                 215                 220
Glu Glu Ala Gly Ala Ser Ala Pro Glu Ser Gln Ala Gly Gly Gly Pro
225                 230                 235                 240
Arg Gly Arg Ala Arg Gly Pro Arg Gln Gln Gly Arg Arg Arg His Gly
                245                 250                 255
Thr Gln Arg Arg Arg Gly Pro Pro Gln Ala Arg Glu Glu Gly Pro Arg
            260                 265                 270
Asp Ala Thr Thr Ile Leu Gly Leu Gly Thr Pro Ser Gly Glu Gln Arg
        275                 280                 285
Ala Asp Gln Ser Gln Ala Leu Pro Ala Leu Ala Gly Ala Ala Ala Ala
    290                 295                 300
His Ala His Ala Ile Pro Gly Ala Gly Pro Ala Ala Ala Pro Val Gly
305                 310                 315                 320
Gly Arg Gly Arg Arg Gly Gly Trp Arg Gly Gly Arg Arg Gly Gly Ser
                325                 330                 335
Ala Gly Ala Gly Gly Gly Gly Arg Gly Gly Arg Gly Arg Gly Arg Gly
            340                 345                 350
Gly Gly Arg Gly Gly Gly Gly Ala Gly Arg Gly Gly Gly Ala Ala Gly
        355                 360                 365
Pro Arg Glu Gly Ala Ser Ser Pro Gly Ala Arg Arg Gly Glu Gln Arg
    370                 375                 380
Arg Arg Gly Arg Gly Pro Pro Ala Ala Gly Ala Ala Gln Val Ser Ala
385                 390                 395                 400
Arg Gly Arg Arg Ala Arg Gly Gln Arg Ala Gly Glu Glu Ala Gln Asp
                405                 410                 415
Gly Leu Leu Pro Arg Gly Arg Asp Arg Leu Pro Leu Arg Pro Gly Asp
            420                 425                 430
Ala Asn Gln Arg Ala Glu Arg Pro Gly Pro Pro Arg Gly Gly His Gly
        435                 440                 445
Pro Val Asn Ala Ser Ser Ala Pro Asp Thr Ser Pro Pro Arg His Pro
    450                 455                 460
Arg Arg Trp Val Ser Gln Gln Arg Gln Arg Leu Trp Arg Gln Phe Arg
465                 470                 475                 480
Val Gly Gly Gly Phe Pro Pro Pro Pro Pro Ser Arg Pro Pro Ala Val
                485                 490                 495
Leu Leu Pro Leu Leu Arg Leu Ala Cys Ala Gly Asp Pro Gly Ala Thr
            500                 505                 510
Arg Pro Gly Pro Arg Arg Pro Ala Arg Arg Pro Arg Gly Glu Leu Ile
        515                 520                 525
Pro Arg Arg Pro Asp Pro Ala Ala Pro Ser Glu Glu Gly Leu Arg Met
    530                 535                 540
Glu Ser Ser Val Asp Asp Gly Ala Thr Ala Thr Thr Ala Asp Ala Ala
545                 550                 555                 560
Ser Gly Glu Ala Pro Glu Ala Gly Pro Ser Pro Ser His Ser Pro Thr
                565                 570                 575
Met Cys Gln Thr Gly Gly Pro Gly Pro Pro Pro Pro Gln Pro Pro Arg
            580                 585                 590
Trp Leu Pro
        595
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<210> 188
<211> 376

388
528
643

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<212> PRT
<213> Homo sapien

<400> 188

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Glu Met Arg Lys Phe Asp Val Pro Ser Met Glu Ser Thr Leu Asn Gln
 1               5                  10                  15
Pro Ala Met Leu Glu Thr Leu Tyr Ser Asp Pro His Tyr Arg Ala His
            20                  25                  30
Phe Pro Asn Pro Arg Pro Asp Thr Asn Lys Asp Val Tyr Lys Val Leu
        35                  40                  45
Pro Glu Ser Lys Lys Ala Pro Gly Ser Gly Ala Val Phe Glu Arg Asn
    50                  55                  60
Gly Pro His Ala Ser Ser Ser Gly Val Leu Pro Leu Gly Leu Gln Pro
65                  70                  75                  80
Ala Pro Gly Leu Ser Lys Ser Leu Ser Ser Gln Val Trp Gln Pro Ser
                85                  90                  95
Pro Asp Pro Trp His Pro Gly Glu Gln Ser Cys Glu Leu Ser Thr Cys
            100                 105                 110
Arg Gln Gln Leu Glu Leu Ile Arg Leu Gln Met Glu Gln Met Gln Leu
        115                 120                 125
Gln Asn Gly Ala Met Cys His His Pro Ala Ala Phe Ala Pro Leu Leu
    130                 135                 140
Pro Thr Leu Glu Pro Ala Gln Trp Leu Ser Ile Leu Asn Ser Asn Glu
145                 150                 155                 160
His Leu Leu Lys Glu Lys Glu Leu Leu Ile Asp Lys Gln Arg Lys His
                165                 170                 175
Ile Ser Gln Leu Glu Gln Lys Val Arg Glu Ser Glu Leu Gln Val His
            180                 185                 190
Ser Ala Leu Leu Gly Arg Pro Ala Pro Phe Gly Asp Val Cys Leu Leu
        195                 200                 205
Arg Leu Gln Glu Leu Gln Arg Glu Asn Thr Phe Leu Arg Ala Gln Phe
    210                 215                 220
Ala Gln Lys Thr Glu Ala Leu Ser Lys Glu Lys Met Glu Leu Glu Lys
225                 230                 235                 240
Lys Leu Ser Ala Ser Glu Val Glu Ile Gln Leu Ile Arg Glu Ser Leu
                245                 250                 255
Lys Val Thr Leu Gln Lys His Ser Glu Glu Gly Lys Lys Gln Glu Glu
            260                 265                 270
Arg Val Lys Gly Arg Asp Lys His Ile Asn Asn Leu Lys Lys Lys Cys
        275                 280                 285
Gln Lys Glu Ser Glu Gln Asn Arg Glu Lys Gln Gln Arg Ile Glu Thr
    290                 295                 300
Leu Glu Arg Tyr Leu Ala Asp Leu Pro Thr Leu Glu Asp His Gln Lys
305                 310                 315                 320
Gln Thr Glu Gln Leu Lys Asp Ala Glu Leu Lys Asn Thr Glu Leu Gln
                325                 330                 335
Glu Arg Val Ala Glu Leu Glu Thr Leu Leu Glu Asp Thr Gln Ala Thr
            340                 345                 350
Cys Arg Glu Lys Glu Val Gln Leu Glu Ser Leu Arg Gln Arg Glu Ala
        355                 360                 365
Asp Leu Ser Ser Ala Arg His Arg
    370                 375
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<210> 189
<211> 160

359
5/29
644

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<212> PRT
<213> Homo sapien

<400> 189
Met Leu Glu Ala His Arg Arg Gln Arg His Pro Phe Leu Leu Leu Gly
1 5 10 15
Thr Thr Ala Asn Arg Thr Gln Ser Leu Asn Tyr Gly Cys Ile Val Glu
20 25 30
Asn Pro Gln Thr His Glu Val Leu His Tyr Val Glu Lys Pro Ser Thr
35 40 45
Phe Ile Ser Asp Ile Ile Asn Cys Gly Ile Tyr Leu Phe Ser Pro Glu
50 55 60
Ala Leu Lys Pro Leu Arg Asp Val Phe Gln Arg Asn Gln Gln Asp Gly
65 70 75 80
Gln Leu Glu Asp Ser Pro Gly Leu Trp Pro Gly Ala Gly Thr Ile Arg
85 90 95
Leu Glu Gln Asp Val Phe Ser Ala Leu Ala Gly Gln Gly Gln Ile Tyr
100 105 110
Val His Leu Thr Asp Gly Ile Trp Ser Gln Ile Lys Ser Ala Gly Ser
115 120 125
Ala Leu Tyr Ala Ser Arg Leu Tyr Leu Ser Arg Tyr Gln Asp Thr His
130 135 140
Pro Glu Arg Leu Ala Lys His Thr Pro Gly Gly Pro Trp Ile Arg Gly
145 150 155 160

<210> 190
<211> 146
<212> PRT
<213> Homo sapien

<400> 190
Met Asp Pro Arg Ala Ser Leu Leu Leu Leu Gly Asn Val Tyr Ile His
1 5 10 15
Pro Thr Ala Lys Val Ala Pro Ser Ala Val Leu Gly Pro Asn Val Ser
20 25 30
Ile Gly Lys Gly Val Thr Val Gly Glu Gly Val Arg Leu Arg Glu Ser
35 40 45
Ile Val Leu His Gly Ala Thr Leu Gln Glu His Thr Cys Val Leu His
50 55 60
Ser Ile Val Gly Trp Gly Ser Thr Val Gly Arg Trp Ala Arg Val Glu
65 70 75 80
Gly Thr Pro Ser Asp Pro Asn Pro Asn Asp Pro Arg Ala Arg Met Asp
85 90 95
Ser Glu Ser Leu Phe Lys Asp Gly Lys Leu Leu Pro Ala Ile Thr Ile
100 105 110
Leu Gly Cys Arg Val Arg Ile Pro Ala Glu Val Leu Ile Leu Asn Ser
115 120 125
Ile Val Leu Pro His Lys Glu Leu Ser Arg Ser Phe Thr Asn Gln Ile
130 135 140
Ile Leu
145

<210> 191
<211> 704
<212> PRT

360
645

09370 38.0800999

<213> Homo sapien

<400> 191

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Glu Gly Gly Cys Ala Ala Gly Arg Gly Arg Glu Leu Glu Pro Glu Leu
 1               5                  10                  15
Glu Pro Gly Pro Gly Pro Gly Ser Ala Leu Glu Pro Gly Glu Glu Phe
            20                  25                  30
Glu Ile Val Asp Arg Ser Gln Leu Pro Gly Pro Gly Asp Leu Arg Ser
        35                  40                  45
Ala Thr Arg Pro Arg Ala Ala Glu Gly Trp Ser Ala Pro Ile Leu Thr
    50                  55                  60
Leu Ala Arg Arg Ala Thr Gly Asn Leu Ser Ala Ser Cys Gly Ser Ala
65                  70                  75                  80
Leu Arg Ala Ala Ala Gly Leu Gly Gly Gly Asp Ser Gly Asp Gly Thr
                85                  90                  95
Ala Arg Ala Ala Ser Lys Cys Gln Met Met Glu Glu Arg Ala Asn Leu
            100                 105                 110
Met His Met Met Lys Leu Ser Ile Lys Val Leu Leu Gln Ser Ala Leu
        115                 120                 125
Ser Leu Gly Arg Ser Leu Asp Ala Asp His Ala Pro Leu Gln Gln Phe
    130                 135                 140
Phe Val Val Met Glu His Cys Leu Lys His Gly Leu Lys Val Lys Lys
145                 150                 155                 160
Ser Phe Ile Gly Gln Asn Lys Ser Phe Phe Gly Pro Leu Glu Leu Val
                165                 170                 175
Glu Lys Leu Cys Pro Glu Ala Ser Asp Ile Ala Thr Ser Val Arg Asn
            180                 185                 190
Leu Pro Glu Leu Lys Thr Ala Val Gly Arg Gly Arg Ala Trp Leu Tyr
        195                 200                 205
Leu Ala Leu Met Gln Lys Lys Leu Ala Asp Tyr Leu Lys Val Leu Ile
    210                 215                 220
Asp Asn Lys His Leu Leu Ser Glu Phe Tyr Glu Pro Glu Ala Leu Met
225                 230                 235                 240
Met Glu Glu Glu Gly Met Val Ile Val Gly Leu Leu Val Gly Leu Asn
                245                 250                 255
Val Leu Asp Ala Asn Leu Cys Leu Lys Gly Glu Asp Leu Asp Ser Gln
            260                 265                 270
Val Gly Val Ile Asp Phe Ser Leu Tyr Leu Lys Asp Val Gln Asp Leu
        275                 280                 285
Asp Gly Gly Lys Glu His Glu Arg Ile Thr Asp Val Leu Asp Gln Lys
    290                 295                 300
Asn Tyr Val Glu Glu Leu Asn Arg His Leu Ser Cys Thr Val Gly Asp
305                 310                 315                 320
Leu Gln Thr Lys Ile Asp Gly Leu Glu Lys Thr Asn Ser Lys Leu Gln
                325                 330                 335
Glu Glu Leu Ser Ala Ala Thr Asp Arg Ile Cys Ser Leu Gln Glu Glu
            340                 345                 350
Gln Gln Gln Leu Arg Glu Gln Asn Glu Leu Ile Arg Glu Arg Ser Glu
        355                 360                 365
Lys Ser Val Glu Ile Thr Lys Gln Asp Thr Lys Val Glu Leu Glu Thr
    370                 375                 380
Tyr Lys Gln Thr Arg Gln Gly Leu Asp Glu Met Tyr Ser Asp Val Trp
385                 390                 395                 400
Lys Gln Leu Lys Glu Glu Lys Lys Val Arg Leu Glu Leu Glu Lys Glu
                405                 410                 415
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367
987
646

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Leu Glu Leu Gln Ile Gly Met Lys Thr Glu Met Glu Ile Ala Met Lys
420 425 430
Leu Leu Glu Lys Asp Thr His Glu Lys Gln Asp Thr Leu Val Ala Leu
435 440 445
Arg Gln Gln Leu Glu Glu Val Lys Ala Ile Asn Leu Gln Met Phe His
450 455 460
Lys Ala Gln Asn Ala Glu Ser Ser Leu Gln Gln Lys Asn Glu Ala Ile
465 470 475 480
Thr Ser Phe Glu Gly Lys Thr Asn Gln Val Met Ser Ser Met Lys Gln
485 490 495
Met Glu Glu Arg Leu Gln His Ser Glu Arg Ala Arg Gln Gly Ala Glu
500 505 510
Glu Arg Ser His Lys Leu Gln Gln Glu Leu Gly Gly Arg Ile Gly Ala
515 520 525
Leu Gln Leu Gln Leu Ser Gln Leu His Glu Gln Cys Ser Ser Leu Glu
530 535 540
Lys Glu Leu Lys Ser Glu Lys Glu Gln Arg Gln Ala Leu Gln Arg Glu
545 550 555 560
Leu Gln His Glu Lys Asp Thr Ser Ser Leu Leu Arg Met Glu Leu Gln
565 570 575
Gln Val Glu Gly Leu Lys Lys Glu Leu Arg Glu Leu Gln Asp Glu Lys
580 585 590
Ala Glu Leu Gln Lys Ile Cys Glu Glu Gln Glu Gln Ala Leu Gln Glu
595 600 605
Met Gly Leu His Leu Ser Gln Ser Lys Leu Lys Met Glu Asp Ile Lys
610 615 620
Glu Val Asn Gln Ala Leu Lys Gly His Ala Trp Leu Lys Asp Asp Glu
625 630 635 640
Ala Thr His Cys Arg Gln Cys Glu Lys Glu Phe Ser Ile Ser Arg Arg
645 650 655
Lys His His Cys Arg Asn Cys Gly His Ile Phe Cys Asn Thr Cys Ser
660 665 670
Ser Asn Glu Leu Ala Leu Pro Ser Tyr Pro Lys Pro Val Arg Val Cys
675 680 685
Asp Ser Cys His Thr Leu Leu Leu Gln Arg Cys Ser Ser Thr Ala Ser
690 695 700

<210> 192
<211> 331
<212> PRT
<213> Homo sapien

<400> 192
Arg Ala Gly Ala Ser Ala Met Ala Leu Arg Lys Glu Leu Leu Lys Ser
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20 25 30
Ser Lys Ser Gln Leu Lys Val Leu Ser His Asn Leu Tyr Thr Val Leu
35 40 45
His Ile Pro His Asp Pro Val Ala Leu Glu Glu His Phe Arg Asp Asp
50 55 60
Asp Asp Gly Pro Val Ser Ser Gln Gly Tyr Met Pro Tyr Leu Asn Lys
65 70 75 80
Tyr Ile Leu Asp Lys Val Glu Glu Gly Ala Phe Val Lys Glu His Phe
85 90 95

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Asp Glu Leu Cys Trp Thr Leu Thr Ala Lys Lys Asn Tyr Arg Ala Asp
100 105 110
Ser Asn Gly Asn Ser Met Leu Ser Asn Gln Asp Ala Phe Arg Leu Trp
115 120 125
Cys Leu Phe Asn Phe Leu Ser Glu Asp Lys Tyr Pro Leu Ile Met Val
130 135 140
Pro Asp Glu Val Glu Tyr Leu Leu Lys Lys Val Leu Ser Ser Met Ser
145 150 155 160
Leu Glu Val Ser Leu Gly Glu Leu Glu Glu Leu Leu Ala Gln Glu Ala
165 170 175
Gln Val Ala Gln Thr Thr Gly Gly Leu Ser Val Trp Gln Phe Leu Glu
180 185 190
Leu Phe Asn Ser Gly Arg Cys Leu Arg Gly Val Gly Arg Asp Thr Leu
195 200 205
Ser Met Ala Ile His Glu Val Tyr Gln Glu Leu Ile Gln Asp Val Leu
210 215 220
Lys Gln Gly Tyr Leu Trp Lys Arg Gly His Leu Arg Arg Asn Trp Ala
225 230 235 240
Glu Arg Trp Phe Gln Leu Gln Pro Ser Cys Leu Cys Tyr Phe Gly Ser
245 250 255
Glu Glu Cys Lys Glu Lys Arg Gly Ile Ile Pro Leu Asp Ala His Cys
260 265 270
Cys Val Glu Val Leu Pro Asp Arg Asp Gly Lys Arg Cys Met Phe Cys
275 280 285
Val Lys Thr Ala Thr Arg Thr Tyr Glu Met Ser Ala Ser Asp Thr Arg
290 295 300
Gln Arg Gln Glu Trp Thr Ala Ala Ile Gln Met Ala Ile Arg Leu Gln
305 310 315 320
Ala Glu Gly Lys Thr Ser Leu His Lys Asp Leu
325 330

<210> 193
<211> 475
<212> PRT
<213> Homo sapien

<400> 193
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1 5 10 15
Asn Asn Arg Asn Val His Leu Glu His Ser Glu Gln Asn Pro Gly Ser
20 25 30
Ser Ala Gly Asp Thr Ser Ala Ala His Gln Val Val Leu Gly Glu Asn
35 40 45
Leu Ile Ala Thr Ala Leu Cys Leu Ser Gly Ser Gly Ser Gln Ser Asp
50 55 60
Leu Lys Asp Val Ala Ser Thr Ala Gly Glu Glu Gly Asp Thr Ser Leu
65 70 75 80
Arg Glu Ser Leu His Pro Val Thr Arg Ser Leu Lys Ala Gly Cys His
85 90 95
Thr Lys Gln Leu Ala Ser Arg Asn Cys Ser Glu Glu Lys Ser Pro Gln
100 105 110
Thr Ser Ile Leu Lys Glu Gly Asn Arg Asp Thr Ser Leu Asp Phe Arg
115 120 125
Pro Val Val Ser Pro Ala Asn Gly Val Glu Gly Val Arg Val Asp Gln
130 135 140

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

      <210> 194
      <211> 241
      <212> PRT
      <213> Homo sapien

      <400> 194
Met Ser Gly Glu Ser Ala Arg Ser Leu Gly Lys Gly Ser Ala Pro Pro
 1               5                  10                  15
Gly Pro Val Pro Glu Gly Ser Ile Arg Ile Tyr Ser Met Arg Phe Cys
            20                  25                  30
Pro Phe Ala Glu Arg Thr Arg Leu Val Leu Lys Ala Lys Gly Ile Arg
        35                  40                  45
```

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649

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

<210> 195
<211> 138
<212> PRT
<213> Homo sapien

<400> 195
Gln Thr Lys Ile Leu Glu Glu Asp Leu Glu Gln Ile Lys Leu Ser Leu
1 5 10 15
Arg Glu Arg Gly Arg Glu Leu Thr Thr Gln Arg Gln Leu Met Gln Glu
20 25 30
Arg Ala Glu Glu Gly Lys Gly Pro Ser Lys Ala Gln Arg Gly Ser Leu
35 40 45
Glu His Met Lys Leu Ile Leu Arg Asp Lys Glu Lys Glu Val Glu Cys
50 55 60
Gln Gln Glu His Ile His Glu Leu Gln Glu Leu Lys Asp Gln Leu Glu
65 70 75 80
Gln Gln Leu Gln Gly Leu His Arg Lys Val Gly Glu Thr Ser Leu Leu
85 90 95
Leu Ser Gln Arg Glu Gln Glu Ile Val Val Leu Gln Gln Gln Leu Gln
100 105 110
Glu Ala Arg Glu Gln Gly Glu Leu Lys Glu Gln Ser Leu Gln Ser Gln
115 120 125
Leu Asp Glu Ala Gln Arg Ala Leu Ala Gln
130 135

<210> 196
<211> 102
<212> PRT

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<213> Homo sapien

<400> 196

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

<210> 197
<211> 138
<212> PRT
<213> Homo sapien

<400> 197

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

<210> 198
<211> 100
<212> PRT
<213> Homo sapien

<400> 198

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

Gly Asn Ser Thr Asn Lys Lys Asp Ala Gln Ser Asn Ala Ala Arg Asp
50 55 60
Phe Val Asn Tyr Leu Val Arg Ile Asn Glu Ile Lys Ser Glu Glu Val
65 70 75 80
Pro Ala Phe Gly Val Ala Ser Pro Pro Pro Leu Thr Asp Thr Pro Asp
85 90 95
Thr Thr Ala Asn
100

<210> 199
<211> 127
<212> PRT
<213> Homo sapien

<400> 199
Met Val Lys Glu Thr Thr Tyr Tyr Asp Val Leu Gly Val Lys Pro Asn
1 5 10 15
Ala Thr Gln Glu Glu Leu Lys Lys Ala Tyr Arg Lys Leu Ala Leu Lys
20 25 30
Tyr His Pro Asp Lys Asn Pro Asn Glu Gly Glu Lys Phe Lys Gln Ile
35 40 45
Ser Gln Ala Tyr Glu Val Leu Ser Asp Ala Lys Lys Arg Glu Leu Tyr
50 55 60
Asp Lys Gly Gly Glu Gln Ala Ile Lys Glu Gly Gly Ala Gly Gly Gly
65 70 75 80
Phe Gly Ser Pro Met Asp Ile Phe Asp Met Phe Phe Gly Gly Gly Gly
85 90 95
Arg Met Gln Arg Glu Arg Arg Gly Lys Asn Val Val His Gln Leu Ser
100 105 110
Val Thr Leu Glu Asp Leu Tyr Asn Gly Ala Thr Arg Lys Leu Ala
115 120 125

<210> 200
<211> 90
<212> PRT
<213> Homo sapien

<400> 200
Met Ala Cys Pro Leu Asp Gln Ala Ile Gly Leu Leu Val Ala Ile Phe
1 5 10 15
His Lys Tyr Ser Gly Arg Glu Gly Asp Lys His Thr Leu Ser Lys Lys
20 25 30
Glu Leu Lys Glu Leu Ile Gln Lys Glu Leu Thr Ile Gly Ser Lys Leu
35 40 45
Gln Asp Ala Glu Ile Ala Arg Leu Met Glu Asp Leu Asp Arg Asn Lys
50 55 60
Asp Gln Glu Val Asn Phe Gln Glu Tyr Val Thr Phe Leu Gly Ala Leu
65 70 75 80
Ala Leu Ile Tyr Asn Glu Ala Leu Lys Gly
85 90

<210> 201
<211> 120
<212> PRT
<213> Homo sapien

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369
637
652

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<400> 201

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

<210> 202
<211> 177
<212> PRT
<213> Homo sapien

<400> 202

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

<210> 203
<211> 164
<212> PRT
<213> Homo sapien

388
653

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<400> 203

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

<210> 204
<211> 241
<212> PRT
<213> Homo sapien

<400> 204

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

654

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```
        195                 200                 205
Asp Pro Thr Val Ser Ala Leu Leu Thr Ser Glu Lys Asp Trp Gln Gly
    210                 215                 220
Phe Leu Glu Leu Tyr Leu Gln Asn Ser Pro Glu Ala Cys Asp Tyr Gly
225                 230                 235                 240
Leu
```

<210> 205
<211> 160
<212> PRT
<213> Homo sapien

<400> 205

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

<210> 206
<211> 197
<212> PRT
<213> Homo sapien

<400> 206

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

Gly Pro Gly Ser Gln Arg His Phe Ala Thr Ser Cys His Gln Asp Glu
115 120 125
Tyr Ser Gln Gln Ile Val Cys His Cys Arg Ala Gly Tyr Thr Gly Leu
130 135 140
Arg Cys Glu Ala Cys Ala Pro Gly His Phe Gly Asp Pro Ser Arg Pro
145 150 155 160
Gly Gly Arg Cys Gln Leu Cys Glu Cys Ser Gly Asn Ile Asp Pro Met
165 170 175
Asp Pro Asp Ala Cys Asp Pro His Thr Gly Gln Cys Leu Arg Cys Leu
180 185 190
His His Thr Glu Gly
195

<210> 207
<211> 175
<212> PRT
<213> Homo sapien

<400> 207
Ile Ile Arg Gln Gln Gly Leu Ala Ser Tyr Asp Tyr Val Arg Arg Arg
1 5 10 15
Leu Thr Ala Glu Asp Leu Phe Glu Ala Arg Ile Ile Ser Leu Glu Thr
20 25 30
Tyr Asn Leu Leu Arg Glu Gly Thr Arg Ser Leu Arg Glu Ala Leu Glu
35 40 45
Ala Glu Ser Ala Trp Cys Tyr Leu Tyr Gly Thr Gly Ser Val Ala Gly
50 55 60
Val Tyr Leu Pro Gly Ser Arg Gln Thr Leu Ser Ile Tyr Gln Ala Leu
65 70 75 80
Lys Lys Gly Leu Leu Ser Ala Glu Val Ala Arg Leu Leu Leu Glu Ala
85 90 95
Gln Ala Ala Thr Gly Phe Leu Leu Asp Pro Val Lys Gly Glu Arg Leu
100 105 110
Thr Val Asp Glu Ala Val Arg Lys Gly Leu Val Gly Pro Glu Leu His
115 120 125
Asp Arg Leu Leu Ser Ala Glu Arg Ala Val Thr Gly Tyr Arg Asp Pro
130 135 140
Tyr Thr Glu Gln Thr Ile Ser Leu Phe Gln Ala Met Lys Lys Glu Leu
145 150 155 160
Ile Pro Thr Glu Glu Ala Leu Arg Leu Trp Met Pro Ser Trp Pro
165 170 175

<210> 208
<211> 177
<212> PRT
<213> Homo sapien

<400> 208
Met Ala Ala Gly Val Glu Ala Ala Ala Glu Val Ala Ala Thr Glu Ile
1 5 10 15
Lys Met Glu Glu Glu Ser Gly Ala Pro Gly Val Pro Ser Gly Asn Gly
20 25 30
Ala Pro Gly Pro Lys Gly Glu Gly Glu Arg Pro Ala Gln Asn Glu Lys
35 40 45
Arg Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr

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94
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656

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

<210> 209
<211> 196
<212> PRT
<213> Homo sapien

<400> 209
Asp Leu Gln Asp Met Phe Ile Val His Thr Ile Glu Glu Ile Glu Gly
1 5 10 15
Leu Ile Ser Ala His Asp Gln Phe Lys Ser Thr Leu Pro Asp Ala Asp
20 25 30
Arg Glu Arg Glu Ala Ile Leu Ala Ile His Lys Glu Ala Gln Arg Ile
35 40 45
Ala Glu Ser Asn His Ile Lys Leu Ser Gly Ser Asn Pro Tyr Thr Thr
50 55 60
Val Thr Pro Gln Ile Ile Asn Ser Lys Trp Glu Lys Val Gln Gln Leu
65 70 75 80
Val Pro Lys Arg Asp His Ala Leu Leu Glu Glu Gln Ser Lys Gln Gln
85 90 95
Ser Asn Glu His Leu Arg Arg Gln Phe Ala Ser Gln Ala Asn Val Val
100 105 110
Gly Pro Trp Ile Gln Thr Lys Met Glu Glu Ile Gly Arg Ile Ser Ile
115 120 125
Glu Met Asn Gly Thr Leu Glu Asp Gln Leu Ser His Leu Lys Gln Tyr
130 135 140
Glu Arg Ser Ile Val Asp Tyr Lys Pro Asn Leu Asp Leu Leu Glu Gln
145 150 155 160
Gln His Gln Leu Ile Gln Glu Ala Leu Ile Phe Asp Asn Lys His Thr
165 170 175
Asn Tyr Thr Met Glu His Ile Arg Val Gly Trp Glu Gln Leu Leu Thr
180 185 190
Thr Ile Ala Arg
195

<210> 210
<211> 156
<212> PRT
<213> Homo sapien

322
656
657

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<400> 210

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

<210> 211
<211> 92
<212> PRT
<213> Homo sapien

<400> 211

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

<210> 212
<211> 142
<212> PRT
<213> Homo sapien

<400> 212

Glu Lys Gln Lys Asn Lys Glu Phe Ser Gln Thr Leu Glu Asn Glu Lys
1 5 10 15
Asn Thr Leu Leu Ser Gln Ile Ser Thr Lys Asp Gly Glu Leu Lys Met
20 25 30
Leu Gln Glu Glu Val Thr Lys Met Asn Leu Leu Asn Gln Gln Ile Gln
35 40 45
Glu Glu Leu Ser Arg Val Thr Lys Leu Lys Glu Thr Ala Glu Glu Glu

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658

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```
    50                  55                  60
Lys Asp Asp Leu Glu Glu Arg Leu Met Asn Gln Leu Ala Glu Leu Asn
65                  70                  75                  80
Gly Ser Ile Gly Asn Tyr Cys Gln Asp Val Thr Asp Ala Gln Ile Lys
                85                  90                  95
Asn Glu Leu Leu Glu Ser Glu Met Lys Asn Leu Lys Lys Cys Val Ser
            100                 105                 110
Glu Leu Glu Glu Glu Lys Gln Gln Leu Val Lys Glu Lys Thr Lys Val
        115                 120                 125
Glu Ser Glu Ile Arg Lys Glu Tyr Leu Glu Lys Ile Gln Gly
    130                 135                 140
```

<210> 213
<211> 142
<212> PRT
<213> Homo sapien

<400> 213

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

<210> 214
<211> 129
<212> PRT
<213> Homo sapien

<400> 214

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

Val Ile Leu Leu Glu Asn Leu Arg Phe His Val Glu Glu Glu Gly Lys
100 105 110
Gly Lys Asp Ala Ser Gly Asn Lys Val Lys Ala Glu Pro Ala Lys Ile
115 120 125
Glu

<210> 215
<211> 148
<212> PRT
<213> Homo sapien

<400> 215
Met Ala Thr Leu Lys Glu Lys Leu Ile Ala Pro Val Ala Glu Glu Glu
1 5 10 15
Ala Thr Val Pro Asn Asn Lys Ile Thr Val Val Gly Val Gly Gln Val
20 25 30
Gly Met Ala Cys Ala Ile Ser Ile Leu Gly Lys Ser Leu Ala Asp Glu
35 40 45
Leu Ala Leu Val Asp Val Leu Glu Asp Lys Leu Lys Gly Glu Met Met
50 55 60
Asp Leu Gln His Gly Ser Leu Phe Leu Gln Thr Pro Lys Ile Val Ala
65 70 75 80
Asp Lys Asp Tyr Ser Val Thr Ala Asn Ser Lys Ile Val Val Val Thr
85 90 95
Ala Gly Val Arg Gln Gln Glu Gly Glu Ser Arg Leu Asn Leu Val Gln
100 105 110
Arg Asn Val Asn Val Phe Lys Phe Ile Ile Pro Gln Ile Val Lys Tyr
115 120 125
Ser Pro Asp Cys Ile Ile Ile Val Val Ser Asn Pro Val Asp Ile Leu
130 135 140
Thr Tyr Val Thr
145

<210> 216
<211> 527
<212> PRT
<213> Homo sapien

<400> 216
Gln Arg Ala Pro Gly Ile Glu Glu Lys Ala Ala Glu Asn Gly Ala Leu
1 5 10 15
Gly Ser Pro Glu Arg Glu Glu Lys Val Leu Glu Asn Gly Glu Leu Thr
20 25 30
Pro Pro Arg Arg Glu Glu Lys Ala Leu Glu Asn Gly Glu Leu Arg Ser
35 40 45
Pro Glu Ala Gly Glu Lys Val Leu Val Asn Gly Gly Leu Thr Pro Pro
50 55 60
Lys Ser Glu Asp Lys Val Ser Glu Asn Gly Gly Leu Arg Phe Pro Arg
65 70 75 80
Asn Thr Glu Arg Pro Pro Glu Thr Gly Pro Trp Arg Ala Pro Gly Pro
85 90 95
Trp Glu Lys Thr Pro Glu Ser Trp Gly Pro Ala Pro Thr Ile Gly Glu
100 105 110
Pro Ala Pro Glu Thr Ser Leu Glu Arg Ala Pro Ala Pro Ser Ala Val

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395
660

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```
        115                 120                 125
Val Ser Ser Arg Asn Gly Gly Glu Thr Ala Pro Gly Pro Leu Gly Pro
    130                 135                 140
Ala Pro Lys Asn Gly Thr Leu Glu Pro Gly Thr Glu Arg Arg Ala Pro
145                 150                 155                 160
Glu Thr Gly Gly Ala Pro Arg Ala Pro Gly Ala Gly Arg Leu Asp Leu
                165                 170                 175
Gly Ser Gly Gly Arg Ala Pro Val Gly Thr Gly Thr Ala Pro Gly Gly
            180                 185                 190
Gly Pro Gly Ser Gly Val Asp Ala Lys Ala Gly Trp Val Asp Asn Thr
        195                 200                 205
Arg Pro Gln Pro Pro Pro Pro Pro Leu Pro Pro Pro Pro Glu Ala Gln
    210                 215                 220
Pro Arg Arg Leu Glu Pro Ala Pro Pro Arg Ala Arg Pro Glu Val Ala
225                 230                 235                 240
Pro Glu Gly Glu Pro Gly Ala Pro Asp Ser Arg Ala Gly Gly Asp Thr
                245                 250                 255
Ala Leu Ser Gly Asp Gly Asp Pro Pro Lys Pro Glu Arg Lys Gly Pro
            260                 265                 270
Glu Met Pro Arg Leu Phe Leu Asp Leu Gly Pro Pro Gln Gly Asn Ser
        275                 280                 285
Glu Gln Ile Lys Ala Arg Leu Ser Arg Leu Ser Leu Ala Leu Pro Pro
    290                 295                 300
Leu Thr Leu Thr Pro Phe Pro Gly Pro Gly Pro Arg Arg Pro Pro Trp
305                 310                 315                 320
Glu Gly Ala Asp Ala Gly Ala Ala Gly Gly Glu Ala Gly Gly Ala Gly
                325                 330                 335
Ala Pro Gly Pro Ala Glu Glu Asp Gly Glu Asp Glu Asp Glu Asp Glu
            340                 345                 350
Glu Glu Asp Glu Glu Ala Ala Ala Pro Gly Ala Ala Ala Gly Pro Arg
        355                 360                 365
Gly Pro Gly Arg Ala Arg Ala Ala Pro Val Pro Val Val Val Ser Ser
    370                 375                 380
Ala Asp Ala Asp Ala Ala Arg Pro Leu Arg Gly Leu Leu Lys Ser Pro
385                 390                 395                 400
Arg Gly Ala Asp Glu Pro Glu Asp Ser Glu Leu Glu Arg Lys Arg Lys
                405                 410                 415
Met Val Ser Phe His Gly Asp Val Thr Val Tyr Leu Phe Asp Gln Glu
            420                 425                 430
Thr Pro Thr Asn Glu Leu Ser Val Gln Ala Pro Pro Glu Gly Asp Thr
        435                 440                 445
Asp Pro Ser Thr Pro Pro Ala Pro Pro Thr Pro Pro His Pro Ala Thr
    450                 455                 460
Pro Gly Asp Gly Phe Pro Ser Asn Asp Ser Gly Phe Gly Gly Ser Phe
465                 470                 475                 480
Glu Trp Ala Glu Asp Phe Pro Leu Leu Pro Pro Pro Gly Pro Pro Leu
                485                 490                 495
Cys Phe Ser Arg Phe Ser Val Ser Pro Ala Leu Glu Thr Pro Gly Pro
            500                 505                 510
Pro Ala Arg Ala Pro Asp Ala Arg Pro Ala Gly Pro Val Glu Asn
        515                 520                 525
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<210> 217
<211> 466
<212> DNA

337
546
661

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<213> Homo sapien

<400> 217

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accaagatgg tcgttactct ctgacctata tctacactgg gctgtccaag catgttgaag 120
acgtccccgc gtttcaggcc cttggctcac tcaatgacct ccagttcttt agatacaaca 180
gtaaagacag gaagtctcag cccatgggac tctggagaca ggtggaagga atggaggatt 240
ggaagcagga cagccaactt cagaaggcca gggaggacat ctttatggag accctgaaag 300
acatcgtgga gtattacaac gacagtaacg ggtctcacgt attgcaggga aggtttggtt 360
gtgagatcga gaataacaga agcagcggag cattctggaa atattactat gatggaaagg 420
actacattga attcaacaaa gaaatcccag cctgggtccc cttcga 466

<210> 218
<211> 381
<212> DNA
<213> Homo sapien

<400> 218

gagtttcctt cgcaagttca tgtggggtac cttcccaggc tgcctggctg accagctggt 60
tttaaagcgc cggggtaacc agttggagat ctgtgccgtg gtcctgaggc agttgtctcc 120
acacaagtac tacttcctcg tgggctacag tgaaactttg ctgtcctact tttacaaatg 180
tcctgtgcga ctccacctcc aaactgtgcc ctcaaaggtt gtgtataagt acctctagaa 240
caatcccctt ttttccatca agctgtagcc tgcagagaat ggaaacgtgg gaaaggaatg 300
gtatgtgggg gaaatgcatc ccctcagagg actgaggcat agtctctcat ctgctattga 360
ataaagacct tctatcttgt a 381

<210> 219
<211> 1293
<212> DNA
<213> Homo sapien

<400> 219

gaggggaggc gcatggcggg gatggcgctg gcgcgggcct ggaagcagat gtcctggttc 60
tactaccagt acctgctggt cacggcgctc tacatgctgg agccctggga gcggacggtg 120
ttcaattcca tgctggtttc cattgtgggg atggcactat acacaggata cgtcttcatg 180
ccccagcaca tcatggcgat attgcactac tttgaaatcg tacaatgacc aagatgcgac 240
caggatcaga ggttccttgg ggaagaccca ccctacgaag ttggaatgag accatcagat 300
gtgataagaa actcttctag atgtcaacat aaccaaccct ataaagacta aaattcatga 360
gtagaacagg aaaatcatcc tgactcatgt gttgtgttct ttatttttaa ttttcaaaga 420
ggctcttgta tagcagtttt tgtctatttt aacattgtag tcatttgtac tttgatatca 480
gtatttttct aacctttgtg actgtttcaa tattaccccc gtgaaagctt ttcttaatgt 540
aactttgagt acattttaat tgccttctat ttttaaaact caaaatcatt agttgggctt 600
tactgttctt gctattgtat ggcatataca tctgcctgga tatatttcta ctcttgacca 660
aagttttgta aagaacaata taagatttcg ggtaggggta tggggaggga agatatttta 720
ttgagaacta cttaacaaaa gatttatctg taagcttgaa ctcaggagta cagttttagc 780
tatctagact ctaacagctt ttgctttaaa attattaaag tgtttcttaa tgaaaaagaa 840
aagatcttgc taaagttaaa ataaggaaca tttcaccttt taaatattta attcttatgt 900
ggacttattt ccagaaaact ttggtgataa ttcttgagac aaaaggtggt taagtagcat 960
tattatgtaa tgcttatata ccatagagtt tttaatagaa gagaaatcca tttcctccga 1020
gggtcactat taacaatgta cttccttaaa tttagtttaa tgattgtaat gggtgctgca 1080
tttgcacatt gcattaagtt atgatgagac gaattgttgt taaaaattat agcaaaaaga 1140
aatgtaaact tggttaaaat cctttcactc tttgtattgt ttttttaag gtttttattc 1200
cttaaatgta aaatgactac ctaatttttt gatgtaaata cattaaattc aaagagaaaa 1260
aaaatcaaaa aaaaaaaaaa aaaaaaactc gag 1293

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<210> 220
<211> 983
<212> DNA
<213> Homo sapien

<400> 220
caggttattc tgatcctgcc gcctgtcttc cctgtaagag tggagcctcg aggtgtacct 60
taaagtgacc ggaatgttag agatgcaatt tgcagagctg gggcaaggaa gggctccttg 120
tcactgtagt tactttcctt gcagtggcca aatgcccaat aagaaggaat acatgaccac 180
tgctgtgggg agtcagcagg tgcgtgatgc agctggccac actccatcca cggccatgac 240
ataaaacaga caagaagtaa ggctggactg taacacctca aggcctgctc cagtgaccca 300
ctttcttcag agaggctcta ccacacacac aaccaccttc caaatttaca ctcagatcac 360
tacaccatgt ctcccaagtt aaaacatgta tccacctaga ctttaaatgt gctttgtaac 420
tgttgatggc actgtacaga gggccaaagt atttcccatc agatagcatt tttctgaacc 480
catgcctctt gggacgagat cacaggactt gacccatcat caaataggac caggtgacct 540
acagagacat cacaatgatg gcttcctaca gtcaagtcca tttccaataa tgctctcatc 600
taagagaacc catgaacctt atttgaatcc tggttcaaac aaaaacctta aattatttat 660
gagacaatta taaacttgat agattttgat gtgtgaaggt atttatgaat atttttagtc 720
agtgatggta tactgttaag gaaaaggttc atattttagg gacaaaggct gaaacattta 780
tggacagagt gatatgatat ctgggatttg ttttaggatg aagtgggagg gaggaaatga 840
atggaaatag tgttgaaaca gtattggcca cgagtcagct attgtgtgct aagacgctcc 900
tcacaccagt ctactctgta tgtgtttgaa tatctctgta ataaacttaa caaggaaaaa 960
aaaaaaaaaa aaaaaaactc gag 983

<210> 221
<211> 373
<212> DNA
<213> Homo sapien

<400> 221
cattttatgg gttaattttt tattaaatag caataagata cttttataac tcaataaaat 60
tattcaatga tacattcgga aaataaatgt ataaaatatg aaaaagtact aaaaagcatt 120
tttcagtact tttaggtaag attaatccaa ctaaacacta gcatatgtta tacagtaata 180
ataaggggaa aatacaataa tgttgagaaa gcaaactcaa agcatagatc aatgaaaaaa 240
ttgagaaatg gacataaatg atttagtatt tttaaagaga gtgaaaaatc attattttat 300
gcttttgtgt agcgttagat gaattaaata acatatgcac atatagcttt gcgatacaaa 360
tttccagacc ata 373

<210> 222
<211> 544
<212> DNA
<213> Homo sapien

<400> 222
cagagatgct gctgctacaa aggatcggtg taagcagtta acccaggaaa tgatgacaga 60
gaaagaaaga agcaatgtgg ttataaacaag gatgaaagat cgaattggaa cattagaaaa 120
ggaacataat gtatttcaaa acaaaataca tgtcagttat caagagactc aacagatgca 180
gatgaagttt cagcaagttc gtgagcagat ggaggcagag atagctcact tgaagcagga 240
aaatggtata ctgagagatg cagtcagcaa cactacaaat caactggaaa gcaagcagtc 300
tgcagaacta aataaactac gccaggatta tgctaggttg gtgaatgagc tgactgagaa 360
aacaggaaag ctacagcaag aggaagtcca aaagaagaat gctgagcaag cagctactca 420
gttgaaggtt caactacaag aagctgagag aaggtgggaa gaagttcaga gctacatcag 480
gaagagaaca gcggaacatg aggcagcaca gctagattta cagagtaaat ttgtggccaa 540
agaa 544

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325
648
663

<210> 223
<211> 316
<212> DNA
<213> Homo sapien

<400> 223
gaggcaaggg atatgcttta gtgcctatta tagttaattc ttcaactcca aagtctaaaa 60
cagttgaatc tgctgaagga aaatctgaag aagtaaatga aacattagtt atacccactg 120
aggaagcaga aatggaagaa agtggacgaa gtgcaactcc tgttaactgt gaacagcctg 180
atatcttggt ttcttctaca ccaataaatg aaggacagac tgtgttagac aaggtggctg 240
agcagtgtga acctgctgaa agtcagccag aagcacttct gagaggaaga tgtttgcaag 300
gtaactctaa cagttg 316

<210> 224
<211> 1583
<212> DNA
<213> Homo sapien

<400> 224
cagaccacgt ctgccctcgc cgctctagcc ctgcgcccca gcccggccgc ggcacctccg 60
cctcgccgcc gctaggtcgg ccggctccgc ccggctgccg cctaggatga atatcatgga 120
cttcaacgtg aagaagctgg cggccgacgc aggcaccttc ctcagtcgcg ccgtgcagtt 180
cacagaagaa aagcttggcc aggctgagaa gacagaattg gatgctcact tagagaacct 240
ccttagcaaa gctgaatgta ccaaaatatg gacagaaaaa ataatgaaac aaactgaagt 300
gttattgcag ccaaatccaa atgccaggat agaagaattt gtttatgaga aactggatag 360
aaaagctcca agtcgtataa acaacccaga acttttggga caatatatga ttgatgcagg 420
gactgagttt ggcccaggaa cagcttatgg taatgccctt attaaatgtg gagaaaccca 480
aaaaagaatt ggaacagcag acagagaact gattcaaacg tcagccttaa attttcttac 540
tcctttaaga aactttatag aaggagatta caaaacaatt gctaaagaaa ggaaactatt 600
gcaaaataag agactggatt tggatgctgc aaaaacgaga ctaaaaaagg caaaagctgc 660
agaaactaga aattcatctg aacaggaatt aagaataact caaagtgaat ttgatcgtca 720
agcagagatt accagacttc tgctagaggg aatcagcagt acacatgccc atcaccttcg 780
ctgtctgaat gactttgtag aagcccagat gacttactat gcacagtgtt accagtatat 840
gttggacctc cagaaacaac tgggaagttt tccatccaat tatcttagta acaacaatca 900
gacttctgtg acacctgtac catcagtttt accaaatgcg attggttctt ctgccatggc 960
ttcaacaagt ggcctagtaa tcacctctcc ttccaacctc agtgacctta aggagtgtag 1020
tggcagcaga aaggccaggg ttctctatga ttatgatgca gcaaacagta ctgaattatc 1080
acttctggca gatgaggtga tcactgtgtt cagtgttgtt ggaatggatt cagactggct 1140
aatgggggaa aggggaaacc agaagggcaa ggtgccaatt acctacttag aactgctcaa 1200
ttaagtaggt ggactatgga aaggttgccc atcatgactt tgtatttata tacaattaac 1260
tctaaataaa gcaggttaag tatcttccat gttaatgtgt taagagactg aaaataccag 1320
ccatcagaaa ctggcctttt tgccaataaa gttgcatggt aaatatttca ttacagaatt 1380
tatgttagag ctttcatgcc aagaatgttt tcttacaaaa ttctcttttt attgaggttt 1440
cactaataag cagcttctac ttttgagcct caacttaaag cagaactgtt ttttactgga 1500
ttttttcatta acagcaagct ttttttttta tgtaaaataa atctattgtg aattgaaaaa 1560
aaaaaaaaaa aaaaaaactc gag 1583

<210> 225
<211> 491
<212> DNA
<213> Homo sapien

<400> 225
gaacaacatc atcttgaatc actagataga ctcttgacgg aaagcaaagg ggaaatgaaa 60
aaggaaaata tgaagaaaga tgaagcttta aaagcattac agaaccaagt atctgaagaa 120

664

acaatcaagg ttaggcaact agattcagca ttggaaattt gtaaggaaga acttgtcttg 180
catttgaatc aattggaagg aaataaggaa aagtttgaaa aacagttaaa gaagaaatct 240
gaagaggtat attgtttaca gaaagagcta aagataaaaa atcacagtct tcaagagact 300
tctgagcaaa acgttattct acagcatact cttcagcaac agcagcaaat gttacaacaa 360
gagacaatta gaaatggaga gctagaagat actcaaacta aacttgaaaa acaggtgtca 420
aaactggaac aagaacttca aaaacaaagg gaaagttcag ctgaaaagtt gagaaaaatg 480
gaggagaaat g 491

<210> 226
<211> 483
<212> DNA
<213> Homo sapien

<400> 226
cagccgcacg ccgcggagca ggggctcgga ggtcccggga ttacggtgct cgagcacgct 60
ggtgggaaag gacccgggac ttgaacagtg ttgtgcggcg ccatgcaggt ctccagcctc 120
aatgaggtga agatttacag cctcagctgc ggcaagtccc ttcctgagtg gctttctgat 180
aggaagaaga gagcgctaca gaagaaagat gtagatgtcc gtaggagaat tgaacttatt 240
caggactttg aaatgcctac tgtgtgtacc actattaagg tgtcaaaaga tggacagtac 300
attttagcaa ctggaacata taaacctcgg gttcgatgtt atgacaccta tcaattatcc 360
ttgaagtttg aaaggtgttt agattcagaa gttgtcacct ttgaaatttt gtctgatgac 420
tactcaaaga ttgtcttctt acataatgat agatacattg aatttcattc gcaatcaggt 480
ttt 483

<210> 227
<211> 486
<212> DNA
<213> Homo sapien

<400> 227
gagcctcgct aagctccgac tctgggcggc accgggcgtc ccacgatgcc gaagaacaag 60
aagcggaaca ctccccaccg cggtagcagt gctggcggcg gcgggtcagg agcagccgca 120
gcgacggcgg cgacagcagg tggccagcat cgaaatgttc agccttttag tgatgaagat 180
gcatcaattg aaacagtgag ccattgcagt ggttatagcg atccttccag ttttgctgaa 240
gatggaccag aagtccttga tgaggaagga actcaagaag acctagagta caagttgaag 300
ggattaattg acctaaccct ggataagagt gcgaagacaa ggcaagcagc tcttgaaggt 360
attaaaaatg cactggcttc aaaaatgctg tatgaattta ttctggaaag gagaatgact 420
ttaactgata gcattgaacg ctgcctgaaa aaaggtaaga gtgatgagca acgtgcagct 480
gcagcg 486

<210> 228
<211> 494
<212> DNA
<213> Homo sapien

<400> 228
gaggccagga ctccgggaat gcgagcaggc cccttattct cccagtggcc tcggtctgtc 60
cccacagcgg cccggtcagg gttgcccgag ccccaaggcg gggggcggca ccggggtgct 120
gaaagggaca gaatgctttg acctccaagc tgttttaaat ctagtagata agccagatcc 180
tgtgttgcca taagcccttg gcccacattt aagtgggaat gcagctagct tggatgtctg 240
aaactttgta agcgccttct gtctgaatcc tgaacacagg caccaagact actgaagaag 300
ctcgtcattc ttgtgcaggg atagccacac aagcaaacat gtttgcaaaa cttgaaagaa 360
agaaaattgc agaaagaaga cttgctgttc ttaagaggcc caggaaggtg ctacttagga 420
atcccaccgg cttgtgaagc aagggaatca agtttgcctt caatggggaa cttgacttca 480
ggaaaatgaa cttt 494

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330
58
665

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<210> 229
<211> 465
<212> DNA
<213> Homo sapien

<400> 229
gtcagagagc tggtataacc tcctgttgga catgcagaac cgactcaata aggtcatcaa 60
aagcgtgggc aagattgagc actccttctg gagatccttt cacactgagc gaaagacaga 120
accagccaca ggcttcatcg atggtgatct gattgaaagt ttcctagata tcagccgccc 180
taagatgcag gaggttgtgg caaacttgca gtatgatgat ggcagtggta tgaagcggga 240
ggcaactgca gatgacctca tcaaagtcgt ggaggaacta actcggatcc attagccaag 300
gacaggatct cttttcctga cctcctcaaa ggcgttgccc tcctatcctc ccttccttgc 360
ccacccttgg tttctttggc atgggaaggt tttccttaac cacttgccct agagccacca 420
gtgaccttgt gtggaaacag ggtttttttt acttaaaaca gttca 465

<210> 230
<211> 495
<212> DNA
<213> Homo sapien

<400> 230
caggggaaag ggtgtttggc cttgaccagc cactgctgac ctcaatctca gacctacaga 60
tggtgaatat ctccctgcga gtgttgtctc gacccaatgc tcaggagctt cctagcatgt 120
accagcgcct agggctggac tacgaggaac gagtgttgcc gtccattgtc aacgaggtgc 180
tcaagagtgt ggtggccaag ttcaatgcct cacagctgat cacccagcgg gcccaggtat 240
ccctgttgat ccgccgggag ctgacagaaa gggccaaagg acttcagcct catcctggat 300
gatgtggcca tcacagactt gagctttagc cgagaagtac acaagctgcc tgtaagaaac 360
ccaaccaagt ggggtgaatt ccaaaaaccc gtgggggtga agggcttctt aagaatgcaa 420
ggaaggagga aaagaattcc atgggggggg ggttccttaa cccaggaaca ggggtttccc 480
ttgaattttt ttcca 495

<210> 231
<211> 498
<212> DNA
<213> Homo sapien

<400> 231
ggcagcttct gagaccaggg ttgctccgtc cgtgctccgc ctcgccatga cttcctacag 60
ctatcgccag tcgtcggcca cgtcgtcctt cggaggcctg ggcggcggct ccgtgcgttt 120
tgggccgggg gtcgcttttc gcgcgcccag cattcacggg ggctccggcg gccgcggcgt 180
atccgtgtcc tccgcccgct ttgtgtcctc gtcctcctcg gggggctacg gcggcggcta 240
cggcggcgtc ctgaccgcgt ccgacgggct gctggcgggc aacgaggagc taaccatgca 300
gaacctcaac gaccgcctgc ctcctacctg gacaaagtgc gcgcctggga agcgggcaac 360
ggcgaactta gaggtgaaag aatcccgcga actggtacca aaaacaaggg gcctggggcc 420
ttccgcgact tacagccaac ttactacacc gaacattcaa gaacttgcgg gaacaaaaat 480
ttttggtgcc acccattt 498

<210> 232
<211> 465
<212> DNA
<213> Homo sapien

<400> 232
caggccggcc gagtaggaaa gctggaggcg cgggtgggga acatgtctga gtcggagctc 60

ggcaggaagt gggaccggtg tctggcggat gcggtcgtga agataggtac tggttttgga 120
ttaggaattg ttttctcact taccttcttt aaaagaagaa tgtggccatt agccttcggt 180
tctggcatgg gattaggaat ggcttattcc aactgtcagc atgatttcca ggctccatat 240
cttctacatg gaaaatatgt caaagagcag gagcagtgac ttcacctgag aacatcccag 300
cgggaggaca agagaaaatc atgtttattc ctcaggaata cttgaagtgc cctggagtaa 360
actgccattc ttctgtaaca atggtatcag taatgcttta aactccagca cctggttatg 420
catttgaaac ccaagtctgg ttcttggttt ggatttctc tctgg 465

<210> 233
<211> 366
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(366)
<223> n = A,T,C or G

<400> 233
cagtaaaaaa ggttatgttt tattaattgc tggacaaccg tgggaaaaca aataagcaat 60
tgacaccacc aaattcttat tacattcaan ataaaanatt tattcacacc acaaaaagat 120
aatcacaaca aaatatacac taacttaaaa aacaaaagat tatagtgaca taaaatgtta 180
tattctcttt ttaagtgggt aaaagtattt tgtttgcttc tacataaatt tctattcatg 240
ananaataac aaatattaaa atacagtgat agtttgcatt tcttctatag aatgaacata 300
gacataaccc tgaagctttt agtttacagg gagtttccat gaagccacaa actaaactaa 360
ttatca 366

<210> 234
<211> 379
<212> DNA
<213> Homo sapien

<400> 234
gagggcagcc ctcctacctg cgcacgtggt gccgccgctg ctgcctcccg ctcgccctga 60
acccagtgcc tgcagccatg gctcccggcc agctcgcctt atttagtgtc tctgacaaaa 120
ccggccttgt ggaatttgca agaaacctga ccgctcttgg tttgaatctg gtcgcttccg 180
gagggactgc aaaagctctc agggatgctg gtctggcagt cacagatgtc tctgagttga 240
cgggatttct gaaatgttgg ggggacgtgt gaaaactttg catcctgcac gatcccatgc 300
tggaatccta gctcctaata ttcagaagat aatgcttgac atgcgccaca cttgattcaa 360
tcttataaca attgttgcc 379

<210> 235
<211> 406
<212> DNA
<213> Homo sapien

<400> 235
caggctgcac catgtacccc accttcagtt taaaagaaaa aaaaaatccc cttcactcct 60
actgggaggt gggacccctt tcattttcag ttttgctcat ctagggaaaa taaggctttg 120
gtttccagtt taattgtttt tgaccttcta aaatgttttt atgttagcac tgatagttgg 180
cattactgtt gttaagcact gtgttccaga ccgtgtctga cttagtgtaa cctaggagat 240
tttatagttt tattttaatg aaaccctgat tgacgcacag cagtggggag aacagcgtct 300
tttacctgtc accgaagcca ggaagccccg tttgtaagcg tgtgttgtgg tgctttattg 360
tacatcctcc agtggcgttc tttttactct aatgttcttt tggttt 406

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397 501 666

<210> 236
<211> 278
<212> DNA
<213> Homo sapien

<400> 236
gagattagca cctgtgaaca atgcgttctc tgatgacact ctgagcatgg accaacgcct 60
tcttaagcta attctgcaaa atcacatatt gaaagtaaaa gttggcctta gcgacctcta 120
caatggacag atactggaaa ccattggagg caaacaactc cgagtctttg tgtatcggac 180
ggctatctgc atagaaaact catgcatggt gagaggaagc aagcagggaa ggaacggtgc 240
cattcacata ttccgagaga tcatccaacc agcagaat 278

<210> 237
<211> 322
<212> DNA
<213> Homo sapien

<400> 237
cagggccgtg gcggaggagg agcgctgcac ggtggagcgt cgggccgacc tcacctacgc 60
ggagttcgtg cagcagtacg tgcgcccctg atcgcggagg tcgcgtcctg ttcaccggcc 120
cgtctgcccc gaccgcccaa ggccgccttc ccctgacctc gcgcgcacgc gtggggctgg 180
ggcggcgagg ctggcggtcc ggcctggccg cgactctgcc cttctttcca gaggttccgg 240
gccctgtgct cccgcgacag gttgctggct tcgtttgggg acagagtggt ccggtgagca 300
ccgccaacac ctactcctac ct 322

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<211> 613
<212> DNA
<213> Homo sapiens

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<222> (399)
<223> n=A,T,C or G

<400> 238
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tcgagccatg gatgaccctg cgtctgcctt catcagtgac agtggtgctg ctgctgctca 540
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<210> 239
<211> 613
<212> DNA
<213> Homo sapiens

<400> 239

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3B
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668

09370838 · 06000999

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taagatcact gta 613

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<211> 585
<212> DNA
<213> Homo sapiens

<400> 240
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<210> 241
<211> 566
<212> DNA
<213> Homo sapiens

<400> 241
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<210> 242
<211> 556
<212> DNA
<213> Homo sapiens

<400> 242
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cgactacaaa cggaacttgc cgcgtcgagg actgtcgggc tacagcatgc tggccatagg 120
gattggaacc ctgatctacg ggcactggag cataatgaag tggaaccgtg agcgcaggcg 180

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ggacgtgccc gactggaagg tggggagtcc tgtgttccac acaacccgct gggtgccccc 360
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cttcatgtgg tacacgtagg ccctgtgccc tccggccacc tggatccctg cccctcccca 480
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aaaaaaaaaa ctcgag 556

<210> 243
<211> 591
<212> DNA
<213> Homo sapiens

<400> 243
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caccagattt acatgcaagg gcaaaccagt ccaccacttc atgaacacca gtacatttac 480
cgagtacaca gtggtggatg aatcttctgt tgctaagatt gatgatgcag ctcctcctga 540
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<210> 244
<211> 594
<212> DNA
<213> Homo sapiens

<400> 244
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aaagactaaa gaagttcgca ttaagatttt ggccacagga atctgtcgca cagatgacca 240
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caagggcaaa ccagtccacc acttcatgaa caccagtaca tttaccgagt acacagtggt 540
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<210> 245
<211> 615
<212> DNA
<213> Homo sapiens

<220>
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<222> (105)
<223> n=A,T,C or G

<400> 245
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09370838 - 08009990

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atttgatgca gctgtttgaa gagtctggga atacagatat agaaggaatc gacacaacta 480
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aaatgctaga cctac 615

<210> 246
<211> 546
<212> DNA
<213> Homo sapiens

<400> 246
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taagga 546

<210> 247
<211> 564
<212> DNA
<213> Homo sapiens

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acaagagaag tttaatctga aagaagaact ggaacgttgt aaagtgcagt cctccacttt 480
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ggaaaaccac cttctcaaag atga 564

<210> 248
<211> 434
<212> DNA
<213> Homo sapiens

<400> 248
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acagctggaa gatgggcgca ccctgtctga ctacaacatc cagaaagagt ccaccctgca 240
cctggtgctc cgtctcagag gtgggatgca aatcttcgtg aagacactca ctggcaagac 300

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catcacccct gaggtggagc ccagtgacac catcgagaac gtcaaagcaa agatccagga 360
caaggaaggc attcctcctg accagcagag gttgatcttt gccggaaagc cagcctggga 420
agatggggcc gcca 434

<210> 249
<211> 416
<212> DNA
<213> Homo sapiens

<400> 249
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cggacaggac ccgcacagca agcacctgta cacggccgac atgttcacgc acgggatcca 120
gagcgccgcg cacttcgtca tgttcttcgc gccctggtgt ggacactgcc agcggctgca 180
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cttccagaca ctggaaaact ggatgctgca gacactgaac gaggagccag tgacac 416

<210> 250
<211> 504
<212> DNA
<213> Homo sapiens

<400> 250
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gtgaagactg ccaggcctag ctct 504

<210> 251
<211> 607
<212> DNA
<213> Homo sapiens

<400> 251
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<210> 252
<211> 618
<212> DNA

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<213> Homo sapiens

<400> 252
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gcttctgatg tttctgtt 618

<210> 253
<211> 1201
<212> DNA
<213> Homo sapiens

<400> 253
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aaactgcagg tactaacacc acaaaaattg gaattggtaa aagcccaact acaacaagaa 540
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<210> 254
<211> 560
<212> DNA
<213> Homo sapiens

<400> 254
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388
SEQ
673

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ttctatcctg gatgtggttc ttctgtgtag caattccttg atgtccagtt tggaaagatg 540
tactcttctc aacaagaaaa 560

<210> 255
<211> 612
<212> DNA
<213> Homo sapiens

<400> 255
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agtatccatt aattattgtg tcagaagaga ttgaatacct gcttaagaag cttacagaag 480
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<210> 256
<211> 1132
<212> DNA
<213> Homo sapiens

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<210> 257
<211> 519
<212> DNA
<213> Homo sapiens

<400> 257

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cccggccggg cccatcctct ccatccgggt ctgcagggac atgatcaccc gccgctcctt 180
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tgatgaaaat ggctccaagg gctatggatt tgtacacttt gaaacacagg aagcagctga 480
aagagctatt gaaaaaatga atgggatgct tctaaatga 519

<210> 258
<211> 596
<212> DNA
<213> Homo sapiens

<400> 258
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gcagtggagg cactcgccac aggctgccac gagaaatgat ttttgttgga agagatgact 120
gtgagctcat gttgcagtct cgtagtgtgg ataagcaaca cgctgtcatc aactatgatg 180
cgtctacgga tgagcattta gtgaaggatt tgggcagcct caatgggact tttgtgaatg 240
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ttaagcatga gaagtttacc attcagcttc agttgtccca aaaatcttca gaatcagaat 420
tatccaaatc tgcaagtgcc aaaagcatag attcaaaggt agcagacgct gctactgaag 480
tgcagcacaa aactactgaa gcactgaaat ccgaggaaaa agccatggat atttctgcta 540
tgccccgtgg tactccatta tatgggcagc cgtcatggtg gggggatgat gaggtg 596

<210> 259
<211> 595
<212> DNA
<213> Homo sapiens

<400> 259
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tcggagaatt tcagaattaa gagaggagct gcaaatggac cagcaagcaa agaaacatct 120
tcaggacgag tttgatgcat gtttggagga gaaagatcag tatatcagtg ttctccagac 180
tcaggtttct cttctaaagc agcgattaca gaatggccca atgaatgttg atgctcccaa 240
acccctccct cccggggagc tccaggcaga agtgcacggt gacacggaga agatggaggg 300
cgtcgggggaa ccagtgggag gtgggacttc cgctaaaacc ctggaaatgc tccagcaaag 360
agtgaaacgt caggagaatc tgcttcagcg ctgtaaggag acaattgggt cccacaagga 420
gcagtgcgca ctgctgctga gtgagaagga ggcactgcag gagcagttgg atgaaaggct 480
gcaggagctg gaaaagatga aggggatggt aataaccgag acgaagcggc aaatgcttga 540
gaccctggaa ctgaaagaag atgaaattgc tcagcttcgt agtcatatca aacag 595

<210> 260
<211> 994
<212> DNA
<213> Homo sapiens

<400> 260
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ttttcgcctt ccctgttctt ccctttctca aacaaacaag acatggcaaa ccgcagtcta 120
acccagcccc ttgaaattat ccatagtttt acagacagct ccaggccatg agccacaatg 180
tccaaaatta ttcttgagca ctgatataaa ttacttagac cttctttgag ggcagaactc 240
agctgttgct ctcatgatgg gcagtgctgg aaagggttct ggtatgtctt caaaatgagt 300

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387
589
674

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tctgaaccat tttttaatac ttgttttgtc atggtgaaat tatagcagtt atcccaaaat 480
gttttaatta tcaaaatact gtctttttaaa aaaaaaaaaa agtaacacct tttaaagcat 540
tagatttcac ttgggtttct tttccaaaaa atgctaggta gacaaggcat tgtaaacatg 600
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agaaataata tctaaagttt aacaactaaa gtaccctcac agaatagcaa ataccctttct 720
gttctggaca tgggttcaaa tttgaatatg gaaataattt ccttggaagt ccctagaggc 780
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tgcttttttat tagatctata taaataagtt aactagcaat ttagttttgt atttaagcta 960
cacttaatct ttttctttgg tgatatttat ttct 994

<210> 261
<211> 594
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (538)
<223> n=A,T,C or G

<400> 261
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caggaacctt cggaacaccc agggaatgct gaaggacaca cagctgcacc tggacgatgc 120
tctcagaggc caggacgacc tgaaagagca gctggccatg gttgagcgca gagccaacct 180
gatgcaggct gagatcgagg agctcagggc atccctggaa cagacagaga ggagcaggag 240
agtggccgag caagagctac tggatgccag tgagcgcgtg cagctcctcc acacccagaa 300
caccagcctc atcaacacca agaagaagct ggagacagac atttcccaaa tccagggaga 360
gatggaagac atcgtccagg aagcccgcaa cgcagaagag aaggccaaga aagccatcac 420
tgatgccgcc atgatggcgg aggagctgaa gaaggagcag gacaccagcg cccacctgga 480
gcggatgaag aagaacatgg agcagaccgt gaaggacctg cagcaccgtc tggacgangc 540
tgagcagctt ggcgctgaag ggcgggcaag aagcagatcc agaaactgga ggct 594

<210> 262
<211> 594
<212> DNA
<213> Homo sapiens

<400> 262
gaaaaggtgg ctggagccaa aggcatagtc agggttaatg ctccttttc tttatcccaa 60
atcagatagt gtttaggctt tttcatcaaa tataaaaacc cagcccagtt catggctcat 120
tcggcagcaa ccctgagacg ctttacagct ctagacccta aaaggtcaaa aggccgtctt 180
atgctcaata tacattttat tacccaatct gccccggaca ttaaataaaa ctccaaaaat 240
taaatccggc cctcaaaccc cacaacagga cttaattgac ctcaccttca aggtgtagaa 300
taataaaaaa aaaaagttgc aattccttgc ctccgctgtg agacaaaccc cagccacatc 360
tccagcacac aagaacttcc aaacgcctga accacagcag ccaggcgttc ctccagaacc 420
tcctccccca ggagcttgct acatgtgccg gaaatctggc cactaggcca aggaatgcct 480
gcagccccgg attcctccta agccgtgtcc catctgtgcg ggaccccact gaaaatcgga 540
ctgttcaact cacctggcag ccactctcag agaccctgga actctggccc aagg 594

<210> 263
<211> 506
<212> DNA

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<213> Homo sapiens

<400> 263
gaattcggca cgagcggaaa cttaggggcc acgtgagcca cggccacggc cgcataggca 60
agcaccggaa gcaccccggc ggccgcggta atgctggtgg tctgcatcac caccggatca 120
acttcgacaa ataccaccca ggctactttg ggaaagttgg tatgaagcat taccacttaa 180
agaggaacca gagcttctgc ccaactgtca accttgacaa attgtggact ttggtcagtg 240
aacagacacg ggtgaatgct gctaaaaaca agactggggc tgctcccatc attgatgtgg 300
tgcgatcggg ctactataaa gttctgggaa agggaaagct cccaaagcag cctgtcatcg 360
tgaaggccaa attcttcagc agaagagctg aggagaagat taagagtgtt gggggggcct 420
gtgtcctggt ggcttgaagc cacatggagg gagtttcatt aaatgctaac tacttttaa 480
aaaaaaaaaa aaaaaaaaaa ctcgag 506

<210> 264
<211> 600
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (32)
<223> n=A,T,C or G

<400> 264
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cggcggcggg gtgtcccgtc ggcggccctg aagtgaccca taaacatgtc ttgtgagagg 120
aaaggcctct cggagctgcg atcggagctc tacttcctca tcgcccggtt cctggaagat 180
ggaccctgtc agcaggcggc tcaggtgctg atccgcgagg tggccgagaa ggagctgctg 240
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tattacagac acttagcacc tgatcacttg ctgcaaatat gtcatcgact aggacctctt 360
cttgaacaag aaattcctca aagtgttcct ggagtacaaa ctttattagg agctggaaga 420
cagtctttac tacgcacaaa taaaagctgc aagcatgttg tgtggaaagg atctgctctg 480
gctgcgttgc actgtggaag accacctgag tcaccagtta actatggtag cccacccagc 540
attgcggata ctctgttttc aaggaagctg aatgggaaat acagacttga gcgacttgtt 600

<210> 265
<211> 534
<212> DNA
<213> Homo sapiens

<400> 265
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gccacggggg agaaagtgct gcgctacgag accttcatca gtgacgtgct gcagcgggac 120
ttgcgaaagg tgctggacca tcgagacaag gtatatgagc agctggccaa ataccttcaa 180
ctgagaaatg tcattgagcg actccaggaa gctaagcact cggagttata tatgcaggtg 240
gatttgggct gtaacttctt cgttgacaca gtggtcccag atacttcacg catctatgtg 300
gccctgggat atggtttttt cctggagttg acactggcag aagctctcaa gttcattgat 360
cgtaagagct ctctcctcac agagctcagc aacagcctca ccaaggactc catgaatatc 420
aaagcccata tccacatgtt gctagagggg cttagagaac tacaaggcct gcagaatttc 480
ccagagaagc ctcaccattg acttcttccc cccatcctca gacattaaag agcc 534

<210> 266
<211> 552
<212> DNA
<213> Homo sapiens

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<400> 266
gaattcggca ccagggcacc tccgcctcgc cgccgctagg tcggccggct ccgcccggct 60
gccgcctagg atgaatatca tggacttcaa cgtgaagaag ctggcggccg acgcaggcac 120
cttcctcagt cgcgccgtgc agttcacaga agaaaagctt ggccaggctg agaagacaga 180
attggatgct cacttagaga acctccttag caaagctgaa tgtaccaaaa tatggacaga 240
aaaaataatg aaacaaactg aagtgttatt gcagccaaat ccaaatgcca ggatagaaga 300
atttgtttat gagaaactgg atagaaaagc tccaagtcgt ataaacaacc cagaactttt 360
gggacaatat atgattgatg cagggactga gtttggccca ggaacagctt atggtaatgc 420
ccttattaaa tgtggagaaa cccaaaaaag aattggaaca gcagacagag aactgattca 480
aacgtcagcc ttaaattttc ttactccttt aagaaacttt atagaaggag attacaaaac 540
aattgctaaa ga 552

<210> 267
<211> 551
<212> DNA
<213> Homo sapiens

<400> 267
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ggaagcggct cggcagatcg agcgtgaggc ccagcagcag cagcacctgt accgggtgaa 120
catcaacaac agcatgcccc caggacgcac gggcatgggg accccgggga gccagatggc 180
ccccgtgagc ctgaatgtgc cccgacccaa ccaggtgagc gggcccgtca tgcccagcat 240
gcctcccggg cagtggcagc aggcgccccc tccccagcag cagcccatgc caggcttgcc 300
caggcctgtg atatccatgc aggcccaggc ggccgtggct gggccccgga tgcccagcgt 360
gcagccaccc aggagcatct cacccagcgc tctgcaagac ctgctgcgga ccctgaagtc 420
gcccagctcc cctcagcagc aacagcaggt gctgaacatt ctcaaatcaa acccgcagct 480
aatggcagct ttcatcaaac agcgcacagc caagtacgtg gccaatcagc ccggcatgca 540
gccccagcct g 551

<210> 268
<211> 573
<212> DNA
<213> Homo sapiens

<400> 268
gaattcggca ccagggttcc ttgtgggcta gaagaatcct gcaaaaatgt ctctctatcc 60
atctctcgaa gacttgaagg tagacaaagt aattcaggct caaactgctt tttctgcaaa 120
ccctgccaat ccagcaattt tgtcagaagc ttctgctcct atccctcacg atggaaatct 180
ctatcccaga ctgtatccag agctctctca atacatgggg ctgagtttaa atgaagaaga 240
aatacgtgca aatgtggccg tggtttctgg tgcaccactt caggggcagt tggtagcaag 300
accttccagt ataaactata tggtggctcc tgtaactggt aatgatgttg gaattcgtag 360
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tggactcagg cttaaatcaa tagataatgg tatatttgtt cagctagtcc aggctaattc 480
tccagcctca ttggttggtc tgagatttgg ggaccaagta cttcagatca atggtgaaaa 540
ctgtgcagga tggagctctg ataaagcgca caa 573

<210> 269
<211> 500
<212> DNA
<213> Homo sapiens

<400> 269
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atgtgggggga gccatgaaga aactaactaa aggggagcct ttggggacca gggggagaca 120

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agtcactatt ttgagggaga aagctctgga ttgattctga caggacactt gagtgtgaac 180
tgtccaagct aagcctctgg gtgtgtagag agagcccctta cagatagata gcacctttgc 240
tttcagagtg gaaggactag ccactaagga ccagaccaag atgcatgtag gtcactgaca 300
agcacctgat gaagaggagg ggtctcctcc aagtttgtgt ttggaactcc tcctgtgttc 360
aatttcctaa aagccataat ccagcaagct gaactcatga gaaggtctgc ttcatgttga 420
gcatggaaga cagaacacag acggaaactg cagtgatggt gtgaagacac cacggatagg 480
ttaggggcag tgaggaggaa 500

<210> 270
<211> 224
<212> DNA
<213> Homo sapiens

<400> 270
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cataactgaa agtagctaag gcaccccagc cggaggaagt gagctctcct ggggcgtggt 120
tgttcgtgat ccttgcatct gttacttagg gtcaaggctt gggtcttgcc ccgcagaccc 180
ttgggacgac ccggccccag cgcagctatg aacctggagc gagt 224

<210> 271
<211> 447
<212> DNA
<213> Homo sapiens

<400> 271
gaattcggca cgaggctggg ccgggcccga gcggatcgcg ggctcgggct gcggggctcc 60
ggctgcgggc gctgggccgc gaggcgcgga gcttgggagc ggagcccagg ccgtgccgcg 120
cggcgccatg aaggggcaagg aggagaagga gggcggcgca cggctgggcg ctggcggcgg 180
aagccccgag aagagcccga gcgcgcagga gctcaaggag cagggcaatc gtctgttcgt 240
gggccgaaag tacccggagg cggcggcctg ctacggccgc gcgatcaccc ggaacccgct 300
ggtggccgtg tattacacca accgggcctt gtgctacctg aagatgcagc agcacgagca 360
ggccctggcc gactgccggc gcgccctgga gctggacggg cagtctgtga aggcgcactt 420
cttcctgggg cagtgccagc tggagat 447

<210> 272
<211> 606
<212> DNA
<213> Homo sapiens

<400> 272
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gaggttattg atttgcttaa acctgaccaa gtagaaggga tccagaaatc tgggactaaa 120
aaactgaaga ccgaaactga caaagaaaat gctgaagtga agtttaaaga ttttcttctg 180
tccttgaaga ctatgatgtt ttctgaagat gaggctcttt gtgttgtaga cttgctaaag 240
gagaagtctg gtgtaataca agatgcttta aagaagtcaa gtaagggaga attgactacg 300
cttatacatc agcttcaaga aaaggacaag ttactcgctg ctgtgaagga agatgctgct 360
gctacaaagg atcggtgtaa gcagttaacc caggaaatga tgacagagaa agaaagaagc 420
aatgtggtta taacaaggat gaaagatcga attggaacat tagaaaagga acataatgta 480
tttcaaaaca aaatacatgt cagttatcaa gagactcaac agatgcagat gaagtttcag 540
caagttcgtg agcagatgga ggcagagata gctcacttga agcaggaaaa tgggtatact 600
ggagaa 606

<210> 273
<211> 598
<212> DNA

379
SEQ
679

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<213> Homo sapiens

<400> 273
gaattcggca ccaggcccgg tcccgcggtc gcagctccag ccgcctcctc cgcgcagccg 60
ccgcctcagc tgctcgctct gtgggtcggt cctctccggc acttgggctc cagtcgcgcc 120
ctccaagccc ttcaggccgc cccagtgtcc tcctccttct ccggccagac ccagccccgc 180
gaagatggtg gaccgcgagc aactggtgca gaaagcccgg ctggccgagc aggcggagcg 240
ctacgacgac atggccgcgg ccatgaagaa cgtgacagag ctgaatgagc cactgtcgaa 300
tgaggaacga aaccttctgt ctgtggccta caagaacgtt gtgggggcac gccgctcttc 360
ctggagggtc atcagtagca ttgagcagaa gacatctgca gacggcaatg agaagaagat 420
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tgtgctgagc ctgctggata actacctgat caagaattgc agcgagaccc agtacgagag 540
caaagtgttc tacctgaaga tgaaagggga ctactaccgc tacctggctg aagtggcc 598

<210> 274
<211> 536
<212> DNA
<213> Homo sapiens

<400> 274
gcaccaagag actaaacaag aaagtggatc agggaagaag aaagcttcat caaagaaaca 60
aaagacagaa aatgtcttcg tagatgaacc ccttattcat gcaactactt atattccttt 120
gatggataat gctgactcaa gtcctgtggt agataagaga gaggttattg atttgcttaa 180
acctgaccaa gtagaaggga tccagaaatc tgggactaaa aaactgaaga ccgaaactga 240
caaagaaaat gctgaagtga agtttaaaga ttttcttctg tccttgaaga ctatgatgtt 300
ttctgaagat gaggctcttt gtgttgtaga cttgctaaag gagaagtctg gtgtaataca 360
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aaaggacaag ttactcgctg ctgtgaagga agatgctgct gctacaaagg atcggtgtaa 480
gcagttaacc caggaaatga tgacagagaa agaaagaagc aatgtggtta taacaa 536

<210> 275
<211> 494
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (379)
<223> n=A,T,C or G

<400> 275
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gcagatcttc gtgaagactc tgactggtaa gaccatcacc ctcgaggttg agcccagtga 120
caccatcgag aatgtcaagg caaagatcca agataaggaa ggcatccctc ctgaccagca 180
gaggctgatc tttgctggaa aacagctgga agatgggcgc accctgtctg actacaacat 240
ccagaaagag tccaccctgc acctggtgct ccgtctcaga ggtgggatgc aaatcttcgt 300
gaagacactc actggcaaga ccatcaccct tgaggtggag cccagtgaca ccatcgagaa 360
cgtcaaagca aagatccang acaaggaagg cattcctcct gaccagcaga ggttgatctt 420
tgccggaaag cagctggaag atgggcgcac cctgtctgac tacaacatcc agaaagagtc 480
taccctgcac ctgg 494

<210> 276
<211> 484
<212> DNA
<213> Homo sapiens

6660 0.8E8D7E60

<400> 276
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agacaaaagg cagtcacagg tgtgcaggga gtgtgggcga ggctttagca ggaagtcaca 120
gctcatcata caccagagga cacacacagg agaaaagcct tatgtctgcg gagagtgtgg 180
gcgaggcttt atagttgagt cagtcctccg caaccacctg agtacacact ccggggagaa 240
accttatgtg tgcagccatt gtgggcgagg ctttagctgc aagccatacc tcatcagaca 300
tcagaggaca cacacaaggg agaaatcgtt tatgtgcaca gtgtgtgggc gaggctttcg 360
tgaaaagtca gagctcatta agcaccagag aattcacacg ggggataagc cttatgtgtg 420
cagagattga ggccgaggct ttgtaaagga gatcatgtct caacacacac cagaggatta 480
catt 484

<210> 277
<211> 513
<212> DNA
<213> Homo sapiens

<400> 277
gcttgaggct gccaatcaga gcttggcaga gctgagagat cagcggcagg gggagcgcct 60
ggaacatgca gcagctttgc gggccctaca agatcaggta tccatccaga gtgcagatgc 120
acaggaacaa gtggaagggc ttttggctga gaacaatgcc ttgaggacta gcctggctgc 180
cctggagcag atccaaacag caaagaccca agaactgaat atgctccggg aacagaccac 240
tgggctggca gctgagttgc agcagcagca ggctgagtac gaggacctta tgggacagaa 300
agatgacctc aactcccagc tccaggagtc attacgggcc aatagtcgac tgctggaaca 360
acttcaagaa atagggcagg agaaggagca gttgacccag gaattacagg aggctcggaa 420
gagtgcggag aagcggaagg ccatgcttgg atgagctagc aatggaaacg ctgcaagaga 480
agtcccacac aaggaagagc ttgggagcag ttc 513

<210> 278
<211> 471
<212> DNA
<213> Homo sapiens

<400> 278
gaattcggca ccagccaagg ccctgtccct ggctcgggcc cttgaagagg ccttggaagc 60
caaagaggaa ctcgagcgga ccaacaaaat gctcaaagcc gaaatggaag acctggtcag 120
ctccaaggat gacgtgggca agaacgtcca tgagctggag aagtccaagc gggccctgga 180
gacccagatg gaggagatga agacgcagct ggaagagctg gaggacgagc tgcaagccac 240
ggaggacgcc aaactgcggc tggaagtcaa catgcaggcg ctcaagggcc agttcgaaag 300
ggatctccaa gcccgggacg agcagaatga ggagaagagg aggcaactgc agagacagct 360
tcacgagtat gagacggaac tggaagacga gcgaaagcaa cgtgccctgg cagctgcagc 420
aaagaagaag ctggaagggg acctgaaaga cctggagctt caggccgact t 471

<210> 279
<211> 497
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (457)
<223> n=A,T,C or G
<221> misc_feature
<222> (471)
<223> n=A,T,C or G

378
681

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<400> 279
gaattcggca cgaggccaca gaggcggcgg agagatggcc ttcagcggtt cccaggctcc 60
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tcagatcact gtcaatggga ccgttctcag ctccagtgga accaggtttg ctgtgaactt 180
tcagactggc ttcagtggaa atgacattgc cttccacttc aaccctcggt ttgaagatgg 240
agggtacgtg gtgtgcaaca cgaggcagaa cggaagctgg gggcccgagg agaggaagac 300
acacatgcct ttccagaagg ggatgccctt tgacctctgc ttcctggtgc agagctcaga 360
tttcaaggtg atggtgaacg ggatcctctt cgtgcagtac ttccaccgcg tgcccttcca 420
ccgtgtggac accatctccg tcaatggctc tgtgcanctg tcctacatca ncttccagac 480
ccagacagtc atccaca 497

<210> 280
<211> 544
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (451)
<223> n=A,T,C or G

<400> 280
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THE UNITED STATES OF AMERICA

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UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

April 12, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: ***09/476,235***
FILING DATE: ***December 30, 1999***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

T. Wallace
T. WALLACE
Certifying Officer

TRADUCCION OFICIAL No. 2000/096
HILDA AGUILERA DE PIERRARITA
INTERPRETE OFICIAL

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PTO/SB/05 (2/98)

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for nonprovisional applications under 37 CFR § 1.53(b))

Attorney Docket No.	210121.475C2
First Inventor or Application Identifier	Steven G. Reed
Title	COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE
Express Mail Label No.	EL414545511US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Box Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

1. [ ] General Authorization Form & Fee Transmittal *(Submit an original and a duplicate for fee processing)*
2. [X] Specification [Total Pages] 75 *(preferred arrangement set forth below)*
   - Descriptive Title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
3. [ ] Drawing(s) (35 USC 113) [Total Sheets]
4. Oath or Declaration [Total Pages]
   a. [ ] Newly executed (original or copy)
   b. [ ] Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional with Box 17 completed)*
      i. [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b)
5. [ ] Incorporation By Reference *(useable if box 4b is checked)* The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered to be part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. [ ] Microfiche Computer Program *(Appendix)*
7. Nucleotide and Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. [X] Computer-Readable Copy
   b. [X] Paper Copy (identical to computer copy)
   c. [X] Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. [ ] Assignment Papers (cover sheet & document(s))
9. [ ] 37 CFR 3.73(b) Statement *(when there is an assignee)* [ ] Power of Attorney
10. [ ] English Translation Document *(if applicable)*
11. [ ] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copies of IDS Citations
12. [ ] Preliminary Amendment
13. [X] Return Receipt Postcard
14. [ ] Small Entity Statement(s) [ ] Statement filed in prior application, Status still proper and desired
15. [ ] Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
16. [X] Other: Certificate of Express Mail

17. If a CONTINUING APPLICATION, *check appropriate box and supply the requisite information below and in a preliminary amendment*

[ ] Continuation [ ] Divisional [X] Continuation-in-Part (CIP) of prior Application No.: 09/370,838

Prior application information: Examiner Not Assigned Group / Art Unit 1817

[ ] Claims the benefit of Provisional Application No. _____

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Respectfully submitted,

TYPED or PRINTED NAME David J. Maki REGISTRATION NO. 31,392

SIGNATURE _____ Date DECEMBER 30, 1999

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09/476235 12/30/99

420 A590 Box seq 686

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Steven G. Reed, Bellevue, Washington; Michael J. Lodes, Seattle, Washington, Raodoh Mohamath, Seattle, Washington and Heather Secrist, Seattle, Washington
Filed	:	December 30, 1999
For	:	COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE

Docket No. : 210121.475C2

Date : December 30, 1999

Box Patent Application
Assistant Commissioner for Patents
Washington, DC 20231

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Assistant Commissioner for Patents:

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Respectfully submitted,

SEED AND BERRY LLP

Elizabeth M. McCarthy

DJM:em

Enclosures:
- Postcard
- Form PTO/SB/05
- Specification, Claims, Abstract (75 pages)
- Declaration regarding Sequence Listing
- Diskette containing Sequence Listing
- Sequence Listing (152 pages)

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COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE

REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Patent Application No. 09/370,838, filed August 9, 1999, which is a continuation-in-part of U.S. Patent Application No. 09/285,323, filed April 2, 1999.

TECHNICAL FIELD

The present invention relates generally to compositions and methods for the treatment of lung cancer. The invention is more specifically related to nucleotide sequences that are preferentially expressed in lung tumor tissue, together with polypeptides encoded by such nucleotide sequences. The inventive nucleotide sequences and polypeptides may be used in vaccines and pharmaceutical compositions for the treatment of lung cancer.

BACKGROUND OF THE INVENTION

Lung cancer is the primary cause of cancer death among both men and women in the U.S., with an estimated 172,000 new cases being reported in 1994. The five-year survival rate among all lung cancer patients, regardless of the stage of disease at diagnosis, is only 13%. This contrasts with a five-year survival rate of 46% among cases detected while the disease is still localized. However, only 16% of lung cancers are discovered before the disease has spread.

Early detection is difficult since clinical symptoms are often not seen until the disease has reached an advanced stage. Currently, diagnosis is aided by the use of chest x-rays, analysis of the type of cells contained in sputum and fiberoptic examination of the bronchial passages. Treatment regimens are determined by the type and stage of the cancer, and include surgery, radiation therapy and/or chemotherapy. In spite of considerable research into therapies for the disease, lung cancer remains difficult to treat.

Accordingly, there remains a need in the art for improved vaccines, treatment methods and diagnostic techniques for lung cancer.

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SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compounds and methods for the therapy and diagnosis of cancer, such as lung cancer. In one aspect, the present invention provides polypeptides comprising at least a portion of a lung tumor protein, or a variant thereof .. Certain portions and other variants are immunogenic, such that the ability of the variant to react with antigen-specific antisera is not substantially diminished. Within certain embodiments, the polypeptide comprises a sequence that is encoded by a polynucleotide sequence selected from the group consisting of: (a) sequences recited in SEQ ID NOS: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 and 361; (b) variants of a sequence recited in SEQ ID NOS: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 and 361; and (c) complements of a sequence of (a) or (b).

The present invention further provides polynucleotides that encode a polypeptide as described above, or a portion thereof (such as a portion encoding at least 15 contiguous amino acid residues of a lung tumor protein), expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, vaccines are provided. Such vaccines comprise a polypeptide or polynucleotide as described above and an immunostimulant.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a lung tumor protein; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

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Within related aspects, vaccines are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

Within related aspects, pharmaceutical compositions comprising a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a physiologically acceptable carrier are provided.

Vaccines are further provided, within other aspects, that comprise a fusion protein, or a polynucleotide encoding a fusion protein, in combination with an immunostimulant.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition or vaccine as recited above.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a lung tumor protein, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a lung tumor protein, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polynucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

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The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating $CD4^+$ and/or $CD8^+$ T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of a lung tumor protein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody. The cancer may be lung cancer.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within

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certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

SEQUENCE IDENTIFIERS

SEQ ID NO: 1 is the determined cDNA sequence for L363C1.cons

SEQ ID NO: 2 is the determined cDNA sequence for L263C2.cons

SEQ ID NO: 3 is the determined cDNA sequence for L263C2c

SEQ ID NO: 4 is the determined cDNA sequence for L263C1.cons

SEQ ID NO: 5 is the determined cDNA sequence for L263C1b

SEQ ID NO: 6 is the determined cDNA sequence for L164C2.cons

SEQ ID NO: 7 is the determined cDNA sequence for L164C1.cons

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SEQ ID NO: 8 is the determined cDNA sequence for L366C1a

SEQ ID NO: 9 is the determined cDNA sequence for L260C1.cons

SEQ ID NO: 10 is the determined cDNA sequence for L163C1c

SEQ ID NO: 11 is the determined cDNA sequence for L163C1b

SEQ ID NO: 12 is the determined cDNA sequence for L255C1.cons

SEQ ID NO: 13 is the determined cDNA sequence for L255C1b

SEQ ID NO: 14 is the determined cDNA sequence for L355C1.cons

SEQ ID NO: 15 is the determined cDNA sequence for L366C1.cons

SEQ ID NO: 16 is the determined cDNA sequence for L163C1a

SEQ ID NO: 17 is the determined cDNA sequence for LT86-1

SEQ ID NO: 18 is the determined cDNA sequence for LT86-2

SEQ ID NO: 19 is the determined cDNA sequence for LT86-3

SEQ ID NO: 20 is the determined cDNA sequence for LT86-4

SEQ ID NO: 21 is the determined cDNA sequence for LT86-5

SEQ ID NO: 22 is the determined cDNA sequence for LT86-6

SEQ ID NO: 23 is the determined cDNA sequence for LT86-7

SEQ ID NO: 24 is the determined cDNA sequence for LT86-8

SEQ ID NO: 25 is the determined cDNA sequence for LT86-9

SEQ ID NO: 26 is the determined cDNA sequence for LT86-10

SEQ ID NO: 27 is the determined cDNA sequence for LT86-11

SEQ ID NO: 28 is the determined cDNA sequence for LT86-12

SEQ ID NO: 29 is the determined cDNA sequence for LT86-13

SEQ ID NO: 30 is the determined cDNA sequence for LT86-14

SEQ ID NO: 31 is the determined cDNA sequence for LT86-15

SEQ ID NO: 32 is the predicted amino acid sequence for LT86-1

SEQ ID NO: 33 is the predicted amino acid sequence for LT86-2

SEQ ID NO: 34 is the predicted amino acid sequence for LT86-3

SEQ ID NO: 35 is the predicted amino acid sequence for LT86-4

SEQ ID NO: 36 is the predicted amino acid sequence for LT86-5

SEQ ID NO: 37 is the predicted amino acid sequence for LT86-6

SEQ ID NO: 38 is the predicted amino acid sequence for LT86-7

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SEQ ID NO: 39 is the predicted amino acid sequence for LT86-8

SEQ ID NO: 40 is the predicted amino acid sequence for LT86-9

SEQ ID NO: 41 is the predicted amino acid sequence for LT86-10

SEQ ID NO: 42 is the predicted amino acid sequence for LT86-11

SEQ ID NO: 43 is the predicted amino acid sequence for LT86-12

SEQ ID NO: 44 is the predicted amino acid sequence for LT86-13

SEQ ID NO: 45 is the predicted amino acid sequence for LT86-14

SEQ ID NO: 46 is the predicted amino acid sequence for LT86-15

SEQ ID NO: 47 is a $(dT)_{12}AG$ primer

SEQ ID NO: 48 is a primer

SEQ ID NO: 49 is the determined 5' cDNA sequence for L86S-3

SEQ ID NO: 50 is the determined 5' cDNA sequence for L86S-12

SEQ ID NO: 51 is the determined 5' cDNA sequence for L86S-16

SEQ ID NO: 52 is the determined 5' cDNA sequence for L86S-25

SEQ ID NO: 53 is the determined 5' cDNA sequence for L86S-36

SEQ ID NO: 54 is the determined 5' cDNA sequence for L86S-40

SEQ ID NO: 55 is the determined 5' cDNA sequence for L86S-46

SEQ ID NO: 56 is the predicted amino acid sequence for L86S-3

SEQ ID NO: 57 is the predicted amino acid sequence for L86S-12

SEQ ID NO: 58 is the predicted amino acid sequence for L86S-16

SEQ ID NO: 59 is the predicted amino acid sequence for L86S-25

SEQ ID NO: 60 is the predicted amino acid sequence for L86S-36

SEQ ID NO: 61 is the predicted amino acid sequence for L86S-40

SEQ ID NO: 62 is the predicted amino acid sequence for L86S-46

SEQ ID NO: 63 is the determined 5' cDNA sequence for L86S-30

SEQ ID NO: 64 is the determined 5' cDNA sequence for L86S-41

SEQ ID NO: 65 is the predicted amino acid sequence from the 5' end of LT86-9

SEQ ID NO: 66 is the determined extended cDNA sequence for LT86-4

SEQ ID NO: 67 is the predicted extended amino acid sequence for LT86-4

SEQ ID NO: 68 is the determined 5' cDNA sequence for LT86-20

SEQ ID NO: 69 is the determined 3' cDNA sequence for LT86-21

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SEQ ID NO: 70 is the determined 5' cDNA sequence for LT86-22

SEQ ID NO: 71 is the determined 5' cDNA sequence for LT86-26

SEQ ID NO: 72 is the determined 5' cDNA sequence for LT86-27

SEQ ID NO: 73 is the predicted amino acid sequence for LT86-20

SEQ ID NO: 74 is the predicted amino acid sequence for LT86-21

SEQ ID NO: 75 is the predicted amino acid sequence for LT86-22

SEQ ID NO: 76 is the predicted amino acid sequence for LT86-26

SEQ ID NO: 77 is the predicted amino acid sequence for LT86-27

SEQ ID NO: 78 is the determined extended cDNA sequence for L86S-12

SEQ ID NO: 79 is the determined extended cDNA sequence for L86S-36

SEQ ID NO: 80 is the determined extended cDNA sequence for L86S-46

SEQ ID NO: 81 is the predicted extended amino acid sequence for L86S-12

SEQ ID NO: 82 is the predicted extended amino acid sequence for L86S-36

SEQ ID NO: 83 is the predicted extended amino acid sequence for L86S-46

SEQ ID NO: 84 is the determined 5'cDNA sequence for L86S-6

SEQ ID NO: 85 is the determined 5'cDNA sequence for L86S-11

SEQ ID NO: 86 is the determined 5'cDNA sequence for L86S-14

SEQ ID NO: 87 is the determined 5'cDNA sequence for L86S-29

SEQ ID NO: 88 is the determined 5'cDNA sequence for L86S-34

SEQ ID NO: 89 is the determined 5'cDNA sequence for L86S-39

SEQ ID NO: 90 is the determined 5'cDNA sequence for L86S-47

SEQ ID NO: 91 is the determined 5'cDNA sequence for L86S-49

SEQ ID NO: 92 is the determined 5'cDNA sequence for L86S-51

SEQ ID NO: 93 is the predicted amino acid sequence for L86S-6

SEQ ID NO: 94 is the predicted amino acid sequence for L86S-11

SEQ ID NO: 95 is the predicted amino acid sequence for L86S-14

SEQ ID NO: 96 is the predicted amino acid sequence for L86S-29

SEQ ID NO: 97 is the predicted amino acid sequence for L86S-34

SEQ ID NO: 98 is the predicted amino acid sequence for L86S-39

SEQ ID NO: 99 is the predicted amino acid sequence for L86S-47

SEQ ID NO: 100 is the predicted amino acid sequence for L86S-49

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SEQ ID NO: 101 is the predicted amino acid sequence for L86S-51

SEQ ID NO: 102 is the determined DNA sequence for SLT-T1

SEQ ID NO: 103 is the determined 5' cDNA sequence for SLT-T2

SEQ ID NO: 104 is the determined 5' cDNA sequence for SLT-T3

SEQ ID NO: 105 is the determined 5' cDNA sequence for SLT-T5

SEQ ID NO: 106 is the determined 5' cDNA sequence for SLT-T7

SEQ ID NO: 107 is the determined 5' cDNA sequence for SLT-T9

SEQ ID NO: 108 is the determined 5' cDNA sequence for SLT-T10

SEQ ID NO: 109 is the determined 5' cDNA sequence for SLT-T11

SEQ ID NO: 110 is the determined 5' cDNA sequence for SLT-T12

SEQ ID NO: 111 is the predicted amino acid sequence for SLT-T1

SEQ ID NO: 112 is the predicted amino acid sequence for SLT-T2

SEQ ID NO: 113 is the predicted amino acid sequence for SLT-T3

SEQ ID NO: 114 is the predicted amino acid sequence for SLT-T10

SEQ ID NO: 115 is the predicted amino acid sequence for SLT-T12

SEQ ID NO: 116 is the determined 5' cDNA sequence for SALT-T3

SEQ ID NO: 117 is the determined 5' cDNA sequence for SALT-T4

SEQ ID NO: 118 is the determined 5' cDNA sequence for SALT-T7

SEQ ID NO: 119 is the determined 5' cDNA sequence for SALT-T8

SEQ ID NO: 120 is the determined 5' cDNA sequence for SALT-T9

SEQ ID NO: 121 is the predicted amino acid sequence for SALT-T3

SEQ ID NO: 122 is the predicted amino acid sequence for SALT-T4

SEQ ID NO: 123 is the predicted amino acid sequence for SALT-T7

SEQ ID NO: 124 is the predicted amino acid sequence for SALT-T8

SEQ ID NO: 125 is the predicted amino acid sequence for SALT-T9

SEQ ID NO: 126 is the determined cDNA sequence for PSLT-1

SEQ ID NO: 127 is the determined cDNA sequence for PSLT-2

SEQ ID NO: 128 is the determined cDNA sequence for PSLT-7

SEQ ID NO: 129 is the determined cDNA sequence for PSLT-13

SEQ ID NO: 130 is the determined cDNA sequence for PSLT-27

SEQ ID NO: 131 is the determined cDNA sequence for PSLT-28

SEQ ID NO: 132 is the determined cDNA sequence for PSLT-30

SEQ ID NO: 133 is the determined cDNA sequence for PSLT-40

SEQ ID NO: 134 is the determined cDNA sequence for PSLT-69

SEQ ID NO: 135 is the determined cDNA sequence for PSLT-71

SEQ ID NO: 136 is the determined cDNA sequence for PSLT-73

SEQ ID NO: 137 is the determined cDNA sequence for PSLT-79

SEQ ID NO: 138 is the determined cDNA sequence for PSLT-03

SEQ ID NO: 139 is the determined cDNA sequence for PSLT-09

SEQ ID NO: 140 is the determined cDNA sequence for PSLT-011

SEQ ID NO: 141 is the determined cDNA sequence for PSLT-041

SEQ ID NO: 142 is the determined cDNA sequence for PSLT-62

SEQ ID NO: 143 is the determined cDNA sequence for PSLT-6

SEQ ID NO: 144 is the determined cDNA sequence for PSLT-37

SEQ ID NO: 145 is the determined cDNA sequence for PSLT-74

SEQ ID NO: 146 is the determined cDNA sequence for PSLT-010

SEQ ID NO: 147 is the determined cDNA sequence for PSLT-012

SEQ ID NO: 148 is the determined cDNA sequence for PSLT-037

SEQ ID NO: 149 is the determined 5' cDNA sequence for SAL-3

SEQ ID NO: 150 is the determined 5' cDNA sequence for SAL-24

SEQ ID NO: 151 is the determined 5' cDNA sequence for SAL-25

SEQ ID NO: 152 is the determined 5' cDNA sequence for SAL-33

SEQ ID NO: 153 is the determined 5' cDNA sequence for SAL-50

SEQ ID NO: 154 is the determined 5' cDNA sequence for SAL-57

SEQ ID NO: 155 is the determined 5' cDNA sequence for SAL-66

SEQ ID NO: 156 is the determined 5' cDNA sequence for SAL-82

SEQ ID NO: 157 is the determined 5' cDNA sequence for SAL-99

SEQ ID NO: 158 is the determined 5' cDNA sequence for SAL-104

SEQ ID NO: 159 is the determined 5' cDNA sequence for SAL-109

SEQ ID NO: 160 is the determined 5' cDNA sequence for SAL-5

SEQ ID NO: 161 is the determined 5' cDNA sequence for SAL-8

SEQ ID NO: 162 is the determined 5' cDNA sequence for SAL-12

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SEQ ID NO: 163 is the determined 5' cDNA sequence for SAL-14

SEQ ID NO: 164 is the determined 5' cDNA sequence for SAL-16

SEQ ID NO: 165 is the determined 5' cDNA sequence for SAL-23

SEQ ID NO: 166 is the determined 5' cDNA sequence for SAL-26

SEQ ID NO: 167 is the determined 5' cDNA sequence for SAL-29

SEQ ID NO: 168 is the determined 5' cDNA sequence for SAL-32

SEQ ID NO: 169 is the determined 5' cDNA sequence for SAL-39

SEQ ID NO: 170 is the determined 5' cDNA sequence for SAL-42

SEQ ID NO: 171 is the determined 5' cDNA sequence for SAL-43

SEQ ID NO: 172 is the determined 5' cDNA sequence for SAL-44

SEQ ID NO: 173 is the determined 5' cDNA sequence for SAL-48

SEQ ID NO: 174 is the determined 5' cDNA sequence for SAL-68

SEQ ID NO: 175 is the determined 5' cDNA sequence for SAL-72

SEQ ID NO: 176 is the determined 5' cDNA sequence for SAL-77

SEQ ID NO: 177 is the determined 5' cDNA sequence for SAL-86

SEQ ID NO: 178 is the determined 5' cDNA sequence for SAL-88

SEQ ID NO: 179 is the determined 5' cDNA sequence for SAL-93

SEQ ID NO: 180 is the determined 5' cDNA sequence for SAL-100

SEQ ID NO: 181 is the determined 5' cDNA sequence for SAL-105

SEQ ID NO: 182 is the predicted amino acid sequence for SAL-3

SEQ ID NO: 183 is the predicted amino acid sequence for SAL-24

SEQ ID NO: 184 is a first predicted amino acid sequence for SAL-25

SEQ ID NO: 185 is a second predicted amino acid sequence for SAL-25

SEQ ID NO: 186 is the predicted amino acid sequence for SAL-33

SEQ ID NO: 187 is a first predicted amino acid sequence for SAL-50

SEQ ID NO: 188 is the predicted amino acid sequence for SAL-57

SEQ ID NO: 189 is a first predicted amino acid sequence for SAL-66

SEQ ID NO: 190 is a second predicted amino acid sequence for SAL-66

SEQ ID NO: 191 is the predicted amino acid sequence for SAL-82

SEQ ID NO: 192 is the predicted amino acid sequence for SAL-99

SEQ ID NO: 193 is the predicted amino acid sequence for SAL-104

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SEQ ID NO: 194 is the predicted amino acid sequence for SAL-5

SEQ ID NO: 195 is the predicted amino acid sequence for SAL-8

SEQ ID NO: 196 is the predicted amino acid sequence for SAL-12

SEQ ID NO: 197 is the predicted amino acid sequence for SAL-14

SEQ ID NO: 198 is the predicted amino acid sequence for SAL-16

SEQ ID NO: 199 is the predicted amino acid sequence for SAL-23

SEQ ID NO: 200 is the predicted amino acid sequence for SAL-26

SEQ ID NO: 201 is the predicted amino acid sequence for SAL-29

SEQ ID NO: 202 is the predicted amino acid sequence for SAL-32

SEQ ID NO: 203 is the predicted amino acid sequence for SAL-39

SEQ ID NO: 204 is the predicted amino acid sequence for SAL-42

SEQ ID NO: 205 is the predicted amino acid sequence for SAL-43

SEQ ID NO: 206 is the predicted amino acid sequence for SAL-44

SEQ ID NO: 207 is the predicted amino acid sequence for SAL-48

SEQ ID NO: 208 is the predicted amino acid sequence for SAL-68

SEQ ID NO: 209 is the predicted amino acid sequence for SAL-72

SEQ ID NO: 210 is the predicted amino acid sequence for SAL-77

SEQ ID NO: 211 is the predicted amino acid sequence for SAL-86

SEQ ID NO: 212 is the predicted amino acid sequence for SAL-88

SEQ ID NO: 213 is the predicted amino acid sequence for SAL-93

SEQ ID NO: 214 is the predicted amino acid sequence for SAL-100

SEQ ID NO: 215 is the predicted amino acid sequence for SAL-105

SEQ ID NO: 216 is a second predicted amino acid sequence for SAL-50

SEQ ID NO: 217 is the determined cDNA sequence for SSLT-4

SEQ ID NO: 218 is the determined cDNA sequence for SSLT-9

SEQ ID NO: 219 is the determined cDNA sequence for SSLT-10

SEQ ID NO: 220 is the determined cDNA sequence for SSLT-12

SEQ ID NO: 221 is the determined cDNA sequence for SSLT-19

SEQ ID NO: 222 is the determined cDNA sequence for SSLT-31

SEQ ID NO: 223 is the determined cDNA sequence for SSLT-38

SEQ ID NO: 224 is the determined cDNA sequence for LT4690-2

SEQ ID NO: 225 is the determined cDNA sequence for LT4690-3

SEQ ID NO: 226 is the determined cDNA sequence for LT4690-22

SEQ ID NO: 227 is the determined cDNA sequence for LT4690-24

SEQ ID NO: 228 is the determined cDNA sequence for LT4690-37

SEQ ID NO: 229 is the determined cDNA sequence for LT4690-39

SEQ ID NO: 230 is the determined cDNA sequence for LT4690-40

SEQ ID NO: 231 is the determined cDNA sequence for LT4690-41

SEQ ID NO: 232 is the determined cDNA sequence for LT4690-49

SEQ ID NO: 233 is the determined 3' cDNA sequence for LT4690-55

SEQ ID NO: 234 is the determined 5' cDNA sequence for LT4690-55

SEQ ID NO: 235 is the determined cDNA sequence for LT4690-59

SEQ ID NO: 236 is the determined cDNA sequence for LT4690-63

SEQ ID NO: 237 is the determined cDNA sequence for LT4690-71

SEQ ID NO: 238 is the determined cDNA sequence for 2LT-3

SEQ ID NO: 239 is the determined cDNA sequence for 2LT-6

SEQ ID NO: 240 is the determined cDNA sequence for 2LT-22

SEQ ID NO: 241 is the determined cDNA sequence for 2LT-25

SEQ ID NO: 242 is the determined cDNA sequence for 2LT-26

SEQ ID NO: 243 is the determined cDNA sequence for 2LT-31

SEQ ID NO: 244 is the determined cDNA sequence for 2LT-36

SEQ ID NO: 245 is the determined cDNA sequence for 2LT-42

SEQ ID NO: 246 is the determined cDNA sequence for 2LT-44

SEQ ID NO: 247 is the determined cDNA sequence for 2LT-54

SEQ ID NO: 248 is the determined cDNA sequence for 2LT-55

SEQ ID NO: 249 is the determined cDNA sequence for 2LT-57

SEQ ID NO: 250 is the determined cDNA sequence for 2LT-58

SEQ ID NO: 251 is the determined cDNA sequence for 2LT-59

SEQ ID NO: 252 is the determined cDNA sequence for 2LT-62

SEQ ID NO: 253 is the determined cDNA sequence for 2LT-63

SEQ ID NO: 254 is the determined cDNA sequence for 2LT-65

SEQ ID NO: 255 is the determined cDNA sequence for 2LT-66

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SEQ ID NO: 256 is the determined cDNA sequence for 2LT-70

SEQ ID NO: 257 is the determined cDNA sequence for 2LT-73

SEQ ID NO: 258 is the determined cDNA sequence for 2LT-74

SEQ ID NO: 259 is the determined cDNA sequence for 2LT-76

SEQ ID NO: 260 is the determined cDNA sequence for 2LT-77

SEQ ID NO: 261 is the determined cDNA sequence for 2LT-78

SEQ ID NO: 262 is the determined cDNA sequence for 2LT-80

SEQ ID NO: 263 is the determined cDNA sequence for 2LT-85

SEQ ID NO: 264 is the determined cDNA sequence for 2LT-87

SEQ ID NO: 265 is the determined cDNA sequence for 2LT-89

SEQ ID NO: 266 is the determined cDNA sequence for 2LT-94

SEQ ID NO: 267 is the determined cDNA sequence for 2LT-95

SEQ ID NO: 268 is the determined cDNA sequence for 2LT-98

SEQ ID NO: 269 is the determined cDNA sequence for 2LT-100

SEQ ID NO: 270 is the determined cDNA sequence for 2LT-103

SEQ ID NO: 271 is the determined cDNA sequence for 2LT-105

SEQ ID NO: 272 is the determined cDNA sequence for 2LT-107

SEQ ID NO: 273 is the determined cDNA sequence for 2LT-108

SEQ ID NO: 274 is the determined cDNA sequence for 2LT-109

SEQ ID NO: 275 is the determined cDNA sequence for 2LT-118

SEQ ID NO: 276 is the determined cDNA sequence for 2LT-120

SEQ ID NO: 277 is the determined cDNA sequence for 2LT-121

SEQ ID NO: 278 is the determined cDNA sequence for 2LT-122

SEQ ID NO: 279 is the determined cDNA sequence for 2LT-124

SEQ ID NO: 280 is the determined cDNA sequence for 2LT-126

SEQ ID NO: 281 is the determined cDNA sequence for 2LT-127

SEQ ID NO: 282 is the determined cDNA sequence for 2LT-128

SEQ ID NO: 283 is the determined cDNA sequence for 2LT-129

SEQ ID NO: 284 is the determined cDNA sequence for 2LT-133

SEQ ID NO: 285 is the determined cDNA sequence for 2LT-137

SEQ ID NO: 286 is the determined cDNA sequence for LT4690-71

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SEQ ID NO: 287 is the determined cDNA sequence for LT4690-82

SEQ ID NO: 288 is the determined full-length cDNA sequence for SSLT-74

SEQ ID NO: 289 is the determined cDNA sequence for SSLT-78

SEQ ID NO: 290 is the determined cDNA sequence for SCC1-8.

SEQ ID NO: 291 is the determined cDNA sequence for SCC1-12.

SEQ ID NO: 292 is the determined cDNA sequence for SCC1-336

SEQ ID NO: 293 is the determined cDNA sequence for SCC1-344

SEQ ID NO: 294 is the determined cDNA sequence for SCC1-345

SEQ ID NO: 295 is the determined cDNA sequence for SCC1-346

SEQ ID NO: 296 is the determined cDNA sequence for SCC1-348

SEQ ID NO: 297 is the determined cDNA sequence for SCC1-350

SEQ ID NO: 298 is the determined cDNA sequence for SCC1-352

SEQ ID NO: 299 is the determined cDNA sequence for SCC1-354

SEQ ID NO: 300 is the determined cDNA sequence for SCC1-355

SEQ ID NO: 301 is the determined cDNA sequence for SCC1-356

SEQ ID NO: 302 is the determined cDNA sequence for SCC1-357

SEQ ID NO: 303 is the determined cDNA sequence for SCC1-501

SEQ ID NO: 304 is the determined cDNA sequence for SCC1-503

SEQ ID NO: 305 is the determined cDNA sequence for SCC1-513

SEQ ID NO: 306 is the determined cDNA sequence for SCC1-516

SEQ ID NO: 307 is the determined cDNA sequence for SCC1-518

SEQ ID NO: 308 is the determined cDNA sequence for SCC1-519

SEQ ID NO: 309 is the determined cDNA sequence for SCC1-522

SEQ ID NO: 310 is the determined cDNA sequence for SCC1-523

SEQ ID NO: 311 is the determined cDNA sequence for SCC1-525

SEQ ID NO: 312 is the determined cDNA sequence for SCC1-527

SEQ ID NO: 313 is the determined cDNA sequence for SCC1-529

SEQ ID NO: 314 is the determined cDNA sequence for SCC1-530

SEQ ID NO: 315 is the determined cDNA sequence for SCC1-531

SEQ ID NO: 316 is the determined cDNA sequence for SCC1-532

SEQ ID NO: 317 is the determined cDNA sequence for SCC1-533

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SEQ ID NO: 318 is the determined cDNA sequence for SCC1-536

SEQ ID NO: 319 is the determined cDNA sequence for SCC1-538

SEQ ID NO: 320 is the determined cDNA sequence for SCC1-539

SEQ ID NO: 321 is the determined cDNA sequence for SCC1-541

SEQ ID NO: 322 is the determined cDNA sequence for SCC1-542

SEQ ID NO: 323 is the determined cDNA sequence for SCC1-546

SEQ ID NO: 324 is the determined cDNA sequence for SCC1-549

SEQ ID NO: 325 is the determined cDNA sequence for SCC1-551

SEQ ID NO: 326 is the determined cDNA sequence for SCC1-552

SEQ ID NO: 327 is the determined cDNA sequence for SCC1-554

SEQ ID NO: 328 is the determined cDNA sequence for SCC1-558

SEQ ID NO: 329 is the determined cDNA sequence for SCC1-559

SEQ ID NO: 330 is the determined cDNA sequence for SCC1-561

SEQ ID NO: 331 is the determined cDNA sequence for SCC1-562

SEQ ID NO: 332 is the determined cDNA sequence for SCC1-564

SEQ ID NO: 333 is the determined cDNA sequence for SCC1-565

SEQ ID NO: 334 is the determined cDNA sequence for SCC1-566

SEQ ID NO: 335 is the determined cDNA sequence for SCC1-567

SEQ ID NO: 336 is the determined cDNA sequence for SCC1-568

SEQ ID NO: 337 is the determined cDNA sequence for SCC1-570

SEQ ID NO: 338 is the determined cDNA sequence for SCC1-572

SEQ ID NO: 339 is the determined cDNA sequence for SCC1-575

SEQ ID NO: 340 is the determined cDNA sequence for SCC1-576

SEQ ID NO: 341 is the determined cDNA sequence for SCC1-577

SEQ ID NO: 342 is the determined cDNA sequence for SCC1-578

SEQ ID NO: 343 is the determined cDNA sequence for SCC1-582

SEQ ID NO: 344 is the determined cDNA sequence for SCC1-583

SEQ ID NO: 345 is the determined cDNA sequence for SCC1-586

SEQ ID NO: 346 is the determined cDNA sequence for SCC1-588

SEQ ID NO: 347 is the determined cDNA sequence for SCC1-590

SEQ ID NO: 348 is the determined cDNA sequence for SCC1-591

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SEQ ID NO: 349 is the determined cDNA sequence for SCC1-592
SEQ ID NO: 350 is the determined cDNA sequence for SCC1-593
SEQ ID NO: 351 is the determined cDNA sequence for SCC1-594
SEQ ID NO: 352 is the determined cDNA sequence for SCC1-595
SEQ ID NO: 353 is the determined cDNA sequence for SCC1-596
SEQ ID NO: 354 is the determined cDNA sequence for SCC1-598
SEQ ID NO: 355 is the determined cDNA sequence for SCC1-599
SEQ ID NO: 356 is the determined cDNA sequence for SCC1-602
SEQ ID NO: 357 is the determined cDNA sequence for SCC1-604
SEQ ID NO: 358 is the determined cDNA sequence for SCC1-605
SEQ ID NO: 359 is the determined cDNA sequence for SCC1-606
SEQ ID NO: 360 is the determined cDNA sequence for SCC1-607
SEQ ID NO: 361 is the determined cDNA sequence for SCC1-608
SEQ ID NO: 362 is the determined cDNA sequence for SCC1-610

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DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the therapy and diagnosis of cancer, such as lung cancer. The compositions described herein may include lung tumor polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (*e.g.*, T cells). Polypeptides of the present invention generally comprise at least a portion (such as an immunogenic portion) of a lung tumor protein or a variant thereof. A "lung tumor protein" is a protein that is expressed in lung tumor cells at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in a normal tissue, as determined using a representative assay provided herein. Certain lung tumor proteins are tumor proteins that react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera of a patient afflicted with lung cancer. Polynucleotides of the subject invention generally comprise a DNA or RNA sequence that encodes all or a portion of such a polypeptide, or that is complementary to such a sequence. Antibodies are generally immune system proteins, or antigen-binding fragments thereof, that are capable of binding to a

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polypeptide as described above. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B-cells that express a polypeptide as described above. T cells that may be employed within such compositions are generally T cells that are specific for a polypeptide as described above.

The present invention is based on the discovery of human lung tumor proteins. Sequences of polynucleotides encoding specific tumor proteins are provided in SEQ ID NOS: 1-31, 49-55, 63,64, 66, 68-72, 78-80, 84-92 and 217-362.

LUNG TUMOR PROTEIN POLYNUCLEOTIDES

Any polynucleotide that encodes a lung tumor protein or a portion or other variant thereof as described herein is encompassed by the present invention. Preferred polynucleotides comprise at least 15 consecutive nucleotides, preferably at least 30 consecutive nucleotides and more preferably at least 45 consecutive nucleotides, that encode a portion of a lung tumor protein. More preferably, a polynucleotide encodes an immunogenic portion of a lung tumor protein. Polynucleotides complementary to any such sequences are also encompassed by the present invention. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a lung tumor protein or a portion thereof) or may comprise a variant of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native tumor protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native lung tumor protein or a portion thereof.

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Two polynucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS 5*:151-153; Myers, E.W. and Muller W. (1988) *CABIOS 4*:11-17; Robinson, E.D. (1971) *Comb. Theor 11*:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol. 4*:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA 80*:726-730.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (i.e. gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (i.e. the window size) and multiplying the results by 100 to yield the percentage of

sequence identity.

Variants may also, or alternatively, be substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are capable of hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding a native lung tumor protein (or a complementary sequence). Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Polynucleotides may be prepared using any of a variety of techniques. For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least five fold greater in a lung tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Alternatively, polypeptides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as lung tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion may be used to isolate a full length gene from a suitable library (*e.g.*, a lung tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (*e.g.*, by nick-translation or end-labeling with ^{32}P) using well known techniques. A bacterial or bacteriophage library is then screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (*see* Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences are then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (*see* Triglia et al., *Nucl. Acids Res. 16*:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a

template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., *PCR Methods Applic.* *1*:111-19, 1991) and walking PCR (Parker et al., *Nucl. Acids. Res.* *19*:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (*e.g.*, NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence.

Certain nucleic acid sequences of cDNA molecules encoding portions of lung tumor proteins are provided in SEQ ID NO: 1-31, 49-55, 63,64, 66, 68-72, 78-80, 84-92 and 217-362. The isolation of these sequences is described in detail below.

Polynucleotide variants may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical synthesis. Modifications in a polynucleotide sequence may also be introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis (see Adelman et al., *DNA* *2*:183, 1983). Alternatively, RNA molecules may be generated by *in vitro* or *in vivo* transcription of DNA sequences encoding a lung tumor protein, or portion thereof, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Certain portions may be used to prepare an encoded polypeptide, as described herein. In addition, or alternatively, a portion may be administered to a patient such that the encoded polypeptide is generated *in vivo* (*e.g.*, by transfecting

antigen-presenting cells, such as dendritic cells, with a cDNA construct encoding a lung tumor polypeptide, and administering the transfected cells to the patient).

A portion of a sequence complementary to a coding sequence (*i.e.*, an antisense polynucleotide) may also be used as a probe or to modulate gene expression. cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells of tissues to facilitate the production of antisense RNA. An antisense polynucleotide may be used, as described herein, to inhibit expression of a tumor protein. Antisense technology can be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (*see* Gee et al., *In* Huber and Carr, *Molecular and Immunologic Approaches*, Futura Publishing Co. (Mt. Kisco, NY; 1994)). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (*e.g.*, promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes.

A portion of a coding sequence, or of a complementary sequence, may also be designed as a probe or primer to detect gene expression. Probes may be labeled with a variety of reporter groups, such as radionuclides and enzymes, and are preferably at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and still more preferably at least 30 nucleotides in length. Primers, as noted above, are preferably 22-30 nucleotides in length.

Any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl-, methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In

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general, a vector will contain an origin of replication functional in at least one organism, convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Such formulations are particularly useful for therapeutic purposes, as described below. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (*e.g.*, avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also be accomplished using an antibody, by methods known to those of ordinary skill in the art.

Other formulations for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

LUNG TUMOR POLYPEPTIDES

Within the context of the present invention, polypeptides may comprise at least an immunogenic portion of a lung tumor protein or a variant thereof, as described herein. As noted above, a "lung tumor protein" is a protein that is expressed by lung tumor cells. Proteins that are lung tumor proteins also react detectably within an immunoassay (such as an ELISA) with antisera from a patient with lung cancer. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further

immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of a protein that is recognized (*i.e.*, specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of a lung tumor protein or a variant thereof. Certain preferred immunogenic portions include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other preferred immunogenic portions may contain a small N- and/or C-terminal deletion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (*i.e.*, they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well known techniques. An immunogenic portion of a native lung tumor protein is a portion that reacts with such antisera and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (*e.g.*, in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ^{125}I-labeled Protein A.

As noted above, a composition may comprise a variant of a native lung tumor protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native lung tumor protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the

ability of a variant to react with antigen-specific antisera may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antigen-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity (determined as described above) to the identified polypeptides.

Preferably, a variant contains conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of

the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (*e.g.*, poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. *See* Merrifield, *J. Am. Chem. Soc.* *85*:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain

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preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused protein, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene 40*:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA 83*:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA

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are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (*see*, for example, Stoute et al. *New Engl. J. Med.*, *336*:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (*e.g.*, the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in *E. coli* (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10*:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

BINDING AGENTS

The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to a lung tumor protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to a lung tumor protein if it reacts at a detectable level (within, for example, an ELISA) with a lung tumor protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a complex is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10^3 L/mol. The binding constant may be determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as lung cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a lung tumor protein will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (*e.g.*, blood, sera, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should

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be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (*e.g.*, mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a

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few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988) and digested by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ^{90}Y, ^{123}I, ^{125}I, ^{131}I, ^{186}Re, ^{188}Re, ^{211}At, and ^{212}Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of

reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody

molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

T CELLS

Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for a lung tumor protein. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the ISOLEX™ system, available from Nexell Therapeutics Inc., Irvine, CA (see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a lung tumor polypeptide, polynucleotide encoding a lung tumor polypeptide and/or an antigen presenting cell (APC) that expresses

such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, a lung tumor polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a lung tumor polypeptide if the T cells kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., *Cancer Res.* *54*:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (*e.g.*, by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a lung tumor polypeptide (100 ng/ml - 100 μg/ml, preferably 200 ng/ml - 25 μg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (*e.g.*, TNF or IFN-γ) is indicative of T cell activation (*see* Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a lung tumor polypeptide, polynucleotide or polypeptide-expressing APC may be $CD4^+$ and/or $CD8^+$. Lung tumor protein-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from either a patient or a related, or unrelated, donor and are administered to the patient following stimulation and expansion.

For therapeutic purposes, $CD4^+$ or $CD8^+$ T cells that proliferate in response to a lung tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a lung tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a lung

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tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of a lung tumor protein can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

PHARMACEUTICAL COMPOSITIONS AND VACCINES

Within certain aspects, polypeptides, polynucleotides, T cells and/or binding agents disclosed herein may be incorporated into pharmaceutical compositions or immunogenic compositions (*i.e.*, vaccines). Pharmaceutical compositions comprise one or more such compounds and a physiologically acceptable carrier. Vaccines may comprise one or more such compounds and an immunostimulant. An immunostimulant may be any substance that enhances or potentiates an immune response to an exogenous antigen. Examples of immunostimulants include adjuvants, biodegradable microspheres (*e.g.*, polylactic galactide) and liposomes (into which the compound is incorporated; *see e.g.*, Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and vaccines within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound, within the composition or vaccine.

A pharmaceutical composition or vaccine may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems 15*:143-198, 1998, and references cited therein. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope. In a preferred embodiment, the DNA may be introduced

using a viral expression system (*e.g.*, vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., *Proc. Natl. Acad. Sci. USA 86*:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci. 569*:86-103, 1989; Flexner et al., *Vaccine 8*:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques 6*:616-627, 1988; Rosenfeld et al., *Science 252*:431-434, 1991; Kolls et al., *Proc. Natl. Acad. Sci. USA 91*:215-219, 1994; Kass-Eisler et al., *Proc. Natl. Acad. Sci. USA 90*:11498-11502, 1993; Guzman et al., *Circulation 88*:2838-2848, 1993; and Guzman et al., *Cir. Res. 73*:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., *Science 259*:1745-1749, 1993 and reviewed by Cohen, *Science 259*:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (*e.g.*, polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Such compositions may also comprise buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione, adjuvants (*e.g.*, aluminum hydroxide) and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate.

Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of immunostimulants may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bortadella pertussis* or *Mycobacterium tuberculosis* derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

Within the vaccines provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (*e.g.*, IFN-γ, TNFα, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (*e.g.*, IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, *Ann. Rev. Immunol.* 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Ribi ImmunoChem Research Inc. (Hamilton, MT) (*see* US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555. Another

preferred adjuvant is a saponin, preferably QS21, which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprises an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210. Any vaccine provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient.

The compositions described herein may be administered as part of a sustained release formulation (*i.e.*, a formulation such as a capsule, sponge or gel (composed of polysaccharides, for example) that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and vaccines to facilitate production of an antigen-specific immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic,

syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med. 50*:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency, and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (*see* Zitvogel et al., *Nature Med. 4*:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFα, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcγ receptor, mannose receptor and DEC-205 marker. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion

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molecules (*e.g.*, CD54 and CD11) and costimulatory molecules (*e.g.*, CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide encoding a lung tumor protein (or portion or other variant thereof) such that the lung tumor polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place *ex vivo*, and a composition or vaccine comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs *in vivo*. *In vivo* and *ex vivo* transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., *Immunology and cell Biology* 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the lung tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (*e.g.*, vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (*e.g.*, a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

CANCER THERAPY

In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as lung cancer. Within such methods, pharmaceutical compositions and vaccines are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and vaccines may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. A cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs.

Within certain embodiments, immunotherapy may be active immunotherapy, in

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which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides disclosed herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as $CD8^+$ cytotoxic T lymphocytes and $CD4^+$ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (*see*, for example, Cheever et al.,

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Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions disclosed herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (*i.e.*, untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells *in vitro*. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a lung tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally

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be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

METHODS FOR DETECTING CANCER

In general, a cancer may be detected in a patient based on the presence of one or more lung tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as lung cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a lung tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the

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binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length lung tumor proteins and portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 μg, and preferably about 100 ng to about 1 μg, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see, e.g.,* Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides

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within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with lung cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic

methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as lung cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent

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is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1μg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use lung tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such lung tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a lung tumor protein in a biological sample. Within certain methods, a biological sample comprising $CD4^+$ and/or $CD8^+$ T cells isolated from a patient is incubated with a lung tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated *in vitro* for 2-9 days (typically 4 days) at 37°C with polypeptide (*e.g.*, 5 - 25 μg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of lung tumor polypeptide to serve as a control. For $CD4^+$ T cells, activation is preferably detected by evaluating proliferation of

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the T cells. For $CD8^+$ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a lung tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a lung tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the lung tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a lung tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a lung tumor protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes will hybridize to a polynucleotide encoding a polypeptide disclosed herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence recited in SEQ ID NOS: 1-31, 49-55, 63,64, 66, 68-72, 78-80, 84-92 and 217-362. Techniques for both PCR based assays and hybridization assays are well known in the art (*see*, for example, Mullis et al., *Cold Spring Harbor Symp. Quant. Biol.*, *51*:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification

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using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the disclosed compositions may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple lung tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

DIAGNOSTIC KITS

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for

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performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a lung tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a lung tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a lung tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a lung tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1

PREPARATION OF LUNG TUMOR-SPECIFIC cDNA SEQUENCES USING DIFFERENTIAL DISPLAY RT-PCR

This example illustrates the preparation of cDNA molecules encoding lung tumor-specific polypeptides using a differential display screen.

Tissue samples were prepared from lung tumor and normal tissue of a patient with lung cancer that was confirmed by pathology after removal of samples from the patient. Normal RNA and tumor RNA was extracted from the samples and mRNA was isolated and converted into cDNA using a $(dT)_{12}AG$ (SEQ ID NO: 47) anchored 3' primer. Differential display PCR was then executed using a randomly chosen primer (SEQ ID NO: 48). Amplification conditions were standard buffer containing 1.5 mM $MgCl_2$, 20 pmol of primer, 500 pmol dNTP and 1 unit of Taq DNA polymerase (Perkin-Elmer, Branchburg, NJ). Forty

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cycles of amplification were performed using 94 °C denaturation for 30 seconds, 42 °C annealing for 1 minute and 72 °C extension for 30 seconds. Bands that were repeatedly observed to be specific to the RNA fingerprint pattern of the tumor were cut out of a silver stained gel, subcloned into the pGEM-T vector (Promega, Madison, WI) and sequenced. The isolated 3' sequences are provided in SEQ ID NO: 1-16.

Comparison of these sequences to those in the public databases using the BLASTN program, revealed no significant homologies to the sequences provided in SEQ ID NO: 1-11. To the best of the inventors' knowledge, none of the isolated DNA sequences have previously been shown to be expressed at a greater level in human lung tumor tissue than in normal lung tissue.

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Example 2

USE OF PATIENT SERA TO IDENTIFY DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by expression screening of lung tumor samples with autologous patient sera.

A human lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a late SCID mouse passaged human squamous epithelial lung carcinoma and poly A+ RNA was isolated using the Message Maker kit (Gibco BRL, Gaithersburg, MD). The resulting library was screened using *E. coli*-absorbed autologous patient serum, as described in Sambrook et al., (*Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989), with the secondary antibody being goat anti-human IgG-A-M (H + L) conjugated with alkaline phosphatase, developed with NBT/BCIP (Gibco BRL). Positive plaques expressing immunoreactive antigens were purified. Phagemid from the plaques was rescued and the nucleotide sequences of the clones was determined.

Fifteen clones were isolated, referred to hereinafter as LT86-1 – LT86-15. The isolated cDNA sequences for LT86-1 – LT86-8 and LT86-10 - LT86-15 are provided in SEQ ID NO: 17-24 and 26-31, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 32-39 and 41-46, respectively. The determined cDNA sequence for LT86-9 is provided in SEQ ID NO: 25, with the corresponding predicted amino acid sequences from the 3' and 5' ends being provided in SEQ ID NO: 40 and 65, respectively. These sequences were compared to those in the gene bank as described above. Clones LT86-3, LT86-6 – LT86-9, LT86-11 – LT86-13 and LT86-15 (SEQ ID NO: 19, 22-25, 27-29 and 31, respectively) were found to show some homology to previously identified expressed sequence tags (ESTs), with clones LT86-6, LT86-8, LT86-11, LT86-12 and LT86-15 appearing to be similar or identical to each other. Clone LT86-3 was found to show some homology with a human transcription repressor. Clones LT86-6, 8, 9, 11, 12 and 15 were found to show some homology to a yeast RNA Pol II transcription regulation mediator.

Clone LT86-13 was found to show some homology with a *C. elegans* leucine aminopeptidase. Clone LT86-9 appears to contain two inserts, with the 5' sequence showing homology to the previously identified antisense sequence of interferon alpha-induced P27, and the 3' sequence being similar to LT86-6. Clone LT86-14 (SEQ ID NO: 30) was found to show some homology to the trithorax gene and has an "RGD" cell attachment sequence and a beta-Lactamase A site which functions in hydrolysis of penicillin. Clones LT86-1, LT86-2, LT86-4, LT86-5 and LT86-10 (SEQ ID NOS: 17, 18, 20, 21 and 26, respectively) were found to show homology to previously identified genes. A subsequently determined extended cDNA sequence for LT86-4 is provided in SEQ ID NO: 66, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 67.

Subsequent studies led to the isolation of five additional clones, referred to as LT86-20, LT86-21, LT86-22, LT86-26 and LT86-27. The determined 5' cDNA sequences for LT86-20, LT86-22, LT86-26 and LT86-27 are provided in SEQ ID NO: 68 and 70-72, respectively, with the determined 3' cDNA sequences for LT86-21 being provided in SEQ ID NO: 69. The corresponding predicted amino acid sequences for LT86-20, LT86-21, LT86-22, LT86-26 and LT86-27 are provided in SEQ ID NO: 73-77, respectively. LT86-22 and LT86-27 were found to be highly similar to each other. Comparison of these sequences to those in the gene bank as described above, revealed no significant homologies to LT86-22 and LT86-27. LT86-20, LT86-21 and LT86-26 were found to show homology to previously identified genes.

In further studies, a cDNA expression library was prepared using mRNA from a lung small cell carcinoma cell line in the lambda ZAP Express expression vector (Stratagene), and screened as described above, with a pool of two lung small cell carcinoma patient sera. The sera pool was adsorbed with *E. coli* lysate and human PBMC lysate was added to the serum to block antibody to proteins found in normal tissue. Seventy-three clones were isolated. The determined cDNA sequences of these clones are provided in SEQ ID NO: 290-362. The sequences of SEQ ID NO: 289-292, 294, 296-297, 300, 302, 303, 305, 307-315, 317-320, 322-325, 327-332, 334, 335, 338-341, 343-352, 354-358, 360 and 362 were found to show some homology to previously isolated genes. The sequences of SEQ ID NO: 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 and 361 were found to show some homology to previously identified ESTs.

Example 3

USE OF MOUSE ANTISERA TO IDENTIFY DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by screening of lung tumor cDNA libraries with mouse anti-tumor sera.

A directional cDNA lung tumor expression library was prepared as described above in Example 2. Sera was obtained from SCID mice containing late passaged human squamous cell and adenocarcinoma tumors. These sera were pooled and injected into normal mice to produce anti-lung tumor serum. Approximately 200,000 PFUs were screened from the unamplified library using this antiserum. Using a goat anti-mouse IgG-A-M (H+L) alkaline phosphatase second antibody developed with NBT/BCIP (BRL Labs.), approximately 40 positive plaques were identified. Phage was purified and phagemid excised for 9 clones with inserts in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined cDNA sequences for 7 of the isolated clones (hereinafter referred to as L86S-3, L86S-12, L86S-16, L86S-25, L86S-36, L86S-40 and L86S-46) are provided in SEQ ID NO: 49-55, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 56-62, respectively. The 5' cDNA sequences for the remaining 2 clones (hereinafter referred to as L86S-30 and L86S-41) are provided in SEQ ID NO: 63 and 64. L86S-36 and L86S-46 were subsequently determined to represent the same gene. Comparison of these sequences with those in the public database as described above, revealed no significant homologies to clones L86S-30, L86S-36 and L86S-46 (SEQ ID NO: 63, 53 and 55, respectively). L86S-16 (SEQ ID NO: 51) was found to show some homology to an EST previously identified in fetal lung and germ cell tumor. The remaining clones were found to show at least some degree of homology to previously identified human genes. Subsequently determined extended cDNA sequences for L86S-12, L86S-36 and L86S-46 are provided in SEQ ID NO: 78-80, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 81-83.

Subsequent studies led to the determination of 5' cDNA sequences for an additional nine clones, referred to as L86S-6, L86S-11, L86S-14, L86S-29, L86S-34, L86S-39, L86S-47, L86S-49 and L86S-51 (SEQ ID NO: 84-92, respectively). The corresponding predicted amino acid sequences are provided in SEQ ID NO: 93-101, respectively. L86S-30,

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L86S-39 and L86S-47 were found to be similar to each other. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to L86S-14. L86S-29 was found to show some homology to a previously identified EST. L86S-6, L86S-11, L86S-34, L86S-39, L86S-47, L86S-49 and L86S-51 were found to show some homology to previously identified genes.

In further studies, a directional cDNA library was constructed using a Stratagene kit with a Lambda Zap Express vector. Total RNA for the library was isolated from two primary squamous lung tumors and poly A+ RNA was isolated using an oligo dT column. Antiserum was developed in normal mice using a pool of sera from three SCID mice implanted with human squamous lung carcinomas. Approximately 700,000 PFUs were screened from the unamplified library with *E. coli* absorbed mouse anti-SCID tumor serum. Positive plaques were identified as described above. Phage was purified and phagemid excised for 180 clones with inserts in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined cDNA sequences for 23 of the isolated clones are provided in SEQ ID NO: 126-148. Comparison of these sequences with those in the public database as described above revealed no significant homologies to the sequences of SEQ ID NO: 139 and 143-148. The sequences of SEQ ID NO: 126-138 and 140-142 were found to show homology to previously identified human polynucleotide sequences.

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Example 4

USE OF MOUSE ANTISERA TO SCREEN LUNG TUMOR LIBRARIES PREPARED FROM SCID MICE

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by screening of lung tumor cDNA libraries prepared from SCID mice with mouse anti-tumor sera.

A directional cDNA lung tumor expression library was prepared using a Stratagene kit with a Lambda Zap Express vector. Total RNA for the library was taken from a late passaged lung adenocarcinoma grown in SCID mice. Poly A+ RNA was isolated using a Message Maker Kit (Gibco BRL). Sera was obtained from two SCID mice implanted with lung adenocarcinomas. These sera were pooled and injected into normal mice to produce anti-lung tumor serum. Approximately 700,000 PFUs were screened from the unamplified library with *E. coli*-absorbed mouse anti-SCID tumor serum. Positive plaques were identified with a goat anti-mouse IgG-A-M (H+L) alkaline phosphatase second antibody developed with NBT/BCIP (Gibco BRL). Phage was purified and phagemid excised for 100 clones with insert in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined 5' cDNA sequences for 33 of the isolated clones are provided in SEQ ID NO: 149-181. The corresponding predicted amino acid sequences for SEQ ID NO: 149, 150, 152-154, 156-158 and 160-181 are provided in SEQ ID NO: 182, 183, 186, 188-193 and 194-215, respectively. The clone of SEQ ID NO: 151 (referred to as SAL-25) was found to contain two open reading frames (ORFs). The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 184 and 185. The clone of SEQ ID NO: 153 (referred to as SAL-50) was found to contain two open reading frames encoding the predicted amino acid sequences of SEQ ID NO: 187 and 216. Similarly, the clone of SEQ ID NO: 155 (referred to as SAL-66) was found to contain two open reading frames encoding the predicted amino acid sequences of SEQ ID NO: 189 and 190. Comparison of the isolated sequences with those in the public database revealed no significant homologies to the sequences of SEQ ID NO: 151, 153 and 154. The sequences of SEQ ID NO: 149, 152, 156, 157 and 158 were found to show some homology to previously isolated expressed sequence tags (ESTs). The sequences of SEQ ID NO: 150, 155 and 159-181 were found to show

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homology to sequences previously identified in humans.

Using the procedures described above, two directional cDNA libraries (referred to as LT46-90 and LT86-21) were prepared from two late passaged lung squamous carcinomas grown in SCID mice and screened with sera obtained from SCID mice implanted with human squamous lung carcinomas. The determined cDNA sequences for the isolated clones are provided in SEQ ID NO: 217-237 and 286-289. SEQ ID NO: 286 was found to be a longer sequence of LT4690-71 (SEQ ID NO: 237). Comparison of these sequences with those in the public databases revealed no known homologies to the sequences of SEQ ID NO: 219, 220, 225, 226, 287 and 288. The sequences of SEQ ID NO: 218, 221, 222 and 224 were found to show some homology to previously identified sequences of unknown function. The sequence of SEQ ID NO: 236 was found to show homology to a known mouse mRNA sequence. The sequences of SEQ ID NO: 217, 223, 227-237, 286 and 289 showed some homology to known human DNA and/or RNA sequences.

In further studies using the techniques described above, one of the cDNA libraries described above (LT86-21) was screened with *E. coli*-absorbed mouse anti-SCID tumor serum. This serum was obtained from normal mice immunized with a pool of 3 sera taken from SCID mice implanted with human squamous lung carcinomas. The determined cDNA sequences for the isolated clones are provided in SEQ ID NO: 238-285. Comparison of these sequences with those in the public databases revealed no significant homologies to the sequences of SEQ ID NO: 253, 260, 277 and 285. The sequences of SEQ ID NO: 249, 250, 256, 266, 276 and 282 were found to show some homology to previously isolated expressed sequence tags (ESTs). The sequences of SEQ ID NO: 238-248, 251, 252, 254, 255, 257-259, 261-263, 265, 267-275, 278-281, 283 and 284 were found to show some homology to previously identified DNA or RNA sequences.

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Example 5

DETERMINATION OF TISSUE SPECIFICITY OF LUNG TUMOR POLYPEPTIDES

Using gene specific primers, mRNA expression levels for representative lung tumor polypeptides were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent. First strand synthesis was carried out using 2 μg of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42 ^{0}C for one hour. The cDNA was then amplified by PCR with gene-specific primers. To ensure the semi-quantitative nature of the RT-PCR, β-actin was used as an internal control for each of the tissues examined. 1 μl of 1:30 dilution of cDNA was employed to enable the linear range amplification of the β-actin template and was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the β-actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in five different types of tumor tissue (lung squamous tumor from 3 patients, lung adenocarcinoma, prostate tumor colon tumor and lung tumor), and different normal tissues, including lung from four patients, prostate, brain, kidney, liver, ovary, skeletal muscle, skin, small intestine, myocardium, retina and testes. L86S-46 was found to be expressed at high levels in lung squamous tumor, colon tumor and prostate tumor, and was undetectable in the other tissues examined. L86S-5 was found to be expressed in the lung tumor samples and in 2 out of 4 normal lung samples, but not in the other normal or tumor tissues tested. L86S-16 was found to be expressed in all tissues except normal liver and normal stomach. Using real-time PCR, L86S-46 was found to be over-expressed in lung squamous tissue and normal tonsil, with expression being low or undetectable in all other tissues examined.

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Example 6

ISOLATION OF DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

DNA sequences encoding antigens potentially involved in squamous cell lung tumor formation were isolated as follows.

A lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a pool of two human squamous epithelial lung carcinomas and poly A+ RNA was isolated using oligo-dT cellulose (Gibco BRL, Gaithersburg, MD). Phagemid were rescued at random and the cDNA sequences of isolated clones were determined.

The determined cDNA sequence for the clone SLT-T1 is provided in SEQ ID NO: 102, with the determined 5' cDNA sequences for the clones SLT-T2, SLT-T3, SLT-T5, SLT-T7, SLT-T9, SLT-T10, SLT-T11 and SLT-T12 being provided in SEQ ID NO: 103-110, respectively. The corresponding predicted amino acid sequence for SLT-T1, SLT-T2, SLT-T3, SLT-T10 and SLT-T12 are provided in SEQ ID NO: 111-115, respectively. Comparison of the sequences for SLT-T2, SLT-T3, SLT-T5, SLT-T7, SLT-T9 and SLT-T11 with those in the public databases as described above, revealed no significant homologies. The sequences for SLT-T10 and SLT-T12 were found to show some homology to sequences previously identified in humans.

The sequence of SLT-T1 was determined to show some homology to a PAC clone of unknown protein function. The cDNA sequence of SLT-T1 (SEQ ID NO: 102) was found to contain a mutator (MUTT) domain. Such domains are known to function in removal of damaged guanine from DNA that can cause A to G transversions (see, for example, el-Deiry, W.S., 1997 *Curr. Opin. Oncol. 9*:79-87; Okamoto, K. et al. 1996 *Int. J. Cancer 65*:437-41; Wu, C. et al. 1995 *Biochem. Biophys. Res. Commun. 214*:1239-45; Porter, D.W. et al. 1996 *Chem. Res. Toxicol. 9*:1375-81). SLT-T1 may thus be of use in the treatment, by gene therapy, of lung cancers caused by, or associated with, a disruption in DNA repair.

In further studies, DNA sequences encoding antigens potentially involved in adenocarcinoma lung tumor formation were isolated as follows. A human lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a late

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SCID mouse passaged human adenocarcinoma and poly A+ RNA was isolated using the Message Maker kit (Gibco BRL, Gaithersburg, MD). Phagemid were rescued at random and the cDNA sequences of isolated clones were determined.

The determined 5' cDNA sequences for five isolated clones (referred to as SALT-T3, SALT-T4, SALT-T7, SALT-T8, and SALT-T9) are provided in SEQ ID NO: 116-120, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 121-125. SALT-T3 was found to show 98% identity to the previously identified human transducin-like enhancer protein TLE2. SALT-T4 appears to be the human homologue of the mouse H beta 58 gene. SALT-T7 was found to have 97% identity to human 3-mercaptopyruvate sulfurtransferase and SALT-T8 was found to show homology to human interferon-inducible protein 1-8U. SALT-T9 shows approximately 90% identity to human mucin MUC 5B.

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Example 7

SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

Example 8

ISOLATION AND CHARACTERIZATION OF DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS BY T-CELL EXPRESSION CLONING

Lung tumor antigens may also be identified by T cell expression cloning. One source of tumor specific T cells is from surgically excised tumors from human patients.

A non-small cell lung carcinoma was minced and enzymatically digested for several hours to release tumor cells and infiltrating lymphocytes (tumor infiltrating T cells, or TILs). The cells were washed in HBSS buffer and passed over a Ficoll (100%/75%/HBSS) discontinuous gradient to separate tumor cells and lymphocytes from non-viable cells. Two bands were harvested from the interfaces; the upper band at the 75%/HBSS interface contained predominantly tumor cells, while the lower band at the 100%/75%/HBSS interface contained a majority of lymphocytes. The TILs were expanded in culture, either in 24-well plates with culture media supplemented with 10 ng/ml IL-7 and 100 U/ml IL-2, or

alternatively, 24-well plates that have been pre-coated with the anti-CD3 monoclonal antibody OKT3. The resulting TIL cultures were analyzed by FACS to confirm that a high percentage were CD8+ T cells (>90% of gated population) with only a small percentage of CD4+ cells.

In addition, non-small cell lung carcinoma cells were expanded in culture using standard techniques to establish a tumor cell line, which was later confirmed to be a lung carcinoma cell line by immunohistochemical analysis. This tumor cell line was transduced with a retroviral vector to express human CD80, and characterized by FACS analysis to confirm high expression levels of CD80, and class I and II MHC molecules.

The specificity of the TIL lines to lung tumor was confirmed by INF-γ and/or TNF-α cytokine release assays. TIL cells from day 21 cultures were co-cultured with either autologous or allogeneic tumor cells, EBV-immortalized LCL, or control cell lines Daudi and K562, and the culture supernatant monitored by ELISA for the presence of cytokines. The TIL specifically recognized autologous tumor but not allogeneic tumor. In addition, there was no recognition of EBV-immortalized LCL or the control cell lines, indicating that the TIL lines are tumor specific and are potentially recognizing a tumor antigen presented by autologous MHC molecules.

The characterized tumor-specific TIL lines were expanded to suitable numbers for T cell expression cloning using soluble anti-CD3 antibody in culture with irradiated EBV transformed LCLs and PBL feeder cells in the presence of 20 U/ml IL-2. Clones from the expanded TIL lines were generated by standard limiting dilution techniques. Specifically, TIL cells were seeded at 0.5 cells/well in a 96-well U bottom plate and stimulated with CD-80-transduced autologous tumor cells, EBV transformed LCL, and PBL feeder cells in the presence of 50 U/ml IL-2. These clones were further analyzed for tumor specificity by ^{51}Cr microcytotoxicity and IFN-γ bioassays. The MHC restriction element recognized by the TIL clones may be determined by antibody blocking studies.

CTL lines or clones prepared as described above may be employed to identify tumor specific antigens. For example, autologous fibroblasts or LCL from a patient may be transfected or transduced with polynucleotide fragments derived from a lung tumor cDNA library to generate target cells expressing tumor polypeptides. The target cells expressing tumor polypeptides in the context of MHC will be recognized by the CTL line or clone, resulting in T-cell activation which can be monitored by cytokine detection assays. The tumor

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gene being expressed by the target cell and recognized by the tumor-specific CTL may then be isolated.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

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Claims

1. An isolated polypeptide comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NO: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 and 361;

(b) sequences that hybridize to a sequence of SEQ ID NO: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 and 361 under moderately stringent conditions; and

(c) a complement of a sequence of (a) or (b).

2. An isolated polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 and 361 or a complement of any of the foregoing polynucleotide sequences.

3. An isolated polynucleotide encoding at least 15 amino acid residues of a lung tumor protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NO: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 and 361 or a complement of any of the foregoing sequences.

4. An isolated polynucleotide encoding a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a

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polynucleotide comprising a sequence recited in any one of SEQ ID NO: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 and 361 or a complement of any of the foregoing sequences.

5. An isolated polynucleotide comprising a sequence recited in any one of SEQ ID NO: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 and 361.

6. An isolated polynucleotide comprising a sequence that hybridizes to a sequence recited in any one of SEQ ID NO: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 and 361 under moderately stringent conditions.

7. An isolated polynucleotide complementary to a polynucleotide according to any one of claims 3-6.

8. An expression vector comprising a polynucleotide according to any one of claims claim 3-7.

9. A host cell transformed or transfected with an expression vector according to claim 8.

10. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a lung tumor protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 and 361 or a complement of any of the foregoing polynucleotide sequences.

11. A fusion protein comprising at least one polypeptide according to

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claim 1.

12. A fusion protein according to claim 11, wherein the fusion protein comprises an expression enhancer that increases expression of the fusion protein in a host cell transfected with a polynucleotide encoding the fusion protein.

13. A fusion protein according to claim 11, wherein the fusion protein comprises a T helper epitope that is not present within the polypeptide of claim 1.

14. A fusion protein according to claim 11, wherein the fusion protein comprises an affinity tag.

15. An isolated polynucleotide encoding a fusion protein according to claim 11.

16. A pharmaceutical composition comprising a physiologically acceptable carrier and at least one component selected from the group consisting of:

(a) a polypeptide according to claim 1;

(b) a polynucleotide according to claim 3;

(c) an antibody according to claim 10;

(d) a fusion protein according to claim 11; and

(e) a polynucleotide according to claim 15.

17. A vaccine comprising an immunostimulant and at least one component selected from the group consisting of:

(a) a polypeptide according to claim 1;

(b) a polynucleotide according to claim 3;

(c) an antibody according to claim 10;

(d) a fusion protein according to claim 11; and

(e) a polynucleotide according to claim 15.

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18. A vaccine according to claim 17, wherein the immunostimulant is an adjuvant.

19. A vaccine according to any claim 17, wherein the immunostimulant induces a predominantly Type I response.

20. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 16.

21. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a vaccine according to claim 19.

22. A pharmaceutical composition comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a pharmaceutically acceptable carrier or excipient.

23. A pharmaceutical composition according to claim 22, wherein the antigen presenting cell is a dendritic cell or a macrophage.

24. A vaccine comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with an immunostimulant.

25. A vaccine according to claim 24, wherein the immunostimulant is an adjuvant.

26. A vaccine according to claim 24, wherein the immunostimulant induces a predominantly Type I response.

27. A vaccine according to claim 24, wherein the antigen-presenting cell is a dendritic cell.

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28. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antigen-presenting cell that expresses a polypeptide encoded by a polynucleotide recited in any one of SEQ ID NO: 217-362, and thereby inhibiting the development of a cancer in the patient.

29. A method according to claim 28, wherein the antigen-presenting cell is a dendritic cell.

30. A method according to any one of claims 20, 21 and 28, wherein the cancer is lung cancer.

31. A method for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NO: 217-362; and

(ii) complements of the foregoing polynucleotides;

wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the antigen from the sample.

32. A method according to claim 31, wherein the biological sample is blood or a fraction thereof.

33. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated according to the method of claim 31.

34. A method for stimulating and/or expanding T cells specific for a lung tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:

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(i) a polypeptide according to claim 1;

(ii) a polypeptide encoded by a polynucleotide comprising a sequence provided in any one of SEQ ID NO: 217-362

(iii) a polynucleotide encoding a polypeptide of (i) or (ii); and

(iv) an antigen presenting cell that expresses a polypeptide of (i) or (ii),

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

35. An isolated T cell population, comprising T cells prepared according to the method of claim 34.

36. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population according to claim 35.

37. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating $CD4^+$ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:

(i) a polypeptide according to claim 1;

(ii) a polypeptide encoded by a polynucleotide comprising a sequence of any one of SEQ ID NO: 217-362;

(iii) a polynucleotide encoding a polypeptide of (i) or (ii); and

(iv) an antigen-presenting cell that expresses a polypeptide of (i) or (ii);

such that T cells proliferate; and

(b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.

38. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

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(a) incubating $CD4^+$ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:

(i) a polypeptide according to claim 1;

(ii) a polypeptide encoded by a polynucleotide comprising a sequence of any one of SEQ ID NO: 217-362;

(iii) a polynucleotide encoding a polypeptide of (i) or (ii); and

(iv) an antigen-presenting cell that expresses a polypeptide of (i) or (ii);

such that T cells proliferate;

(b) cloning at least one proliferated cell to provide cloned T cells; and

(c) administering to the patient an effective amount of the cloned T cells, and thereby inhibiting the development of a cancer in the patient.

39. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with a binding agent that binds to a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NO: 217-362; and

(ii) complements of the foregoing polynucleotides;

(b) detecting in the sample an amount of polypeptide that binds to the binding agent; and

(c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

40. A method according to claim 39, wherein the binding agent is an antibody.

41. A method according to claim 42, wherein the antibody is a monoclonal antibody.

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42. A method according to claim 39, wherein the cancer is lung cancer.

43. A method for monitoring the progression of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 217-362 or a complement of any of the foregoing polynucleotides;

(b) detecting in the sample an amount of polypeptide that binds to the binding agent;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polypeptide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

44. A method according to claim 43, wherein the binding agent is an antibody.

45. A method according to claim 44, wherein the antibody is a monoclonal antibody.

46. A method according to claim 43, wherein the cancer is a lung cancer.

47. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 217-362 or a complement of any of the foregoing polynucleotides;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to

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the oligonucleotide; and

(c) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

48. A method according to claim 47, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

49. A method according to claim 47, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.

50. A method for monitoring the progression of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 217-362 or a complement of any of the foregoing polynucleotides;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

51. A method according to claim 50, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

52. A method according to claim 50, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.

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53. A diagnostic kit, comprising:

(a) one or more antibodies according to claim 10; and

(b) a detection reagent comprising a reporter group.

54. A kit according to claim 53, wherein the antibodies are immobilized on a solid support.

55. A kit according to claim 53, wherein the detection reagent comprises an anti-immunoglobulin, protein G, protein A or lectin.

56. A kit according to claim 53, wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.

57. An oligonucleotide comprising 10 to 40 contiguous nucleotides that hybridize under moderately stringent conditions to a polynucleotide that encodes a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NO: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 and 361 or a complement of any of the foregoing polynucleotides.

58. A oligonucleotide according to claim 57, wherein the oligonucleotide comprises 10-40 contiguous nucleotides recited in any one of SEQ ID NO: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 and 361.

59. A diagnostic kit, comprising:

(a) an oligonucleotide according to claim 58; and

(b) a diagnostic reagent for use in a polymerase chain reaction or hybridization assay.

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COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE

Abstract of the Disclosure

Compositions and methods for the therapy and diagnosis of cancer, such as lung cancer, are disclosed. Compositions may comprise one or more lung tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a lung tumor protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as lung cancer. Diagnostic methods based on detecting a lung tumor protein, or mRNA encoding such a protein, in a sample are also provided.

SEQUENCE LISTING

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Lodes, Michael J.
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Secrist, Heather

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caaatagagg gcctgggcaa aaaaaaaaa 449

<210> 10
<211> 538
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(538)
<223> n = A,T,C or G

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gctcactact gtggatatgt atgtnttgac cgatnacaca ggctgattta gggaagagat 420

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<210> 11
<211> 543
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(543)
<223> n = A,T,C or G

<400> 11
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aaa 543

<210> 12
<211> 329
<212> DNA
<213> Homo sapien

<400> 12
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tgatgttcaa ggcaagttgc aagtcatcg 329

<210> 13
<211> 314
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(314)
<223> n = A,T,C or G

<400> 13
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atcccaagtc atcg 314

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768

<210> 14
<211> 691
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(691)
<223> n = A,T,C or G

<400> 14
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<210> 15
<211> 355
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(355)
<223> n = A,T,C or G

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<210> 16
<211> 522
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(522)
<223> n = A,T,C or G

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<211> 317
<212> DNA
<213> Homo sapien

<400> 17
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gtgtttatgg caagtcactt tgacagacat tattgtggca aatgttgtct gacccactgt 240
ttcaactaac cagaagacaa gtaactgtat gagttaatta aagacatgaa ctaaaaaaaa 300
aaaaaaaaaa actcgag 317

<210> 18
<211> 392
<212> DNA
<213> Homo sapien

<400> 18
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cggacatccc agagaagccc caagacccca cg 392

<210> 19
<211> 2624
<212> DNA
<213> Homo sapien

<400> 19
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52
723
769

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<210> 20
<211> 488
<212> DNA
<213> Homo sapien

<400> 20
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cctaaccc 488

<210> 21
<211> 391
<212> DNA
<213> Homo sapien

<400> 21
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<210> 22
<211> 1320
<212> DNA
<213> Homo sapien

<400> 22
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<210> 23
<211> 633
<212> DNA
<213> Homo sapien

<400> 23
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<210> 24

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<211> 1328
<212> DNA
<213> Homo sapien

<400> 24

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<211> 1758
<212> DNA
<213> Homo sapien

<400> 25

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gaggttgccc tgagctgatt atcatgctgt tgcactccag cttgggcgac agagcgagac 1560
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<210> 26
<211> 493
<212> DNA
<213> Homo sapien

<400> 26
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acacgtcgag ccccgcacag gcaagggtcc ggaacttagc ccaaagcacg tttcccctgg 180
cagcgcagga gacgccccgc cgcgcgccgg cgcacgcccc cctctcctcc tttgttccgg 240
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gcgcagccgc gaagattccg ttggaactga cgcagagccg agtgcagaag atctgggtgc 360
ccgtggacca caggccctcg ttgcccagat cctgtgggcc aaagctgacc aactcccccg 420
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tactcgctgc ctc 493

<210> 27
<211> 1331
<212> DNA
<213> Homo sapien

<400> 27
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aacatgtaat aatgaagtgg tcaaaatgca gaggctaaca ttagaacact tgaatcagat 180
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agggtattgg tggcacttca aagatcatga agagcaagat aaagtcagac ctaaagccaa 480
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ggagaccaca aagaatgtac aacagacagt gagtgctaaa ggccccccctg aaaaacggat 720
gagacttcag tgagtactgg acaaaagaga agcctggaag actcctcatg ctagttatca 780
tacctcagta ctgtggctct tgagctttga agtactttat tgtaaccttc ttatttgtat 840
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ccagcacttt gggaggccat ggcgggtgga tcacttgagg tcagaagttc aagaccagcc 960
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aaaaactcga g 1331

<210> 28
<211> 1333
<212> DNA
<213> Homo sapien

<400> 28
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acagaacatg taataatgaa gtggtcaaaa tgcagaggct aacattagaa cacttgaatc 180
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ccaaagggta ttggtggcac ttcaaagatc atgaagagca agataaagtc agacctaaag 480
ccaaaaggaa agaagaacca agctctattt ttcagagaca acgtgtggat gctttacttt 540
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agaaggagac cacaaagaat gtacaacaga cagtgagtgc taaaggcccc cctgaaaaac 720
ggatgagact tcagtgagta ctggacaaaa gagaagcctg gaagactcct catgctagtt 780
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atatttgtga tatgtcttct gtaacctttc ctctcccgga cttgagcaac ctacacactc 1260
acatgtttac tggtagatat gtttaaaagc aaaataaagg tatttgtata aaaaaaaaaa 1320
aaaaaaactc gag 1333

<210> 29
<211> 813
<212> DNA
<213> Homo sapien

<400> 29
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actggcccgg ggtctgggtc cacctggaca tcgctgctcc agtgcatgct ggcgagcgag 180
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taaccagccc tgggtagatg tgactggctg ttagggaccc cattctgtga agcaggagac 720
cctcacagct cccaccaacc cccagttcac ttgaagttga attaaatatg gccacaacat 780
aaaaaaaaaa aaaaaaaaaa aaaaaaactc gag 813

<210> 30
<211> 1316

<212> DNA
<213> Homo sapien

<400> 30

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gtggagtcaa atatactttt caccatcagg aaatatagtt gctcatgaaa actgtttgct 180
gtattcatca ggactggtgg agtgtgagac tcttgatcta cgtaatacaa ttagaaactt 240
tgatgtcaaa tctgtaaaga aagagatctg gagaggaaga agattgaaat gctcattctg 300
taacaaagga ggcgccaccg tggggtgtga tttatggttc tgtaagaaga gttaccacta 360
tgtctgtgcc aaaaaggacc aagcaattct tcaagttgat ggaaaccatg gaacttacaa 420
attattttgc ccagaacatt ctccagaaca agaagaggcc actgaaagtg ctgatgaccc 480
aagcatgaag aagaagagag gaaaaaacaa acgcctctca tcaggccctc ctgcacagcc 540
aaaaacgatg aaatgtagta acgccaaaag acatatgaca gaagagcctc atggtcacac 600
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tgcctcagag tcggactatg aagggatcga gaccttactg tttgactgtg gattatttaa 780
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gcaaaggcag atgaagcagc agcttgaggc acttgcagac ttacaacaaa gcttgtgctc 900
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tttagcacac ttaataaatg cttgtcaaaa cccaaaaaaa aaaaaaaaaa ctcgag 1316

<210> 31
<211> 1355
<212> DNA
<213> Homo sapien

<400> 31

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acagaacatg taataatgaa gtggtcaaaa tgcagaggct aacattagaa cacttgaatc 180
agatggttgg aatcgagtac atccttttgc atgctcaaga gcccattctt ttcatcattc 240
ggaagcaaca gcggcagtcc cctgcccaag ttatcccact agctgattac tatatcattg 300
ctggagtgat ctatcaggca ccagacttgg gatcagttat aaactctaga gtgcttactg 360
cagtgcatgg tattcagtca gcttttgatg aagctatgtc atactgtcga tatcatcctt 420
ccaaagggta ttggtggcac ttcaaagatc atgaagagca agataaagtc agacctaaag 480
ccaaaaggaa agaagaacca agctctattt ttcagagaca acgtgtggat gctttacttt 540
tagacctcag acaaaaattt ccacccaaat ttgtgcagct aaagcctgga gaaaagcctg 600
ttccagtgga tcaaacaaag aaagaggcag aacctatacc agaaactgta aaacctgagg 660
agaaggagac cacaaagaat gtacaacaga cagtgagtgc taaaggcccc cctgaaaaac 720
ggatgagact tcagtgagta ctggacaaaa gagaagcctg gaagactcct catgctagtt 780
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aatcccagca ctttgggagg ccatggcggg tggatcactt gaggtcagaa gttcaagacc 960
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aatatttgtt atatgtcttc tggtaacctt tcctctcccg gacttgaagc aacctcacac 1260
actcacatgt ttactggtag atatgtttta aaagcaaaat aaaggtattt gtttttccaa 1320

aaaaaaaaaa aaaaaaaaaa aaaaaaaaac tcgag 1355

<210> 32
<211> 80
<212> PRT
<213> Homo sapien

<400> 32
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1 5 10 15
Thr Thr Pro Lys Lys Asp Lys His Gln Arg Lys Lys Val Gln Pro Ala
20 25 30
Val Leu Lys Tyr Tyr Lys Val Asp Glu Asn Gly Lys Ile Ser Cys Leu
35 40 45
Arg Arg Glu Cys Pro Ser Asp Glu Cys Gly Ala Gly Val Phe Met Ala
50 55 60
Ser His Phe Asp Arg His Tyr Cys Gly Lys Cys Cys Leu Thr His Cys
65 70 75 80

<210> 33
<211> 130
<212> PRT
<213> Homo sapien

<400> 33
Glu Ile Ser Asn Glu Val Arg Lys Phe Arg Thr Leu Thr Glu Leu Ile
1 5 10 15
Leu Asp Ala Gln Glu His Val Lys Asn Pro Tyr Lys Gly Lys Lys Leu
20 25 30
Lys Lys His Pro Asp Phe Pro Lys Lys Pro Leu Thr Pro Tyr Phe Arg
35 40 45
Phe Phe Met Glu Lys Arg Ala Lys Tyr Ala Lys Leu His Pro Gln Met
50 55 60
Ser Asn Leu Asp Leu Thr Lys Ile Leu Ser Lys Lys Tyr Lys Glu Leu
65 70 75 80
Pro Glu Lys Lys Lys Met Lys Tyr Val Pro Asp Phe Gln Arg Arg Glu
85 90 95
Thr Gly Val Arg Ala Lys Pro Gly Pro Ile Gln Gly Gly Ser Pro Pro
100 105 110
Pro Tyr Pro Glu Cys Gln Glu Ser Asp Ile Pro Glu Lys Pro Gln Asp
115 120 125
Pro Pro
130

<210> 34
<211> 506
<212> PRT
<213> Homo sapien

<400> 34
Asn Ser Glu Lys Glu Ile Pro Val Leu Asn Glu Leu Pro Val Pro Met
1 5 10 15
Val Ala Arg Tyr Ile Arg Ile Asn Pro Gln Ser Trp Phe Asp Asn Gly
20 25 30
Ser Ile Cys Met Arg Met Glu Ile Leu Gly Cys Pro Leu Pro Asp Pro

510
78
777

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        35                  40                  45
Asn Asn Tyr Tyr His Arg Arg Asn Glu Met Thr Thr Thr Asp Asp Leu
    50                  55                  60
Asp Phe Lys His His Asn Tyr Lys Glu Met Arg Gln Leu Met Lys Val
65                  70                  75                  80
Val Asn Glu Met Cys Pro Asn Ile Thr Arg Ile Tyr Asn Ile Gly Lys
                85                  90                  95
Ser His Gln Gly Leu Lys Leu Tyr Ala Val Glu Ile Ser Asp His Pro
            100                 105                 110
Gly Glu His Glu Val Gly Glu Pro Glu Phe His Tyr Ile Ala Gly Ala
        115                 120                 125
His Gly Asn Glu Val Leu Gly Arg Glu Leu Leu Leu Leu Leu Leu His
    130                 135                 140
Phe Leu Cys Gln Glu Tyr Ser Ala Gln Asn Ala Arg Ile Val Arg Leu
145                 150                 155                 160
Val Glu Glu Thr Arg Ile His Ile Leu Pro Ser Leu Asn Pro Asp Gly
                165                 170                 175
Tyr Glu Lys Ala Tyr Glu Gly Gly Ser Glu Leu Gly Gly Trp Ser Leu
            180                 185                 190
Gly Arg Trp Thr His Asp Gly Ile Asp Ile Asn Asn Asn Phe Pro Asp
        195                 200                 205
Leu Asn Ser Leu Leu Trp Glu Ala Glu Asp Gln Gln Asn Ala Pro Arg
    210                 215                 220
Lys Val Pro Asn His Tyr Ile Ala Ile Pro Glu Trp Phe Leu Ser Glu
225                 230                 235                 240
Asn Ala Thr Val Ala Thr Glu Thr Arg Ala Val Ile Ala Trp Met Glu
                245                 250                 255
Lys Ile Pro Phe Val Leu Gly Gly Asn Leu Gln Gly Gly Glu Leu Val
            260                 265                 270
Val Ala Tyr Pro Tyr Asp Met Val Arg Ser Leu Trp Lys Thr Gln Glu
        275                 280                 285
His Thr Pro Thr Pro Asp Asp His Val Phe Arg Trp Leu Ala Tyr Ser
    290                 295                 300
Tyr Ala Ser Thr His Arg Leu Met Thr Asp Ala Arg Arg Arg Val Cys
305                 310                 315                 320
His Thr Glu Asp Phe Gln Lys Glu Glu Gly Thr Val Asn Gly Ala Ser
                325                 330                 335
Trp His Thr Val Ala Gly Ser Leu Asn Asp Phe Ser Tyr Leu His Thr
            340                 345                 350
Asn Cys Phe Glu Leu Ser Ile Tyr Val Gly Cys Asp Lys Tyr Pro His
        355                 360                 365
Glu Ser Glu Leu Pro Glu Glu Trp Glu Asn Asn Arg Glu Ser Leu Ile
    370                 375                 380
Val Phe Met Glu Gln Val His Arg Gly Ile Lys Gly Ile Val Arg Asp
385                 390                 395                 400
Leu Gln Gly Lys Gly Ile Ser Asn Ala Val Ile Ser Val Glu Gly Val
                405                 410                 415
Asn His Asp Ile Arg Thr Ala Ser Asp Gly Asp Tyr Trp Arg Leu Leu
            420                 425                 430
Asn Pro Gly Glu Tyr Val Val Thr Ala Lys Ala Glu Gly Phe Ile Thr
        435                 440                 445
Ser Thr Lys Asn Cys Met Val Gly Tyr Asp Met Gly Ala Thr Arg Cys
    450                 455                 460
Asp Phe Thr Leu Thr Lys Thr Asn Leu Ala Arg Ile Arg Glu Ile Met
465                 470                 475                 480
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Glu Thr Phe Gly Lys Gln Pro Val Ser Leu Pro Ser Arg Arg Leu Lys
485 490 495
Leu Arg Gly Arg Lys Arg Arg Gln Arg Gly
500 505

<210> 35
<211> 96
<212> PRT
<213> Homo sapien

<400> 35
Met Asn Gly Glu Ala Asp Cys Pro Thr Asp Leu Glu Met Ala Ala Pro
1 5 10 15
Arg Gly Gln Asp Arg Trp Ser Gln Glu Asp Met Leu Thr Leu Leu Glu
20 25 30
Cys Met Lys Asn Asn Leu Pro Ser Asn Asp Ser Ser Gln Phe Lys Thr
35 40 45
Thr Gln Thr His Met Asp Arg Glu Lys Val Ala Leu Lys Asp Phe Ser
50 55 60
Gly Asp Met Cys Lys Leu Lys Trp Val Glu Ile Ser Asn Glu Val Arg
65 70 75 80
Lys Phe Arg Thr Leu Thr Glu Leu Ile Leu Asp Thr Gln Glu His Val
85 90 95

<210> 36
<211> 129
<212> PRT
<213> Homo sapien

<400> 36
Gly Ile Val Val Phe Ser Leu Gly Ser Met Val Ser Glu Ile Pro Glu
1 5 10 15
Lys Lys Ala Val Ala Ile Ala Asp Ala Leu Gly Lys Ile Pro Gln Thr
20 25 30
Val Leu Trp Arg Tyr Thr Gly Thr Arg Pro Ser Asn Leu Ala Asn Asn
35 40 45
Thr Ile Leu Val Gln Trp Leu Pro Gln Asn Asp Leu Leu Gly His Pro
50 55 60
Met Thr Arg Ala Phe Ile Thr His Ala Ser Ser His Gly Val Asn Glu
65 70 75 80
Ser Ile Cys Asn Gly Val Pro Met Val Met Ile Pro Leu Phe Gly Asp
85 90 95
Gln Met Asp Asn Ala Lys Arg Arg Glu Thr Lys Gly Ala Gly Val Thr
100 105 110
Leu Asn Val Leu Glu Met Thr Ser Glu Asp Leu Glu Asp Ala Leu Lys
115 120 125
Ser

<210> 37
<211> 238
<212> PRT
<213> Homo sapien

<400> 37

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Asn Leu Leu Gly Ile Ser Trp Val Asp Ser Ser Trp Ile Pro Ile Leu
 1               5                  10                  15
Asn Ser Gly Ser Val Leu Asp Tyr Phe Ser Glu Arg Ser Asn Pro Phe
            20                  25                  30
Tyr Asp Arg Thr Cys Asn Asn Glu Val Val Lys Met Gln Arg Leu Thr
        35                  40                  45
Leu Glu His Leu Asn Gln Met Val Gly Ile Glu Tyr Ile Leu Leu His
    50                  55                  60
Ala Gln Glu Pro Ile Leu Phe Ile Ile Arg Lys Gln Gln Arg Gln Ser
65                  70                  75                  80
Pro Ala Gln Val Ile Pro Leu Ala Asp Tyr Tyr Ile Ile Ala Gly Val
                85                  90                  95
Ile Tyr Gln Ala Pro Asp Leu Gly Ser Val Ile Asn Ser Arg Val Leu
            100                 105                 110
Thr Ala Val His Gly Ile Gln Ser Ala Phe Asp Glu Ala Met Ser Tyr
        115                 120                 125
Cys Arg Tyr His Pro Ser Lys Gly Tyr Trp Trp His Phe Lys Asp His
    130                 135                 140
Glu Glu Gln Asp Lys Val Arg Pro Lys Ala Lys Arg Lys Glu Glu Pro
145                 150                 155                 160
Ser Ser Ile Phe Gln Arg Gln Arg Val Asp Ala Leu Leu Leu Asp Leu
                165                 170                 175
Arg Gln Lys Phe Pro Pro Lys Phe Val Gln Leu Lys Pro Gly Glu Lys
            180                 185                 190
Pro Val Pro Val Asp Gln Thr Lys Lys Glu Ala Glu Pro Ile Pro Glu
        195                 200                 205
Thr Val Lys Pro Glu Glu Lys Glu Thr Thr Lys Asn Val Gln Gln Thr
    210                 215                 220
Val Ser Ala Lys Gly Pro Pro Glu Lys Arg Met Arg Leu Gln
225                 230                 235
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<210> 38
<211> 202
<212> PRT
<213> Homo sapien

<400> 38

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Lys Gly Ser Glu Gly Glu Asn Pro Leu Thr Val Pro Gly Arg Glu Lys
 1               5                  10                  15
Glu Gly Met Leu Met Gly Val Lys Pro Gly Glu Asp Ala Ser Gly Pro
            20                  25                  30
Ala Glu Asp Leu Val Arg Arg Ser Glu Lys Asp Thr Ala Ala Val Val
        35                  40                  45
Ser Arg Gln Gly Ser Ser Leu Asn Leu Phe Glu Asp Val Gln Ile Thr
    50                  55                  60
Glu Pro Glu Ala Glu Pro Glu Ser Lys Ser Glu Pro Arg Pro Pro Ile
65                  70                  75                  80
Ser Ser Pro Arg Ala Pro Gln Thr Arg Ala Val Lys Pro Arg Leu His
                85                  90                  95
Pro Val Lys Pro Met Asn Ala Thr Ala Thr Lys Val Ala Asn Cys Ser
            100                 105                 110
Leu Gly Thr Ala Thr Ile Ile Gly Glu Asn Leu Asn Asn Glu Val Met
        115                 120                 125
Met Lys Lys Tyr Ser Pro Ser Asp Pro Ala Phe Ala Tyr Ala Gln Leu
    130                 135                 140
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Thr His Asp Glu Leu Ile Gln Leu Val Leu Lys Gln Lys Glu Thr Ile
145                 150                 155                 160
Ser Lys Lys Glu Phe Gln Val Arg Glu Leu Glu Asp Tyr Ile Asp Asn
                165                 170                 175
Leu Leu Val Arg Val Met Glu Glu Thr Pro Asn Ile Leu Arg Ile Pro
            180                 185                 190
Thr Gln Val Gly Lys Lys Ala Gly Lys Met
        195                 200
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<210> 39
<211> 243
<212> PRT
<213> Homo sapien

<400> 39

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Val Asn Ala Leu Gly Ile Met Ala Ala Val Asp Ile Arg Asp Asn Leu
 1               5                  10                  15
Leu Gly Ile Ser Trp Val Asp Ser Ser Trp Ile Pro Ile Leu Asn Ser
            20                  25                  30
Gly Ser Val Leu Asp Tyr Phe Ser Glu Arg Ser Asn Pro Phe Tyr Asp
        35                  40                  45
Arg Thr Cys Asn Asn Glu Val Val Lys Met Gln Arg Leu Thr Leu Glu
    50                  55                  60
His Leu Asn Gln Met Val Gly Ile Glu Tyr Ile Leu Leu His Ala Gln
65                  70                  75                  80
Glu Pro Ile Leu Phe Ile Ile Arg Lys Gln Gln Arg Gln Ser Pro Ala
                85                  90                  95
Gln Val Ile Pro Leu Ala Asp Tyr Tyr Ile Ile Ala Gly Val Ile Tyr
            100                 105                 110
Gln Ala Pro Asp Leu Gly Ser Val Ile Asn Ser Arg Val Leu Thr Ala
        115                 120                 125
Val His Gly Ile Gln Ser Ala Phe Asp Glu Ala Met Ser Tyr Cys Arg
    130                 135                 140
Tyr His Pro Ser Lys Gly Tyr Trp Trp His Phe Lys Asp His Glu Glu
145                 150                 155                 160
Gln Asp Lys Val Arg Pro Lys Ala Lys Arg Lys Glu Glu Pro Ser Ser
                165                 170                 175
Ile Phe Gln Arg Gln Arg Val Asp Ala Leu Leu Leu Asp Leu Arg Gln
            180                 185                 190
Lys Ile Ser Thr Gln Ile Cys Ala Val Asp Gln Thr Lys Lys Glu Ala
        195                 200                 205
Glu Pro Ile Pro Glu Thr Val Lys Pro Glu Glu Lys Glu Thr Thr Lys
    210                 215                 220
Asn Val Gln Gln Thr Val Ser Ala Lys Gly Pro Pro Glu Lys Arg Met
225                 230                 235                 240
Arg Leu Gln
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<210> 40
<211> 245
<212> PRT
<213> Homo sapien

<400> 40

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Ala Ala Val Asp Ile Arg Asp Asn Leu Leu Gly Ile Ser Trp Val Asp
```

```
 1               5                  10                  15
Ser Ser Trp Ile Pro Ile Leu Asn Ser Gly Ser Val Leu Asp Tyr Phe
            20                  25                  30
Ser Glu Arg Ser Asn Pro Phe Tyr Asp Arg Thr Cys Asn Asn Glu Val
        35                  40                  45
Val Lys Met Gln Arg Leu Thr Leu Glu His Leu Asn Gln Met Val Gly
    50                  55                  60
Ile Glu Tyr Ile Leu Leu His Ala Gln Glu Pro Ile Leu Phe Ile Ile
65                  70                  75                  80
Arg Lys Gln Gln Arg Gln Ser Pro Ala Gln Val Ile Pro Leu Ala Asp
                85                  90                  95
Tyr Tyr Ile Ile Ala Gly Val Ile Tyr Gln Ala Pro Asp Leu Gly Ser
            100                 105                 110
Val Ile Asn Ser Arg Val Leu Thr Ala Val His Gly Ile Gln Ser Ala
        115                 120                 125
Phe Asp Glu Ala Met Ser Tyr Cys Arg Tyr His Pro Ser Lys Gly Tyr
    130                 135                 140
Trp Trp His Phe Lys Asp His Glu Glu Gln Asp Lys Val Arg Pro Lys
145                 150                 155                 160
Ala Lys Arg Lys Glu Glu Pro Ser Ser Ile Phe Gln Arg Gln Arg Val
                165                 170                 175
Asp Ala Leu Leu Leu Asp Leu Arg Gln Lys Phe Pro Pro Lys Phe Val
            180                 185                 190
Gln Leu Lys Pro Gly Glu Lys Pro Val Pro Val Asp Gln Thr Lys Lys
        195                 200                 205
Glu Ala Glu Pro Ile Pro Glu Thr Val Lys Pro Glu Glu Lys Glu Thr
    210                 215                 220
Thr Lys Asn Val Gln Gln Thr Val Ser Ala Lys Gly Pro Pro Glu Lys
225                 230                 235                 240
Arg Met Arg Leu Gln
                245
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<210> 41
<211> 163
<212> PRT
<213> Homo sapien

<400> 41

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Gly Glu Arg Gln Gly Leu Val Ala Arg Ala Arg Leu Ser Leu Arg Pro
 1               5                  10                  15
Ser Ile Pro Glu Leu Ser Glu Arg Thr Ser Arg Pro Cys Arg Ala Ser
            20                  25                  30
Pro Ala Ser Leu Pro Ser Gln His Thr Ser Ser Pro Ala Gln Ala Arg
        35                  40                  45
Val Arg Asn Leu Ala Gln Ser Thr Phe Pro Leu Ala Ala Gln Glu Thr
    50                  55                  60
Pro Gly Arg Ala Pro Ala His Ala Pro Leu Ser Ser Phe Val Pro Gly
65                  70                  75                  80
Val Gly Gly Arg Ser Pro Ala Ser Val Gly Ile Ser Ala Pro Gly Gly
                85                  90                  95
Gly Pro Ser Gly Ala Ala Ala Lys Ile Pro Leu Glu Leu Thr Gln Ser
            100                 105                 110
Arg Val Gln Lys Ile Trp Val Pro Val Asp His Arg Pro Ser Leu Pro
        115                 120                 125
Arg Ser Cys Gly Pro Lys Leu Thr Asn Ser Pro Ala Val Phe Val Met
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```
    130                 135                 140
Val Gly Leu Pro Arg Pro Gly Gln Asp Leu Leu Leu His Glu Ser Leu
145                 150                 155                 160
Leu Ala Ala
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<210> 42
<211> 243
<212> PRT
<213> Homo sapien

<400> 42

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

<210> 43
<211> 244
<212> PRT
<213> Homo sapien

<400> 43

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

<210> 44
<211> 109
<212> PRT
<213> Homo sapien

<400> 44
Glu Leu His Phe Ser Glu Phe Thr Ser Ala Val Ala Asp Met Lys Asn
1 5 10 15
Ser Val Ala Asp Arg Asp Asn Ser Pro Ser Ser Cys Ala Gly Leu Phe
20 25 30
Ile Ala Ser His Ile Gly Phe Asp Trp Pro Gly Val Trp Val His Leu
35 40 45
Asp Ile Ala Ala Pro Val His Ala Gly Glu Arg Ala Thr Gly Phe Gly
50 55 60
Val Ala Leu Leu Leu Ala Leu Phe Gly Arg Ala Ser Glu Asp Pro Leu
65 70 75 80
Leu Asn Leu Val Ser Pro Leu Asp Cys Glu Val Asp Ala Gln Glu Gly
85 90 95
Asp Asn Met Gly Arg Asp Ser Lys Arg Arg Arg Leu Val
100 105

<210> 45
<211> 324
<212> PRT
<213> Homo sapien

517
788
784

<400> 45
Arg Arg Pro Val Met Ala Gln Glu Thr Ala Pro Pro Cys Gly Pro Val
1 5 10 15
Ser Arg Gly Asp Ser Pro Ile Ile Glu Lys Met Glu Lys Arg Thr Cys
20 25 30
Ala Leu Cys Pro Glu Gly His Glu Trp Ser Gln Ile Tyr Phe Ser Pro
35 40 45
Ser Gly Asn Ile Val Ala His Glu Asn Cys Leu Leu Tyr Ser Ser Gly
50 55 60
Leu Val Glu Cys Glu Thr Leu Asp Leu Arg Asn Thr Ile Arg Asn Phe
65 70 75 80
Asp Val Lys Ser Val Lys Lys Glu Ile Trp Arg Gly Arg Arg Leu Lys
85 90 95
Cys Ser Phe Cys Asn Lys Gly Gly Ala Thr Val Gly Cys Asp Leu Trp
100 105 110
Phe Cys Lys Lys Ser Tyr His Tyr Val Cys Ala Lys Lys Asp Gln Ala
115 120 125
Ile Leu Gln Val Asp Gly Asn His Gly Thr Tyr Lys Leu Phe Cys Pro
130 135 140
Glu His Ser Pro Glu Gln Glu Glu Ala Thr Glu Ser Ala Asp Asp Pro
145 150 155 160
Ser Met Lys Lys Lys Arg Gly Lys Asn Lys Arg Leu Ser Ser Gly Pro
165 170 175
Pro Ala Gln Pro Lys Thr Met Lys Cys Ser Asn Ala Lys Arg His Met
180 185 190
Thr Glu Glu Pro His Gly His Thr Asp Ala Ala Val Lys Ser Pro Phe
195 200 205
Leu Lys Lys Cys Gln Glu Ala Gly Leu Leu Thr Glu Leu Phe Glu His
210 215 220
Ile Leu Glu Asn Met Asp Ser Val His Gly Arg Leu Val Asp Glu Thr
225 230 235 240
Ala Ser Glu Ser Asp Tyr Glu Gly Ile Glu Thr Leu Leu Phe Asp Cys
245 250 255
Gly Leu Phe Lys Asp Thr Leu Arg Lys Phe Gln Glu Val Ile Lys Ser
260 265 270
Lys Ala Cys Glu Trp Glu Glu Arg Gln Arg Gln Met Lys Gln Gln Leu
275 280 285
Glu Ala Leu Ala Asp Leu Gln Gln Ser Leu Cys Ser Phe Gln Glu Asn
290 295 300
Gly Asp Leu Asp Cys Ser Ser Ser Thr Ser Gly Ser Leu Leu Pro Pro
305 310 315 320
Glu Asp His Gln

<210> 46
<211> 244
<212> PRT
<213> Homo sapien

<400> 46
Ala Val Asp Ile Arg Asp Asn Leu Leu Gly Ile Ser Trp Val Asp Ser
1 5 10 15
Ser Trp Ile Pro Ile Leu Asn Ser Gly Ser Val Leu Asp Tyr Phe Ser
20 25 30
Glu Arg Ser Asn Pro Phe Tyr Asp Arg Thr Cys Asn Asn Glu Val Val

```
        35                  40                  45
Lys Met Gln Arg Leu Thr Leu Glu His Leu Asn Gln Met Val Gly Ile
    50                  55                  60
Glu Tyr Ile Leu Leu His Ala Gln Glu Pro Ile Leu Phe Ile Ile Arg
65                  70                  75                  80
Lys Gln Gln Arg Gln Ser Pro Ala Gln Val Ile Pro Leu Ala Asp Tyr
                85                  90                  95
Tyr Ile Ile Ala Gly Val Ile Tyr Gln Ala Pro Asp Leu Gly Ser Val
            100                 105                 110
Ile Asn Ser Arg Val Leu Thr Ala Val His Gly Ile Gln Ser Ala Phe
        115                 120                 125
Asp Glu Ala Met Ser Tyr Cys Arg Tyr His Pro Ser Lys Gly Tyr Trp
    130                 135                 140
Trp His Phe Lys Asp His Glu Glu Gln Asp Lys Val Arg Pro Lys Ala
145                 150                 155                 160
Lys Arg Lys Glu Glu Pro Ser Ser Ile Phe Gln Arg Gln Arg Val Asp
                165                 170                 175
Ala Leu Leu Leu Asp Leu Arg Gln Lys Phe Pro Pro Lys Phe Val Gln
            180                 185                 190
Leu Lys Pro Gly Glu Lys Pro Val Pro Val Asp Gln Thr Lys Lys Glu
        195                 200                 205
Ala Glu Pro Ile Pro Glu Thr Val Lys Pro Glu Glu Lys Glu Thr Thr
    210                 215                 220
Lys Asn Val Gln Gln Thr Val Ser Ala Lys Gly Pro Pro Glu Lys Arg
225                 230                 235                 240
Met Arg Leu Gln
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<210> 47
<211> 14
<212> DNA
<213> Homo sapien

<400> 47
ttttttttt ttag 14

<210> 48
<211> 10
<212> DNA
<213> Homo sapien

<400> 48
cttcaaccctc 10

<210> 49
<211> 496
<212> DNA
<213> Homo sapien

<400> 49
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ccgcagcctt agcttcggct cccggcttgg gtggcgcggc cgtgccctcg ttttggcctc 120
cgaacgcggc tcgaatggca agccaaaatt ccttccggat agaatatgat acctttggtg 180
aactaaaggt gccaaatgat aagtattatg gcgcccagac cgtgagatct acgatgaact 240
ttaagattgg aggtgtgaca gaacgcatgc caacccccagt tattaaagct tttggcatct 300

tgaagcgagc ggccgctgaa gtaaaccagg attatggtct tgatccaaag attgctaatg 360
caataatgaa ggcagcagat gaggtagctg aaggtaaatt aaatgatcat tttcctctcg 420
tggtatggca gactggatca ggaactcaga caaatatgaa tgtaaatgaa gtcattagcc 480
aatagagcaa ttgaaa 496

<210> 50
<211> 499
<212> DNA
<213> Homo sapien

<400> 50
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gaaaagttat taaatgcaaa gcagctgtgc tttgggagca gaagcaaccc ttctccattg 120
aggaaataga agttgcccca ccaaagacta aagaagttcg cattaagatt ttggccacag 180
gaatctgtcg cacagatgac catgtgataa aaggaacaat ggtgtccaag tttccagtga 240
ttgtgggaca tgaggcaact gggattgtag agagcattgg agaaggagtg actacagtga 300
aaccaggtga caaagtcatc cctctctttc tgccacaatg tagagaatgc aatgcttgtc 360
gcaacccaga tggcaacctt tgcattagga gcgatattac tggtcgtgga gtactggctg 420
atggcaccac cagatttaca tgcaagggcg aaccagtcca ccacttcatg aacaccagta 480
catttaccga gtacacagt 499

<210> 51
<211> 887
<212> DNA
<213> Homo sapien

<400> 51
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gtggccagtg accagataga gatgaatcgc ctgaaggctc agctggagaa tgaaaagcag 120
aaagtggcag agctgtattc tatccataac tctggagaca aatctgatat tcaggacctc 180
ctggagagtg tcaggctgga caaagaaaaa gcagagactt tggctagtag cttgcaggaa 240
gatctggctc ataccgaaa tgatgccaat cgattacagg atgccattgc taaggtagag 300
gatgaatacc gagccttcca agaagaagct aagaaacaaa ttgaagattt gaatatgacg 360
ttagaaaaat taagatcaga cctggatgaa aaagaaacag aaaggagtga catgaaagaa 420
accatctttg aacttgaaga tgaagtagaa caacatcgtg ctgtgaaact tcatgacaac 480
ctcattattt ctgatctaga gaatacagtt aaaaaactcc aggaccaaaa gcacgacatg 540
gaaagagaaa taaagacact ccacagaaga cttcgggaag aatctgcgga atggcggcag 600
tttcaggctg atctccagac tgcagtagtc attgcaaatg acattaaatc tgaagcccaa 660
gaggagattg gtgatctaaa gcgccggtta catgaggctc aagaaaaaaa tgagaaactc 720
acaaaagaat tggaggaaat aaagtcacgc aagcaagagg aggagcgagg cgggtataca 780
attacatgaa tgccgttgag agagatttgg cagccttaag gcagggaatg ggactgagta 840
gaaggtcctc gacttcctca gagccaactc ctacagtaaa aaccctc 887

<210> 52
<211> 491
<212> DNA
<213> Homo sapien

<400> 52
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aaggaacctt tcactcttga ggcctactac agctctcctc aggatttgcc ctatccagat 120
cctgctatag ctcagttttc agttcagaaa gtcactcctc agtctgatgg ctccagttca 180
aaagtgaaag tcaaagttcg agtaaatgtc catggcattt tcagtgtgtc cagtgcatct 240
ttagtggagg ttcacaagtc tgaggaaaat gaggagccaa tggaaacaga tcagaatgca 300
aaggaggaag agaagatgca agtggaccag gaggaaccac atgttgaaga gcaacagcag 360

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559
296
786

cagacaccag gcagaaaata aggcagagtc tgaagaaatg gagacctctc aagctggatc 420
caaggataaa aagatggacc aaccacccca agccaagaag gcaaaagtga agaccagtac 480
tgtggacctg g 491

<210> 53
<211> 787
<212> DNA
<213> Homo sapien

<400> 53
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cacgtgtaac ttcgacttca agatttctga atccatatgt agtatgtttc attgtcgtcg 120
caggggtagt gatcctggca gtcaccatag ctctacttgt ttacttttta gcttttgatc 180
aaaaatctta cttttatagg agcagttttc aactcctaaa tgttgaatat aatagtcagt 240
taaattcacc agctacacag gaatacagga ctttgagtgg aagaattgaa tctctgatta 300
ctaaaacatt caaagaatca aatttaagaa atcagttcat cagagctcat gttgccaaac 360
tgaggcaaga tggtagtggt gtgagagcgg atgttgtcat gaaatttcaa ttcactagaa 420
ataacaatgg agcatcaatg aaaagcagaa ttgagtctgt tttacgacaa atgctgaata 480
actctggaaa cctggaaata aacccttcaa ctgagataac atcacttact gaccaggctg 540
cagcaaattg gcttattaat gaatgtgggg ccggtccaga cctaataaca ttgtctgagc 600
agagaatcct tggaggcact gaggctgagg agggaagctg gccgtggcaa gtcagtctgc 660
ggctcaataa tgcccaccac tgtggaggca gcctgatcaa taacatgtgg atcctgacag 720
cagctcactg cttcagaagc aactctaatc ctcgtgactg gattgccacg tctggtattt 780
ccacaac 787

<210> 54
<211> 386
<212> DNA
<213> Homo sapien

<400> 54
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gagccaatgg aaacagatca gaatgcaaag gaggaagaga agatgcaagt ggaccaggag 120
gaaccacatg ttgaagagca acagcagcag acaccagcag aaaataaggc agagtctgaa 180
gaaatggaga cctctcaagc tggatccaag gataaaaaga tggaccaacc accccaagcc 240
aagaaggcaa aagtgaagac cagtactgtg gacctgccaa tcgagaatca gctattatgg 300
cagatagaca gagagatgct caacttgtac attgaaaatg agggtaagat gatcatgcag 360
gataaactgg agaaggagcg gaatga 386

<210> 55
<211> 1462
<212> DNA
<213> Homo sapien

<400> 55
aagcagttga gtaggcagaa aaaagaacct ctccattaag gattaaaatg tataggccag 60
cacgtgtaac ttcgacttca agatttctga atccatatgt agtatgtttc attgtcgtcg 120
caggggtagt gatcctggca gtcaccatag ctctacttgt ttacttttta gcttttgatc 180
aaaaatctta cttttatagg agcagttttc aactcctaaa tgttgaatat aatagtcagt 240
taaattcacc agctacacag gaatacagga ctttgagtgg aagaattgaa tctctgatta 300
ctaaaacatt caaagaatca aatttaagaa atcagttcat cagagctcat gttgccaaac 360
tgaggcaaga tggtagtggt gtgagagcgg atgttgtcat gaaatttcaa ttcactagaa 420
ataacaatgg agcatcaatg aaaagcagaa ttgagtctgt tttacgacaa atgctgaata 480
actctggaaa cctggaaata aacccttcaa ctgagataac atcacttact gaccaggctg 540
cagcaaattg gcttattaat gaatgtgggg ccggtccaga cctaataaca ttgtctgagc 600

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agagaatcct tggaggcact gaggctgagg agggaagctg gccgtggcaa gtcagtctgc     660
ggctcaataa tgcccaccac tgtggaggca gcctgatcaa taacatgtgg atcctgacag     720
cagctcactg cttcagaagc aactctaatc ctcgtgactg gattgccacg tctggtattt     780
ccacaacatt tcctaaacta agaatgagag taagaaatat tttaattcat aacaattata     840
aatctgcaac tcatgaaaat gacattgcac ttgtgagact tgagaacagt gtcaccttta     900
ccaaagatat ccatagtgtg tgtctcccag ctgctaccca gaatattcca cctggctcta     960
ctgcttatgt aacaggatgg ggcgctcaag aatatgctgg ccacacagtt ccagagctaa    1020
ggcaaggaca ggtcagaata ataagtaatg atgtatgtaa tgcaccacat agttataatg    1080
gagccatctt gtctggaatg ctgtgtgctg gagtacctca aggtggagtg gacgcatgtc    1140
agggtgactc tggtggccca ctagtacaag aagactcacg gcggctttgg tttattgtgg    1200
ggatagtaag ctggggagat cagtgtggcc tgccggataa gccaggagtg tatactcgag    1260
tgacagcata cattgactgg attaggcaac aaactgggat ctagtgcaac aagtgcatcc    1320
ctgttgcaaa gtctgtatgc aggtgtgcct gtcttaaatt ccaaagcttt acatttcaac    1380
tgaaaaagaa actagaaatg tcctaattta acatcttgtt acataaatat ggtttaacaa    1440
aaaaaaaaaa aaaaaactcg ag                                             1462
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<210> 56
<211> 159
<212> PRT
<213> Homo sapien

<400> 56

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Thr Met Tyr Arg Ala Leu Arg Leu Leu Ala Arg Ser Arg Pro Leu Val
 1               5                  10                  15
Arg Ala Pro Ala Ala Ala Leu Ala Ser Ala Pro Gly Leu Gly Gly Ala
            20                  25                  30
Ala Val Pro Ser Phe Trp Pro Pro Asn Ala Ala Arg Met Ala Ser Gln
        35                  40                  45
Asn Ser Phe Arg Ile Glu Tyr Asp Thr Phe Gly Glu Leu Lys Val Pro
    50                  55                  60
Asn Asp Lys Tyr Tyr Gly Ala Gln Thr Val Arg Ser Thr Met Asn Phe
65                  70                  75                  80
Lys Ile Gly Gly Val Thr Glu Arg Met Pro Thr Pro Val Ile Lys Ala
                85                  90                  95
Phe Gly Ile Leu Lys Arg Ala Ala Ala Glu Val Asn Gln Asp Tyr Gly
            100                 105                 110
Leu Asp Pro Lys Ile Ala Asn Ala Ile Met Lys Ala Ala Asp Glu Val
        115                 120                 125
Ala Glu Gly Lys Leu Asn Asp His Phe Pro Leu Val Val Trp Gln Thr
    130                 135                 140
Gly Ser Gly Thr Gln Thr Asn Met Asn Val Asn Glu Val Ile Ser
145                 150                 155
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<210> 57
<211> 165
<212> PRT
<213> Homo sapien

<400> 57

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

<210> 58
<211> 259
<212> PRT
<213> Homo sapien

<400> 58
Glu Ser Glu Gln Lys Gly Lys Ala Ala Leu Ala Ala Thr Leu Glu Glu
1 5 10 15
Tyr Lys Ala Thr Val Ala Ser Asp Gln Ile Glu Met Asn Arg Leu Lys
20 25 30
Ala Gln Leu Glu Asn Glu Lys Gln Lys Val Ala Glu Leu Tyr Ser Ile
35 40 45
His Asn Ser Gly Asp Lys Ser Asp Ile Gln Asp Leu Leu Glu Ser Val
50 55 60
Arg Leu Asp Lys Glu Lys Ala Glu Thr Leu Ala Ser Ser Leu Gln Glu
65 70 75 80
Asp Leu Ala His Thr Arg Asn Asp Ala Asn Arg Leu Gln Asp Ala Ile
85 90 95
Ala Lys Val Glu Asp Glu Tyr Arg Ala Phe Gln Glu Glu Ala Lys Lys
100 105 110
Gln Ile Glu Asp Leu Asn Met Thr Leu Glu Lys Leu Arg Ser Asp Leu
115 120 125
Asp Glu Lys Glu Thr Glu Arg Ser Asp Met Lys Glu Thr Ile Phe Glu
130 135 140
Leu Glu Asp Glu Val Glu Gln His Arg Ala Val Lys Leu His Asp Asn
145 150 155 160
Leu Ile Ile Ser Asp Leu Glu Asn Thr Val Lys Lys Leu Gln Asp Gln
165 170 175
Lys His Asp Met Glu Arg Glu Ile Lys Thr Leu His Arg Arg Leu Arg
180 185 190
Glu Glu Ser Ala Glu Trp Arg Gln Phe Gln Ala Asp Leu Gln Thr Ala
195 200 205
Val Val Ile Ala Asn Asp Ile Lys Ser Glu Ala Gln Glu Glu Ile Gly
210 215 220
Asp Leu Lys Arg Arg Leu His Glu Ala Gln Glu Lys Asn Glu Lys Leu
225 230 235 240
Thr Lys Glu Leu Glu Glu Ile Lys Ser Arg Lys Gln Glu Glu Glu Arg
245 250 255

09/129,439

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TRADUCCIÓN OFICIAL No.2000/096 de un documento escrito en inglés, el cual para su identificación se sella con el sello del traductor al tiempo con la presente. Esta traducción ha sido preparada por Hilda Aguilera de Piedrahita traductora e intérprete oficial debidamente reconocida por el Ministerio de Relaciones Exteriores y autorizada por el Ministerio de Justicia y del Derecho, por resolución número 323 de 1980.

(Se traduce el certificado de la Oficina de Patentes y Marcas de los Estados Unidos de América, correspondiente a la solicitud 09/476,235 y el capítulo reivindicatorio, escritos en inglés.)

ESTADOS UNIDOS DE AMÉRICA

A TODOS A QUIENES ESTOS PRESENTES LLEGAREN:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS

Abril 12, 2000

POR EL PRESENTE CERTIFICO QUE ADJUNTA SE ENCUENTRA UNA COPIA FIEL DE LOS ARCHIVOS DE LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE AMÉRICA DE AQUELLOS PAPELES DE LA SOLICITUD DE PATENTE IDENTIFICADA ABAJO Y QUE CUMPLIERON CON

TRADUCCION OFICIAL No. 2000/096
HILDA AGUILERA DE PIEDRAHITA
INTERPRETE OFICIAL
Res. No. 323 DEL MIN. DE JUSTICIA

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99

791

LOS REQUISITOS PARA QUE SE LES OTORGARA UNA FECHA DE SOLICITUD BAJO EL CÓDIGO DE COMERCIO DE LOS ESTADOS UNIDOS DE AMÉRICA TÍTULO 35 SECCIÓN 111.

NUMERO DE SOLICITUD: ***09/476,235***

FECHA DE PRESENTACIÓN: ***Diciembre 30, 1999***

Por autoridad del

COMISARIO DE PATENTES Y MARCAS

(Firmado.) T. WALLACE

Funcionario que Certifica

(SELLO DE OBLEA DE LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE AMÉRICA)

(Nota: al margen aparece un sello a tinta en todas las páginas: 09476235.123099)

REPRODUCCION OFICIAL No. 2004/696
BILDA ARGUELLES DE PIEDRAHITA
INTERPRETE OFICIAL
RES No. 223 DEL MIN. DE JUSTICIA

Reivindicaciones

1. Un polipéptido aislado que incluye por lo menos una porción inmunogénica de una proteína de tumor pulmonar, o una variante de ella, donde la proteína de tumor incluye una secuencia de aminoácidos que

660
9/22

792

está codificada por una secuencia polinucleótida seleccionada del grupo consistente de:

(a) Las secuencias presentadas en los NOS SEQ ID 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 y 361;

(b) Las secuencias presentadas en los NOS SEQ ID 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 y 361; bajo condiciones moderadamente severas; y

(c) Un complemento de la secuencia (a) o (b).

2. Un polipéptido aislado de acuerdo con la reivindicación 1, donde el polipéptido incluye una secuencia de aminoácidos codificada por una secuencia polinucleótida presentada en cualesquiera de los NOS SEQ ID 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 y 361 o un complemento de cualesquiera de las anteriores secuencias polinucleótidas.

3. Un polinucleótido aislado que codifica por lo menos 15 residuos aminoácidos de proteína de tumor pulmonar, o una variante de ellos que

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difiere en una o más sustituciones, supresiones, adiciones, y/o inserciones tales que la habilidad de la variante para reaccionar con antisera antígeno específico no se disminuye sustancialmente, donde la proteína de tumor incluye una secuencia de aminoácidos que está codificada por un polinucleótido que incluye la secuencia presentada en cualesquiera de los NOS SEQ ID 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 y 361 o un complemento de cualesquiera de las secuencias anteriores.

4. Un polinucleótido aislado que codifica una proteína de tumor pulmonar, o una variante de ella, donde la proteína de tumor incluye una secuencia de aminoácidos que está codificada por un polinucleótido que incluye la secuencia presentada en cualesquiera de los NOS SEQ ID 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 y 361 o un complemento de cualesquiera de las secuencias anteriores.

5. Un polinucleótido aislado que incluye una secuencia presentada en cualesquiera de los NOS SEQ 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 y 361.

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6. Un polinucleótido aislado que incluye una secuencia que hibridiza a una secuencia presentada en cualesquiera de los NOS SEQ ID 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 y 361 bajo condiciones moderadamente severas.

7. Un polinucleótido aislado complementario a un polinucleótido de acuerdo con cualesquiera de las reivindicaciones 3-6.

8. Un vector de expresión que incluye un polinucleótido de acuerdo con cualesquiera de las reivindicaciones 3-7.

9. Una célula anfitriona transformada o transfectada con un vector de expresión de acuerdo con la reivindicación 8.

10. Un anticuerpo aislado, o fragmento de antígeno ligante del mismo, que específicamente se liga a una proteína de tumor pulmonar que incluye una secuencia de aminoácidos que es codificada por una secuencia polinucleótida presentada en cualesquiera de los NOS SEQ ID 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 y 361 o un complemento de cualesquiera de las anteriores secuencias polinucleótidas.

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11. Una proteína de fusión que incluye por lo menos un polipéptido de acuerdo con la reivindicación 1.

12. Una proteína de fusión de acuerdo con la reivindicación 11, donde la proteína de fusión incluye una expresión mejoradora, que aumenta la expresión de la proteína de fusión en una célula anfitriona transfectada con un polinucleótido codificando la proteína de fusión.

13. Una proteína de fusión de acuerdo con la reivindicación 11, donde la proteína de fusión incluye un ayudador T epitope que no está presente dentro del polipéptido de la reivindicación 1.

14. Una proteína de fusión de acuerdo con la reivindicación 11, donde la proteína de fusión incluye una etiqueta de afinidad.

15. Un polinucleótido aislado que codifica la proteína de fusión de acuerdo con la reivindicación 11.

16. Una composición farmacéutica que incluye un portador fisiológicamente aceptable y por lo menos un componente seleccionado del grupo que consiste de:

(a) un polipéptido de acuerdo con la reivindicación 1;

(b) un polinucleótido de acuerdo con la reivindicación 3;

(c) un anticuerpo de acuerdo con la reivindicación 10;

(d) una proteína de fusión de acuerdo con la reivindicación 11; y

(e) un polinucleótido de acuerdo con la reivindicación 15.

17. Una vacuna que incluye un inmunoestimulante y por lo menos un componente seleccionado del grupo que consiste de:

(a) un polipéptido de acuerdo con la reivindicación 1;

(b) un polinucleótido de acuerdo con la reivindicación 3;

(c) un anticuerpo de acuerdo con la reivindicación 10;

(d) una proteína de fusión de acuerdo con la reivindicación 11; y

(e) un polinucleótido de acuerdo con la reivindicación 15.

18. Una vacuna de acuerdo con la reivindicación 17, donde el inmunoestimulante es un adyuvante.

19. Una vacuna de acuerdo con la reivindicación 17 donde el inmunoestimulante induce una respuesta predominantemente Tipo I.

20. Un método para inhibir el desarrollo de cáncer en un paciente, que incluye la administración al paciente, de una cantidad efectiva de la composición farmacéutica de acuerdo con la reivindicación 16.

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21. Un método para inhibir el desarrollo de cáncer en un paciente, que incluye la administración al paciente, de una cantidad efectiva de la vacuna de acuerdo con la reivindicación 19.

22. Una composición farmacéutica que incluye una célula que presenta antígeno que expresa un polipéptido de acuerdo con la reivindicación 1, en combinación con un portador o excipiente farmacéuticamente aceptable.

23. Una composición farmacéutica de acuerdo con la reivindicación 22, donde la célula que presenta antígeno es una célula dendrítica o macrófaga.

24. Una vacuna que incluye una célula que presenta antígeno que expresa un polipéptido de acuerdo con la reivindicación 1, en combinación con un inmunoestimulante.

25. Una vacuna de acuerdo con la reivindicación 24, donde el inmunoestimulante es un adyuvante.

26. Una vacuna de acuerdo con la reivindicación 24, donde el inmunoestimulante induce una respuesta predominantemente de Tipo I.

27. Una vacuna de acuerdo con la reivindicación 24 donde la célula que presenta antígeno es una célula dendrítica.

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28. Un método para inhibir el desarrollo de cáncer en un paciente, que incluye la administración al paciente, de una cantidad efectiva de una célula que presenta antígeno que expresa un polipéptido codificado por un polinucleótido presentado en cualesquiera de los NO SEQ ID: 217-362, y así inhibir el desarrollo de un cáncer en el paciente.

29. Un método de acuerdo con la reivindicación 28 donde la célula que presenta antígeno es una célula dendrítica.

30. Un método de acuerdo con las reivindicaciones 20, 21 y 28, donde el cáncer es cáncer de pulmón.

31. Un método para remover células tumor de una muestra biológica, que incluye poner en contacto una muestra biológica con células T que reaccionan específicamente con una proteína de tumor pulmonar, donde la proteína de tumor incluye una secuencia de aminoácidos que es codificada por una secuencia de polinucleótido seleccionada del grupo consistente de:

(i) polinucleótidos presentados en cualesquiera de NOS SEQ ID: 217-362 y

(ii) complementos de los anteriores polinucleótidos;

donde la etapa de contacto se lleva a cabo bajo condiciones y por un tiempo suficiente para permitir la remoción de las células que expresan el antígeno de la muestra.

32. Un método de acuerdo con la reivindicación 31, donde la muestra biológica es sangre o una fracción de la misma.

33. Un método para inhibir el desarrollo de cáncer en un paciente, que incluye la administración al paciente, de una muestra biológica tratada de acuerdo con el método de la reivindicación 31.

34. Un método para estimular y/o expandir las células T específicas para una proteína de tumor pulmonar, que incluye poner en contacto células T con por lo menos un componente seleccionado del grupo que consiste de:

(i) un polipéptido de acuerdo con la reivindicación 1;

(ii) un polipéptido codificado por un polinucleótido que incluye una secuencia presentada en cualesquiera de los NO SEQ ID: 217-362

(iii) un polinucleótido que codifica un polipéptido de (i) o (ii); y

(iv) un antígeno presente en la célula que expresa un polipéptido de (i) o (ii);

bajo condiciones y por un tiempo suficiente para permitir la estimulación y/o expansión de las células T.

35. Una población de células T aisladas, que incluyen células T preparadas de acuerdo con el método de la reivindicación 34.

36. Un método para inhibir el desarrollo de cáncer en un paciente, que incluye la administración al paciente una cantidad efectiva de una población de células T de acuerdo con la reivindicación 35.

37. Un método para inhibir el desarrollo de cáncer en un paciente, que incluye las etapas de:

(a) incubar células T $CD4^+$ y /o $CD8^+$ aisladas de un paciente con por lo menos un componente seleccionado del grupo consistente de:

(i) un polipéptido de acuerdo con la reivindicación 1;

(ii) un polipéptido codificado por un polinucleótido que incluye una secuencia presentada en cualesquiera de los NO SEQ ID: 217-362;

(iii) un polinucleótido que codifica un polipéptido de (i) o (ii); y

(iv) una célula que presenta antígeno que expresa un polipéptido de (i) o (ii);

tal que las células T proliferen; y

(b) administrar al paciente una cantidad efectiva células T proliferadas, y así inhibir el desarrollo de cáncer en un paciente.

38. Un método para inhibir el desarrollo de cáncer en un paciente, que incluye las etapas de:

(a) incubar células T $CD4^+$ y /o $CD8^+$ aisladas de un paciente con por lo menos un componente seleccionado del grupo consistente de:

(i) un polipéptido de acuerdo con la reivindicación 1;

(ii) un polipéptido codificado por un polinucleótido que incluye una secuencia presentada en cualesquiera de los NO SEQ ID: 217-362;

(iii) un polinucleótido que codifica un polipéptido de (i) o (ii); y

(iv) una célula que presenta antígeno que expresa un polipéptido de (i) o (ii);

tal que las células T proliferen; y

(b) clonar por lo menos una célula proliferada para suministrar células T clonadas; y

(c) administrar al paciente una cantidad efectiva células T clonadas, y así inhibir el desarrollo de cáncer en un paciente.

39. Un método para determinar la presencia o ausencia de cáncer en un paciente, que incluye las etapas de:

(a) poner en contacto una muestra biológica obtenida de un paciente con un agente ligante que se liga a una proteína de tumor pulmonar, donde la proteína de tumor incluye una secuencia de aminoácidos que es codificada por una secuencia de polinucleótido seleccionado del grupo que consiste de:

(i) polinucleótidos presentados en cualesquiera de NOS SEQ ID: 217-362; y

(ii) complementos de los anteriores polinucleótidos;

(b) detectar en la muestra una cantidad de polipéptido que se liga al agente ligante; y

(c) comparar la cantidad de polipéptido a un valor de corte predeterminado, y así determinar la presencia o ausencia de cáncer en el paciente.

40. Un método de acuerdo con la reivindicación 39, donde el agente ligante es un anticuerpo.

41. Un método de acuerdo con la reivindicación 42, donde el anticuerpo es un anticuerpo monoclonal.

42. Un método de acuerdo a la reivindicación 39, donde el cáncer es cáncer de pulmón.

43. Un método para monitorear la progresión de cáncer en un paciente, que incluye las etapas de:

(a) poner en contacto una muestra biológica obtenida de un paciente a un primer punto en tiempo con un agente ligante que se liga a una proteína de tumor pulmonar, donde la proteína de tumor incluye una secuencia de aminoácidos que es codificada por una secuencia de polinucleótido presentada en cualesquiera de NOS SEQ ID: 217-362 o un complemento de cualesquiera de los anteriores polinucleótidos;

(b) detectar en la muestra una cantidad de polipéptido que se liga al agente ligante;

(c) repetir las etapas (a) y (b) usando una muestra biológica obtenida del paciente a un punto subsiguiente en el tiempo; y

(d) comparar la cantidad de polipéptido detectado en la etapa (c) con la cantidad detectada en la etapa (b) y desde allí supervisar la progresión del cáncer en el paciente.

44. Un método de acuerdo con la reivindicación 43, donde el agente ligante es un anticuerpo.

45. Un método de acuerdo con la reivindicación 44, donde el anticuerpo es un anticuerpo monoclonal.

46. Un método de acuerdo con la reivindicación 43, donde el cáncer es cáncer de pulmón.

47. Un método para determinar la presencia o ausencia de un cáncer en un paciente, que incluye las etapas de:

(a) poner en contacto una muestra biológica obtenida de un paciente con un oligonucleótido que hibridiza a un polinucleótido que codifica una proteína de tumor pulmonar, donde la proteína de tumor incluye una secuencia de aminoácidos que es codificada por una secuencia de polinucleótido presentada en cualesquiera de NOS SEQ ID: 217-362 o un complemento de cualesquiera de los anteriores polinucleótidos;

(b) detectar en la muestra una cantidad de polinucleótido que hibridiza al oligonucleótido; y

(c) comparar la cantidad de polinucleótido que hibridiza al oligonucleótido a un valor predeterminado de corte, y desde allí determinar la presencia o ausencia de cáncer en un paciente.

48. Un método de acuerdo con la reivindicación 47, donde la cantidad de polinucleótido que hibridiza al oligonucleótido es determinada usando una reacción de polimerasa en cadena.

49. Un método de acuerdo con la reivindicación 47, donde la cantidad de polinucleótido que hibridiza al oligonucleótido es determinada usando un ensayo de hibridización.

50. Un método para monitorear la progresión de cáncer en un paciente, que incluye las etapas de :

(a) poner en contacto una muestra biológica obtenida de un paciente con un oligonucleótido que hibridiza a un polinucleótido que codifica una proteína de tumor pulmonar, donde la proteína de tumor incluye una secuencia de aminoácidos que es codificada por una secuencia de polinucleótido presentada en cualesquiera de NOS SEQ ID: 217-362 o un complemento de cualesquiera de los anteriores polinucleótidos;

(b) detectar en la muestra una cantidad de polinucleótido que hibridiza al oligonucleótido; y

(c) repetir las etapas (a) y (b) usando una muestra biológica obtenida del paciente a un punto subsiguiente en el tiempo; y

(d) comparar la cantidad de polinucleótido detectado en la etapa (c) con la cantidad detectada en la etapa (b) y desde allí monitorear la progresión del cáncer en el paciente.

51. Un método de acuerdo con la reivindicación 50, donde la cantidad de polinucleótido que hibridiza al oligonucleótido es determinada usando una reacción en cadena de polimerasa.

52. Un método de acuerdo con la reivindicación 50, donde la cantidad de polinucleótido que hibridiza al oligonucleótido es determinada usando un ensayo de hibridización.

53. Un conjunto de diagnóstico, que incluye:

(a) uno o más anticuerpos de acuerdo con la reivindicación 10; y

(b) un agente de detección que incluye un grupo reportero.

54. Un conjunto de acuerdo con la reivindicación 53, donde los anticuerpos son inmovilizados sobre un soporte sólido.

55. Un conjunto de acuerdo con la reivindicación 53, donde el agente de detección incluye un anti-inmunoglobulina, proteína G, proteína A o lectina.

56. Un conjunto de acuerdo con la reivindicación 53, donde el grupo reportero es seleccionado del grupo que consiste de radioisótopos, grupos fluorescentes, grupos luminiscentes, enzimas, biotina y partículas de tinte.

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57. Un oligonucleótido que incluye de 10 a 40 nucleótidos contiguos que hibridiza bajo condiciones moderadamente severas a un polinucleótido que codifica una proteína de tumor pulmonar, donde la proteína de tumor incluye una secuencia de aminoácidos que es codificada por una secuencia de polinucleótido presentada en cualesquiera de los NOS SEQ ID 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 y 361 o un complemento de cualesquiera de las anteriores secuencias polinucleótidas.

58. Un oligonucleótido de acuerdo con la reivindicación 57, donde el oligonucleótido incluye de 10 a 40 nucleótidos contiguos presentada en cualesquiera de los NOS SEQ ID 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336; 337, 342, 353, 359 y 361.

59. Un conjunto de diagnóstico, que incluye:

(a) un oligonucleótido de acuerdo con la reivindicación 58; y

(b) un agente de diagnóstico para ser usado en una reacción de polimerasa en cadena o un ensayo de hibridización.

ES TRADUCCIÓN FIEL Y COMPLETA de la cual se deja copia en los archivos de esta oficina para su confrontación y a la cual me remito.

Santafé de Bogotá, 6 de Junio del 2000.

2000/096

PTO 261486

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

June 12, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: ***09/518,809***
FILING DATE: ***March 03, 2000***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

T. Lawrence

T. LAWRENCE
Certifying Officer

Please type a plus sign (+) inside this box [+] 03-06-00

A/BOX SEQ

PTO/SB/05 (2/98)

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for nonprovisional applications under 37 CFR § 1.53(b))

Attorney Docket No.	210121.475C3
First Inventor or Application Identifier	Steven G. Reed
Title	COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE
Express Mail Label No.	EL487465258US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Box Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

1. [ ] General Authorization Form & Fee Transmittal *(Submit an original and a duplicate for fee processing)*
2. [X] Specification [Total Pages] 84 *(preferred arrangement set forth below)*
   - Descriptive Title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
3. [ ] Drawing(s) *(35 USC 113)* [Total Sheets]
4. Oath or Declaration [Total Pages]
   a. [ ] Newly executed (original or copy)
   b. [ ] Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional with Box 17 completed)*
      i. [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b)
5. [ ] Incorporation By Reference *(useable if box 4b is checked)* The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered to be part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. [ ] Microfiche Computer Program *(Appendix)*
7. Nucleotide and Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. [X] Computer-Readable Copy
   b. [X] Paper Copy (identical to computer copy)
   c. [X] Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. [ ] Assignment Papers (cover sheet & document(s))
9. [ ] 37 CFR 3.73(b) Statement *(when there is an assignee)* [ ] Power of Attorney
10. [ ] English Translation Document *(if applicable)*
11. [ ] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copies of IDS Citations
12. [ ] Preliminary Amendment
13. [X] Return Receipt Postcard
14. [ ] Small Entity Statement(s) [ ] Statement filed in prior application, Status still proper and desired
15. [ ] Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
16. [X] Other: Certificate of Express Mail

17. If a CONTINUING APPLICATION, *check appropriate box and supply the requisite information below and in a preliminary amendment*

[ ] Continuation [ ] Divisional [X] Continuation-In-Part (CIP) of prior Application No.: 09/476,235 filed December 30, 1999

Prior application information: Examiner _____ Group / Art Unit _____

[ ] Claims the benefit of Provisional Application No. _____

CORRESPONDENCE ADDRESS

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Respectfully submitted,

TYPED or PRINTED NAME David J. Maki REGISTRATION NO. 31,392

SIGNATURE _____ Date 3/3/00

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EXPRESS MAIL NO. EL487465258US

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Steven G. Reed, Michael J. Lodes, Raodoh Mohamath and Heather Secrist
Filed	:	March 3, 2000
For	:	COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE
Docket No.	:	210121.475C3
Date	:	March 3, 2000

Box Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

09518 09/030200

DECLARATION

Sir:

I, Lawrence Teague, in accordance with 37 C.F.R. § 1.821(f) do hereby declare that, to the best of my knowledge, the content of the paper entitled "Sequence Listing" and the computer readable copy contained within the floppy disk are the same.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated this 3rd day of March, 2000.

Lawrence Teague
Legal Assistant

701 Fifth Avenue, Suite 6300
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(206) 622-4900
FAX (206) 682-6031

[illegible]

PATENT

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Steven G. Reed, Michael J. Lodes, Raodoh Mohamath, and Heather Secrist
Filed	:	March 3, 2000
For	:	COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE

Docket No.	:	210121.475C3
Date	:	March 3, 2000

Box Patent Application
Assistant Commissioner for Patents
Washington, DC 20231

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

Assistant Commissioner for Patents:

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Respectfully submitted,

Seed Intellectual Property Law Group PLLC

Judith A. Breaks/Jeanette West/Susan Johnson

DJM:jab1

Enclosures:

Postcard
Form PTO/SB/05
Specification,Claims, Abstract (84 pages)
Hard copy of Sequence Listing
Declaration re Sequence Listing
Diskette containing Sequence Listing

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COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE

REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Patent Application No. 09/476,235 filed December 30, 1999, which is a continuation-in-part of U.S. Patent Application No. 09/370,838, filed August 9, 1999, which is a continuation-in-part of U.S. Patent Application No. 09/285,323, filed April 2, 1999.

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TECHNICAL FIELD

The present invention relates generally to compositions and methods for the treatment of lung cancer. The invention is more specifically related to nucleotide sequences that are preferentially expressed in lung tumor tissue, together with polypeptides encoded by such nucleotide sequences. The inventive nucleotide sequences and polypeptides may be used in vaccines and pharmaceutical compositions for the treatment of lung cancer.

BACKGROUND OF THE INVENTION

Lung cancer is the primary cause of cancer death among both men and women in the U.S., with an estimated 172,000 new cases being reported in 1994. The five-year survival rate among all lung cancer patients, regardless of the stage of disease at diagnosis, is only 13%. This contrasts with a five-year survival rate of 46% among cases detected while the disease is still localized. However, only 16% of lung cancers are discovered before the disease has spread.

Early detection is difficult since clinical symptoms are often not seen until the disease has reached an advanced stage. Currently, diagnosis is aided by the use of chest x-rays, analysis of the type of cells contained in sputum and fiberoptic examination of the bronchial passages. Treatment regimens are determined by the type and stage of the cancer, and include surgery, radiation therapy and/or chemotherapy. In spite of considerable research into therapies for the disease, lung cancer remains difficult to treat.

Accordingly, there remains a need in the art for improved vaccines, treatment methods and diagnostic techniques for lung cancer.

SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compounds and methods for the therapy and diagnosis of cancer, such as lung cancer. In one aspect, the present invention provides polypeptides comprising at least a portion of a lung tumor protein, or a variant thereof. Certain portions and other variants are immunogenic, such that the ability of the variant to react with antigen-specific antisera is not substantially diminished. Within certain embodiments, the polypeptide comprises a sequence that is encoded by a polynucleotide sequence selected from the group consisting of: (a) sequences recited in SEQ ID NOS: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379 and 386; (b) variants of a sequence recited in SEQ ID NOS: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379 and 386; and (c) complements of a sequence of (a) or (b).

The present invention further provides polynucleotides that encode a polypeptide as described above, or a portion thereof (such as a portion encoding at least 15 contiguous amino acid residues of a lung tumor protein), expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, vaccines are provided. Such vaccines comprise a polypeptide or polynucleotide as described above and an immunostimulant.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a lung tumor protein; and (b) a physiologically acceptable carrier.

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Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, vaccines are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

Within related aspects, pharmaceutical compositions comprising a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a physiologically acceptable carrier are provided.

Vaccines are further provided, within other aspects, that comprise a fusion protein, or a polynucleotide encoding a fusion protein, in combination with an immunostimulant.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition or vaccine as recited above.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a lung tumor protein, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a lung tumor protein, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polynucleotide encoding such a polypeptide;

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and/or (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating $CD4^+$ and/or $CD8^+$ T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of a lung tumor protein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

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Within further aspects, the present invention provides methods for determining the presence or absence of a cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody. The cancer may be lung cancer.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the

cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed

herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

SEQUENCE IDENTIFIERS

SEQ ID NO: 1 is the determined cDNA sequence for L363C1.cons
SEQ ID NO: 2 is the determined cDNA sequence for L263C2.cons
SEQ ID NO: 3 is the determined cDNA sequence for L263C2c
SEQ ID NO: 4 is the determined cDNA sequence for L263C1.cons
SEQ ID NO: 5 is the determined cDNA sequence for L263C1b
SEQ ID NO: 6 is the determined cDNA sequence for L164C2.cons
SEQ ID NO: 7 is the determined cDNA sequence for L164C1.cons
SEQ ID NO: 8 is the determined cDNA sequence for L366C1a
SEQ ID NO: 9 is the determined cDNA sequence for L260C1.cons
SEQ ID NO: 10 is the determined cDNA sequence for L163C1c
SEQ ID NO: 11 is the determined cDNA sequence for L163C1b
SEQ ID NO: 12 is the determined cDNA sequence for L255C1.cons
SEQ ID NO: 13 is the determined cDNA sequence for L255C1b
SEQ ID NO: 14 is the determined cDNA sequence for L355C1.cons
SEQ ID NO: 15 is the determined cDNA sequence for L366C1.cons
SEQ ID NO: 16 is the determined cDNA sequence for L163C1a
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SEQ ID NO: 18 is the determined cDNA sequence for LT86-2
SEQ ID NO: 19 is the determined cDNA sequence for LT86-3
SEQ ID NO: 20 is the determined cDNA sequence for LT86-4
SEQ ID NO: 21 is the determined cDNA sequence for LT86-5
SEQ ID NO: 22 is the determined cDNA sequence for LT86-6
SEQ ID NO: 23 is the determined cDNA sequence for LT86-7
SEQ ID NO: 24 is the determined cDNA sequence for LT86-8

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SEQ ID NO: 25 is the determined cDNA sequence for LT86-9

SEQ ID NO: 26 is the determined cDNA sequence for LT86-10

SEQ ID NO: 27 is the determined cDNA sequence for LT86-11

SEQ ID NO: 28 is the determined cDNA sequence for LT86-12

SEQ ID NO: 29 is the determined cDNA sequence for LT86-13

SEQ ID NO: 30 is the determined cDNA sequence for LT86-14

SEQ ID NO: 31 is the determined cDNA sequence for LT86-15

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SEQ ID NO: 35 is the predicted amino acid sequence for LT86-4

SEQ ID NO: 36 is the predicted amino acid sequence for LT86-5

SEQ ID NO: 37 is the predicted amino acid sequence for LT86-6

SEQ ID NO: 38 is the predicted amino acid sequence for LT86-7

SEQ ID NO: 39 is the predicted amino acid sequence for LT86-8

SEQ ID NO: 40 is the predicted amino acid sequence for LT86-9

SEQ ID NO: 41 is the predicted amino acid sequence for LT86-10

SEQ ID NO: 42 is the predicted amino acid sequence for LT86-11

SEQ ID NO: 43 is the predicted amino acid sequence for LT86-12

SEQ ID NO: 44 is the predicted amino acid sequence for LT86-13

SEQ ID NO: 45 is the predicted amino acid sequence for LT86-14

SEQ ID NO: 46 is the predicted amino acid sequence for LT86-15

SEQ ID NO: 47 is a $(dT)_{12}AG$ primer

SEQ ID NO: 48 is a primer

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SEQ ID NO: 51 is the determined 5' cDNA sequence for L86S-16

SEQ ID NO: 52 is the determined 5' cDNA sequence for L86S-25

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SEQ ID NO: 53 is the determined 5' cDNA sequence for L86S-36

SEQ ID NO: 54 is the determined 5' cDNA sequence for L86S-40

SEQ ID NO: 55 is the determined 5' cDNA sequence for L86S-46

SEQ ID NO: 56 is the predicted amino acid sequence for L86S-3

SEQ ID NO: 57 is the predicted amino acid sequence for L86S-12

SEQ ID NO: 58 is the predicted amino acid sequence for L86S-16

SEQ ID NO: 59 is the predicted amino acid sequence for L86S-25

SEQ ID NO: 60 is the predicted amino acid sequence for L86S-36

SEQ ID NO: 61 is the predicted amino acid sequence for L86S-40

SEQ ID NO: 62 is the predicted amino acid sequence for L86S-46

SEQ ID NO: 63 is the determined 5' cDNA sequence for L86S-30

SEQ ID NO: 64 is the determined 5' cDNA sequence for L86S-41

SEQ ID NO: 65 is the predicted amino acid sequence from the 5' end of LT86-9

SEQ ID NO: 66 is the determined extended cDNA sequence for LT86-4

SEQ ID NO: 67 is the predicted extended amino acid sequence for LT86-4

SEQ ID NO: 68 is the determined 5' cDNA sequence for LT86-20

SEQ ID NO: 69 is the determined 3' cDNA sequence for LT86-21

SEQ ID NO: 70 is the determined 5' cDNA sequence for LT86-22

SEQ ID NO: 71 is the determined 5' cDNA sequence for LT86-26

SEQ ID NO: 72 is the determined 5' cDNA sequence for LT86-27

SEQ ID NO: 73 is the predicted amino acid sequence for LT86-20

SEQ ID NO: 74 is the predicted amino acid sequence for LT86-21

SEQ ID NO: 75 is the predicted amino acid sequence for LT86-22

SEQ ID NO: 76 is the predicted amino acid sequence for LT86-26

SEQ ID NO: 77 is the predicted amino acid sequence for LT86-27

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SEQ ID NO: 79 is the determined extended cDNA sequence for L86S-36

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SEQ ID NO: 81 is the predicted extended amino acid sequence for L86S-12

SEQ ID NO: 82 is the predicted extended amino acid sequence for L86S-36

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SEQ ID NO: 84 is the determined 5'cDNA sequence for L86S-6

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SEQ ID NO: 86 is the determined 5'cDNA sequence for L86S-14

SEQ ID NO: 87 is the determined 5'cDNA sequence for L86S-29

SEQ ID NO: 88 is the determined 5'cDNA sequence for L86S-34

SEQ ID NO: 89 is the determined 5'cDNA sequence for L86S-39

SEQ ID NO: 90 is the determined 5'cDNA sequence for L86S-47

SEQ ID NO: 91 is the determined 5'cDNA sequence for L86S-49

SEQ ID NO: 92 is the determined 5'cDNA sequence for L86S-51

SEQ ID NO: 93 is the predicted amino acid sequence for L86S-6

SEQ ID NO: 94 is the predicted amino acid sequence for L86S-11

SEQ ID NO: 95 is the predicted amino acid sequence for L86S-14

SEQ ID NO: 96 is the predicted amino acid sequence for L86S-29

SEQ ID NO: 97 is the predicted amino acid sequence for L86S-34

SEQ ID NO: 98 is the predicted amino acid sequence for L86S-39

SEQ ID NO: 99 is the predicted amino acid sequence for L86S-47

SEQ ID NO: 100 is the predicted amino acid sequence for L86S-49

SEQ ID NO: 101 is the predicted amino acid sequence for L86S-51

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SEQ ID NO: 103 is the determined 5' cDNA sequence for SLT-T2

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SEQ ID NO: 105 is the determined 5' cDNA sequence for SLT-T5

SEQ ID NO: 106 is the determined 5' cDNA sequence for SLT-T7

SEQ ID NO: 107 is the determined 5' cDNA sequence for SLT-T9

SEQ ID NO: 108 is the determined 5' cDNA sequence for SLT-T10

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SEQ ID NO: 109 is the determined 5' cDNA sequence for SLT-T11

SEQ ID NO: 110 is the determined 5' cDNA sequence for SLT-T12

SEQ ID NO: 111 is the predicted amino acid sequence for SLT-T1

SEQ ID NO: 112 is the predicted amino acid sequence for SLT-T2

SEQ ID NO: 113 is the predicted amino acid sequence for SLT-T3

SEQ ID NO: 114 is the predicted amino acid sequence for SLT-T10

SEQ ID NO: 115 is the predicted amino acid sequence for SLT-T12

SEQ ID NO: 116 is the determined 5' cDNA sequence for SALT-T3

SEQ ID NO: 117 is the determined 5' cDNA sequence for SALT-T4

SEQ ID NO: 118 is the determined 5' cDNA sequence for SALT-T7

SEQ ID NO: 119 is the determined 5' cDNA sequence for SALT-T8

SEQ ID NO: 120 is the determined 5' cDNA sequence for SALT-T9

SEQ ID NO: 121 is the predicted amino acid sequence for SALT-T3

SEQ ID NO: 122 is the predicted amino acid sequence for SALT-T4

SEQ ID NO: 123 is the predicted amino acid sequence for SALT-T7

SEQ ID NO: 124 is the predicted amino acid sequence for SALT-T8

SEQ ID NO: 125 is the predicted amino acid sequence for SALT-T9

SEQ ID NO: 126 is the determined cDNA sequence for PSLT-1

SEQ ID NO: 127 is the determined cDNA sequence for PSLT-2

SEQ ID NO: 128 is the determined cDNA sequence for PSLT-7

SEQ ID NO: 129 is the determined cDNA sequence for PSLT-13

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SEQ ID NO: 131 is the determined cDNA sequence for PSLT-28

SEQ ID NO: 132 is the determined cDNA sequence for PSLT-30

SEQ ID NO: 133 is the determined cDNA sequence for PSLT-40

SEQ ID NO: 134 is the determined cDNA sequence for PSLT-69

SEQ ID NO: 135 is the determined cDNA sequence for PSLT-71

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SEQ ID NO: 137 is the determined cDNA sequence for PSLT-79

SEQ ID NO: 138 is the determined cDNA sequence for PSLT-03

SEQ ID NO: 139 is the determined cDNA sequence for PSLT-09

SEQ ID NO: 140 is the determined cDNA sequence for PSLT-011

SEQ ID NO: 141 is the determined cDNA sequence for PSLT-041

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SEQ ID NO: 143 is the determined cDNA sequence for PSLT-6

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SEQ ID NO: 147 is the determined cDNA sequence for PSLT-012

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SEQ ID NO: 156 is the determined 5' cDNA sequence for SAL-82

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SEQ ID NO: 158 is the determined 5' cDNA sequence for SAL-104

SEQ ID NO: 159 is the determined 5' cDNA sequence for SAL-109

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SEQ ID NO: 161 is the determined 5' cDNA sequence for SAL-8

SEQ ID NO: 162 is the determined 5' cDNA sequence for SAL-12

SEQ ID NO: 163 is the determined 5' cDNA sequence for SAL-14

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SEQ ID NO: 195 is the predicted amino acid sequence for SAL-8

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SEQ ID NO: 202 is the predicted amino acid sequence for SAL-32

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SEQ ID NO: 204 is the predicted amino acid sequence for SAL-42

SEQ ID NO: 205 is the predicted amino acid sequence for SAL-43

SEQ ID NO: 206 is the predicted amino acid sequence for SAL-44

SEQ ID NO: 207 is the predicted amino acid sequence for SAL-48

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SEQ ID NO: 209 is the predicted amino acid sequence for SAL-72

SEQ ID NO: 210 is the predicted amino acid sequence for SAL-77

SEQ ID NO: 211 is the predicted amino acid sequence for SAL-86

SEQ ID NO: 212 is the predicted amino acid sequence for SAL-88

SEQ ID NO: 213 is the predicted amino acid sequence for SAL-93

SEQ ID NO: 214 is the predicted amino acid sequence for SAL-100

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SEQ ID NO: 216 is a second predicted amino acid sequence for SAL-50

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SEQ ID NO: 232 is the determined cDNA sequence for LT4690-49

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SEQ ID NO: 236 is the determined cDNA sequence for LT4690-63

SEQ ID NO: 237 is the determined cDNA sequence for LT4690-71

SEQ ID NO: 238 is the determined cDNA sequence for 2LT-3

SEQ ID NO: 239 is the determined cDNA sequence for 2LT-6

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SEQ ID NO: 284 is the determined cDNA sequence for 2LT-133

SEQ ID NO: 285 is the determined cDNA sequence for 2LT-137

SEQ ID NO: 286 is the determined cDNA sequence for LT4690-71

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SEQ ID NO: 360 is the determined cDNA sequence for SCC1-607

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SEQ ID NO: 361 is the determined cDNA sequence for SCC1-608

SEQ ID NO: 362 is the determined cDNA sequence for SCC1-610

SEQ ID NO: 363 is the determined cDNA sequence for clone DMS79T1

SEQ ID NO: 364 is the determined cDNA sequence for clone DMS79T2

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SEQ ID NO: 366 is the determined cDNA sequence for clone DMS79T5

SEQ ID NO: 367 is the determined cDNA sequence for clone DMS79T6

SEQ ID NO: 368 is the determined cDNA sequence for clone DMS79T7

SEQ ID NO: 369 is the determined cDNA sequence for clone DMS79T9

SEQ ID NO: 370 is the determined cDNA sequence for clone DMS79T10

SEQ ID NO: 371 is the determined cDNA sequence for clone DMS79T11

SEQ ID NO: 372 is the determined cDNA sequence for clone 128T1

SEQ ID NO: 373 is the determined cDNA sequence for clone 128T2

SEQ ID NO: 374 is the determined cDNA sequence for clone 128T3

SEQ ID NO: 375 is the determined cDNA sequence for clone 128T4

SEQ ID NO: 376 is the determined cDNA sequence for clone 128T5

SEQ ID NO: 377 is the determined cDNA sequence for clone 128T7

SEQ ID NO: 378 is the determined cDNA sequence for clone 128T9

SEQ ID NO: 379 is the determined cDNA sequence for clone 128T10

SEQ ID NO: 380 is the determined cDNA sequence for clone 128T11

SEQ ID NO: 381 is the determined cDNA sequence for clone 128T12

SEQ ID NO: 382 is the determined cDNA sequence for clone NCIH69T3

SEQ ID NO: 383 is the determined cDNA sequence for clone NCIH69T5

SEQ ID NO: 384 is the determined cDNA sequence for clone NCIH69T6

SEQ ID NO: 385 is the determined cDNA sequence for clone NCIH69T7

SEQ ID NO: 386 is the determined cDNA sequence for clone NCIH69T9

SEQ ID NO: 387 is the determined cDNA sequence for clone NCIH69T10

SEQ ID NO: 388 is the determined cDNA sequence for clone NCIH69T11

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SEQ ID NO: 389 is the determined cDNA sequence for clone NCIH69T12

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the therapy and diagnosis of cancer, such as lung cancer. The compositions described herein may include lung tumor polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (*e.g.*, T cells). Polypeptides of the present invention generally comprise at least a portion (such as an immunogenic portion) of a lung tumor protein or a variant thereof. A "lung tumor protein" is a protein that is expressed in lung tumor cells at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in a normal tissue, as determined using a representative assay provided herein. Certain lung tumor proteins are tumor proteins that react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera of a patient afflicted with lung cancer. Polynucleotides of the subject invention generally comprise a DNA or RNA sequence that encodes all or a portion of such a polypeptide, or that is complementary to such a sequence. Antibodies are generally immune system proteins, or antigen-binding fragments thereof, that are capable of binding to a polypeptide as described above. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B-cells that express a polypeptide as described above. T cells that may be employed within such compositions are generally T cells that are specific for a polypeptide as described above.

The present invention is based on the discovery of human lung tumor proteins. Sequences of polynucleotides encoding specific tumor proteins are provided in SEQ ID NOS: 1-31, 49-55, 63,64, 66, 68-72, 78-80, 84-92 and 217-389.

LUNG TUMOR PROTEIN POLYNUCLEOTIDES

Any polynucleotide that encodes a lung tumor protein or a portion or other variant thereof as described herein is encompassed by the present invention. Preferred polynucleotides comprise at least 15 consecutive nucleotides, preferably at least 30 consecutive nucleotides and

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more preferably at least 45 consecutive nucleotides, that encode a portion of a lung tumor protein. More preferably, a polynucleotide encodes an immunogenic portion of a lung tumor protein. Polynucleotides complementary to any such sequences are also encompassed by the present invention. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

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Polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes a lung tumor protein or a portion thereof) or may comprise a variant of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native tumor protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native lung tumor protein or a portion thereof.

Two polynucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison,

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WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS 5*:151-153; Myers, E.W. and Muller W. (1988) *CABIOS 4*:11-17; Robinson, E.D. (1971) *Comb. Theor 11*:105; Santoo, N. Nes, M. (1987) *Mol. Biol. Evol. 4*:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA 80*:726-730.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (i.e. gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (i.e. the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Variants may also, or alternatively, be substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are capable of hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding a native lung tumor protein (or a complementary sequence). Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

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It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Polynucleotides may be prepared using any of a variety of techniques. For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least five fold greater in a lung tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Alternatively, polypeptides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as lung tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion may be used to isolate a full length gene from a suitable library (*e.g.*, a lung tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (*e.g.*, by nick-

translation or end-labeling with ^{32}P) using well known techniques. A bacterial or bacteriophage library is then screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (*see* Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences are then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (*see* Triglia et al., *Nucl. Acids Res. 16*:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that

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initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., *PCR Methods Applic. 1*:111-19, 1991) and walking PCR (Parker et al., *Nucl. Acids. Res. 19*:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (*e.g.*, NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence.

Certain nucleic acid sequences of cDNA molecules encoding portions of lung tumor proteins are provided in SEQ ID NO: 1-31, 49-55, 63,64, 66, 68-72, 78-80, 84-92 and 217-389. The isolation of these sequences is described in detail below.

Polynucleotide variants may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical synthesis. Modifications in a polynucleotide sequence may also be introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis (*see* Adelman et al., *DNA 2*:183, 1983). Alternatively, RNA molecules may be generated by *in vitro* or *in vivo* transcription of DNA sequences encoding a lung tumor protein, or portion thereof, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Certain portions may be used to prepare an encoded polypeptide, as described herein. In addition, or alternatively, a portion may be administered to a patient such that the encoded polypeptide is generated *in vivo* (*e.g.*, by transfecting antigen-presenting cells, such as dendritic cells, with a cDNA construct encoding a lung tumor polypeptide, and administering the transfected cells to the patient).

A portion of a sequence complementary to a coding sequence (*i.e.*, an antisense

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polynucleotide) may also be used as a probe or to modulate gene expression. cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells of tissues to facilitate the production of antisense RNA. An antisense polynucleotide may be used, as described herein, to inhibit expression of a tumor protein. Antisense technology can be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (*see* Gee et al., *In* Huber and Carr, ***Molecular and Immunologic Approaches***, Futura Publishing Co. (Mt. Kisco, NY; 1994)). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (*e.g.*, promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes.

A portion of a coding sequence, or of a complementary sequence, may also be designed as a probe or primer to detect gene expression. Probes may be labeled with a variety of reporter groups, such as radionuclides and enzymes, and are preferably at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and still more preferably at least 30 nucleotides in length. Primers, as noted above, are preferably 22-30 nucleotides in length.

Any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl-, methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In general, a vector will contain an origin of replication functional in at least one organism,

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convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Such formulations are particularly useful for therapeutic purposes, as described below. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (*e.g.*, avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also be accomplished using an antibody, by methods known to those of ordinary skill in the art.

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Other formulations for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

LUNG TUMOR POLYPEPTIDES

Within the context of the present invention, polypeptides may comprise at least an immunogenic portion of a lung tumor protein or a variant thereof, as described herein. As noted above, a "lung tumor protein" is a protein that is expressed by lung tumor cells. Proteins that are lung tumor proteins also react detectably within an immunoassay (such as an ELISA) with antisera from a patient with lung cancer. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic

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properties.

An "immunogenic portion," as used herein is a portion of a protein that is recognized (*i.e.*, specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of a lung tumor protein or a variant thereof. Certain preferred immunogenic portions include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other preferred immunogenic portions may contain a small N- and/or C-terminal deletion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

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Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (*i.e.*, they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well known techniques. An immunogenic portion of a native lung tumor protein is a portion that reacts with such antisera and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (*e.g.*, in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ^{125}I-labeled Protein A.

As noted above, a composition may comprise a variant of a native lung tumor protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native lung

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tumor protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with antigen-specific antisera may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antigen-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

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Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity (determined as described above) to the identified polypeptides.

Preferably, a variant contains conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or

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addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (*e.g.*, poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

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Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. *See* Merrifield, *J. Am. Chem. Soc. 85*:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin

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Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

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Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused protein, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged

residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene 40*:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA 83*:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (*see*, for example, Stoute et al. *New Engl. J. Med., 336*:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (*e.g.*, the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in *E. coli* (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments

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Gly Gly Tyr

<210> 59
<211> 125
<212> PRT
<213> Homo sapien

<400> 59

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Gly Thr Ser Phe Ser Lys Asn His Ala Ala Pro Phe Ser Lys Val Leu
 1               5                  10                  15
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            20                  25                  30
Pro Gln Asp Leu Pro Tyr Pro Asp Pro Ala Ile Ala Gln Phe Ser Val
        35                  40                  45
Gln Lys Val Thr Pro Gln Ser Asp Gly Ser Ser Ser Lys Val Lys Val
    50                  55                  60
Lys Val Arg Val Asn Val His Gly Ile Phe Ser Val Ser Ser Ala Ser
65                  70                  75                  80
Leu Val Glu Val His Lys Ser Glu Glu Asn Glu Glu Pro Met Glu Thr
                85                  90                  95
Asp Gln Asn Ala Lys Glu Glu Glu Lys Met Gln Val Asp Gln Glu Glu
            100                 105                 110
Pro His Val Glu Glu Gln Gln Gln Gln Thr Pro Gly Arg
        115                 120                 125
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<210> 60
<211> 246
<212> PRT
<213> Homo sapien

<400> 60

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

<210> 61
<211> 128
<212> PRT
<213> Homo sapien

<400> 61

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            20                  25                  30
Glu Lys Met Gln Val Asp Gln Glu Glu Pro His Val Glu Glu Gln Gln
        35                  40                  45
Gln Gln Thr Pro Ala Glu Asn Lys Ala Glu Ser Glu Glu Met Glu Thr
    50                  55                  60
Ser Gln Ala Gly Ser Lys Asp Lys Lys Met Asp Gln Pro Pro Gln Ala
65                  70                  75                  80
Lys Lys Ala Lys Val Lys Thr Ser Thr Val Asp Leu Pro Ile Glu Asn
                85                  90                  95
Gln Leu Leu Trp Gln Ile Asp Arg Glu Met Leu Asn Leu Tyr Ile Glu
            100                 105                 110
Asn Glu Gly Lys Met Ile Met Gln Asp Lys Leu Glu Lys Glu Arg Asn
        115                 120                 125
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<210> 62
<211> 418
<212> PRT
<213> Homo sapien

<400> 62

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

```
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
    130                 135                 140
Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145                 150                 155                 160
Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
                165                 170                 175
Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
            180                 185                 190
Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
        195                 200                 205
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
    210                 215                 220
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225                 230                 235                 240
Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
                245                 250                 255
Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
            260                 265                 270
Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
        275                 280                 285
His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
    290                 295                 300
Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
305                 310                 315                 320
Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
                325                 330                 335
Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
            340                 345                 350
Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
        355                 360                 365
Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
    370                 375                 380
Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
385                 390                 395                 400
Val Tyr Thr Arg Val Thr Ala Tyr Ile Asp Trp Ile Arg Gln Gln Thr
                405                 410                 415
Gly Ile
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<210> 63
<211> 776
<212> DNA
<213> Homo sapien

<400> 63

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cacagatggt gatagaggaa tccatcttgc agtcagataa agccctcact gatagagaga      60
aggcagtagc agtggatcgg gccaagaagg aggcagctga gaaggaacag gaacttttaa     120
aacagaaatt acaggagcag ccagcaacag atggaggctc aagataagag tcgcaaggaa     180
aactagccaa ctgaaggaga agctgcagat ggagagagaa cacctactga gagagcagat     240
tatgatgttg gagcacacgc agaaggtcca aaatgattgg cttcatgaag gatttaagaa     300
gaagtatgag gagatgaatg cagagataag tcaatttaaa cgtatgattg atactacaaa     360
aaatgatgat actcctgga ttgcacgaac cttggacaac cttgccgatg agctaactgc     420
aatattgtct gctcctgcta aattaattgg tcatggtgtc aaaggtgtga gctcactctt     480
taaaaagcat aagctccct tttaaggata ttatagattg tacatatatg ctttggacta     540
tttttgatct gtatgttttt cattttcatt cagcaagttt ttttttttt tcagagtctt     600
```

actctgttgc ccaggctgga gtacagtggt gcaatctcag ctcactgcaa cctctgcctc 660
ctgggttcaa gagattcacc tgcctcagcc ccctagtagc tgggattata ggtgtacacc 720
accacaccca gctaattttt gtatttttag tagagatggg gtttcactat gttggc 776

<210> 64
<211> 160
<212> DNA
<213> Homo sapien

<400> 64
gcagcgctct cggttgcagt acccactgga aggacttagg cgctcgcgtg gacaccgcaa 60
gcccctcagt agcctcggcc caagaggcct gctttccact cgctagcccc gccgggggtc 120
cgtgtcctgt ctcggtggcc ggacccgggc ccgagcccga 160

<210> 65
<211> 72
<212> PRT
<213> Homo sapien

<400> 65
Leu Ser Ala Met Gly Phe Thr Ala Ala Gly Ile Ala Ser Ser Ser Ile
1 5 10 15
Ala Ala Lys Met Met Ser Ala Ala Ala Ile Ala Asn Gly Gly Gly Val
20 25 30
Ala Ser Gly Ser Leu Val Ala Thr Leu Gln Ser Leu Gly Ala Thr Gly
35 40 45
Leu Ser Gly Leu Thr Lys Phe Ile Leu Gly Ser Ile Gly Ser Ala Ile
50 55 60
Ala Ala Val Ile Ala Arg Phe Tyr
65 70

<210> 66
<211> 2581
<212> DNA
<213> Homo sapien

<400> 66
ctttcaaccc gcgctcgccg gctccagccc cgcgcgcccc cacccccttgc cctcccggcg 60
gctccgcagg gtgaggtggc tttgaccccg ggttgcccgg ccagcacgac cgaggaggtg 120
gctggacagc tggaggatga acggagaagc cgactgcccc acagacctgg aaatggccgc 180
ccccaaaggc caagaccgtt ggtcccagga agacatgctg actttgctgg aatgcatgaa 240
gaacaacctt ccatccaatg acagctccaa gttcaaaacc accgaatcac acatggactg 300
ggaaaaagta gcatttaaag acttttctgg agacatgtgc aagctcaaat gggtggagat 360
ttctaatgag gtgaggaagt tccgtacatt gacagaattg atcctcgatg ctcaggaaca 420
tgttaaaaat ccttacaaag gcaaaaaact caagaaacac ccagacttcc caaagaagcc 480
cctgacccct tatttccgct tcttcatgga gaagcgggcc aagtatgcga aactccaccc 540
tgagatgagc aacctggacc taaccaagat tctgtccaag aaatacaagg agcttccgga 600
gaagaagaag atgaaatata ttcaggactt ccagagagag aaacaggagt tcgagcgaaa 660
cctggcccga ttcagggagg atcaccccga cctaatccag aatgccaaga aatcggacat 720
cccagagaag cccaaaaccc cccagcagct gtggtacacc cacgagaaga aggtgtatct 780
caaagtgcgg ccagatgcca ctacgaagga ggtgaaggac tccctgggga agcagtggtc 840
tcagctctcg gacaaaaaga ggctgaaatg gattcataag gccctggagc agcggaagga 900
gtacgaggag atcatgagag actatatcca gaagcaccca gagctgaaca tcagtgagga 960
gggtatcacc aagtccaccc tcaccaaggc cgaacgccag ctcaaggaca agtttgacgg 1020
gcgacccacc aagccacctc cgaacagcta ctcgctgtac tgcgcagagc tcatggccaa 1080

```
catgaaggac gtgcccagca cagagcgcat ggtgctgtgc agccagcagt ggaagctgct    1140
gtcccagaag gagaaggacg cctatcacaa gaagtgtgat cagaaaaaga aagattacga    1200
ggtggagctg ctccgtttcc tcgagagcct gcctgaggag gagcagcagc gggtcttggg    1260
ggaagagaag atgctgaaca tcaacaagaa gcaggccacc agccccgcct ccaagaagcc    1320
agcccaggaa gggggcaagg gcggctccga gaagcccaag cggcccgtgt cggccatgtt    1380
catcttctcg gaggagaaac ggcggcagct gcaggaggag cggcctgagc tctccgagag    1440
cgagctgacc cgcctgctgg cccgaatgtg gaacgacctg tctgagaaga agaaggccaa    1500
gtacaaggcc cgagaggcgg cgctcaaggc tcagtcggag aggaagcccg gcggggagcg    1560
cgaggaacgg ggcaagctgc ccgagtcccc caaaagagct gaggagatct ggcaacagag    1620
cgttatcggc gactacctgg cccgcttcaa gaatgaccgg gtgaaggcct tgaaagccat    1680
ggaaatgacc tggaataaca tggaaaagaa ggagaaactg atgtggatta agaaggcagc    1740
cgaagaccaa aagcgatatg agagagagct gagtgagatg cgggcacctc cagctgctac    1800
aaattcttcc aagaagatga aattccaggg agaacccaag aagcctccca tgaacggtta    1860
ccagaagttc tcccaggagc tgctgtccaa tggggagctg aaccacctgc cgctgaagga    1920
gcgcatggtg gagatcggca gtcgctggca gcgcatctcc cagagccaga aggagcacta    1980
caaaaagctg gccgaggagc agcaaaagca gtacaaggtg cacctggacc tctgggttaa    2040
gagcctgtct ccccaggacc gtgcagcata taaagagtac atctccaata aacgtaagag    2100
catgaccaag ctgcgaggcc caaaccccaa atccagccgg actactctgc agtccaagtc    2160
ggagtccgag gaggatgatg aagaggatga ggatgacgag gacgaggatg aagaagagga    2220
agatgatgag aatggggact cctctgaaga tggcggcgac tcctctgagt ccagcagcga    2280
ggacgagagc gaggatgggg atgagaatga agaggatgac gaggacgaag acgacgacga    2340
ggatgacgat gaggatgaag ataatgagtc cgagggcagc agctccagct cctcctcctt    2400
aggggactcc tcagactttg actccaactg aggcttagcc ccaccccagg ggagccaggg    2460
agagcccagg agctcccctc cccaactgac caccttttgtt tcttccccat gttctgtccc    2520
ttgccccccct ggcctccccc actttctttc tttctttaaa aaaaaaaaaa aaaaactcga    2580
g                                                                    2581
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<210> 67
<211> 764
<212> PRT
<213> Homo sapien

<400> 67

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

SEQ 795 849

Ala Arg Phe Arg Glu Asp His Pro Asp Leu Ile Gln Asn Ala Lys Lys
180 185 190
Ser Asp Ile Pro Glu Lys Pro Lys Thr Pro Gln Gln Leu Trp Tyr Thr
195 200 205
His Glu Lys Lys Val Tyr Leu Lys Val Arg Pro Asp Ala Thr Thr Lys
210 215 220
Glu Val Lys Asp Ser Leu Gly Lys Gln Trp Ser Gln Leu Ser Asp Lys
225 230 235 240
Lys Arg Leu Lys Trp Ile His Lys Ala Leu Glu Gln Arg Lys Glu Tyr
245 250 255
Glu Glu Ile Met Arg Asp Tyr Ile Gln Lys His Pro Glu Leu Asn Ile
260 265 270
Ser Glu Glu Gly Ile Thr Lys Ser Thr Leu Thr Lys Ala Glu Arg Gln
275 280 285
Leu Lys Asp Lys Phe Asp Gly Arg Pro Thr Lys Pro Pro Pro Asn Ser
290 295 300
Tyr Ser Leu Tyr Cys Ala Glu Leu Met Ala Asn Met Lys Asp Val Pro
305 310 315 320
Ser Thr Glu Arg Met Val Leu Cys Ser Gln Gln Trp Lys Leu Leu Ser
325 330 335
Gln Lys Glu Lys Asp Ala Tyr His Lys Lys Cys Asp Gln Lys Lys Lys
340 345 350
Asp Tyr Glu Val Glu Leu Leu Arg Phe Leu Glu Ser Leu Pro Glu Glu
355 360 365
Glu Gln Gln Arg Val Leu Gly Glu Glu Lys Met Leu Asn Ile Asn Lys
370 375 380
Lys Gln Ala Thr Ser Pro Ala Ser Lys Lys Pro Ala Gln Glu Gly Gly
385 390 395 400
Lys Gly Gly Ser Glu Lys Pro Lys Arg Pro Val Ser Ala Met Phe Ile
405 410 415
Phe Ser Glu Glu Lys Arg Arg Gln Leu Gln Glu Glu Arg Pro Glu Leu
420 425 430
Ser Glu Ser Glu Leu Thr Arg Leu Leu Ala Arg Met Trp Asn Asp Leu
435 440 445
Ser Glu Lys Lys Lys Ala Lys Tyr Lys Ala Arg Glu Ala Ala Leu Lys
450 455 460
Ala Gln Ser Glu Arg Lys Pro Gly Gly Glu Arg Glu Glu Arg Gly Lys
465 470 475 480
Leu Pro Glu Ser Pro Lys Arg Ala Glu Glu Ile Trp Gln Gln Ser Val
485 490 495
Ile Gly Asp Tyr Leu Ala Arg Phe Lys Asn Asp Arg Val Lys Ala Leu
500 505 510
Lys Ala Met Glu Met Thr Trp Asn Asn Met Glu Lys Lys Glu Lys Leu
515 520 525
Met Trp Ile Lys Lys Ala Ala Glu Asp Gln Lys Arg Tyr Glu Arg Glu
530 535 540
Leu Ser Glu Met Arg Ala Pro Pro Ala Ala Thr Asn Ser Ser Lys Lys
545 550 555 560
Met Lys Phe Gln Gly Glu Pro Lys Lys Pro Pro Met Asn Gly Tyr Gln
565 570 575
Lys Phe Ser Gln Glu Leu Leu Ser Asn Gly Glu Leu Asn His Leu Pro
580 585 590
Leu Lys Glu Arg Met Val Glu Ile Gly Ser Arg Trp Gln Arg Ile Ser
595 600 605
Gln Ser Gln Lys Glu His Tyr Lys Lys Leu Ala Glu Glu Gln Gln Lys

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```
    610                 615                 620
Gln Tyr Lys Val His Leu Asp Leu Trp Val Lys Ser Leu Ser Pro Gln
625                 630                 635                 640
Asp Arg Ala Ala Tyr Lys Glu Tyr Ile Ser Asn Lys Arg Lys Ser Met
                645                 650                 655
Thr Lys Leu Arg Gly Pro Asn Pro Lys Ser Ser Arg Thr Thr Leu Gln
            660                 665                 670
Ser Lys Ser Glu Ser Glu Glu Asp Asp Glu Glu Asp Glu Asp Asp Glu
        675                 680                 685
Asp Glu Asp Glu Glu Glu Glu Asp Asp Glu Asn Gly Asp Ser Ser Glu
    690                 695                 700
Asp Gly Gly Asp Ser Ser Glu Ser Ser Ser Glu Asp Glu Ser Glu Asp
705                 710                 715                 720
Gly Asp Glu Asn Glu Glu Asp Asp Glu Asp Glu Asp Asp Asp Glu Asp
                725                 730                 735
Asp Asp Glu Asp Glu Asp Asn Glu Ser Glu Gly Ser Ser Ser Ser Ser
            740                 745                 750
Ser Ser Leu Gly Asp Ser Ser Asp Phe Asp Ser Asn
        755                 760
```

<210> 68
<211> 434
<212> DNA
<213> Homo sapien

<400> 68

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ctaagatgct ggatgctgaa gacatcgtcg gaactgcccg gccagatgag aaagccatta     60
tgacttatgt gtctagcttc tatcatgcct tctctggagc ccagaaggca gaaacagcag    120
ccaatcgcat ctgcaaagtg ttggcggtca atcaagagaa cgagcagctt atggaagact    180
atgagaagct ggccagtgat ctgttggagt ggatccgccg caccatccca tggctggaga    240
atcgggtgcc tgagaacacc atgcatgcca tgcagcagaa gctggaggac ttccgagact    300
atagacgcct gcacaagccg cccaaggtgc aggagaagtg ccagctggag atcaacttta    360
acacgctgca gaccaaactg cggctcagca accggcctgc cttcatgccc tccgagggca    420
ggatggtctc ggat                                                      434
```

<210> 69
<211> 244
<212> DNA
<213> Homo sapien

<400> 69

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aggcagcatg ctcgttgaga gtcatcacca ctccctaatc tcaagtacgc agggacacaa     60
acactgcgga aggccgcagg gtcctctgcc taggaaaacc agagaccttt gttcacttgt    120
ttatgtgctg accttccctc cactattgtc ctgtgaccct gccaaatccc cctttgtgag    180
aaacacccaa gaatgatcaa taaaaaataa attaatttag gaaaaaaaaa aaaaaaaact    240
cgag                                                                 244
```

<210> 70
<211> 437
<212> DNA
<213> Homo sapien

<400> 70

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ctgggacggg agcgtccagc gggactcgaa ccccagatgt gaaggcgttt ctggaaagtc     60
cttggtccct ggatccagcg tcggccagcc cagagcccgt gccgcacatc cttgcgtcct    120
```

851

ccaggcagtg ggaccccgcg agctgcacgt ccctgggcac ggacaagtgt gaggcactgt 180
tggggctgtg ccaggtgcgg ggtgggctgc ccccttttct agaaccttcc agcctggtgc 240
cgtggccccc aggccggagt cttcctaagg ctgtgaggcc acccctgtcc tggcctccgt 300
tctcgcagca gcagaccttg cccgtgatga gcggggaggc ccttggctgg ctgggccagg 360
ctggttcccc ggccatgggg gctgcacctc tgggggagcc agccaaggag gaccccatgc 420
tggcgcagga agccggg 437

<210> 71
<211> 271
<212> DNA
<213> Homo sapien

<400> 71
gcgcagagtt ctgtcgtcca ccatcgagtg aggaagagag cattggttcc cctgagatag 60
aagagatggc tctcttcagt gcccagtctc catacattaa cccgatcatc ccctttactg 120
gaccaatcca aggagggctg caggagggac ttcaggtgac cctccagggg actaccgaga 180
gttttgcaca aaagtttgtg gtgaactttt cagaacagct tcaatggaga tgacttggcc 240
ttccacttca accccggtta tgaggaagga g 271

<210> 72
<211> 290
<212> DNA
<213> Homo sapien

<400> 72
ccgagcccta cccggaggtc tccagaatcc ccaccgtcag gggatgcaac ggctccctgt 60
ctggtgccct ctcctgctgc gaggactcgg cccagggctc gggcccgccc aaggccccta 120
cggtggccga gggtcccagc tcctgccttc ggcggaacgt gatcagcgag agggagcgca 180
ggaagcggat gtcgttgagc tgtgagcgtc tgcgggccct gctgccccag ttcgatggcc 240
ggcgggagga catggcctcg gtcctggaga tgtctgttgc aattcctgcg 290

<210> 73
<211> 144
<212> PRT
<213> Homo sapien

<400> 73

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

<210> 74
<211> 64
<212> PRT
<213> Homo sapien

<400> 74
Gly Ser Met Leu Val Glu Ser His His His Ser Leu Ile Ser Ser Thr
1 5 10 15
Gln Gly His Lys His Cys Gly Arg Pro Gln Gly Pro Leu Pro Arg Lys
20 25 30
Thr Arg Asp Leu Cys Ser Leu Val Tyr Val Leu Thr Phe Pro Pro Leu
35 40 45
Leu Ser Cys Asp Pro Ala Lys Ser Pro Phe Val Arg Asn Thr Gln Glu
50 55 60

<210> 75
<211> 145
<212> PRT
<213> Homo sapien

<400> 75
Gly Thr Gly Ala Ser Ser Gly Thr Arg Thr Pro Asp Val Lys Ala Phe
1 5 10 15
Leu Glu Ser Pro Trp Ser Leu Asp Pro Ala Ser Ala Ser Pro Glu Pro
20 25 30
Val Pro His Ile Leu Ala Ser Ser Arg Gln Trp Asp Pro Ala Ser Cys
35 40 45
Thr Ser Leu Gly Thr Asp Lys Cys Glu Ala Leu Leu Gly Leu Cys Gln
50 55 60
Val Arg Gly Gly Leu Pro Pro Phe Ser Glu Pro Ser Ser Leu Val Pro
65 70 75 80
Trp Pro Pro Gly Arg Ser Leu Pro Lys Ala Val Arg Pro Pro Leu Ser
85 90 95
Trp Pro Pro Phe Ser Gln Gln Gln Thr Leu Pro Val Met Ser Gly Glu
100 105 110
Ala Leu Gly Trp Leu Gly Gln Ala Gly Ser Leu Ala Met Gly Ala Ala
115 120 125
Pro Leu Gly Glu Pro Ala Lys Glu Asp Pro Met Leu Ala Gln Glu Ala
130 135 140
Gly
145

<210> 76
<211> 69
<212> PRT
<213> Homo sapien

<400> 76
Ala Glu Phe Cys Arg Pro Pro Ser Ser Glu Glu Glu Ser Ile Gly Ser
1 5 10 15
Pro Glu Ile Glu Glu Met Ala Leu Phe Ser Ala Gln Ser Pro Tyr Ile
20 25 30
Asn Pro Ile Ile Pro Phe Thr Gly Pro Ile Gln Gly Gly Leu Gln Glu
35 40 45

Gly Leu Gln Val Thr Leu Gln Gly Thr Thr Glu Ser Phe Ala Gln Lys
50 55 60
Phe Val Val Asn Phe
65

<210> 77
<211> 96
<212> PRT
<213> Homo sapien

<400> 77
Glu Pro Tyr Pro Glu Val Ser Arg Ile Pro Thr Val Arg Gly Cys Asn
1 5 10 15
Gly Ser Leu Ser Gly Ala Leu Ser Cys Cys Glu Asp Ser Ala Gln Gly
20 25 30
Ser Gly Pro Pro Lys Ala Pro Thr Val Ala Glu Gly Pro Ser Ser Cys
35 40 45
Leu Arg Arg Asn Val Ile Ser Glu Arg Glu Arg Arg Lys Arg Met Ser
50 55 60
Leu Ser Cys Glu Arg Leu Arg Ala Leu Leu Pro Gln Phe Asp Gly Arg
65 70 75 80
Arg Glu Asp Met Ala Ser Val Leu Glu Met Ser Val Ala Ile Pro Ala
85 90 95

<210> 78
<211> 2076
<212> DNA
<213> Homo sapien

<400> 78
agaaaaagtc tatgtttgca gaaatacaga tccaagacaa agacaggatg ggcactgctg 60
gaaaagttat taaatgcaaa gcagctgtgc tttgggagca gaagcaaccc ttctccattg 120
aggaaataga agttgcccca ccaaagacta aagaagttcg cattaagatt ttggccacag 180
gaatctgtcg cacagatgac catgtgataa aaggaacaat ggtgtccaag tttccagtga 240
ttgtgggaca tgaggcaact gggattgtag agagcattgg agaaggagtg actacagtga 300
aaccaggtga caaagtcatc cctctctttc tgccacaatg tagagaatgc aatgcttgtc 360
gcaacccaga tggcaacctt tgcattagga gcgatattac tggtcgtgga gtactggctg 420
atggcaccac cagatttaca tgcaagggca aaccagtcca ccacttcatg aacaccagta 480
catttaccga gtacacagtg gtggatgaat cttctgttgc taagattgat gatgcagctc 540
ctcctgagaa agtctgttta attggctgtg ggttttccac tggatatggc gctgctgtta 600
aaactggcaa ggtcaaacct ggttccactt gcgtcgtctt tggcctgaga ggagttggcc 660
tgtcagtcat catgggctgt aagtcagctg gtgcatctag gatcattggg attgacctca 720
acaaagacaa atttgagaag gccatggctg taggtgccac tgagtgtatc agtcccaagg 780
actctaccaa acccatcagt gaggtgctgt cagaaatgac aggcaacaac gtgggataca 840
cctttgaagt tattgggcat cttgaaacca tgattgatgc cctggcatcc tgccacatga 900
actatgggac cagcgtggtt gtaggagttc ctccatcagc caagatgctc acctatgacc 960
cgatgttgct cttcactgga cgcacatgga agggatgtgt ctttggaggt ttgaaaagca 1020
gagatgatgt cccaaaacta gtgactgagt tcctggcaaa gaaatttgac ctggaccagt 1080
tgataactca tgtcttacca tttaaaaaaa tcagtgaagg atttgagctg ctcaattcag 1140
gacaaagcat tcgaacggtc ctgacgtttt gagatccaaa gtggcaggag gtctgtgttg 1200
tcatggtgaa ctggagtttc tcttgtgaga gttccctcat ctgaaatcat gtatctgtct 1260
cacaaataca agcataagta gaagatttgt tgaagacata gaacccttat aaagaattat 1320
taacctttat aaacatttaa agtcttgtga gcacctggga attagtataa taacaatgtt 1380
aatatttttg atttacattt tgtaaggcta taattgtatc ttttaagaaa acatacactt 1440
ggatttctat gttgaaatgg agatttttaa gagttttaac cagctgctgc agatatatat 1500

ctcaaaacag atatagcgta taaagatata gtaaatgcat ctcctagagt aatattcact 1560
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<213> Homo sapien

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<210> 81
<211> 386
<212> PRT
<213> Homo sapien

<400> 81
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Pro Phe Ser Ile Glu Glu Ile Glu Val Ala Pro Pro Lys Thr Lys Glu
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Val Arg Ile Lys Ile Leu Ala Thr Gly Ile Cys Arg Thr Asp Asp His

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595
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856

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Lys Pro Gly Asp Lys Val Ile Pro Leu Phe Leu Pro Gln Cys Arg Glu
            100                 105                 110
Cys Asn Ala Cys Arg Asn Pro Asp Gly Asn Leu Cys Ile Arg Ser Asp
        115                 120                 125
Ile Thr Gly Arg Gly Val Leu Ala Asp Gly Thr Thr Arg Phe Thr Cys
    130                 135                 140
Lys Gly Lys Pro Val His His Phe Met Asn Thr Ser Thr Phe Thr Glu
145                 150                 155                 160
Tyr Thr Val Val Asp Glu Ser Ser Val Ala Lys Ile Asp Asp Ala Ala
                165                 170                 175
Pro Pro Glu Lys Val Cys Leu Ile Gly Cys Gly Phe Ser Thr Gly Tyr
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Gly Ala Ala Val Lys Thr Gly Lys Val Lys Pro Gly Ser Thr Cys Val
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Val Phe Gly Leu Arg Gly Val Gly Leu Ser Val Ile Met Gly Cys Lys
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Asp Ser Thr Lys Pro Ile Ser Glu Val Leu Ser Glu Met Thr Gly Asn
            260                 265                 270
Asn Val Gly Tyr Thr Phe Glu Val Ile Gly His Leu Glu Thr Met Ile
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Asp Ala Leu Ala Ser Cys His Met Asn Tyr Gly Thr Ser Val Val Val
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Gly Val Pro Pro Ser Ala Lys Met Leu Thr Tyr Asp Pro Met Leu Leu
305                 310                 315                 320
Phe Thr Gly Arg Thr Trp Lys Gly Cys Val Phe Gly Gly Leu Lys Ser
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Arg Asp Asp Val Pro Lys Leu Val Thr Glu Phe Leu Ala Lys Lys Phe
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Asp Leu Asp Gln Leu Ile Thr His Val Leu Pro Phe Lys Lys Ile Ser
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Glu Gly Phe Glu Leu Leu Asn Ser Gly Gln Ser Ile Arg Thr Val Leu
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Thr Phe
385
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<210> 82
<211> 418
<212> PRT
<213> Homo sapien

<400> 82

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Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
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902
857

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Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65                  70                  75                  80
Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
                85                  90                  95
Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
            100                 105                 110
Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
        115                 120                 125
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
    130                 135                 140
Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145                 150                 155                 160
Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
                165                 170                 175
Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
            180                 185                 190
Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
        195                 200                 205
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
    210                 215                 220
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225                 230                 235                 240
Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
                245                 250                 255
Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
            260                 265                 270
Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
        275                 280                 285
His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
    290                 295                 300
Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
305                 310                 315                 320
Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
                325                 330                 335
Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
            340                 345                 350
Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
        355                 360                 365
Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
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Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
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<210> 83
<211> 418
<212> PRT
<213> Homo sapien

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<400> 83

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Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
        35                  40                  45
Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
    50                  55                  60
Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65                  70                  75                  80
Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
                85                  90                  95
Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
            100                 105                 110
Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
        115                 120                 125
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
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Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
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Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
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Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
            180                 185                 190
Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
        195                 200                 205
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
    210                 215                 220
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225                 230                 235                 240
Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
                245                 250                 255
Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
            260                 265                 270
Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
        275                 280                 285
His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
    290                 295                 300
Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
305                 310                 315                 320
Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
                325                 330                 335
Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
            340                 345                 350
Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
        355                 360                 365
Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
    370                 375                 380
Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
385                 390                 395                 400
Val Tyr Thr Arg Val Thr Ala Tyr Leu Asp Trp Ile Arg Gln Gln Thr
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Gly Ile
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859

<210> 84
<211> 489
<212> DNA
<213> Homo sapien

<400> 84
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<210> 85
<211> 304
<212> DNA
<213> Homo sapien

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<210> 86
<211> 296
<212> DNA
<213> Homo sapien

<400> 86
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<210> 87
<211> 904
<212> DNA
<213> Homo sapien

<400> 87
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<211> 387
<212> DNA
<213> Homo sapien

<400> 88
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<210> 89
<211> 481
<212> DNA
<213> Homo sapien

<400> 89
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<210> 90
<211> 491
<212> DNA
<213> Homo sapien

<400> 90
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WO 01/23541 PCT/US00/26910

<210> 91
<211> 488
<212> DNA
<213> Homo sapien

<400> 91
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<211> 384
<212> DNA
<213> Homo sapien

<400> 92
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tcaccaccat ggagaaggct gggg 384

<210> 93
<211> 162
<212> PRT
<213> Homo sapien

<400> 93
Lys Gly Lys Leu Asp Asp Tyr Gln Glu Arg Met Asn Lys Gly Glu Arg
1 5 10 15
Leu Asn Gln Asp Gln Leu Asp Ala Val Ser Lys Tyr Gln Glu Val Thr
20 25 30
Asn Asn Leu Glu Phe Ala Lys Glu Leu Gln Arg Ser Phe Met Ala Leu
35 40 45
Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln
50 55 60
Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu
65 70 75 80
Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp
85 90 95
Leu Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu
100 105 110Ser Leu Leu Asp Glu
Phe Tyr Lys Leu Val Asp Pro Glu Arg Asp Met
115 120 125
Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp
130 135 140

Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys Gly Thr Thr Tyr Lys
145 150 155 160
Val Leu

<210> 94
<211> 100
<212> PRT
<213> Homo sapien

<400> 94
Asp Leu Glu Glu Ala Thr Leu Gln His Glu Ala Thr Ala Ala Thr Leu
1 5 10 15
Arg Lys Lys His Ala Asp Ser Val Ala Glu Leu Gly Glu Gln Ile Asp
20 25 30
Asn Leu Gln Arg Val Lys Gln Lys Leu Glu Lys Glu Lys Ser Glu Met
35 40 45
Lys Met Glu Ile Asp Asp Leu Ala Cys Asn Met Glu Val Ile Ser Lys
50 55 60
Ser Lys Gly Asn Leu Glu Lys Met Cys Arg Thr Leu Glu Asp Gln Val
65 70 75 80
Ser Glu Leu Lys Thr Gln Glu Glu Glu Gln Gln Arg Leu Ile Asn Glu
85 90 95
Leu Thr Ala Gln
100

<210> 95
<211> 99
<212> PRT
<213> Homo sapien

<400> 95
Lys Ile Leu Pro Leu Asn Gly Asn Leu Gln Ala Val Glu Leu Gly Glu
1 5 10 15
Lys Arg Thr Ser Ser Leu Arg Ile Lys Met Phe Arg Ala Thr Arg Val
20 25 30
Thr Ser Thr Ser Arg Phe Leu Asn Pro Tyr Val Val Cys Phe Leu Val
35 40 45
Leu Pro Gly Val Val Ile Leu Ala Val Pro Ile Ala Leu Leu Val Tyr
50 55 60
Phe Leu Ala Phe Asp Gln Lys Ser Tyr Phe Tyr Trp Ser Asn Phe Pro
65 70 75 80
Leu Pro Asn Val Glu Tyr Asn Ser Pro Phe Asn Ser Pro Ala Ser Pro
85 90 95
Gly Ile Pro

<210> 96
<211> 257
<212> PRT
<213> Homo sapien

<400> 96
Val Gln Glu Thr Ile His Glu His Asn Lys Leu Ala Ala Asn Ser Asp
1 5 10 15

full
8/5
863

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

<210> 97
<211> 128
<212> PRT
<213> Homo sapien

<400> 97
Ser Leu Pro Gln Phe Ala Val His Pro Glu Arg Ser Gly Leu Ala Asp
1 5 10 15
Ser Gly Asp Gly Gly Asn Met Ser Val Ala Phe Ala Ala Pro Arg Gln
20 25 30
Arg Gly Lys Gly Glu Ile Thr Pro Ala Ala Ile Gln Lys Met Leu Asp
35 40 45
Asp Asn Asn His Leu Ile Gln Cys Ile Met Asp Ser Gln Asn Lys Gly
50 55 60
Lys Thr Ser Glu Cys Ser Gln Tyr Gln Gln Met Leu His Thr Asn Leu
65 70 75 80
Val Tyr Leu Ala Thr Ile Ala Asp Ser Asn Gln Asn Met Gln Ser Leu
85 90 95
Leu Pro Ala Pro Pro Thr Gln Asn Met Pro Met Gly Pro Gly Gly Met
100 105 110
Asn Gln Ser Gly Pro Pro Pro Pro Pro Arg Ser His Asn Met Pro Ser
115 120 125

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548 864

<210> 98
<211> 159
<212> PRT
<213> Homo sapien

<400> 98

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Phe Leu Asp Leu Arg Cys Tyr Arg Ala Gly Ser Ser Arg Leu Ala Val
 1               5                  10                  15
Ala Met Glu Ser Gly Pro Lys Met Leu Ala Pro Val Cys Leu Val Glu
            20                  25                  30
Asn Asn Asn Glu Gln Leu Leu Val Asn Gln Gln Ala Ile Gln Ile Leu
        35                  40                  45
Glu Lys Ile Ser Gln Pro Val Val Val Val Ala Ile Val Gly Leu Tyr
    50                  55                  60
Arg Thr Gly Lys Ser Tyr Leu Met Asn His Leu Ala Gly Gln Asn His
65                  70                  75                  80
Gly Phe Pro Leu Gly Ser Thr Val Gln Ser Glu Thr Lys Gly Ile Trp
                85                  90                  95
Met Trp Cys Val Pro His Pro Ser Lys Pro Asn His Thr Leu Val Leu
            100                 105                 110
Leu Asp Thr Glu Gly Leu Gly Asp Val Glu Lys Gly Asp Pro Lys Asn
        115                 120                 125
Asp Ser Trp Ile Phe Ala Leu Ala Val Leu Leu Cys Ser Thr Phe Val
    130                 135                 140
Tyr Asn Ser Met Ser Thr Ile Asn His Gln Ala Leu Glu Gln Leu
145                 150                 155
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<210> 99
<211> 147
<212> PRT
<213> Homo sapien

<400> 99

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Met Glu Ser Gly Pro Lys Met Leu Ala Pro Val Cys Leu Val Glu Asn
 1               5                  10                  15
Asn Asn Glu Gln Leu Leu Val Asn Gln Gln Ala Ile Gln Ile Leu Glu
            20                  25                  30
Lys Ile Ser Gln Pro Val Val Val Val Ala Ile Val Gly Leu Tyr Arg
        35                  40                  45
Thr Gly Lys Ser Tyr Leu Met Asn His Leu Ala Gly Gln Asn His Gly
    50                  55                  60
Phe Pro Leu Gly Ser Thr Val Gln Ser Glu Thr Lys Gly Ile Trp Met
65                  70                  75                  80
Trp Cys Val Pro His Pro Ser Lys Pro Asn His Thr Leu Val Leu Leu
                85                  90                  95
Asp Thr Glu Gly Leu Gly Asp Val Glu Lys Gly Asp Pro Lys Asn Asp
            100                 105                 110
Ser Trp Ile Phe Ala Leu Ala Val Leu Leu Cys Ser Thr Phe Val Tyr
        115                 120                 125
Asn Ser Met Ser Thr Ile Asn His Gln Ala Leu Glu Gln Leu His Tyr
    130                 135                 140
Val Thr Asp
145
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<210> 100
<211> 124
<212> PRT
<213> Homo sapien

<400> 100
Met Gly Lys Val Lys Val Gly Val Asn Gly Phe Gly Arg Ile Gly Arg
1 5 10 15
Leu Val Thr Arg Ala Ala Phe Asn Ser Gly Lys Val Asp Ile Val Ala
20 25 30
Ile Asn Asp Pro Phe Ile Asp Leu Asn Tyr Met Val Tyr Met Phe Gln
35 40 45
Tyr Asp Ser Thr His Gly Lys Phe His Gly Thr Val Glu Ala Glu Asn
50 55 60
Gly Lys Leu Val Ile Asn Gly Asn Pro Ile Thr Ile Phe Gln Glu Arg
65 70 75 80
Asp Pro Ser Lys Ile Lys Trp Gly Asp Ala Gly Ala Glu Tyr Val Val
85 90 95
Glu Ser Thr Gly Val Phe Thr Thr Met Glu Lys Ala Gly Ala His Leu
100 105 110
Gln Gly Gly Ala Lys Arg Val Ile Ile Ser Ala Pro
115 120

<210> 101
<211> 127
<212> PRT
<213> Homo sapien

<400> 101
Gln Ser Ala Ala Ser Ser Phe Ala Ser Pro Ala Glu Pro His Arg Ser
1 5 10 15
Asp Thr Met Gly Lys Val Lys Val Gly Val Asn Gly Phe Gly Arg Ile
20 25 30
Gly Arg Leu Val Thr Arg Ala Ala Phe Asn Ser Gly Lys Val Asp Ile
35 40 45
Val Ala Ile Asn Asp Pro Phe Ile Asp Leu Asn Tyr Met Val Tyr Met
50 55 60
Phe Gln Tyr Asp Ser Thr His Gly Lys Phe His Gly Thr Val Glu Ala
65 70 75 80
Glu Asn Gly Lys Leu Val Ile Asn Gly Asn Pro Ile Thr Ile Phe Gln
85 90 95
Glu Arg Asp Pro Ser Lys Ile Lys Trp Gly Asp Thr Gly Ala Glu Tyr
100 105 110
Val Val Glu Ser Thr Gly Val Phe Thr Thr Met Glu Lys Ala Gly
115 120 125

<210> 102
<211> 1225
<212> DNA
<213> Homo sapien

<400> 102
atggcggcgc ggtcgtcgtc gggggtggcg gcggcagagg gggcggcggc cctggcggca 60
gcggagacgg cagccgtgac ggtggcagcg gcggcgcggg acctgggcct gggggaatga 120
ggcggccgcg gcgggccagc ggcggagccg tgtagcggag aagctccccc tccctgcttc 180

866

ccttggccga gccgggggcg cgcgcgcacg cggccgtcca gagcgggctc cccacccctc 240
gactcctgcg acccgcaccg caccccccacc cgggcccgga ggatgatgaa gctcaagtcg 300
aaccagaccc gcacctacga cggcgacggc tacaagaagc gggccgcatg cctgtgtttc 360
cgcagcgaga gcgaggagga ggtgctactc gtgagcagta gtcgccatcc agacagatgg 420
attgtccctg gaggaggcat ggagcccgag gaggagccaa gtgtggcagc agttcgtgaa 480
gtctgtgagg aggctggagt aaaagggaca ttgggaagat tagttggaat ttttgagaac 540
caggagagga agcacaggac gtatgtctat gtgctcattg tcactgaagt gctggaagac 600
tgggaagatt cagttaacat tggaaggaag agggaatggt ttaaaatagа agacgccata 660
aaagtgctgc agtatcacaa acccgtgcag gcatcatatt ttgaaacatt gaggcaaggc 720
tactcagcca acaatggcac cccagtcgtg gccaccacat actcggtttc tgctcagagc 780
tcgatgtcag gcatcagatg actgaagact tcctgtaaga gaaatggaaa ttggaaacta 840
gactgaagtg caaatcttcc ctctcaccct ggctctttcc acttctcaca ggcctcctct 900
ttcaaataag gcatggtggg cagcaaagaa agggtgtatt gataatgttg ctgtttggtg 960
ttaagtgatg gggctttttc ttctgttttt attgagggtg ggggttgggt gtgtaatttg 1020
taagtacttt tgtgcatgat ctgtcccctcc ctcttcccac ccctgcagtc ctctgaagag 1080
aggccaacag ccttcccctg ccttggattc tgaagtgttc ctgtttgtct tatcctggcc 1140
ctggccagac gttttctttg atttttaatt ttttttttt attaaaagat accagtatga 1200
gaaaaaaaaa aaaaaaaaac tcgag 1225

<210> 103
<211> 741
<212> DNA
<213> Homo sapien

<400> 103
agaaacctca atcggattca gcaaaggaat ggtgttatta tcactacata ccaaatgtta 60
atcaataact ggcagcaact ttcaagcttt aggggccaag agtttgtgtg ggactatgtc 120
atcctcgatg aagcacataa aataaaaacc tcatctacta agtcagcaat atgtgctcgt 180
gctattcctg caagtaatcg cctcctcctc acaggaaccc caatccagaa taatttacaa 240
gaactatggt ccctatttga ttttgcttgt caagggtccc tgctgggaac attaaaaact 300
tttaagatgg agtatgaaaa tcctattact agagcaagag agaaggatgc taccccagga 360
gaaaaagcct tgggatttaa aatatctgaa aacttaatgg caatcataaa accctatttt 420
ctcaggagga ctaaagaaga cgtacagaag aaaaagtcaa gcaacccaga ggccagactt 480
aatgaaaaga atccagatgt tgatgccatt tgtgaaatgc cttccctttc caggagaaat 540
gatttaatta tttggatacg acttgtgcct ttacaagaag aaatatacag gaaatttgtg 600
tctttagatc atatcaagga gttgctaatg gagacgcgct caccttggc tgagctaggt 660
gtcttaaaga agctgtgtga tcatcctagg ctgctgtctg cacgggcttg ttgtttgcta 720
aatcttggga cattctctgc t 741

<210> 104
<211> 321
<212> DNA
<213> Homo sapien

<400> 104
ttgctctgcg tcatcaaaga caccaaactg ctgtgctata aaagttccaa ggaccagcag 60
cctcagatgg aactgccact ccaaggctgt aacattacgt acatcccgaa agacagcaaa 120
aagaagaagc acgagctgaa gattactcag cagggcacgg acccgcttgt tctcgccgtc 180
cagagcaagg aacaggccga gcagtggctg aaggtgatca aagaagccta cagtggttgt 240
agtggccccg tggattcaga gtgtcctcct ccaccaagct ccccggtgca caaggcagaa 300
ctggagaaga aactgtcttc a 321

<210> 105
<211> 389
<212> DNA

GGGCCT-SEQ#2140

<213> Homo sapien

<400> 105
cagcactggc cacactataa aattcaggtt cagaaaaaca gggtaagtca cagacagcaa 60
cgcttccagc atttatttte tttgcaccca tgggcaattt gagaaaattt acctttagaa 120
cgaactctgt taaaggtaca gacagtacaa tacttttttat tcagaaggtt tctgcataaa 180
ggtgatagtc ttttgactta atatattatt gtctcctgcc ttgtgtttct ggaatgaatg 240
aaggtcatta tttagaagat aatctgggtt gtatttgtgt cgtcagattg aattttcatt 300
gcacatgcta cttaatgtct ttaccaaata ataacaaagg gaaagaaaac caaatataga 360
tgtataataa ggaaaagctg gcctataga 389

<210> 106
<211> 446
<212> DNA
<213> Homo sapien

<400> 106
gccacatttg ccctggtcat agtttaaaca ccaggtcctg tgtcacatct ttttggtgcc 60
acaagtatca ctccattgtt cagagagtaa tgtattagtt ctgcccaatt cattcttcac 120
ttttatttct tccatttcat tagcatttat atcagctcaa gaagttaagg ttagaaaatt 180
ttccacttca aattttcagt acagaaatgt gctgtgatgt ttgacaagac tatttcatag 240
taagtgagtt aatgtttatt ggcctctgct ctcctctgtg tcagacctag gaagcctgag 300
gattacttag ttgttctgtc tctgggtcca caggcagaat ttggcccatc caaagactgg 360
ccaagtgcca aaaaaaggcc tgattaggcc ctgaaattca gtgaaattct gcctgaagaa 420
acctcttatt gaatttgaaa accata 446

<210> 107
<211> 467
<212> DNA
<213> Homo sapien

<400> 107
ccgccgctgc cgtcgccttc ctgggattgg agtctcgagc tttcttcgtt cgttcgccgg 60
cgggttcgcg ccctctcgc gcctcggggc tgcgaggctg gggaaggggt tggaggggc 120
tgttgatcgc cgcgtttaag ttgcgctcgg ggcggccatg tcggccggcg aggtcgagcg 180
cctagtgtcg gagctgagcg gcgggaccgg aggggatgag gaggaagagt ggctctatgg 240
cgatgaagat gaagttgaaa ggccagaaga agaaaatgcc agtgctaatc ctccatctgg 300
aattgaagat gaaactgctg aaaatggtgt accaaaaccg aaagtgactg agaccgaaga 360
tgatagtgat agtgacagcg atgatgatga agatgatgtg catgtcacta taggagacat 420
taaaacggga gcaccacagt atgggagtta tggtacagca cctgtaa 467

<210> 108
<211> 491
<212> DNA
<213> Homo sapien

<400> 108
gaaagataca acttccccaa cccaaacccg tttgtggagg acgacatgga taagaatgaa 60
atcgcctctg ttgcgtaccg ttaccgcagg tggaagcttg gagatgatat tgaccttatt 120
gtccgttgtg agcacgatgg cgtcatgact ggagccaacg gggaagtgtc cttcatcaac 180
atcaagacac tcaatgagtg ggattccagg cactgtaatg gcgttgactg gcgtcagaag 240
ctggactctc agcgaggggc tgtcattgcc acggagctga agaacaacag ctacaagttg 300
gcccggtgga cctgctgtgc tttgctggct ggatctgagt acctcaagct tggttatgtg 360
tctcggtacc acgtgaaaga ctcctcacgc cacgtcatcc taggcaccca gcagttcaag 420
cctaatgagt ttgccagcca gatcaacctg agcgtggaga atgcctgagg cattttacgc 480

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tgcgtcattg a 491

<210> 109
<211> 489
<212> DNA
<213> Homo sapien

<400> 109
ctcagatagt actgaaccct ttatcaacta tgtttttca gtctgacaac caaggcggct 60
actaagtgac taaggggcag gtagtataca gtgtggataa gcaggacaaa ggggtgattc 120
acatcccagg caggacagag caggagatca tgagatttca tcactcagga tggcttgtga 180
tttatttttat tttattcttt ttttttttg agatggagtc tcactcttgc ccaggctgga 240
gtgcagtggt gcgatcttgg ctcactgcaa cctctgcctc ctgggttcaa gcagttctcc 300
tgcctcagcc tcccaagtag ctgggattac aggcgtccgc caccatgccc agccaatttt 360
tgtacttta gtagagatgg ggtttcacca tgttggccag gctggtctcg aactcctgac 420
ctcaggtgat ccactcgcct cggcctccca aagtgctggg attataggca tgcgccacca 480
tgcccgggc 489

<210> 110
<211> 391
<212> DNA
<213> Homo sapien

<400> 110
gcggagtccg ctggctgacc cgagcgctgg tctccgccgg gaaccctggg gcatggagag 60
gtctgagtac ctcggccgcg gcgcacgctg catcgcggag ccaggctgcc gctgtcccag 120
tggagttcca ggagcaccac ctgagtgagg tgcagaatat ggcatctgag gagaagccgg 180
agcaggtgct gagttccatg aaggagaaca aagtggccat cattggaaag attcataccc 240
cgatggagta taaggggggag ctagcctcct atgatatgcg gctgaggcgt aagttggact 300
tatttgccaa cgtaatccat gtgaagtcac ttcctgggta tatgactcgg cacaacaatc 360
tagacctggt gatcattcga gagcagacag a 391

<210> 111
<211> 172
<212> PRT
<213> Homo sapien

<400> 111
Met Met Lys Leu Lys Ser Asn Gln Thr Arg Thr Tyr Asp Gly Asp Gly
1 5 10 15
Tyr Lys Lys Arg Ala Ala Cys Leu Cys Phe Arg Ser Glu Ser Glu Glu
20 25 30
Glu Val Leu Leu Val Ser Ser Ser Arg His Pro Asp Arg Trp Ile Val
35 40 45
Pro Gly Gly Gly Met Glu Pro Glu Glu Glu Pro Ser Val Ala Ala Val
50 55 60
Arg Glu Val Cys Glu Glu Ala Gly Val Lys Gly Thr Leu Gly Arg Leu
65 70 75 80
Val Gly Ile Phe Glu Asn Gln Glu Arg Lys His Arg Thr Tyr Val Tyr
85 90 95
Val Leu Ile Val Thr Glu Val Leu Glu Asp Trp Glu Asp Ser Val Asn
100 105 110
Ile Gly Arg Lys Arg Glu Trp Phe Lys Ile Glu Asp Ala Ile Lys Val
115 120 125
Leu Gln Tyr His Lys Pro Val Gln Ala Ser Tyr Phe Glu Thr Leu Arg

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```
    130                 135                 140
Gln Gly Tyr Ser Ala Asn Asn Gly Thr Pro Val Val Ala Thr Thr Tyr
145                 150                 155                 160
Ser Val Ser Ala Gln Ser Ser Met Ser Gly Ile Arg
                165                 170
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<210> 112
<211> 247
<212> PRT
<213> Homo sapien

<400> 112

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

<210> 113
<211> 107
<212> PRT
<213> Homo sapien

<400> 113

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Leu Leu Cys Val Ile Lys Asp Thr Lys Leu Leu Cys Tyr Lys Ser Ser
 1               5                  10                  15
Lys Asp Gln Gln Pro Gln Met Glu Leu Pro Leu Gln Gly Cys Asn Ile
            20                  25                  30
```

Thr Tyr Ile Pro Lys Asp Ser Lys Lys Lys Lys His Glu Leu Lys Ile
35 40 45
Thr Gln Gln Gly Thr Asp Pro Leu Val Leu Ala Val Gln Ser Lys Glu
50 55 60
Gln Ala Glu Gln Trp Leu Lys Val Ile Lys Glu Ala Tyr Ser Gly Cys
65 70 75 80
Ser Gly Pro Val Asp Ser Glu Cys Pro Pro Pro Pro Ser Ser Pro Val
85 90 95
His Lys Ala Glu Leu Glu Lys Lys Leu Ser Ser
100 105

<210> 114
<211> 155
<212> PRT
<213> Homo sapien

<400> 114
Glu Arg Tyr Asn Phe Pro Asn Pro Asn Pro Phe Val Glu Asp Asp Met
1 5 10 15
Asp Lys Asn Glu Ile Ala Ser Val Ala Tyr Arg Tyr Arg Arg Trp Lys
20 25 30
Leu Gly Asp Asp Ile Asp Leu Ile Val Arg Cys Glu His Asp Gly Val
35 40 45
Met Thr Gly Ala Asn Gly Glu Val Ser Phe Ile Asn Ile Lys Thr Leu
50 55 60
Asn Glu Trp Asp Ser Arg His Cys Asn Gly Val Asp Trp Arg Gln Lys
65 70 75 80
Leu Asp Ser Gln Arg Gly Ala Val Ile Ala Thr Glu Leu Lys Asn Asn
85 90 95
Ser Tyr Lys Leu Ala Arg Trp Thr Cys Cys Ala Leu Leu Ala Gly Ser
100 105 110
Glu Tyr Leu Lys Leu Gly Tyr Val Ser Arg Tyr His Val Lys Asp Ser
115 120 125
Ser Arg His Val Ile Leu Gly Thr Gln Gln Phe Lys Pro Asn Glu Phe
130 135 140
Ala Ser Gln Ile Asn Leu Ser Val Glu Asn Ala
145 150 155

<210> 115
<211> 129
<212> PRT
<213> Homo sapien

<400> 115
Gly Val Arg Trp Leu Thr Arg Ala Leu Val Ser Ala Gly Asn Pro Gly
1 5 10 15
Ala Trp Arg Gly Leu Ser Thr Ser Ala Ala Ala His Ala Ala Ser Arg
20 25 30
Ser Gln Ala Ala Ala Val Pro Val Glu Phe Gln Glu His His Leu Ser
35 40 45
Glu Val Gln Asn Met Ala Ser Glu Glu Lys Leu Glu Gln Val Leu Ser
50 55 60
Ser Met Lys Glu Asn Lys Val Ala Ile Ile Gly Lys Ile His Thr Pro
65 70 75 80
Met Glu Tyr Lys Gly Glu Leu Ala Ser Tyr Asp Met Arg Leu Arg Arg

```
                85                  90                  95
Lys Leu Asp Leu Phe Ala Asn Val Ile His Val Lys Ser Leu Pro Gly
            100                 105                 110
Tyr Met Thr Arg His Asn Asn Leu Asp Leu Val Ile Ile Arg Glu Gln
        115                 120                 125
Thr
```

<210> 116
<211> 550
<212> DNA
<213> Homo sapien

<400> 116

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gaattcggca ccagcctcag agccccccag cccggctacc acccccctgcg gaaaggtacc      60
catctgcatt cctgcccgtc gggacctggt ggacagtcca gcctccttgg cctctagcct     120
tggctcaccg ctgcctagag ccaaggagct catcctgaat gaccttcccg ccagcactcc     180
tgcctccaaa tcctgtgact cctccccgcc ccaggacgct tccaccccca ggcccagctc     240
ggccagtcac ctctgccagc ttgctgccaa gccagcacct tccacggaca gcgtcgccct     300
gaggagcccc ctgactctgt ccagtccctt caccacgtcc ttcagcctgg gctcccacag     360
cactctcaac ggagacctct ccgtgcccag ctcctacgtc agcctccacc tgtcccccca     420
ggtcagcagc tctgtggtgt acggacgctc ccccgtgatg gcatttgagt ctcatcccca     480
tctccgaggg ccatccgtct cttcctccct acccagcatc cctgggggaa agccggccta     540
ctccttccac                                                           550
```

<210> 117
<211> 154
<212> DNA
<213> Homo sapien

<400> 117

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ttctgaggga aagccgagtg gagtgggcga cccggcggcg gtgacaatga gttttcttgg      60
aggcttttt ggtcccattt gtgagattga tgttgccctt aatgatgggg aaaccaggaa     120
aatggcagaa atgaaaactg aggatggcaa agta                                154
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<210> 118
<211> 449
<212> DNA
<213> Homo sapien

<400> 118

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gaattcggca ccagggcccg cagcccgagt gtcgccgcca tggcttcgcc gcagctctgc      60
cgcgcgctgg tgtcggcgca atgggtggcg gaggcgctgc gggccccgcg cgctgggcag     120
cctctgcagc tgctggacgc ctcctggtac ctgccgaagc tggggcgcga cgcgcgacgc     180
gagttcgagg agcgccacat cccgggcgcc gctttcttcg acatcgacca gtgcagcgac     240
cgcacctcgc cctacgacca catgctgccc ggggccgagc atttcgcgga gtacgcaggc     300
cgcctgggcg tgggcgcggc cacccacgtc gtgatctacg acgccagcga ccagggcctc     360
tactccgccc cgcgcgtctg gtggatgttc cgcgccttcg gccaccacgc cgtgtcactg     420
cttgatggcg gcctccgcca ctggctgcg                                       449
```

<210> 119
<211> 642
<212> DNA
<213> Homo sapien

<400> 119
gaattcggca cgagcagtaa cccgaccgcc gctggtcttc gctggacacc atgaatcaca 60
ctgtccaaac cttcttctct cctgtcaaca gtggccagcc ccccaactat gagatgctca 120
aggaggagca cgaggtggct gtgctggggg cgccccacaa ccctgctccc ccgacgtcca 180
ccgtgatcca catccgcagc gagacctccg tgcccgacca tgtcgtctgg tccctgttca 240
acaccctctt catgaacccc tgctgcctgg gcttcatagc attcgcctac tccgtgaagt 300
ctagggacag gaagatggtt ggcgacgtga ccggggccca ggcctatgcc tccaccgcca 360
agtgcctgaa catctgggcc ctgattctgg gcatcctcat gaccattctg ctcatcgtca 420
tcccagtgct gatcttccag gcctatggat agatcaggag gcatcactgg ggccaggagc 480
tctgcccatg acctgtatcc cacgtactcc aacttccatt cctcgccctg ccccggagc 540
cgagtcctgt atcagccctt tatcctcaca cgcttttcta caatggcatt caataaagtg 600
cacgtgtttc tggtgaaaaa aaaaaaaaaa aaaaaactcg ag 642

<210> 120
<211> 603
<212> DNA
<213> Homo sapien

<400> 120
gaattcggca cgagccacaa cagccactac gactgcatcc actggatcca cggccacccc 60
gtcctccacc ccgggaacag ctcccctcc caaagtgctg accagcccgg ccaccacacc 120
catgtccacc atgtccacaa tccacacctc ctctacttcca gagaccaccc acacctccac 180
agtgctgacc accacagcca ccatgacaag ggccaccaat tccacggcca cacctctctc 240
cactctgggg acgacccgga tcctcactga gctgaccaca acagccacta caactgcagc 300
cactggatcc acggccaccc tgtcctccac cccagggacc acctggatcc tcacagagcc 360
gagcactata gccaccgtga tggtgcccac cggttccacg gccaccgcct cctccactct 420
gggaacagct cacacccca aagtggtgac caccatggcc actatgccca cagccactgc 480
ctccacggtt cccagctcgt ccaccgtggg gaccacccgc accctgcag tgctccccag 540
cagcctgcca accttcagcg tgtccactgt gtcctcctca gtcctcacca ccctgagacc 600
cac 603

<210> 121
<211> 178
<212> PRT
<213> Homo sapien

<400> 121
Ser Glu Pro Pro Ser Pro Ala Thr Thr Pro Cys Gly Lys Val Pro Ile
1 5 10 15
Cys Ile Pro Ala Arg Arg Asp Leu Val Asp Ser Pro Ala Ser Leu Ala
20 25 30
Ser Ser Leu Gly Ser Pro Leu Pro Arg Ala Lys Glu Leu Ile Leu Asn
35 40 45
Asp Leu Pro Ala Ser Thr Pro Ala Ser Lys Ser Cys Asp Ser Ser Pro
50 55 60
Pro Gln Asp Ala Ser Thr Pro Arg Pro Ser Ser Ala Ser His Leu Cys
65 70 75 80
Gln Leu Ala Ala Lys Pro Ala Pro Ser Thr Asp Ser Val Ala Leu Arg
85 90 95
Ser Pro Leu Thr Leu Ser Ser Pro Phe Thr Thr Ser Phe Ser Leu Gly
100 105 110
Ser His Ser Thr Leu Asn Gly Asp Leu Ser Val Pro Ser Ser Tyr Val
115 120 125
Ser Leu His Leu Ser Pro Gln Val Ser Ser Ser Val Val Tyr Gly Arg
130 135 140

Ser Pro Val Met Ala Phe Glu Ser His Pro His Leu Arg Gly Ser Ser
145 150 155 160
Val Ser Ser Ser Leu Pro Ser Ile Pro Gly Gly Lys Pro Ala Tyr Ser
165 170 175
Phe His

<210> 122
<211> 36
<212> PRT
<213> Homo sapien

<400> 122
Met Ser Phe Leu Gly Gly Phe Phe Gly Pro Ile Cys Glu Ile Asp Val
1 5 10 15
Ala Leu Asn Asp Gly Glu Thr Arg Lys Met Ala Glu Met Lys Thr Glu
20 25 30
Asp Gly Lys Val
35

<210> 123
<211> 136
<212> PRT
<213> Homo sapien

<400> 123
Met Ala Ser Pro Gln Leu Cys Arg Ala Leu Val Ser Ala Gln Trp Val
1 5 10 15
Ala Glu Ala Leu Arg Ala Pro Arg Ala Gly Gln Pro Leu Gln Leu Leu
20 25 30
Asp Ala Ser Trp Tyr Leu Pro Lys Leu Gly Arg Asp Ala Arg Arg Glu
35 40 45
Phe Glu Glu Arg His Ile Pro Gly Ala Ala Phe Phe Asp Ile Asp Gln
50 55 60
Cys Ser Asp Arg Thr Ser Pro Tyr Asp His Met Leu Pro Gly Ala Glu
65 70 75 80
His Phe Ala Glu Tyr Ala Gly Arg Leu Gly Val Gly Ala Ala Thr His
85 90 95
Val Val Ile Tyr Asp Ala Ser Asp Gln Gly Leu Tyr Ser Ala Pro Arg
100 105 110
Val Trp Trp Met Phe Arg Ala Phe Gly His His Ala Val Ser Leu Leu
115 120 125
Asp Gly Gly Leu Arg His Trp Leu
130 135

<210> 124
<211> 133
<212> PRT
<213> Homo sapien

<400> 124
Met Asn His Thr Val Gln Thr Phe Phe Ser Pro Val Asn Ser Gly Gln
1 5 10 15
Pro Pro Asn Tyr Glu Met Leu Lys Glu Glu His Glu Val Ala Val Leu
20 25 30

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

<210> 125
<211> 195
<212> PRT
<213> Homo sapien

<400> 125
Thr Thr Ala Thr Thr Thr Ala Ser Thr Gly Ser Thr Ala Thr Pro Ser
1 5 10 15
Ser Thr Pro Gly Thr Ala Pro Pro Pro Lys Val Leu Thr Ser Pro Ala
20 25 30
Thr Thr Pro Met Ser Thr Met Ser Thr Ile His Thr Ser Ser Thr Pro
35 40 45
Glu Thr Thr His Thr Ser Thr Val Leu Thr Thr Thr Ala Thr Met Thr
50 55 60
Arg Ala Thr Asn Ser Thr Ala Thr Pro Ser Ser Thr Leu Gly Thr Thr
65 70 75 80
Arg Ile Leu Thr Glu Leu Thr Thr Thr Ala Thr Thr Thr Ala Ala Thr
85 90 95
Gly Ser Thr Ala Thr Leu Ser Ser Thr Pro Gly Thr Thr Trp Ile Leu
100 105 110
Thr Glu Pro Ser Thr Ile Ala Thr Val Met Val Pro Thr Gly Ser Thr
115 120 125
Ala Thr Ala Ser Ser Thr Leu Gly Thr Ala His Thr Pro Lys Val Val
130 135 140
Thr Thr Met Ala Thr Met Pro Thr Ala Thr Ala Ser Thr Val Pro Ser
145 150 155 160
Ser Ser Thr Val Gly Thr Thr Arg Thr Pro Ala Val Leu Pro Ser Ser
165 170 175
Leu Pro Thr Phe Ser Val Ser Thr Val Ser Ser Ser Val Leu Thr Thr
180 185 190
Leu Arg Pro
195

<210> 126
<211> 509
<212> DNA
<213> Homo sapien

<400> 126
gaattcggca cgagccaagt acccccctgag gaatctgcag cctgcatctg agtacaccgt 60

554
875

atccctcgtg gccataaagg gcaaccaaga gagccccaaa gccactggag tctttaccac 120
actgcagcct gggagctcta ttccaccttа caacaccgag gtgactgaga ccaccattgt 180
gatcacatgg acgcctgctc caagaattgg ttttaagctg ggtgtacgac caagccaggg 240
aggagaggca ccacgagaag tgacttcaga ctcaggaagc atcgttgtgt ccggcttgac 300
tccaggagta gaatacgtct acaccatcca agtcctgaga gatggacagg aaagagatgc 360
gccaattgta aacaaagtgg tgacaccatt gtctccacca acaaacttgc atctggaggc 420
aaaccctgac actggagtgc tcacagtctc ctggagagga gcaccacccc agacattact 480
gggtatagaa ttaccacaac ccctacaaa 509

<210> 127
<211> 500
<212> DNA
<213> Homo sapien

<400> 127
gaattcggca cgagccactg atgtccgggg agtcagccag gagcttgggg aagggaagcg 60
cgccccggg gccggtcccg gagggctcga tccgcatcta cagcatgagg ttctgcccgt 120
ttgctgagag gacgcgtcta gtcctgaagg ccaagggaat caggcatgaa gtcatcaata 180
tcaacctgaa aaataagcct gagtggttct ttaagaaaaa tccctttggt ctggtgccag 240
ttctggaaaa cagtcagggt cagctgatct acgagtctgc catcacctgt gagtacctgg 300
atgaagcata cccagggaag aagctgttgc cggatgaccc ctatgagaaa gcttgccaga 360
agatgatctt agagttgttt tctaaggtgc catccttggt aggaagcttt attagaagcc 420
aaaataaaga agactatgct ggcctaaaag aagaatttcg taaagaattt accaagctag 480
aggaggttct gactaataag 500

<210> 128
<211> 500
<212> DNA
<213> Homo sapien

<400> 128
agctttcctc tgctgccgct cggtcacgct tgtgccctgaa ggaggaaaca gtgacagacc 60
tggagactgc agttctctat ccttcacaca gctctttcac catgcctgga tcacttcctt 120
tgaatgcaga agcttgctgg ccaaaagatg tgggaattgt tgcccttgag atctatttttc 180
cttctcaata tgttgatcaa gcagagttgg aaaaatatga tggtgtagat gctggaaagt 240
ataccattgg cttgggccag gccaagatgg gcttctgcac agatagagaa gatattaact 300
ctctttgcat gactgtggtt cagaatctta tggagagaaa taacctttcc tatgattgca 360
ttgggcggct ggaagttgga acagagacaa tcatcgacaa atcaaagtct gtgaagacta 420
atttgatgca gctgtttgaa gagtctgggа atacagatat agaaggaatc gacacaacta 480
atgcatgcta tggaggcaca 500

<210> 129
<211> 497
<212> DNA
<213> Homo sapien

<400> 129
gaattcggca cgagcagagg tctccagagc cttctctctc ctgtgcaaaa tggcaactct 60
taaggaaaaa ctcattgcac cagttgcgga agaagaggca acagttccaa acaataagat 120
cactgtagtg ggtgttggac aagttggtat ggcgtgtgct atcagcattc tgggaaagtc 180
tctggctgat gaacttgctc ttgtggatgt tttggaagat aagcttaaag gagaaatgat 240
ggatctgcag catgggagct tatttcttca gacacctaaa attgtggcag ataaagatta 300
ttctgtgacc gccaattcta agattgtagt ggtaactgca ggagtccgtc agcaagaagg 360
ggagagtcgg ctcaatctgg tgcagagaaa tgttaatgtc ttcaaattca ttattcctca 420
gatcgtcaag tacagtcctg attgcatcat aattgtggtt tccaacccag tggacattct 480

09117852 - 4230CT

tacgtatgtt acctgga 497

<210> 130
<211> 383
<212> DNA
<213> Homo sapien

<400> 130
gaattcggca cgagggccgc ggctgccgac tgggtccccc gccgctgtcg ccaccatggc 60
tccgcaccgc cccgcgcccg cgctgctttg cgcgctgtcc ctggcgctgt gcgcgctgtc 120
gctgcccgtc cgcgcggcca ctgcgtcgcg gggggcgtcc caggcggggg cgccccaggg 180
gcgggtgccc gaggcgcggc ccaacagcat ggtggtggaa caccccgagt tcctcaaggc 240
agggaaggag cctggcctgc agatctggcg tgtggagaaa gttcgatctg gtggcccgtg 300
cccaccaacc tttatggaga cttcttcacg ggcgacgcct acgtcatcct gaagacagtg 360
cagcttaaga acggaaaatc ttg 383

<210> 131
<211> 509
<212> DNA
<213> Homo sapien

<400> 131
gaattcggca cgagagtcag ccgcatcttc ttttgcgtcg ccagccgagc cacatcgctc 60
agacaccatg gggaaggtga aggtcggagt caacggattt ggtcgtattg ggcgcctggt 120
caccagggct gcttttaact ctggtaaagt ggatattgtt gccatcaatg acccattcat 180
tgacctcaac tacatggttt acatgttcca atatgattcc acccatggca aattccatgg 240
caccgtcaag gctgagaacg ggaagcttgt catcaatgga aatcccatca ccatcttcca 300
ggagcgagat ccctccaaaa tcaagtgggg cgatgctggc gctgagtacg tcgtggagtc 360
cactggcgct cttcaccacc atggagaagg ctggggctca tttgcagggg ggagccaaaa 420
gggtcatcat ctctgccccc tctgctgacg ccccatgttc cgtcatgggt gtgaaccatg 480
agaagtatga caacagcctc aagatcatc 509

<210> 132
<211> 357
<212> DNA
<213> Homo sapien

<400> 132
gaattcggca cgagtaagaa gaagccccta gaccacagct ccacaccatg gactggacct 60
ggaggatcct cttcttggtg gcagcagcaa caggtgccca ctcccaggtg caactggtgc 120
aatctgggtc tgagttgaag aagcctgggg cctcagtgaa ggtttcctgc aaggcttctg 180
gacacatctt cagtatctat ggtttgaatt gggtgcgaca ggcccctggt caaggccttg 240
agtggatggg atggatcaaa gtcgacactg cgaacccaac gtatgcccag ggcttcacag 300
gacgatttgt cttctccctg gacacctctg tcagcacggc atatctgcag atcagca 357

<210> 133
<211> 468
<212> DNA
<213> Homo sapien

<400> 133
gaattcggca cgaggcgccc cgaaccgtcc tcctgctgct ctcggcggcc ctggccctga 60
ccgagaccctg ggccggctcc cactccatga ggtatttcga caccgccatg tccccggccg 120
gccgcgggga gccccgcttc atctcagtgg gctacgtgga cgacacgcag ttcgtgaggt 180
tcgacagcga cgccgcgagt ccgagagagg agccgcgggc gccgtggata gagcaggagg 240

ggccggagta ttgggaccgg aacacacaga tcttcaagac caacacacag actgaccgag 300
agagcctgcg gaacctgcgc ggctactaca accagagcga ggccgggtct cacaccctcc 360
agagcatgta cggctgcgac gtggggccgg acgggcgcct cctccgcggg cataaccagt 420
acgcctacga cggcaaggat tacatcgccc tgaacgagga cctgcgct 468

<210> 134
<211> 214
<212> DNA
<213> Homo sapien

<400> 134
gaattcggca cgagctgcgt cctgctgagc tctgttctct ccagcacctc ccaaccccact 60
agtgcctggt tctcttgctc caccaggaac aagccaccat gtctcgccag tcaagtgtgt 120
ccttccggag cgggggcagt cgtagcttca gcaccgcctc tgccatcacc ccgtctgtct 180
cccgcaccag cttcacctcc gtgtcccggt ccgg 214

<210> 135
<211> 355
<212> DNA
<213> Homo sapien

<400> 135
gaattcggca cgaggtgaac aggacccgtc gccatgggcc gtgtgatccg tggacagagg 60
aagggcgccg ggtctgtgtt ccgcgcgcac gtgaagcacc gtaaaggcgc tgcgcgcctg 120
cgcgccgtgg atttcgctga gcggcacggc tacatcaagg gcatcgtcaa ggacatcatc 180
cacgacccgg gccgcggcgc gcccctcgcc aaggtggtct tccgggatcc gtatcggttt 240
aagaagcgga cggagctgtt cattgccgcc gagggcattc acacgggcca gtttgtgtat 300
tgcggcaaga aggccccagct caacattggc aatgtgctcc ctgtgggcac catgc 355

<210> 136
<211> 242
<212> DNA
<213> Homo sapien

<400> 136
gaattcggca cgagccagct cctaaccgcg agtgatccgc cagcctccgc ctcccgaggt 60
gcccggattg cagacggagt ctccttcact cagtgctcaa tggtgcccag gctggagtgc 120
agtggtgtga tctcggctcg ctacaacatc cacctcccag cagcctgcct tggcctccca 180
aagcgccgag attgcagctc tctgcccggc cgccaccccct gtctgggaag tgaggatgct 240
gt 242

<210> 137
<211> 424
<212> DNA
<213> Homo sapien

<400> 137
gaattcggca cgagcccaga tcccgaggtc cgacagcgcc cggcccagat ccccacgcct 60
gccaggagca agccgagagc cagccggccg gcgcactccg actccgagca gtctctgtcc 120
ttcgacccga gccccgcgcc ctttccggga cccctgcccc gcgggcagcg ctgccaacct 180
gccggccatg gagaccccgt cccagcggcg cgccacccgc agcggggcgc aggccagctc 240
cactccgctg tcgcccaccc gcatcacccg gctgcaggag aaggaggacc tgcaggagct 300
caatgatcgc ttggcggtct acatcgaccg tgtgcgctcg ctggaaacgg agaacgcagg 360
gctgcgcctt cgcatcaccg agtctgaaga ggtggtcagc cgcgaggtgt ccggcatcaa 420
ggcc 424

<210> 138
<211> 448
<212> DNA
<213> Homo sapien

<400> 138
gaattcggca cgagcctgtg ttccaggagc cgaatcagaa atgtcatcct caggcacgcc 60
agacttacct gtcctactca ccgatttgaa gattcaatat actaagatct tcataaacaa 120
tgaatggcat gattcagtga gtggcaagaa atttcctgtc tttaatcctg caactgagga 180
ggagctctgc caggtagaag aaggagataa ggaggatgtt gacaaggcag tgaaggccgc 240
aagacaggct tttcagattg gatccccgtg gcgtactatg gatgcttccg agaggggcg 300
actattatac aagttggctg atttaatcga aagagatcgt ctgctgctgg ccgacaatgg 360
agtcaatgaa tggtggaaaa ctctattcca atgcatatct gaatgattta gcaggctgca 420
tcaaaacatt gcgctactgt gcaggttg 448

<210> 139
<211> 510
<212> DNA
<213> Homo sapien

<400> 139
gaattcggca cgaggttccg tgcagctcac ggagaagcga atggacaaag tcggcaagta 60
ccccaaggag ctgcgcaagt gctgcgagga cggcatgcgg gagaacccca tgaggttctc 120
gtgccagcgc cggacccgtt tcatctccct ggcgaggcgt gcaagaaggt cttcctggac 180
tgctgcaact acatcacaga gctgcggcgg cagcacgcgc gggccagcca cctggcctgc 240
caggagtaac ctggatgagg acatcattgc agaagagaac atcgtttccc gaagtgagtt 300
cccagagagc tggctgtgga acgttgagga cttgaaagag ccaccgaaaa atggaatctc 360
tacgaagctc atgaatatat ttttgaaaga ctccatcacc acgtgggaga ttctggctgt 420
gagcatgtcg gacaagaaag ggatctgtgt ggcagacccc ttcgaggtca cagtaatgca 480
ggacttcttc atcgacctgc ggctacccta 510

<210> 140
<211> 360
<212> DNA
<213> Homo sapien

<400> 140
gaattcggca cgagcggtaa ctaccccggc tgcgcacagc tcggcgctcc ttcccgctcc 60
ctcacacacc ggcctcagcc cgcaccggca gtagaagatg gtgaaagaaa caacttacta 120
cgatgttttg ggggtcaaac ccaatgctac tcaggaagaa ttgaaaaagg cttataggaa 180
actggctttg aagtaccatc ctgataagaa cccaaatgaa ggagagaagt ttaaacagat 240
ttctcaagct tacgaagttc tctctgatgc aaagaaaagg gaattatatg acaaaggagg 300
agaacaggca attaaagagg gtggagcagg tggcggtttt ggctccccca tggacatctt 360

<210> 141
<211> 483
<212> DNA
<213> Homo sapien

<400> 141
gaattcggca cgagagcaga ggctgatctt tgctggaaaa cagctggaag atgggctgca 60
ccctgtctga ctacaacatc cagaaagagt ccacccctgca cctggtgctc cgtctcagag 120
gtgggatgca aatcttcgtg aagacactca ctggcaagac catcaccctt gaggtggagc 180
ccagtgacac catcgagaac gtcaaagcaa agatccagga caaggaaggc attcctcctg 240

854
879
879

accagcagag gttgatcttt gccggaaagc agctggaaga tgggcgcacc ctgtctgact 300
acaacatcca gaaagagtct accctgcacc tggtgctccg tctcagaggt gggatgcaga 360
tcttcgtgaa gaccctgact ggtaagacca tcaccctcga ggtggagccc agtgacacca 420
tcgagaatgt caaggcaaag atccaagata aggaaggcat tcctcctgat cagcagaggt 480
tga 483

<210> 142
<211> 500
<212> DNA
<213> Homo sapien

<400> 142
gaattcggca cgaggcggcg acgaccgccg ggagcgtgtg cagcggcggc ggcggaagtg 60
gccggcgagc ccggtccccg ccggcaccat gcttcccttg tcactgctga agacggctca 120
gaatcacccc atgttggtgg agctgaaaaa tggggagacg tacaatggac acctggtgag 180
ctgcgacaac tggatgaaca ttaacctgcg agaagtcatc tgcacgtcca gggacgggga 240
caagttctgg cggatgcccg agtgctacat ccgcggcagc accatcaagt acctgcgcat 300
ccccgacgag atcatcgaca tggtcaagga ggaggtggtg gccaagggcc gcggccgcgg 360
aggcctgcag cagcagaagc agcagaaagg ccgcggcatg ggcggcgctg gccgaggtgt 420
gtttggtggc cggggccgag gtgggatccc gggcacaggc agaagccagc cagagaagaa 480
gcctggcaga caggcgggca 500

<210> 143
<211> 400
<212> DNA
<213> Homo sapien

<400> 143
gaattcggca cgagctcgga tgtcagcagg cgtcccaacc cagcaggaac tggctcaatt 60
ctcagaagaa agcgatcggc cccgaggcag gaaggccggc tccggtgcag ggcgccgccgc 120
ctgcgggctg cttcgggcca gggtcgaccc gagggccagc gcaagcagcg gcaacaggag 180
cgccaggagg acatgaggct ctgcctgcag tcagcaactt ggaatattca gacttcagac 240
cagcatcaca gattataacc ctccgtaaat catctgcatc ccagctccca tcaaaagcca 300
gcctgaagga cccatggaca cgtgactcca gtgttctcaa caacatctta gatcaagttg 360
gtttgcacaa catttgcatc tacttgggac aaagcaagaa 400

<210> 144
<211> 243
<212> DNA
<213> Homo sapien

<400> 144
gaattcggca cgagccagct cctaaccgcg agtgatccgc cagcctccgc ctcccgaggt 60
gcccggattg cagacggagt ctccttcact cagtgctcaa tggtgcccag gctggagtgc 120
agtggtgtga tctcggctcg ctacaacatc cacctcccag cagcctgcct tggcctccca 180
aagtgccgag attgcagcct ctgcccggcc gtcaccccgt ctgggaagtg aggagcgttt 240
ctg 243

<210> 145
<211> 450
<212> DNA
<213> Homo sapien

<400> 145
gaattcggca cgaggacagc aggaccgtgg aggccgcggc aggggtggca gtggtggcgg 60

cggcggcggc ggcggtggtg gttacaaccg cagcagtggt ggctatgaac ccagaggtcg 120
tggaggtggc cgtggaggca gaggtggcat gggcggaagt gaccgtggtg gcttcaataa 180
atttggtggc cctcgggacc aaggatcacg tcatgactcc gaacaggata attcagacaa 240
caacaccatc tttgtgcaag gcctgggtga gaatgttaca attgagtctg tggctgatta 300
cttcaagcag attggtatta ttaagacaaa caagaaaacg ggacagccca tgattaattt 360
gtacacagac agggaaactg gcaagctgaa gggagaggca acggtctctt ttgatgaccc 420
accttcagct aaagcagcct attgactggt 450

<210> 146
<211> 451
<212> DNA
<213> Homo sapien

<400> 146
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<211> 400
<212> DNA
<213> Homo sapien

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<211> 503
<212> DNA
<213> Homo sapien

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<211> 1061

<212> DNA
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<212> DNA
<213> Homo sapien

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<212> DNA
<213> Homo sapien

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561
882
882

US006232459B1

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<211> 2179
<212> DNA
<213> Homo sapien

502
855
883

09/742,855 12/20/2000

<400> 152

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<211> 2109
<212> DNA
<213> Homo sapien

<400> 153

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<211> 1411
<212> DNA
<213> Homo sapien

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<210> 155
<211> 678
<212> DNA
<213> Homo sapien

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<211> 2668
<212> DNA
<213> Homo sapien

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886
886

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<210> 157
<211> 2313
<212> DNA
<213> Homo sapien

<400> 157
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<210> 158
<211> 2114
<212> DNA
<213> Homo sapien

<400> 158
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gacacctcag cagcgcacca ggtggtttta ggagaaaact tgatagccac agccctttgt 180
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cgggagtact tcta 2114

<210> 159

<211> 278
<212> DNA
<213> Homo sapien

<400> 159
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tctctatgca gaaggaaata tcacctatat gacatcatca tcatctattg atacttgctg 240
gcagtgctaa taatggtttt aatgccaatt tgtaagaa 278

<210> 160
<211> 848
<212> DNA
<213> Homo sapien

<400> 160
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aactcgag 848

<210> 161
<211> 432
<212> DNA
<213> Homo sapien

<400> 161
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cttgagagag cgaggccggg agctgaccac tcagaggcag ctgatgcagg aacgggcaga 120
ggaagggaag ggcccaagta aagcacagcg cgggagccta gagcacatga agctgatcct 180
gcgtgataag gagaaggagg tggaatgtca gcaggagcat atccatgaac tccaggagct 240
caaagaccag ctggagcagc agctccaggg cctgcacagg aaggtaggtg agaccagcct 300
cctcctgtcc cagcgagagc aggaaatagt ggtcctgcag cagcaactgc aggaagccag 360
ggaacaaggg gagctgaagg agcagtcact tcagagtcaa ctggatgagg cccagagagc 420
cctagcccag ag 432

<210> 162
<211> 433
<212> DNA
<213> Homo sapien

<400> 162
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ttcaagctgg gagagggctc tagtccctgg ttctgaacac tctggggttc tcgggtgcag 120
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actggaaaat tacgtaaact ggaaaagatt cggcaggatg atacgagttc atccatcaat 420
ttcctgactc gag 433

<210> 163
<211> 432
<212> DNA
<213> Homo sapien

<400> 163
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cacctacagt gagtgtgaga ccttcacgga cgaggacacc agcaccctgg tgcaccctga 120
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ccccgctttc ctcacgccca gtccgacaaa gcggctctcc agcaegaagg tggcaaggta 420
cctgcaccag tc 432

<210> 164
<211> 395
<212> DNA
<213> Homo sapien

<400> 164
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atgaccccat cctatgaaat tagagcagtg gggaacaaaa acaggcagaa attcatgtgt 120
gaggttcagg tggaaggtta taattacact ggcatgggaa attccaccaa taaaaaagat 180
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ggttcctgaa aaaaaaaaaa aaaaaaaaac tcgag 395

<210> 165
<211> 503
<212> DNA
<213> Homo sapien

<400> 165
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acagctcggc gctccttccc gctccctcac acaccggcct cagcccgcac cggcagtaga 120
agatggtgaa agaaacaact tactacgatg ttttgggggt caaacccaat gctactcagg 180
aagaattgaa aaaggcttat aggaaactgg ccttgaagta ccatcctgat aagaacccaa 240
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gttttggctc ccccatggac atctttgata tgtttttttgg aggaggagga aggatgcaga 420
gagaaaggag aggtaaaaat gttgtacatc agctctcagt aaccctagaa gacttatata 480
atggtgcaac aagaaaactg gct 503

<210> 166
<211> 893

09712935 - 050201

<212> DNA
<213> Homo sapien

<400> 166
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gctgggccag aggtgccaac atggggaaac tgaggctcgg ctcggaaggg tgagagtgag 120
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aacggaagta gttgtaggta gtggtatggt ggtatgagtc tgttttctgt tacttataac 240
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ggaagatgga gacaccctct gggggtcctc tctgagtcaa atccagtggt gggtaattgt 840
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<210> 167
<211> 549
<212> DNA
<213> Homo sapien

<400> 167
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gcgcgcccgc ctgcagctgg agctgagcaa agtgcgtgaa gagtttaagg agctgaaagc 540
gcgcaatac 549

<210> 168
<211> 547
<212> DNA
<213> Homo sapien

<400> 168
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tcaaaatgga ggaagaggagc ggcgcgcccg gcgtgccgag cggcaacggg gctccgggcc 120
ctaagggtga aggagaacga cctgctcaga atgaggaagag gaaggaggaaa aacataaaaa 180
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caaacatacc ttttgatgtg aaatggcagt cacttaaaga cctggttaaa gaaaaagttg 300
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caatgcaaaa ggctggaaga cttggaagca cagtatttgt agcaaatctg gattataaag 540
ttggctg 547

<210> 169

<211> 547
<212> DNA
<213> Homo sapien

<400> 169
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aaaccte 547

<210> 170
<211> 838
<212> DNA
<213> Homo sapien

<400> 170
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gagcttgggg aagggaagcg cgcccccggg gccggtcccg gagggctcga tccgcatcta 120
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aggaagcttt attagaagcc aaaataaaga agactatgat ggcctaaaag aagaatttcg 480
taaagaattt accaagctag aggaggttct gactaataag aagacgacct tctttggtgg 540
caattctatc tctatgattg attacctcat ctggccctgg tttgaacggc tggaagcaat 600
gaagttaaat gagtgtgtag accacactcc aaaactgaaa ctgtggatgg cagccatgaa 660
ggaagatccc acagtctcag ccctgcttac tagtgagaaa gactggcaag gtttcctaga 720
gctctactta cagaacagcc ctgaggcctg tgactatggg ctctgaaggg ggcaggagtc 780
agcaataaag ctatgtctga tatttttctt cactaaaaaa aaaaaaaaaa aactcgag 838

<210> 171
<211> 547
<212> DNA
<213> Homo sapien

<400> 171
gaattcggca ccagcgggat ttgggtcgca gttcttgttt gtggattgct gtgatcgtca 60
cttgacaatg cagatcttcg tgaagactct gactggtaag accatcaccc tcgaggttga 120
gcccagtgac accatcgaga atgtcaaggc aaagatccaa gataaggaag gcatccctcc 180
tgaccagcag aggctgatct ttgctggaaa acagctggaa gatgggcgca ccctgtctga 240
ctacaacatc cagaaagagt ccaccctgca cctggtgctc cgtctcagag gtgggatgca 300
aatcttcgtg aagacactca ctggcaagac catcaccctt gaggtcgagc ccagtgacac 360
catcgagaac gtcaaagcaa agatccagga caaggaaggc attcctcctg accagcagag 420
gttgatcttt gccggaaagc agctggaaga tgggcgcacc ctgtctgact acaacatcca 480
gaaagagtct accctgcacc tggtgctccg tctcagaggt gggatgcaga tcttcgtgaa 540
gaccctg 547

<210> 172

<211> 608
<212> DNA
<213> Homo sapien

<400> 172
gaattcggca ccagagactt ctcccctctga ggcctgcgca cccctcctca tcagcctgtc 60
caccctcatc tacaatggtg ccctgccatg tcagtgcaac cctcaaggtt cactgagttc 120
tgagtgcaac cctcatggtg gtcagtgcct gtgcaagcct ggagtggttg ggcgccgctg 180
tgaccctctgt gcccctggct actatggctt tggccccaca ggctgtcaag gcgcttgcct 240
gggctgccgt gatcacacag ggggtgagca ctgtgaaagg tgcattgctg gtttccacgg 300
ggacccacgg ctgccatatg ggggccagtg ccggccctgt ccctgtcctg aaggccctgg 360
gagccaacgg cactttgcta cttcttgcca ccaggatgaa tattcccagc agattgtgtg 420
ccactgccgg gcaggctata cggggctgcg atgtgaagct tgtgcccctg ggcactttgg 480
ggacccatca aggccaggtg gccggtgcca actgtgtgag tgcagtggga acattgaccc 540
aatggatcct gatgcctgtg acccccacac ggggcaatgc ctgcgctgtt tacaccacac 600
agagggtc 608

<210> 173
<211> 543
<212> DNA
<213> Homo sapien

<400> 173
gaattcggca ccagagatca tccgccagca gggtctggcc tcctacgact acgtgcgccg 60
ccgcctcacg gctgaggacc tgttcgaggc tcggatcatc ttctctgaga cctacgacct 120
gctccgggag ggcgaccagg gcctccgtga ggctctgcag gcggagtccg cctggtgcta 180
cctctatggc acgggctccg tggctggtgt ctacctgccc ggttccaggc agacactgag 240
catctaccag gctctcaaga aagggctgct gagtgccgag gtggcccgcc tgctgctgga 300
ggcacaggca gccacaggct tcctgctgga cccggtgaag ggggaacggc tgactgtgga 360
tgaagctgtg cggaagggcc tcgtggggcc cgaactgcac gaccgcctgc tctcggctga 420
gcgggcggtc accggctacc gtgacccctа caccgagcag accatctcgc tcttccaggc 480
catgaagaag gaactgatcc ctactgagga ggccctgcgg ctgtggatgc ccagctggcc 540
acc 543

<210> 174
<211> 548
<212> DNA
<213> Homo sapien

<400> 174
gaattcggca cgagaaatgg cggcaggggt cgaagcggcg gcggaggtgg cggcgacgga 60
gatcaaaatg gaggaagaga gcggcgcgcc cggcgtgccg agcggcaacg gggctccggg 120
ccctaagggt gaaggagaac gacctgctca gaatgagaag aggaaggaga aaaacataaa 180
aagaggaggc aatcgctttg agccatatgc caatccaact aaaagataca gagccttcat 240
tacaaacata ccttttgatg tgaaatggca gtcacttaaa gacctggtta aagaaaaagt 300
tggtgaggta acatacgtgg agctcttaat ggacgctgaa ggaaagtcaa ggggatgtgc 360
tgttgttgaa ttcaagatgg aagagagcat gaaaaaagct gcggaagtcc taaacaagca 420
tagtctgagc ggaagaccac tgaaagtcaa agaagatcct gatggtgaac atgccaggag 480
agcaatgcaa aaggtgatgg ctacgactgg tgggatgggt atgggaccag gtggcccagg 540
aatgatta 548

<210> 175
<211> 604
<212> DNA
<213> Homo sapien

572
893
893

<400> 175
gaattcggca ccagaggacc tccaggacat gttcatcgtc cataccatcg aggagattga 60
gggcctgatc tcagcccatg accagttcaa gtccaccctg ccggacgccg atagggagcg 120
cgaggccatc ctggccatcc acaaggaggc ccagaggatc gctgagagca accacatcaa 180
gctgtcgggc agcaacccct acaccaccgt caccccgcaa atcatcaact ccaagtggga 240
gaaggtgcag cagctggtgc caaaacggga ccatgccctc ctggaggagc agagcaagca 300
gcagtccaac gagcacctgc gccgccagtt cgccagccag gccaatgttg tggggccctg 360
gatccagacc aagatggagg agatcgggcg catctccatt gagatgaacg ggaccctgga 420
ggaccagctg agccacctga agcagtatga acgcagcatc gtggactaca agcccaacct 480
ggacctgctg gagcagcagc accagcttat ccaggaggcc ctcatcttcg acaacaagca 540
caccaactat accatggagc acatccgcgt gggctgggag cagctgctca ccaccattgc 600
ccgg 604

<210> 176
<211> 486
<212> DNA
<213> Homo sapien

<400> 176
gaattcggca ccagccaagc tcactattga atccacgccg ttcaatgtcg cagaggggaa 60
ggaggttctt ctactcgccc acaacctgcc ccagaatcgt attggttaca gctggtacaa 120
aggcgaaaga gtggatggca acagtctaat tgtaggatat gtaataggaa ctcaacaagc 180
taccccaggg cccgcataca gtggtcgaga gacaatatac cccaatgcat ccctgctgat 240
ccagaacgtc acccagaatg acacaggatt ctatacccta caagtcataa agtcagatct 300
tgtgaatgaa gaagcaaccg gacagttcca tgtatacccg gagctgccca agccctccat 360
ctccagcaac aactccaacc ccgtggagga caaggatgct gtggccttca cctgtgaacc 420
tgaggttcag aacacaacct acctgtggtg ggtaaatggt cagagcctcc cggtcagtcc 480
caaggc 486

<210> 177
<211> 387
<212> DNA
<213> Homo sapien

<400> 177
gaattcggca ccagggacag cagaccagac agtcacagca gccttgacaa aacgttcctg 60
gaactcaagc tcttctccac agaggaggac agagcagaca gcagagacca tggagtctcc 120
ctcggccccc ccccacagat ggtgcatccc ctggcagagg ctcctgctca cagcctcact 180
tctaaccttc tggaacccgc ccaccactgc caagctcact attgaatcca cgccgttcaa 240
tgtcgcagag gggaaggagg tgcttctact tgtccacaat ctgccccagc atcttttttgg 300
ctacagctgg tacaaaggtg aaagagtgga tggcaaccgt caaattatag gatatgtaat 360
aggaactcaa caagctaccc cagggcc 387

<210> 178
<211> 440
<212> DNA
<213> Homo sapien

<400> 178
gaattcggca cgaggagaag cagaaaaaca aggaatttag ccagacttta gaaaatgaga 60
aaaatacctt actgagtcag atatcaacaa aggatggtga actaaaaatg cttcaggagg 120
aagtaaccaa aatgaacctg ttaaatcagc aaatccaaga agaactctct agagttacca 180
aactaaagga gacagcagaa gaagagaaag atgatttgga agagaggctt atgaatcaat 240
tagcagaact taatggaagc attgggaatt actgtcagga tgttacagat gcccaaataa 300

aaaatgagct attggaatct gaaatgaaga accttaaaaa gtgtgtgagt gaattggaag 360
aagaaaagca gcagttagtc aaggaaaaaa ctaaggtgga atcagaaata cgaaaggaat 420
atttggagaa aatacaaggt 440

<210> 179
<211> 443
<212> DNA
<213> Homo sapien

<400> 179
gaattcggca ccagcggggg gctacggcgg cggctacggc ggcgtcctga ccgcgtccga 60
cgggctgctg gcgggcaacg agaagctaac catgcagaac ctcaacgacc gcctggcctc 120
ctacctggac aaggtgcgcg ccctggaggc ggccaacggc gagctagagg tgaagatccg 180
cgactggtac cagaagcagg ggcctgggcc ctcccgcgac tacagccact actacacgac 240
catccaggac ctgcgggaca agattcttgg tgccaccatt gagaactcca ggattgtcct 300
gcagatcgac aacgcccgtc tggctgcaga tgacttccga accaagtttg agacggaaca 360
ggctctgcgc atgagcgtgg aggccgacat caacggcctg cgcagggtgc tggatgagct 420
gaccctggcc aggaccgacc tgg 443

<210> 180
<211> 403
<212> DNA
<213> Homo sapien

<400> 180
gaattcggca cgaggttatg agagtcgact tcaatgttcc tatgaagaac aaccagataa 60
caaacaacca gaggattaag gctgctgtcc caagcatcaa attctgcttg gacaatggag 120
ccaagtcggt agtccttatg agccacctag gccggcctga tggtgtgccc atgcctgaca 180
agtactcctt agagccagtt gctgtagaac tcagatctct gctgggcaag gatgttctgt 240
tcttgaagga ctgtgtaggc ccagaagtgg agaaagcctg tgccaaccca gctgctgggt 300
ctgtcatcct gctggagaac ctccgctttc atgtggagga agaagggaag ggaaaagatg 360
cttctgggaa caaggttaaa gccgagccag ccaaaataga agc 403

<210> 181
<211> 493
<212> DNA
<213> Homo sapien

<400> 181
gaattcggca ccagcagagg tctccagagc cttctctctc ctgtgcaaaa tggcaactct 60
taaggaaaaa ctcattgcac cagttgcgga agaagaggca acagttccaa acaataagat 120
cactgtagtg ggtgttggac aagttggtat ggcgtgtgct atcagcattc tgggaaagtc 180
tctggctgat gaacttgctc ttgtggatgt tttggaagat aagcttaaag gagaaatgat 240
ggatctgcag catgggagct tatttcttca gacacctaaa attgtggcag ataaagatta 300
ttctgtgacc gccaattcta agattgtagt ggtaactgca ggagtccgtc agcaagaagg 360
ggagagtcgg ctcaatctgg tgcagagaaa tgttaatgtc ttcaaattca ttattcctca 420
gatcgtcaag tacagtcctg attgcatcat aattgtggtt tccaacccag tggacattct 480
tacgtatgtt acc 493

<210> 182
<211> 209
<212> PRT
<213> Homo sapien

<400> 182

09172525.1423500

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

<210> 183
<211> 255
<212> PRT
<213> Homo sapien

<400> 183

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

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

<210> 184
<211> 188
<212> PRT
<213> Homo sapien

<400> 184
Leu Ser Gly Ser Cys Ile Arg Arg Glu Gln Thr Pro Glu Lys Glu Lys
1 5 10 15
Gln Val Val Leu Phe Glu Glu Ala Ser Trp Thr Cys Thr Pro Ala Cys
20 25 30
Gly Asp Glu Pro Arg Thr Val Ile Leu Leu Ser Ser Met Leu Ala Asp
35 40 45
His Arg Leu Lys Leu Glu Asp Tyr Lys Asp Arg Leu Lys Ser Gly Glu
50 55 60
His Leu Asn Pro Asp Gln Leu Glu Ala Val Glu Lys Tyr Glu Glu Val
65 70 75 80
Leu His Asn Leu Glu Phe Ala Lys Glu Leu Gln Lys Thr Phe Ser Gly
85 90 95
Leu Ser Leu Asp Leu Leu Lys Ala Gln Lys Lys Ala Gln Arg Arg Glu
100 105 110
His Met Leu Lys Leu Glu Ala Glu Lys Lys Lys Leu Arg Thr Ile Leu
115 120 125
Gln Val Gln Tyr Val Leu Gln Asn Leu Thr Gln Glu His Val Gln Lys
130 135 140
Asp Phe Lys Gly Gly Leu Asn Gly Ala Val Tyr Leu Pro Ser Lys Glu
145 150 155 160
Leu Asp Tyr Leu Ile Lys Phe Ser Lys Leu Thr Cys Pro Glu Arg Asn
165 170 175
Glu Ser Leu Arg Gln Thr Leu Glu Gly Ser Thr Val
180 185

<210> 185
<211> 746
<212> PRT
<213> Homo sapien

<400> 185
Asp Lys His Leu Lys Asp Leu Leu Ser Lys Leu Leu Asn Ser Gly Tyr
1 5 10 15
Phe Glu Ser Ile Pro Val Pro Lys Asn Ala Lys Glu Lys Glu Val Pro
20 25 30
Leu Glu Glu Glu Met Leu Ile Gln Ser Glu Lys Lys Thr Gln Leu Ser

```
        35                  40                  45
Lys Thr Glu Ser Val Lys Glu Ser Glu Ser Leu Met Glu Phe Ala Gln
    50                  55                  60
Pro Glu Ile Gln Pro Gln Glu Phe Leu Asn Arg Arg Tyr Met Thr Glu
65                  70                  75                  80
Val Asp Tyr Ser Asn Lys Gln Gly Glu Glu Gln Pro Trp Glu Ala Asp
                85                  90                  95
Tyr Ala Arg Lys Pro Asn Leu Pro Lys Arg Trp Asp Met Leu Thr Glu
            100                 105                 110
Pro Asp Gly Gln Glu Lys Lys Gln Glu Ser Phe Lys Ser Trp Glu Ala
        115                 120                 125
Ser Gly Lys His Gln Glu Val Ser Lys Pro Ala Val Ser Leu Glu Gln
    130                 135                 140
Arg Lys Gln Asp Thr Ser Lys Leu Arg Ser Thr Leu Pro Glu Glu Gln
145                 150                 155                 160
Lys Lys Gln Glu Ile Ser Lys Ser Lys Pro Ser Pro Ser Gln Trp Lys
                165                 170                 175
Gln Asp Thr Pro Lys Ser Lys Ala Gly Tyr Val Gln Glu Glu Gln Lys
            180                 185                 190
Lys Gln Glu Thr Pro Lys Leu Trp Pro Val Gln Leu Gln Lys Glu Gln
        195                 200                 205
Asp Pro Lys Lys Gln Thr Pro Lys Ser Trp Thr Pro Ser Met Gln Ser
    210                 215                 220
Glu Gln Asn Thr Thr Lys Ser Trp Thr Thr Pro Met Cys Glu Glu Gln
225                 230                 235                 240
Asp Ser Lys Gln Pro Glu Thr Pro Lys Ser Trp Glu Asn Asn Val Glu
                245                 250                 255
Ser Gln Lys His Ser Leu Thr Ser Gln Ser Gln Ile Ser Pro Lys Ser
            260                 265                 270
Trp Gly Val Ala Thr Ala Ser Leu Ile Pro Asn Asp Gln Leu Leu Pro
        275                 280                 285
Arg Lys Leu Asn Thr Glu Pro Lys Asp Val Pro Lys Pro Val His Gln
    290                 295                 300
Pro Val Gly Ser Ser Ser Thr Leu Pro Lys Asp Pro Val Leu Arg Lys
305                 310                 315                 320
Glu Lys Leu Gln Asp Leu Met Thr Gln Ile Gln Gly Thr Cys Asn Phe
                325                 330                 335
Met Gln Glu Ser Val Leu Asp Phe Asp Lys Pro Ser Ser Ala Ile Pro
            340                 345                 350
Thr Ser Gln Pro Pro Ser Ala Thr Pro Gly Ser Pro Val Ala Ser Lys
        355                 360                 365
Glu Gln Asn Leu Ser Ser Gln Ser Asp Phe Leu Gln Glu Pro Leu Gln
    370                 375                 380
Val Phe Asn Val Asn Ala Pro Leu Pro Pro Arg Lys Glu Gln Glu Ile
385                 390                 395                 400
Lys Glu Ser Pro Tyr Ser Pro Gly Tyr Asn Gln Ser Phe Thr Thr Ala
                405                 410                 415
Ser Thr Gln Thr Pro Pro Gln Cys Gln Leu Pro Ser Ile His Val Glu
            420                 425                 430
Gln Thr Val His Ser Gln Glu Thr Ala Ala Asn Tyr His Pro Asp Gly
        435                 440                 445
Thr Ile Gln Val Ser Asn Gly Ser Leu Ala Phe Tyr Pro Ala Gln Thr
    450                 455                 460
Asn Val Phe Pro Arg Pro Thr Gln Pro Phe Val Asn Ser Arg Gly Ser
465                 470                 475                 480
```

Val Arg Gly Cys Thr Arg Gly Gly Arg Leu Ile Thr Asn Ser Tyr Arg
485 490 495
Ser Pro Gly Gly Tyr Lys Gly Phe Asp Thr Tyr Arg Gly Leu Pro Ser
500 505 510
Ile Ser Asn Gly Asn Tyr Ser Gln Leu Gln Phe Gln Ala Arg Glu Tyr
515 520 525
Ser Gly Ala Pro Tyr Ser Gln Arg Asp Asn Phe Gln Gln Cys Tyr Lys
530 535 540
Arg Gly Gly Thr Ser Gly Gly Pro Arg Ala Asn Ser Arg Ala Gly Trp
545 550 555 560
Ser Asp Ser Ser Gln Val Ser Ser Pro Glu Arg Asp Asn Glu Thr Phe
565 570 575
Asn Ser Gly Asp Ser Gly Gln Gly Asp Ser Arg Ser Met Thr Pro Val
580 585 590
Asp Val Pro Val Thr Asn Pro Ala Ala Thr Ile Leu Pro Val His Val
595 600 605
Tyr Pro Leu Pro Gln Gln Met Arg Val Ala Phe Ser Ala Ala Arg Thr
610 615 620
Ser Asn Leu Ala Pro Gly Thr Leu Asp Gln Pro Ile Val Phe Asp Leu
625 630 635 640
Leu Leu Asn Asn Leu Gly Glu Thr Phe Asp Leu Gln Leu Gly Arg Phe
645 650 655
Asn Cys Pro Val Asn Gly Thr Tyr Val Phe Ile Phe His Met Leu Lys
660 665 670
Leu Ala Val Asn Val Pro Leu Tyr Val Asn Leu Met Lys Asn Glu Glu
675 680 685
Val Leu Val Ser Ala Tyr Ala Asn Asp Gly Ala Pro Asp His Glu Thr
690 695 700
Ala Ser Asn His Ala Ile Leu Gln Leu Phe Gln Gly Asp Gln Ile Trp
705 710 715 720
Leu Arg Leu His Arg Gly Ala Ile Tyr Gly Ser Ser Trp Lys Tyr Ser
725 730 735
Thr Phe Ser Gly Tyr Leu Leu Tyr Gln Asp
740 745

<210> 186
<211> 705
<212> PRT
<213> Homo sapien

<400> 186
Ala Leu Leu Asn Val Arg Gln Pro Pro Ser Thr Thr Thr Phe Val Leu
1 5 10 15
Asn Gln Ile Asn His Leu Pro Pro Leu Gly Ser Thr Ile Val Met Thr
20 25 30
Lys Thr Pro Pro Val Thr Thr Asn Arg Gln Thr Ile Thr Leu Thr Lys
35 40 45
Phe Ile Gln Thr Thr Ala Ser Thr Arg Pro Ser Val Ser Ala Pro Thr
50 55 60
Val Arg Asn Ala Met Thr Ser Ala Pro Ser Lys Asp Gln Val Gln Leu
65 70 75 80
Lys Asp Leu Leu Lys Asn Asn Ser Leu Asn Glu Leu Met Lys Leu Lys
85 90 95
Pro Pro Ala Asn Ile Ala Gln Pro Val Ala Thr Ala Ala Thr Asp Val
100 105 110

576
846
899

WO 92/14829 PCT/US92/01403

```
Ser Asn Gly Thr Val Lys Lys Glu Ser Ser Asn Lys Glu Gly Ala Arg
        115                 120                 125
Met Trp Ile Asn Asp Met Lys Met Arg Ser Phe Ser Pro Thr Met Lys
    130                 135                 140
Val Pro Val Val Lys Glu Asp Asp Glu Pro Glu Glu Glu Asp Glu Glu
145                 150                 155                 160
Glu Met Gly His Ala Glu Thr Tyr Ala Glu Tyr Met Pro Ile Lys Leu
                165                 170                 175
Lys Ile Gly Leu Arg His Pro Asp Ala Val Val Glu Thr Ser Ser Leu
            180                 185                 190
Ser Ser Val Thr Pro Pro Asp Val Trp Tyr Lys Thr Ser Ile Ser Glu
        195                 200                 205
Glu Thr Ile Asp Asn Gly Trp Leu Ser Ala Leu Gln Leu Glu Ala Ile
    210                 215                 220
Thr Tyr Ala Ala Gln Gln His Glu Thr Phe Leu Pro Asn Gly Asp Arg
225                 230                 235                 240
Ala Gly Phe Leu Ile Gly Asp Gly Ala Gly Val Gly Lys Gly Arg Thr
                245                 250                 255
Ile Ala Gly Ile Ile Tyr Glu Asn Tyr Leu Leu Ser Arg Lys Arg Ala
            260                 265                 270
Leu Trp Phe Ser Val Ser Asn Asp Leu Lys Tyr Asp Ala Glu Arg Asp
        275                 280                 285
Leu Arg Asp Ile Gly Ala Lys Asn Ile Leu Val His Ser Leu Asn Lys
    290                 295                 300
Phe Lys Tyr Gly Lys Ile Ser Ser Lys His Asn Gly Ser Val Lys Lys
305                 310                 315                 320
Gly Val Ile Phe Ala Thr Tyr Ser Ser Leu Ile Gly Glu Ser Gln Ser
                325                 330                 335
Gly Gly Lys Tyr Lys Thr Arg Leu Lys Gln Leu Leu His Trp Cys Gly
            340                 345                 350
Asp Asp Phe Asp Gly Val Ile Val Phe Asp Glu Cys His Lys Ala Lys
        355                 360                 365
Asn Leu Cys Pro Val Gly Ser Ser Lys Pro Thr Lys Thr Gly Leu Ala
    370                 375                 380
Val Leu Glu Leu Gln Asn Lys Leu Pro Lys Ala Arg Val Val Tyr Ala
385                 390                 395                 400
Ser Ala Thr Gly Ala Ser Glu Pro Arg Asn Met Ala Tyr Met Asn Arg
                405                 410                 415
Leu Gly Ile Trp Gly Glu Gly Thr Pro Phe Arg Glu Phe Ser Asp Phe
            420                 425                 430
Ile Gln Ala Val Glu Arg Arg Gly Val Gly Ala Met Glu Ile Val Ala
        435                 440                 445
Met Asp Met Lys Leu Arg Gly Met Tyr Ile Ala Arg Gln Leu Ser Phe
    450                 455                 460
Thr Gly Val Thr Phe Lys Ile Glu Glu Val Leu Leu Ser Gln Ser Tyr
465                 470                 475                 480
Val Lys Met Tyr Asn Lys Ala Val Lys Leu Trp Val Ile Ala Arg Glu
                485                 490                 495
Arg Phe Gln Gln Ala Ala Asp Leu Ile Asp Ala Glu Gln Arg Met Lys
            500                 505                 510
Lys Ser Met Trp Gly Gln Phe Trp Ser Ala His Gln Arg Phe Phe Lys
        515                 520                 525
Tyr Leu Cys Ile Ala Ser Lys Val Lys Arg Val Val Gln Leu Ala Arg
    530                 535                 540
Glu Glu Ile Lys Asn Gly Lys Cys Val Val Ile Gly Leu Gln Ser Thr
```

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

<210> 187
<211> 595
<212> PRT
<213> Homo sapien

<400> 187

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

```
    210                 215                 220
Glu Glu Ala Gly Ala Ser Ala Pro Glu Ser Gln Ala Gly Gly Gly Pro
225                 230                 235                 240
Arg Gly Arg Ala Arg Gly Pro Arg Gln Gln Gly Arg Arg Arg His Gly
                245                 250                 255
Thr Gln Arg Arg Arg Gly Pro Pro Gln Ala Arg Glu Glu Gly Pro Arg
            260                 265                 270
Asp Ala Thr Thr Ile Leu Gly Leu Gly Thr Pro Ser Gly Glu Gln Arg
        275                 280                 285
Ala Asp Gln Ser Gln Ala Leu Pro Ala Leu Ala Gly Ala Ala Ala Ala
    290                 295                 300
His Ala His Ala Ile Pro Gly Ala Gly Pro Ala Ala Ala Pro Val Gly
305                 310                 315                 320
Gly Arg Gly Arg Arg Gly Gly Trp Arg Gly Gly Arg Arg Gly Gly Ser
                325                 330                 335
Ala Gly Ala Gly Gly Gly Gly Arg Gly Gly Arg Gly Arg Gly Arg Gly
            340                 345                 350
Gly Gly Arg Gly Gly Gly Gly Ala Gly Arg Gly Gly Gly Ala Ala Gly
        355                 360                 365
Pro Arg Glu Gly Ala Ser Ser Pro Gly Ala Arg Arg Gly Glu Gln Arg
    370                 375                 380
Arg Arg Gly Arg Gly Pro Pro Ala Ala Gly Ala Ala Gln Val Ser Ala
385                 390                 395                 400
Arg Gly Arg Arg Ala Arg Gly Gln Arg Ala Gly Glu Glu Ala Gln Asp
                405                 410                 415
Gly Leu Leu Pro Arg Gly Arg Asp Arg Leu Pro Leu Arg Pro Gly Asp
            420                 425                 430
Ala Asn Gln Arg Ala Glu Arg Pro Gly Pro Pro Arg Gly Gly His Gly
        435                 440                 445
Pro Val Asn Ala Ser Ser Ala Pro Asp Thr Ser Pro Pro Arg His Pro
    450                 455                 460
Arg Arg Trp Val Ser Gln Gln Arg Gln Arg Leu Trp Arg Gln Phe Arg
465                 470                 475                 480
Val Gly Gly Gly Phe Pro Pro Pro Pro Pro Ser Arg Pro Pro Ala Val
                485                 490                 495
Leu Leu Pro Leu Leu Arg Leu Ala Cys Ala Gly Asp Pro Gly Ala Thr
            500                 505                 510
Arg Pro Gly Pro Arg Arg Pro Ala Arg Arg Pro Arg Gly Glu Leu Ile
        515                 520                 525
Pro Arg Arg Pro Asp Pro Ala Ala Pro Ser Glu Glu Gly Leu Arg Met
    530                 535                 540
Glu Ser Ser Val Asp Asp Gly Ala Thr Ala Thr Thr Ala Asp Ala Ala
545                 550                 555                 560
Ser Gly Glu Ala Pro Glu Ala Gly Pro Ser Pro Ser His Ser Pro Thr
                565                 570                 575
Met Cys Gln Thr Gly Gly Pro Gly Pro Pro Pro Pro Gln Pro Pro Arg
            580                 585                 590
Trp Leu Pro
        595
```

<210> 188
<211> 376
<212> PRT
<213> Homo sapien

584
902

<400> 188

```
Glu Met Arg Lys Phe Asp Val Pro Ser Met Glu Ser Thr Leu Asn Gln
 1               5                  10                  15
Pro Ala Met Leu Glu Thr Leu Tyr Ser Asp Pro His Tyr Arg Ala His
            20                  25                  30
Phe Pro Asn Pro Arg Pro Asp Thr Asn Lys Asp Val Tyr Lys Val Leu
        35                  40                  45
Pro Glu Ser Lys Lys Ala Pro Gly Ser Gly Ala Val Phe Glu Arg Asn
    50                  55                  60
Gly Pro His Ala Ser Ser Ser Gly Val Leu Pro Leu Gly Leu Gln Pro
65                  70                  75                  80
Ala Pro Gly Leu Ser Lys Ser Leu Ser Ser Gln Val Trp Gln Pro Ser
                85                  90                  95
Pro Asp Pro Trp His Pro Gly Glu Gln Ser Cys Glu Leu Ser Thr Cys
            100                 105                 110
Arg Gln Gln Leu Glu Leu Ile Arg Leu Gln Met Glu Gln Met Gln Leu
        115                 120                 125
Gln Asn Gly Ala Met Cys His His Pro Ala Ala Phe Ala Pro Leu Leu
    130                 135                 140
Pro Thr Leu Glu Pro Ala Gln Trp Leu Ser Ile Leu Asn Ser Asn Glu
145                 150                 155                 160
His Leu Leu Lys Glu Lys Glu Leu Leu Ile Asp Lys Gln Arg Lys His
                165                 170                 175
Ile Ser Gln Leu Glu Gln Lys Val Arg Glu Ser Glu Leu Gln Val His
            180                 185                 190
Ser Ala Leu Leu Gly Arg Pro Ala Pro Phe Gly Asp Val Cys Leu Leu
        195                 200                 205
Arg Leu Gln Glu Leu Gln Arg Glu Asn Thr Phe Leu Arg Ala Gln Phe
    210                 215                 220
Ala Gln Lys Thr Glu Ala Leu Ser Lys Glu Lys Met Glu Leu Glu Lys
225                 230                 235                 240
Lys Leu Ser Ala Ser Glu Val Glu Ile Gln Leu Ile Arg Glu Ser Leu
                245                 250                 255
Lys Val Thr Leu Gln Lys His Ser Glu Glu Gly Lys Lys Gln Glu Glu
            260                 265                 270
Arg Val Lys Gly Arg Asp Lys His Ile Asn Asn Leu Lys Lys Lys Cys
        275                 280                 285
Gln Lys Glu Ser Glu Gln Asn Arg Glu Lys Gln Gln Arg Ile Glu Thr
    290                 295                 300
Leu Glu Arg Tyr Leu Ala Asp Leu Pro Thr Leu Glu Asp His Gln Lys
305                 310                 315                 320
Gln Thr Glu Gln Leu Lys Asp Ala Glu Leu Lys Asn Thr Glu Leu Gln
                325                 330                 335
Glu Arg Val Ala Glu Leu Glu Thr Leu Leu Glu Asp Thr Gln Ala Thr
            340                 345                 350
Cys Arg Glu Lys Glu Val Gln Leu Glu Ser Leu Arg Gln Arg Glu Ala
        355                 360                 365
Asp Leu Ser Ser Ala Arg His Arg
    370                 375
```

<210> 189
<211> 160
<212> PRT
<213> Homo sapien

582
883
903

<400> 189
Met Leu Glu Ala His Arg Arg Gln Arg His Pro Phe Leu Leu Leu Gly
1 5 10 15
Thr Thr Ala Asn Arg Thr Gln Ser Leu Asn Tyr Gly Cys Ile Val Glu
20 25 30
Asn Pro Gln Thr His Glu Val Leu His Tyr Val Glu Lys Pro Ser Thr
35 40 45
Phe Ile Ser Asp Ile Ile Asn Cys Gly Ile Tyr Leu Phe Ser Pro Glu
50 55 60
Ala Leu Lys Pro Leu Arg Asp Val Phe Gln Arg Asn Gln Gln Asp Gly
65 70 75 80
Gln Leu Glu Asp Ser Pro Gly Leu Trp Pro Gly Ala Gly Thr Ile Arg
85 90 95
Leu Glu Gln Asp Val Phe Ser Ala Leu Ala Gly Gln Gly Gln Ile Tyr
100 105 110
Val His Leu Thr Asp Gly Ile Trp Ser Gln Ile Lys Ser Ala Gly Ser
115 120 125
Ala Leu Tyr Ala Ser Arg Leu Tyr Leu Ser Arg Tyr Gln Asp Thr His
130 135 140
Pro Glu Arg Leu Ala Lys His Thr Pro Gly Gly Pro Trp Ile Arg Gly
145 150 155 160

<210> 190
<211> 146
<212> PRT
<213> Homo sapien

<400> 190
Met Asp Pro Arg Ala Ser Leu Leu Leu Leu Gly Asn Val Tyr Ile His
1 5 10 15
Pro Thr Ala Lys Val Ala Pro Ser Ala Val Leu Gly Pro Asn Val Ser
20 25 30
Ile Gly Lys Gly Val Thr Val Gly Glu Gly Val Arg Leu Arg Glu Ser
35 40 45
Ile Val Leu His Gly Ala Thr Leu Gln Glu His Thr Cys Val Leu His
50 55 60
Ser Ile Val Gly Trp Gly Ser Thr Val Gly Arg Trp Ala Arg Val Glu
65 70 75 80
Gly Thr Pro Ser Asp Pro Asn Pro Asn Asp Pro Arg Ala Arg Met Asp
85 90 95
Ser Glu Ser Leu Phe Lys Asp Gly Lys Leu Leu Pro Ala Ile Thr Ile
100 105 110
Leu Gly Cys Arg Val Arg Ile Pro Ala Glu Val Leu Ile Leu Asn Ser
115 120 125
Ile Val Leu Pro His Lys Glu Leu Ser Arg Ser Phe Thr Asn Gln Ile
130 135 140
Ile Leu
145

<210> 191
<211> 704
<212> PRT
<213> Homo sapien

<400> 191

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```
Glu Gly Gly Cys Ala Ala Gly Arg Gly Arg Glu Leu Glu Pro Glu Leu
 1               5                  10                  15
Glu Pro Gly Pro Gly Pro Gly Ser Ala Leu Glu Pro Gly Glu Glu Phe
            20                  25                  30
Glu Ile Val Asp Arg Ser Gln Leu Pro Gly Pro Gly Asp Leu Arg Ser
        35                  40                  45
Ala Thr Arg Pro Arg Ala Ala Glu Gly Trp Ser Ala Pro Ile Leu Thr
    50                  55                  60
Leu Ala Arg Arg Ala Thr Gly Asn Leu Ser Ala Ser Cys Gly Ser Ala
65                  70                  75                  80
Leu Arg Ala Ala Ala Gly Leu Gly Gly Gly Asp Ser Gly Asp Gly Thr
                85                  90                  95
Ala Arg Ala Ala Ser Lys Cys Gln Met Met Glu Glu Arg Ala Asn Leu
            100                 105                 110
Met His Met Met Lys Leu Ser Ile Lys Val Leu Leu Gln Ser Ala Leu
        115                 120                 125
Ser Leu Gly Arg Ser Leu Asp Ala Asp His Ala Pro Leu Gln Gln Phe
    130                 135                 140
Phe Val Val Met Glu His Cys Leu Lys His Gly Leu Lys Val Lys Lys
145                 150                 155                 160
Ser Phe Ile Gly Gln Asn Lys Ser Phe Phe Gly Pro Leu Glu Leu Val
                165                 170                 175
Glu Lys Leu Cys Pro Glu Ala Ser Asp Ile Ala Thr Ser Val Arg Asn
            180                 185                 190
Leu Pro Glu Leu Lys Thr Ala Val Gly Arg Gly Arg Ala Trp Leu Tyr
        195                 200                 205
Leu Ala Leu Met Gln Lys Lys Leu Ala Asp Tyr Leu Lys Val Leu Ile
    210                 215                 220
Asp Asn Lys His Leu Leu Ser Glu Phe Tyr Glu Pro Glu Ala Leu Met
225                 230                 235                 240
Met Glu Glu Glu Gly Met Val Ile Val Gly Leu Leu Val Gly Leu Asn
                245                 250                 255
Val Leu Asp Ala Asn Leu Cys Leu Lys Gly Glu Asp Leu Asp Ser Gln
            260                 265                 270
Val Gly Val Ile Asp Phe Ser Leu Tyr Leu Lys Asp Val Gln Asp Leu
        275                 280                 285
Asp Gly Gly Lys Glu His Glu Arg Ile Thr Asp Val Leu Asp Gln Lys
    290                 295                 300
Asn Tyr Val Glu Glu Leu Asn Arg His Leu Ser Cys Thr Val Gly Asp
305                 310                 315                 320
Leu Gln Thr Lys Ile Asp Gly Leu Glu Lys Thr Asn Ser Lys Leu Gln
                325                 330                 335
Glu Glu Leu Ser Ala Ala Thr Asp Arg Ile Cys Ser Leu Gln Glu Glu
            340                 345                 350
Gln Gln Gln Leu Arg Glu Gln Asn Glu Leu Ile Arg Glu Arg Ser Glu
        355                 360                 365
Lys Ser Val Glu Ile Thr Lys Gln Asp Thr Lys Val Glu Leu Glu Thr
    370                 375                 380
Tyr Lys Gln Thr Arg Gln Gly Leu Asp Glu Met Tyr Ser Asp Val Trp
385                 390                 395                 400
Lys Gln Leu Lys Glu Glu Lys Lys Val Arg Leu Glu Leu Glu Lys Glu
                405                 410                 415
Leu Glu Leu Gln Ile Gly Met Lys Thr Glu Met Glu Ile Ala Met Lys
            420                 425                 430
Leu Leu Glu Lys Asp Thr His Glu Lys Gln Asp Thr Leu Val Ala Leu
```

584
825
905

09/12/2000 14:15:09

```
        435                 440                 445
Arg Gln Gln Leu Glu Glu Val Lys Ala Ile Asn Leu Gln Met Phe His
    450                 455                 460
Lys Ala Gln Asn Ala Glu Ser Ser Leu Gln Gln Lys Asn Glu Ala Ile
465                 470                 475                 480
Thr Ser Phe Glu Gly Lys Thr Asn Gln Val Met Ser Ser Met Lys Gln
                485                 490                 495
Met Glu Glu Arg Leu Gln His Ser Glu Arg Ala Arg Gln Gly Ala Glu
            500                 505                 510
Glu Arg Ser His Lys Leu Gln Gln Glu Leu Gly Gly Arg Ile Gly Ala
        515                 520                 525
Leu Gln Leu Gln Leu Ser Gln Leu His Glu Gln Cys Ser Ser Leu Glu
    530                 535                 540
Lys Glu Leu Lys Ser Glu Lys Glu Gln Arg Gln Ala Leu Gln Arg Glu
545                 550                 555                 560
Leu Gln His Glu Lys Asp Thr Ser Ser Leu Leu Arg Met Glu Leu Gln
                565                 570                 575
Gln Val Glu Gly Leu Lys Lys Glu Leu Arg Glu Leu Gln Asp Glu Lys
            580                 585                 590
Ala Glu Leu Gln Lys Ile Cys Glu Glu Gln Glu Gln Ala Leu Gln Glu
        595                 600                 605
Met Gly Leu His Leu Ser Gln Ser Lys Leu Lys Met Glu Asp Ile Lys
    610                 615                 620
Glu Val Asn Gln Ala Leu Lys Gly His Ala Trp Leu Lys Asp Asp Glu
625                 630                 635                 640
Ala Thr His Cys Arg Gln Cys Glu Lys Glu Phe Ser Ile Ser Arg Arg
                645                 650                 655
Lys His His Cys Arg Asn Cys Gly His Ile Phe Cys Asn Thr Cys Ser
            660                 665                 670
Ser Asn Glu Leu Ala Leu Pro Ser Tyr Pro Lys Pro Val Arg Val Cys
        675                 680                 685
Asp Ser Cys His Thr Leu Leu Leu Gln Arg Cys Ser Ser Thr Ala Ser
    690                 695                 700
```

<210> 192
<211> 331
<212> PRT
<213> Homo sapien

<400> 192

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

885 88 406

WO 00/22129 PCT/US99/23743

```
        115                 120                 125
Cys Leu Phe Asn Phe Leu Ser Glu Asp Lys Tyr Pro Leu Ile Met Val
    130                 135                 140
Pro Asp Glu Val Glu Tyr Leu Leu Lys Lys Val Leu Ser Ser Met Ser
145                 150                 155                 160
Leu Glu Val Ser Leu Gly Glu Leu Glu Glu Leu Leu Ala Gln Glu Ala
                165                 170                 175
Gln Val Ala Gln Thr Thr Gly Gly Leu Ser Val Trp Gln Phe Leu Glu
            180                 185                 190
Leu Phe Asn Ser Gly Arg Cys Leu Arg Gly Val Gly Arg Asp Thr Leu
        195                 200                 205
Ser Met Ala Ile His Glu Val Tyr Gln Glu Leu Ile Gln Asp Val Leu
    210                 215                 220
Lys Gln Gly Tyr Leu Trp Lys Arg Gly His Leu Arg Arg Asn Trp Ala
225                 230                 235                 240
Glu Arg Trp Phe Gln Leu Gln Pro Ser Cys Leu Cys Tyr Phe Gly Ser
                245                 250                 255
Glu Glu Cys Lys Glu Lys Arg Gly Ile Ile Pro Leu Asp Ala His Cys
            260                 265                 270
Cys Val Glu Val Leu Pro Asp Arg Asp Gly Lys Arg Cys Met Phe Cys
        275                 280                 285
Val Lys Thr Ala Thr Arg Thr Tyr Glu Met Ser Ala Ser Asp Thr Arg
    290                 295                 300
Gln Arg Gln Glu Trp Thr Ala Ala Ile Gln Met Ala Ile Arg Leu Gln
305                 310                 315                 320
Ala Glu Gly Lys Thr Ser Leu His Lys Asp Leu
                325                 330
```

<210> 193
<211> 475
<212> PRT
<213> Homo sapien

<400> 193

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

584
BDS
907

WO 00/24744 PCT/US99/24907

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

      <210> 194
      <211> 241
      <212> PRT
      <213> Homo sapien

      <400> 194
Met Ser Gly Glu Ser Ala Arg Ser Leu Gly Lys Gly Ser Ala Pro Pro
 1               5                  10                  15
Gly Pro Val Pro Glu Gly Ser Ile Arg Ile Tyr Ser Met Arg Phe Cys
            20                  25                  30
Pro Phe Ala Glu Arg Thr Arg Leu Val Leu Lys Ala Lys Gly Ile Arg
        35                  40                  45
His Glu Val Ile Asn Ile Asn Leu Lys Asn Lys Pro Glu Trp Phe Phe
    50                  55                  60
Lys Lys Asn Pro Phe Gly Leu Val Pro Val Leu Glu Asn Ser Gln Gly
```

587
408

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

<210> 195
<211> 138
<212> PRT
<213> Homo sapien

<400> 195
Gln Thr Lys Ile Leu Glu Glu Asp Leu Glu Gln Ile Lys Leu Ser Leu
1 5 10 15
Arg Glu Arg Gly Arg Glu Leu Thr Thr Gln Arg Gln Leu Met Gln Glu
20 25 30
Arg Ala Glu Glu Gly Lys Gly Pro Ser Lys Ala Gln Arg Gly Ser Leu
35 40 45
Glu His Met Lys Leu Ile Leu Arg Asp Lys Glu Lys Glu Val Glu Cys
50 55 60
Gln Gln Glu His Ile His Glu Leu Gln Glu Leu Lys Asp Gln Leu Glu
65 70 75 80
Gln Gln Leu Gln Gly Leu His Arg Lys Val Gly Glu Thr Ser Leu Leu
85 90 95
Leu Ser Gln Arg Glu Gln Glu Ile Val Val Leu Gln Gln Gln Leu Gln
100 105 110
Glu Ala Arg Glu Gln Gly Glu Leu Lys Glu Gln Ser Leu Gln Ser Gln
115 120 125
Leu Asp Glu Ala Gln Arg Ala Leu Ala Gln
130 135

<210> 196
<211> 102
<212> PRT
<213> Homo sapien

<400> 196

5505214.1 2005-12-23

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

<210> 197
<211> 138
<212> PRT
<213> Homo sapien

<400> 197

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

<210> 198
<211> 100
<212> PRT
<213> Homo sapien

<400> 198

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

910

65 70 75 80
Pro Ala Phe Gly Val Ala Ser Pro Pro Pro Leu Thr Asp Thr Pro Asp
85 90 95
Thr Thr Ala Asn
100

<210> 199
<211> 127
<212> PRT
<213> Homo sapien

<400> 199
Met Val Lys Glu Thr Thr Tyr Tyr Asp Val Leu Gly Val Lys Pro Asn
1 5 10 15
Ala Thr Gln Glu Glu Leu Lys Lys Ala Tyr Arg Lys Leu Ala Leu Lys
20 25 30
Tyr His Pro Asp Lys Asn Pro Asn Glu Gly Glu Lys Phe Lys Gln Ile
35 40 45
Ser Gln Ala Tyr Glu Val Leu Ser Asp Ala Lys Lys Arg Glu Leu Tyr
50 55 60
Asp Lys Gly Gly Glu Gln Ala Ile Lys Glu Gly Gly Ala Gly Gly Gly
65 70 75 80
Phe Gly Ser Pro Met Asp Ile Phe Asp Met Phe Phe Gly Gly Gly Gly
85 90 95
Arg Met Gln Arg Glu Arg Arg Gly Lys Asn Val Val His Gln Leu Ser
100 105 110
Val Thr Leu Glu Asp Leu Tyr Asn Gly Ala Thr Arg Lys Leu Ala
115 120 125

<210> 200
<211> 90
<212> PRT
<213> Homo sapien

<400> 200
Met Ala Cys Pro Leu Asp Gln Ala Ile Gly Leu Leu Val Ala Ile Phe
1 5 10 15
His Lys Tyr Ser Gly Arg Glu Gly Asp Lys His Thr Leu Ser Lys Lys
20 25 30
Glu Leu Lys Glu Leu Ile Gln Lys Glu Leu Thr Ile Gly Ser Lys Leu
35 40 45
Gln Asp Ala Glu Ile Ala Arg Leu Met Glu Asp Leu Asp Arg Asn Lys
50 55 60
Asp Gln Glu Val Asn Phe Gln Glu Tyr Val Thr Phe Leu Gly Ala Leu
65 70 75 80
Ala Leu Ile Tyr Asn Glu Ala Leu Lys Gly
85 90

<210> 201
<211> 120
<212> PRT
<213> Homo sapien

<400> 201
Met Glu Thr Pro Ser Gln Arg Arg Ala Thr Arg Ser Gly Ala Gln Ala

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

<210> 202
<211> 177
<212> PRT
<213> Homo sapien

<400> 202

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

<210> 203
<211> 164
<212> PRT
<213> Homo sapien

<400> 203

```
Met Arg Leu Ala Val Gly Ala Leu Leu Val Cys Ala Val Leu Gly Leu
 1               5                  10                  15
```

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

<210> 204
<211> 241
<212> PRT
<213> Homo sapien

<400> 204
Met Ser Gly Glu Ser Ala Arg Ser Leu Gly Lys Gly Ser Ala Pro Pro
1 5 10 15
Gly Pro Val Pro Glu Gly Ser Ile Arg Ile Tyr Ser Met Arg Phe Cys
20 25 30
Pro Phe Ala Glu Arg Thr Arg Leu Val Leu Lys Ala Lys Gly Ile Arg
35 40 45
His Glu Val Ile Asn Ile Asn Leu Lys Asn Lys Pro Glu Trp Phe Phe
50 55 60
Lys Lys Asn Pro Phe Gly Leu Val Pro Val Leu Glu Asn Ser Gln Gly
65 70 75 80
Gln Leu Ile Tyr Glu Ser Ala Ile Thr Cys Glu Tyr Leu Asp Glu Ala
85 90 95
Tyr Pro Gly Lys Lys Leu Leu Pro Asp Asp Pro Tyr Glu Lys Ala Cys
100 105 110
Gln Lys Met Ile Leu Glu Leu Phe Ser Lys Val Pro Ser Leu Val Gly
115 120 125
Ser Phe Ile Arg Ser Gln Asn Lys Glu Asp Tyr Asp Gly Leu Lys Glu
130 135 140
Glu Phe Arg Lys Glu Phe Thr Lys Leu Glu Glu Val Leu Thr Asn Lys
145 150 155 160
Lys Thr Thr Phe Phe Gly Gly Asn Ser Ile Ser Met Ile Asp Tyr Leu
165 170 175
Ile Trp Pro Trp Phe Glu Arg Leu Glu Ala Met Lys Leu Asn Glu Cys
180 185 190
Val Asp His Thr Pro Lys Leu Lys Leu Trp Met Ala Ala Met Lys Glu
195 200 205
Asp Pro Thr Val Ser Ala Leu Leu Thr Ser Glu Lys Asp Trp Gln Gly
210 215 220

Phe Leu Glu Leu Tyr Leu Gln Asn Ser Pro Glu Ala Cys Asp Tyr Gly
225 230 235 240
Leu

<210> 205
<211> 160
<212> PRT
<213> Homo sapien

<400> 205
Met Gln Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu
1 5 10 15
Val Glu Pro Ser Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp
20 25 30
Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys
35 40 45
Gln Leu Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu
50 55 60
Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe
65 70 75 80
Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val Glu Pro Ser
85 90 95
Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp Lys Glu Gly Ile
100 105 110
Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu Glu Asp
115 120 125
Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu Ser Thr Leu His
130 135 140
Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe Val Lys Thr Leu
145 150 155 160

<210> 206
<211> 197
<212> PRT
<213> Homo sapien

<400> 206
Thr Ser Pro Ser Glu Ala Cys Ala Pro Leu Leu Ile Ser Leu Ser Thr
1 5 10 15
Leu Ile Tyr Asn Gly Ala Leu Pro Cys Gln Cys Asn Pro Gln Gly Ser
20 25 30
Leu Ser Ser Glu Cys Asn Pro His Gly Gly Gln Cys Leu Cys Lys Pro
35 40 45
Gly Val Val Gly Arg Arg Cys Asp Leu Cys Ala Pro Gly Tyr Tyr Gly
50 55 60
Phe Gly Pro Thr Gly Cys Gln Gly Ala Cys Leu Gly Cys Arg Asp His
65 70 75 80
Thr Gly Gly Glu His Cys Glu Arg Cys Ile Ala Gly Phe His Gly Asp
85 90 95
Pro Arg Leu Pro Tyr Gly Gly Gln Cys Arg Pro Cys Pro Cys Pro Glu
100 105 110
Gly Pro Gly Ser Gln Arg His Phe Ala Thr Ser Cys His Gln Asp Glu
115 120 125
Tyr Ser Gln Gln Ile Val Cys His Cys Arg Ala Gly Tyr Thr Gly Leu

593 B6C

914

```
    130                 135                 140
Arg Cys Glu Ala Cys Ala Pro Gly His Phe Gly Asp Pro Ser Arg Pro
145                 150                 155                 160
Gly Gly Arg Cys Gln Leu Cys Glu Cys Ser Gly Asn Ile Asp Pro Met
                165                 170                 175
Asp Pro Asp Ala Cys Asp Pro His Thr Gly Gln Cys Leu Arg Cys Leu
            180                 185                 190
His His Thr Glu Gly
        195
```

<210> 207
<211> 175
<212> PRT
<213> Homo sapien

<400> 207

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

<210> 208
<211> 177
<212> PRT
<213> Homo sapien

<400> 208

```
Met Ala Ala Gly Val Glu Ala Ala Ala Glu Val Ala Ala Thr Glu Ile
 1               5                  10                  15
Lys Met Glu Glu Glu Ser Gly Ala Pro Gly Val Pro Ser Gly Asn Gly
            20                  25                  30
Ala Pro Gly Pro Lys Gly Glu Gly Glu Arg Pro Ala Gln Asn Glu Lys
        35                  40                  45
Arg Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr
    50                  55                  60
Ala Asn Pro Thr Lys Arg Tyr Arg Ala Phe Ile Thr Asn Ile Pro Phe
65                  70                  75                  80
```

Asp Val Lys Trp Gln Ser Leu Lys Asp Leu Val Lys Glu Lys Val Gly
85 90 95
Glu Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg
100 105 110
Gly Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala
115 120 125
Ala Glu Val Leu Asn Lys His Ser Leu Ser Gly Arg Pro Leu Lys Val
130 135 140
Lys Glu Asp Pro Asp Gly Glu His Ala Arg Arg Ala Met Gln Lys Val
145 150 155 160
Met Ala Thr Thr Gly Gly Met Gly Met Gly Pro Gly Gly Pro Gly Met
165 170 175
Ile

<213> 209
<211> 196
<212> PRT
<213> Homo sapien

<400> 209
Asp Leu Gln Asp Met Phe Ile Val His Thr Ile Glu Glu Ile Glu Gly
1 5 10 15
Leu Ile Ser Ala His Asp Gln Phe Lys Ser Thr Leu Pro Asp Ala Asp
20 25 30
Arg Glu Arg Glu Ala Ile Leu Ala Ile His Lys Glu Ala Gln Arg Ile
35 40 45
Ala Glu Ser Asn His Ile Lys Leu Ser Gly Ser Asn Pro Tyr Thr Thr
50 55 60
Val Thr Pro Gln Ile Ile Asn Ser Lys Trp Glu Lys Val Gln Gln Leu
65 70 75 80
Val Pro Lys Arg Asp His Ala Leu Leu Glu Glu Gln Ser Lys Gln Gln
85 90 95
Ser Asn Glu His Leu Arg Arg Gln Phe Ala Ser Gln Ala Asn Val Val
100 105 110
Gly Pro Trp Ile Gln Thr Lys Met Glu Glu Ile Gly Arg Ile Ser Ile
115 120 125
Glu Met Asn Gly Thr Leu Glu Asp Gln Leu Ser His Leu Lys Gln Tyr
130 135 140
Glu Arg Ser Ile Val Asp Tyr Lys Pro Asn Leu Asp Leu Leu Glu Gln
145 150 155 160
Gln His Gln Leu Ile Gln Glu Ala Leu Ile Phe Asp Asn Lys His Thr
165 170 175
Asn Tyr Thr Met Glu His Ile Arg Val Gly Trp Glu Gln Leu Leu Thr
180 185 190
Thr Ile Ala Arg
195

<210> 210
<211> 156
<212> PRT
<213> Homo sapien

<400> 210
Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly Lys Glu

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

<210> 211
<211> 92
<212> PRT
<213> Homo sapien

<400> 211

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

<210> 212
<211> 142
<212> PRT
<213> Homo sapien

<400> 212

```
Glu Lys Gln Lys Asn Lys Glu Phe Ser Gln Thr Leu Glu Asn Glu Lys
 1               5                  10                  15
Asn Thr Leu Leu Ser Gln Ile Ser Thr Lys Asp Gly Glu Leu Lys Met
            20                  25                  30
Leu Gln Glu Glu Val Thr Lys Met Asn Leu Leu Asn Gln Gln Ile Gln
        35                  40                  45
Glu Glu Leu Ser Arg Val Thr Lys Leu Lys Glu Thr Ala Glu Glu Glu
    50                  55                  60
Lys Asp Asp Leu Glu Glu Arg Leu Met Asn Gln Leu Ala Glu Leu Asn
65                  70                  75                  80
```

Gly Ser Ile Gly Asn Tyr Cys Gln Asp Val Thr Asp Ala Gln Ile Lys
85 90 95
Asn Glu Leu Leu Glu Ser Glu Met Lys Asn Leu Lys Lys Cys Val Ser
100 105 110
Glu Leu Glu Glu Glu Lys Gln Gln Leu Val Lys Glu Lys Thr Lys Val
115 120 125
Glu Ser Glu Ile Arg Lys Glu Tyr Leu Glu Lys Ile Gln Gly
130 135 140

<210> 213
<211> 142
<212> PRT
<213> Homo sapien

<400> 213
Gly Gly Tyr Gly Gly Gly Tyr Gly Gly Val Leu Thr Ala Ser Asp Gly
1 5 10 15
Leu Leu Ala Gly Asn Glu Lys Leu Thr Met Gln Asn Leu Asn Asp Arg
20 25 30
Leu Ala Ser Tyr Leu Asp Lys Val Arg Ala Leu Glu Ala Ala Asn Gly
35 40 45
Glu Leu Glu Val Lys Ile Arg Asp Trp Tyr Gln Lys Gln Gly Pro Gly
50 55 60
Pro Ser Arg Asp Tyr Ser His Tyr Tyr Thr Thr Ile Gln Asp Leu Arg
65 70 75 80
Asp Lys Ile Leu Gly Ala Thr Ile Glu Asn Ser Arg Ile Val Leu Gln
85 90 95
Ile Asp Asn Ala Arg Leu Ala Ala Asp Asp Phe Arg Thr Lys Phe Glu
100 105 110
Thr Glu Gln Ala Leu Arg Met Ser Val Glu Ala Asp Ile Asn Gly Leu
115 120 125
Arg Arg Val Leu Asp Glu Leu Thr Leu Ala Arg Thr Asp Leu
130 135 140

<210> 214
<211> 129
<212> PRT
<213> Homo sapien

<400> 214
Val Met Arg Val Asp Phe Asn Val Pro Met Lys Asn Asn Gln Ile Thr
1 5 10 15
Asn Asn Gln Arg Ile Lys Ala Ala Val Pro Ser Ile Lys Phe Cys Leu
20 25 30
Asp Asn Gly Ala Lys Ser Val Val Leu Met Ser His Leu Gly Arg Pro
35 40 45
Asp Gly Val Pro Met Pro Asp Lys Tyr Ser Leu Glu Pro Val Ala Val
50 55 60
Glu Leu Arg Ser Leu Leu Gly Lys Asp Val Leu Phe Leu Lys Asp Cys
65 70 75 80
Val Gly Pro Glu Val Glu Lys Ala Cys Ala Asn Pro Ala Ala Gly Ser
85 90 95
Val Ile Leu Leu Glu Asn Leu Arg Phe His Val Glu Glu Glu Gly Lys
100 105 110
Gly Lys Asp Ala Ser Gly Asn Lys Val Lys Ala Glu Pro Ala Lys Ile

115 120 125
Glu

<210> 215
<211> 148
<212> PRT
<213> Homo sapien

<400> 215
Met Ala Thr Leu Lys Glu Lys Leu Ile Ala Pro Val Ala Glu Glu Glu
1 5 10 15
Ala Thr Val Pro Asn Asn Lys Ile Thr Val Val Gly Val Gly Gln Val
20 25 30
Gly Met Ala Cys Ala Ile Ser Ile Leu Gly Lys Ser Leu Ala Asp Glu
35 40 45
Leu Ala Leu Val Asp Val Leu Glu Asp Lys Leu Lys Gly Glu Met Met
50 55 60
Asp Leu Gln His Gly Ser Leu Phe Leu Gln Thr Pro Lys Ile Val Ala
65 70 75 80
Asp Lys Asp Tyr Ser Val Thr Ala Asn Ser Lys Ile Val Val Val Thr
85 90 95
Ala Gly Val Arg Gln Gln Glu Gly Glu Ser Arg Leu Asn Leu Val Gln
100 105 110
Arg Asn Val Asn Val Phe Lys Phe Ile Ile Pro Gln Ile Val Lys Tyr
115 120 125
Ser Pro Asp Cys Ile Ile Ile Val Val Ser Asn Pro Val Asp Ile Leu
130 135 140
Thr Tyr Val Thr
145

<210> 216
<211> 527
<212> PRT
<213> Homo sapien

<400> 216
Gln Arg Ala Pro Gly Ile Glu Glu Lys Ala Ala Glu Asn Gly Ala Leu
1 5 10 15
Gly Ser Pro Glu Arg Glu Glu Lys Val Leu Glu Asn Gly Glu Leu Thr
20 25 30
Pro Pro Arg Arg Glu Glu Lys Ala Leu Glu Asn Gly Glu Leu Arg Ser
35 40 45
Pro Glu Ala Gly Glu Lys Val Leu Val Asn Gly Gly Leu Thr Pro Pro
50 55 60
Lys Ser Glu Asp Lys Val Ser Glu Asn Gly Gly Leu Arg Phe Pro Arg
65 70 75 80
Asn Thr Glu Arg Pro Pro Glu Thr Gly Pro Trp Arg Ala Pro Gly Pro
85 90 95
Trp Glu Lys Thr Pro Glu Ser Trp Gly Pro Ala Pro Thr Ile Gly Glu
100 105 110
Pro Ala Pro Glu Thr Ser Leu Glu Arg Ala Pro Ala Pro Ser Ala Val
115 120 125
Val Ser Ser Arg Asn Gly Gly Glu Thr Ala Pro Gly Pro Leu Gly Pro
130 135 140

919

```
Ala Pro Lys Asn Gly Thr Leu Glu Pro Gly Thr Glu Arg Arg Ala Pro
145                 150                 155                 160
Glu Thr Gly Gly Ala Pro Arg Ala Pro Gly Ala Gly Arg Leu Asp Leu
                165                 170                 175
Gly Ser Gly Gly Arg Ala Pro Val Gly Thr Gly Thr Ala Pro Gly Gly
            180                 185                 190
Gly Pro Gly Ser Gly Val Asp Ala Lys Ala Gly Trp Val Asp Asn Thr
        195                 200                 205
Arg Pro Gln Pro Pro Pro Pro Pro Leu Pro Pro Pro Pro Glu Ala Gln
    210                 215                 220
Pro Arg Arg Leu Glu Pro Ala Pro Pro Arg Ala Arg Pro Glu Val Ala
225                 230                 235                 240
Pro Glu Gly Glu Pro Gly Ala Pro Asp Ser Arg Ala Gly Gly Asp Thr
                245                 250                 255
Ala Leu Ser Gly Asp Gly Asp Pro Pro Lys Pro Glu Arg Lys Gly Pro
            260                 265                 270
Glu Met Pro Arg Leu Phe Leu Asp Leu Gly Pro Pro Gln Gly Asn Ser
        275                 280                 285
Glu Gln Ile Lys Ala Arg Leu Ser Arg Leu Ser Leu Ala Leu Pro Pro
    290                 295                 300
Leu Thr Leu Thr Pro Phe Pro Gly Pro Gly Pro Arg Arg Pro Pro Trp
305                 310                 315                 320
Glu Gly Ala Asp Ala Gly Ala Ala Gly Gly Glu Ala Gly Gly Ala Gly
                325                 330                 335
Ala Pro Gly Pro Ala Glu Glu Asp Gly Glu Asp Glu Asp Glu Asp Glu
            340                 345                 350
Glu Glu Asp Glu Glu Ala Ala Ala Pro Gly Ala Ala Ala Gly Pro Arg
        355                 360                 365
Gly Pro Gly Arg Ala Arg Ala Ala Pro Val Pro Val Val Val Ser Ser
    370                 375                 380
Ala Asp Ala Asp Ala Ala Arg Pro Leu Arg Gly Leu Leu Lys Ser Pro
385                 390                 395                 400
Arg Gly Ala Asp Glu Pro Glu Asp Ser Glu Leu Glu Arg Lys Arg Lys
                405                 410                 415
Met Val Ser Phe His Gly Asp Val Thr Val Tyr Leu Phe Asp Gln Glu
            420                 425                 430
Thr Pro Thr Asn Glu Leu Ser Val Gln Ala Pro Pro Glu Gly Asp Thr
        435                 440                 445
Asp Pro Ser Thr Pro Pro Ala Pro Pro Thr Pro Pro His Pro Ala Thr
    450                 455                 460
Pro Gly Asp Gly Phe Pro Ser Asn Asp Ser Gly Phe Gly Gly Ser Phe
465                 470                 475                 480
Glu Trp Ala Glu Asp Phe Pro Leu Leu Pro Pro Pro Gly Pro Pro Leu
                485                 490                 495
Cys Phe Ser Arg Phe Ser Val Ser Pro Ala Leu Glu Thr Pro Gly Pro
            500                 505                 510
Pro Ala Arg Ala Pro Asp Ala Arg Pro Ala Gly Pro Val Glu Asn
        515                 520                 525
```

<210> 217
<211> 466
<212> DNA
<213> Homo sapien

<400> 217

gaatggtgcc tgtcctgctg tctctgctgc tgcttctggg tcctgctgtc ccccaggaga 60
accaagatgg tcgttactct ctgacctata tctacactgg gctgtccaag catgttgaag 120
acgtccccgc gtttcaggcc cttggctcac tcaatgacct ccagttcttt agatacaaca 180
gtaaagacag gaagtctcag cccatgggac tctggagaca ggtggaagga atggaggatt 240
ggaagcagga cagccaactt cagaaggcca gggaggacat ctttatggag accctgaaag 300
acatcgtgga gtattacaac gacagtaacg ggtctcacgt attgcaggga aggtttggtt 360
gtgagatcga gaataacaga agcagcggag cattctggaa atattactat gatggaaagg 420
actacattga attcaacaaa gaaatcccag cctgggtccc cttcga 466

<210> 218
<211> 381
<212> DNA
<213> Homo sapien

<400> 218
gagtttcctt cgcaagttca tgtggggtac cttcccaggc tgcctggctg accagctggt 60
tttaaagcgc cggggtaacc agttggagat ctgtgccgtg gtcctgaggc agttgtctcc 120
acacaagtac tacttcctcg tgggctacag tgaaactttg ctgtcctact tttacaaatg 180
tcctgtgcga ctccacctcc aaactgtgcc ctcaaaggtt gtgtataagt acctctagaa 240
caatcccctt ttttccatca agctgtagcc tgcagagaat ggaaacgtgg gaaaggaatg 300
gtatgtgggg gaaatgcatc ccctcagagg actgaggcat agtctctcat ctgctattga 360
ataaagacct tctatcttgt a 381

<210> 219
<211> 1293
<212> DNA
<213> Homo sapien

<400> 219
gaggggaggc gcatggcggg gatggcgctg gcgcgggcct ggaagcagat gtcctggttc 60
tactaccagt acctgctggt cacggcgctc tacatgctgg agccctggga gcggacggtg 120
ttcaattcca tgctggtttc cattgtgggg atggcactat acacaggata cgtcttcatg 180
ccccagcaca tcatggcgat attgcactac tttgaaatcg tacaatgacc aagatgcgac 240
caggatcaga ggttccttgg ggaagaccca ccctacgaag ttggaatgag accatcagat 300
gtgataagaa actcttctag atgtcaacat aaccaacctt ataaagacta aaattcatga 360
gtagaacagg aaaatcatcc tgactcatgt gttgtgttct ttatttttaa ttttcaaaga 420
ggctcttgta tagcagtttt tgtctatttt aacattgtag tcatttgtac tttgatatca 480
gtattttctt aaccttttgtg actgtttcaa tattacccccc gtgaaagctt ttcttaatgt 540
aactttgagt acattttaat tgccttctat ttttaaaact caaaatcatt agttgggctt 600
tactgttcct gctattgtat ggcatataca tctgcctgga tatatttcta ctcttgacca 660
aagttttgta aagaacaata taagatttcg ggtaggggta tggggaggga agatatttta 720
ttgagaacta cttaacaaaa gatttatctg taagcttgaa ctcaggagta cagttttagc 780
tatctagact ctaacagctt ttgctttaaa attattaaag tgtttcttaa tgaaaaagaa 840
aagatcttgc taaagttaaa ataaggaaca tttcaccttt taaatatttta attcttatgt 900
ggacttattt ccagaaaact ttggtgataa ttcttgagac aaaaggtggt taagtagcat 960
tattatgtaa tgcttatata ccatagagtt tttaatagaa gagaaatcca tttcctccga 1020
gggtcactat taacaatgta cttccttaaa tttagtttaa tgattgtaat gggtgctgca 1080
tttgcacatt gcattaagtt atgatgagac gaattgttgt taaaaattat agcaaaaaga 1140
aatgtaaact tggttaaaat cctttcactc tttgtattgt ttttttaag gtttttattc 1200
cttaaatgta aaatgactac ctaatttttt gatgtaaata cattaaattc aaagagaaaa 1260
aaaatcaaaa aaaaaaaaaa aaaaaaactc gag 1293

<210> 220
<211> 983
<212> DNA

600
821
921

<213> Homo sapien

<400> 220

caggttattc tgatcctgcc gcctgtcttc cctgtaagag tggagcctcg aggtgtacct 60
taaagtgacc ggaatgttag agatgcaatt tgcagagctg gggcaaggaa gggctccttg 120
tcactgtagt tactttcctt gcagtggcca aatgcccaat aagaaggaat acatgaccac 180
tgctgtgggg agtcagcagg tgcgtgatgc agctggccac actccatcca cggccatgac 240
ataaaacaga caagaagtaa ggctggactg taacacctca aggcctgctc cagtgaccca 300
ctttcttcag agaggctcta ccacacacac aaccaccttc caaatttaca ctcagatcac 360
tacaccatgt ctcccaagtt aaaacatgta tccacctaga ctttaaatgt gctttgtaac 420
tgttgatggc actgtacaga gggccaaagt atttcccatc agatagcatt tttctgaacc 480
catgcctctt gggacgagat cacaggactt gacccatcat caaataggac caggtgacct 540
acagagacat cacaatgatg gcttcctaca gtcaagtcca tttccaataa tgctctcatc 600
taagagaacc catgaacctt atttgaatcc tggttcaaac aaaaaccttа aattatttat 660
gagacaatta taaacttgat agattttgat gtgtgaaggt atttatgaat atttttagtc 720
agtgatggta tactgttaag gaaaaggttc atattttagg gacaaaggct gaaacattta 780
tggacagagt gatatgatat ctgggatttg ttttaggatg aagtgggagg gaggaaatga 840
atggaaatag tgttgaaaca gtattggcca cgagtcagct attgtgtgct aagacgctcc 900
tcacaccagt ctactctgta tgtgtttgaa tatctctgta ataaacttaa caaggaaaaa 960
aaaaaaaaaa aaaaaaactc gag 983

<210> 221
<211> 373
<212> DNA
<213> Homo sapien

<400> 221

cattttatgg gttaattttt tattaaatag caatagata ctttcataac tcaataaaat 60
tattcaatga tacattcgga aaataaatgt ataaaatatg aaaaagtact aaaaagcatt 120
tttcagtact tttaggtaag attaatccaa ctaaacacta gcatatgtta tacagtaata 180
ataaggggaa aatacaataa tgttgagaaa gcaaactcaa agcatagatc aatgaaaaaa 240
ttgagaaatg gacataaatg atttagtatt tttaaagaga gtgaaaaatc attattttat 300
gcttttgtgt agcgttagat gaattaaata acatatgcac atatagcttt gcgatacaaa 360
tttccagacc ata 373

<210> 222
<211> 544
<212> DNA
<213> Homo sapien

<400> 222

cagagatgct gctgctacaa aggatcggtg taagcagtta acccaggaaa tgatgacaga 60
gaaagaaaga agcaatgtgg ttataacaag gatgaaagat cgaattggaa cattagaaaa 120
ggaacataat gtatttcaaa acaaaataca tgtcagttat caagagactc aacagatgca 180
gatgaagttt cagcaagttc gtgagcagat ggaggcagag atagctcact tgaagcagga 240
aaatggtata ctgagagatg cagtcagcaa cactacaaat caactggaaa gcaagcagtc 300
tgcagaacta aataaactac gccaggatta tgctaggttg gtgaatgagc tgactgagaa 360
aacaggaaag ctacagcaag aggaagtcca aaagaagaat gctgagcaag cagctactca 420
gttgaaggtt caactacaag aagctgagag aaggtgggaa gaagttcaga gctacatcag 480
gaagagaaca gcggaacatg aggcagcaca gctagattta cagagtaaat ttgtggccaa 540
agaa 544

<210> 223
<211> 316
<212> DNA

<213> Homo sapien

<400> 223

gaggcaaggg atatgcttta gtgcctatta tagttaattc ttcaactcca aagtctaaaa 60
cagttgaatc tgctgaagga aaatctgaag aagtaaatga aacattagtt atacccactg 120
aggaagcaga aatggaagaa agtggacgaa gtgcaactcc tgttaactgt gaacagcctg 180
atatcttggt ttcttctaca ccaataaatg aaggacagac tgtgttagac aaggtggctg 240
agcagtgtga acctgctgaa agtcagccag aagcacttct gagaggaaga tgtttgcaag 300
gtaactctaa cagttg 316

<210> 224
<211> 1583
<212> DNA
<213> Homo sapien

<400> 224

cagaccacgt ctgccctcgc cgctctagcc ctgcgcccca gcccggccgc ggcacctccg 60
cctcgccgcc gctaggtcgg ccggctccgc ccggctgccg cctaggatga atatcatgga 120
cttcaacgtg aagaagctgg cggccgacgc aggcaccttc ctcagtcgcg ccgtgcagtt 180
cacagaagaa aagcttggcc aggctgagaa gacagaattg gatgctcact tagagaacct 240
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gactgagttt ggcccaggaa cagcttatgg taatgccctt attaattgtg gagaaaccca 480
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tccttttaaga aactttatag aaggagatta caaaacaatt gctaaagaaa ggaaactatt 600
gcaaaataag agactggatt tggatgctgc aaaaacgaga ctaaaaaagg caaaagctgc 660
agaaactaga aattcatctg aacaggaatt aagaataact caaagtgaat ctgatcgtca 720
agcagagatt accagacttc tgctagaggg aatcagcagt acacatgccc atcaccttcg 780
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<210> 225
<211> 491
<212> DNA
<213> Homo sapien

<400> 225

gaacaacatc atcttgaatc actagataga ctcttgacgg aaagcaaagg ggaaatgaaa 60
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acaatcaagg ttaggcaact agattcagca ttggaaattt gtaaggaaga acttgtcttg 180
catttgaatc aattggaagg aaataaggaa aagtttgaaa aacagttaaa gaagaaatct 240
gaagaggtat attgtttaca gaaagagcta aagataaaaa atcacagtct tcaagagact 300

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tctgagcaaa acgttattct acagcatact cttcagcaac agcagcaaat gttacaacaa 360
gagacaatta gaaatggaga gctagaagat actcaaacta aacttgaaaa acaggtgtca 420
aaactggaac aagaacttca aaaacaaagg gaaagttcag ctgaaaagtt gagaaaaatg 480
gaggagaaat g 491

<210> 226
<211> 483
<212> DNA
<213> Homo sapien

<400> 226
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ggtgggaaag gacccgggac ttgaacagtg ttgtgcggcg ccatgcaggt ctccagcctc 120
aatgaggtga agatttacag cctcagctgc ggcaagtccc ttcctgagtg gctttctgat 180
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caggactttg aaatgcctac tgtgtgtacc actattaagg tgtcaaaaga tggacagtac 300
attttagcaa ctggaacata taaacctcgg gttcgatgtt atgacaccta tcaattatcc 360
ttgaagtttg aaaggtgttt agattcagaa gttgtcacct ttgaaatttt gtctgatgac 420
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ttt 483

<210> 227
<211> 486
<212> DNA
<213> Homo sapien

<400> 227
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gcgacggcgg cgacagcagg tggccagcat cgaaatgttc agccttttag tgatgaagat 180
gcatcaattg aaacagtgag ccattgcagt ggttatagcg atccttccag ttttgctgaa 240
gatggaccag aagtccttga tgaggaagga actcaagaag acctagcgta caagttgaag 300
ggattaactg acctaaccct ggataagagt gcgaagacaa ggcaagcagc tcttgaaggt 360
attaaaaatg cactggcttc aaaaatgctg tatgaattta ttctggaaag gagaatgact 420
ttaactgata gcattgaacg ctgcctgaaa aaaggtaaga gtgatgagca acgtgcagct 480
gcagcg 486

<210> 228
<211> 494
<212> DNA
<213> Homo sapien

<400> 228
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cccacagcgg cccggtccgg gttgcccgag ccccaaggcg gggggcggca ccggggtgct 120
gaaagggaca gaatgctttg acctccaagc tgttttaaat ctagtagata agccagatcc 180
tgtgttgcca taagcccttg gcccacattt aagtgggaat gcagctagct tggatgtctg 240
aaactttgta agcgccttct gtctgaatcc tgaacacagg caccaagact actgaagaag 300
ctcgtcattc ttgtgcaggg atagccacac aagcaaacat gtttgcaaaa cttgaaagaa 360
agaaaattgc agaaagaaga cttgctgttc ttaagaggcc caggaaggtg ctacttagga 420
atcccaccgg cttgtgaagc aagggaatca agtttgcctt caatggggaa cttgacttca 480
ggaaaatgaa cttt 494

<210> 229
<211> 465

<212> DNA
<213> Homo sapien

<400> 229
gtcagagagc tggtataacc tcctgttgga catgcagaac cgactcaata aggtcatcaa 60
aagcgtgggc aagattgagc actccttctg gagatccttt cacactgagc gaaagacaga 120
accagccaca ggcttcatcg atggtgatct gattgaaagt ttcctagata tcagccgccc 180
taagatgcag gaggttgtgg caaacttgca gtatgatgat ggcagtggta tgaagcggga 240
ggcaactgca gatgacctca tcaaagtcgt ggaggaacta actcggatcc attagccaag 300
gacaggatct cttttcctga ccctcctaaa ggcgttgccc tcctatcctc ccttccttgc 360
ccacccttgg tttctttggc atgggaaggt tttccttaac cacttgcccc agagccacca 420
gtgaccttgt gtggaaacag ggtttttttt acttaaaaca gttca 465

<210> 230
<211> 435
<212> DNA
<213> Homo sapien

<400> 230
caggggaaag ggtgtttggc cttgaccagc cactgctgac ctcaatctca gacctacaga 60
tggtgaatat ctccctgcga gtgttgtctc gacccaatgc tcaggagctt cctagcatgt 120
accagcgcct agggctggac tacgaggaac gagtgttgcc gtccattgtc aacgaggtgc 180
tcaagagtgt ggtggccaag ttcaatgcct cacagctgat cacccagcgg gcccaggtat 240
ccctgttgat ccgccgggag ctgacagaaa gggccaaagg acttcagcct catcctggat 300
gatgtggcca tcacagactt gagctttagc cgagaagtac acaagctgcc tgtaagaaac 360
ccaaccaagt ggggtgaatt tcaaaaaccc gtgggggtga agggcttctt aagaatgcaa 420
ggaaggagga aaagaattcc atgggggggg ggttccttaa cccaggaaca ggggtttccc 480
ttgaattttt ttcca 495

<210> 231
<211> 498
<212> DNA
<213> Homo sapien

<400> 231
ggcagcttct gagaccaggg ttgctccgtc cgtgctccgc ctcgccatga cttcctacag 60
ctatcgccag tcgtcggcca cgtcgtcctt cggaggcctg ggcggcggct ccgtgcgttt 120
tgggccgggg gtcgcttttc gcgcgcccag cattcacggg ggctccggcg gccgcggcgt 180
atccgtgtcc tccgcccgct ttgtgtcctc gtcctcctcg gggggctacg gcggcggcta 240
cggcggcgtc ctgaccgcgt ccgacgggct gctggcgggc aacgagaagc taaccatgca 300
gaacctcaac gaccgcctgc ctcctacctg gacaaagtgc gcgccctgga agcgggcaac 360
ggcgaactta gaggtgaaag aatcccgcga actggtacca aaaacaaggg gcctgggggc 420
ttccgcgact tacagccaac ttactacacc gaacattcaa gaacttgcgg gaacaaaaat 480
ttttggtgcc acccattt 498

<210> 232
<211> 465
<212> DNA
<213> Homo sapien

<400> 232
caggccggcc gagtaggaaa gctggaggcg cgggtgggga acatgtctga gtcggagctc 60
ggcaggaagt gggaccggtg tctggcggat gcggtcgtga agataggtac tggttttgga 120
ttaggaattg ttttctcact taccttcttt aaaagaagaa tgtggccatt agccttcggt 180
tctggcatgg gattaggaat ggcttattcc aactgtcagc atgatttcca ggctccatat 240

cttctacatg gaaaatatgt caaagagcag gagcagtgac ttcacctgag aacatcccag 300
cgggaggaca agagaaaatc atgtttattc ctcaggaata cttgaagtgc cctggagtaa 360
actgccattc ttctgtaaca atggtatcag taatgcttta aactccagca cctggttatg 420
catttgaaac ccaagtctgg ttcttggttt ggatttttct tctgg 465

<210> 233
<211> 366
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(366)
<223> n = A,T,C or G

<400> 233
cagtaaaaaa ggttatgttt tattaattgc tggacaaccg tgggaaaaca aataagcaat 60
tgacaccacc aaattcttat tacattcaan ataaaanatt tattcacacc acaaaaagat 120
aatcacaaca aaatatacac taacttaaaa aacaaaagat tatagtgaca taaaatgtta 180
tattctcttt ttaagtgggt aaaagtattt tgtttgcttc tacataaatt tctattcatg 240
anaaaataac aaatattaaa atacagtgat agtttgcatt tcttctatag aatgaacata 300
gacataaccc tgaagctttt agtttacagg gagtttccat gaagccacaa actaaactaa 360
ttatca 366

<210> 234
<211> 379
<212> DNA
<213> Homo sapien

<400> 234
gagggcagcc ctcctacctg cgcacgtggt gccgccgctg ctgcctcccg ctcgccctga 60
acccagtgcc tgcagccatg gctcccggcc agctcgcctt atttagtgtc tctgacaaaa 120
ccggccttgt ggaatttgca agaaacctga ccgctcttgg tttgaatctg gtcgcttccg 180
gagggactgc aaaagctctc agggatgctg gtctggcagt cacagatgtc tctgagttga 240
cgggatttct gaaatgttgg ggggacgtgt gaaaactttg catcctgcac gatcccatgc 300
tggaatccta gctcctaata ttcagaagat aatgcttgac atgcgccaca cttgattcaa 360
tcttataaca attgttgcc 379

<210> 235
<211> 406
<212> DNA
<213> Homo sapien

<400> 235
caggctgcac catgtacccc accttcagtt taaaagaaaa aaaaaatccc cttcactcct 60
actgggaggt gggacccctt tcattttcag ttttgctcat ctagggaaaa taaggctttg 120
gtttccagtt taattgtttt tgaccttcta aaatgttttt atgttagcac tgatagttgg 180
cattactgtt gttaagcact gtgttccaga ccgtgtctga cttagtgtaa cctaggagat 240
tttatagttt tattttaatg aaaccctgat tgacgcacag cagtggggag aacagcgtct 300
tttacctgtc accgaagcca ggaagccccg tttgtaagcg tgtgttgtgg tgctttattg 360
tacatcctcc agtggcgttc tttttactct aatgttcttt tggttt 406

<210> 236
<211> 278
<212> DNA

926

<213> Homo sapien

<400> 236
gagattagca cctgtgaaca atgcgttctc tgatgacact ctgagcatgg accaacgcct 60
tcttaagcta attctgcaaa atcacatatt gaaagtaaaa gttggcctta gcgacctcta 120
caatggacag atactggaaa ccattggagg caaacaactc cgagtctttg tgtatcggac 180
ggctatctgc atagaaaact catgcatggt gagaggaagc aagcagggaa ggaacggtgc 240
cattcacata ttccgagaga tcatccaacc agcagaat 278

<210> 237
<211> 322
<212> DNA
<213> Homo sapien

<400> 237
cagggccgtg gcggaggagg agcgctgcac ggtggagcgt cgggccgacc tcacctacgc 60
ggagttcgtg cagcagtacg tgcgcccctg atcgcggagg tcgcgtcctg ttcaccggcc 120
cgtctgcccc gaccgcccaa ggccgccttc ccctgacctc gcgcgcacgc gtggggctgg 180
ggcggcgagg ctggcggtcc ggcctggccg cgactctgcc cttctttcca gaggttccgg 240
gccctgtgct cccgcgacag gttgctggct tcgtttgggg acagagtggt ccggtgagca 300
ccgccaacac ctactcctac ct 322

<210> 238
<211> 613
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (399)
<223> n=A,T,C or G

<400> 238
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agacaaatct cccacacctc ctaatttacc tagcgataaa atctaccctc cttctgggtc 180
ccccgaagag aataccagca cagccaccat gacttacatg acaactactc cagcaacagc 240
ccaaatgagc accaaggaag ccagctggga tgtggctgaa caacccacca ctgctgattt 300
tgctgctgcc acacttcagc gcacgcacag aactaatcgt ccccttcccc ctccgccttc 360
ccagagatct gcagagcagc caccagttgt ggggcaggna caagcagcaa ccaatatagg 420
attaaataat tcccacaagg ttcaaggagt agttccagtt ccagagaggc cacctgaacc 480
tcgagccatg gatgaccctg cgtctgcctt catcagtgac agtggtgctg ctgctgctca 540
gtgtcccatg gctacagctg tccagccagg cctgcctgag aaagtgcggg acggtgcccg 600
ggtcccgctg ctg 613

<210> 239
<211> 613
<212> DNA
<213> Homo sapiens

<400> 239
gaattcggca ccaggggaca ctggtgctga gctggatgat gatcagcact ggtctgacag 60
cccgtcggat gctgacagag agctgcgttt gccgtgccca gctgaggggg aagcagagct 120
ggagctgagg gtgtcggaag atgaggagaa gctgcccgcc tcaccgaagc accaagagag 180

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tccagtccac agccccctcaa cagaggggcc ccaactccca cctgtccctg ccgccaccca 300
ggagaaatca cctgaggagc gccttttccc tgagcctttg ctccccaaag agaagcccaa 360
agctgatgcc ccctcggatc tgaaagctgt gcactctccc atccgatcac agccagtgac 420
cctgccagaa gctaggactc ctgtctcacc agggagcccg cagccccagc cacccgtggc 480
ggcctccacg ccccaccca gcgaggtctc cagagccttc tctctcctgt gcaaaatggc 540
aactcttaag gaaaaactca ttgcaccagt tgcggaagaa gaggcaacag ttccaaacaa 600
taagatcact gta 613

<210> 240
<211> 585
<212> DNA
<213> Homo sapiens

<400> 240
gaattcggca cgaggtgaga tctacgatga actttaagat tggaggtgtg acagaacgca 60
tgccaacccc agttattaaa gcttttggca tcttgaagcg agcggccgct gaagtaaacc 120
aggattatgg tcttgatcca aagattgcta atgcaataat gaaggcagca gatgaggtag 180
ctgaaggtaa attaaatgat cattttcctc tcgtggtatg gcagactgga tcaggaactc 240
agacaaatat gaatgtaaat gaagtcatta gcaatagagc aattgaaatg ttaggaggtg 300
aacttggcag caagatacct gtgcatccca acgatcatgt taataaaagc cagagctcaa 360
atgatacttt tccccacagca atgcacattg ctgctgcaat agaagttcat gaagtactgt 420
taccaggact acagaagtta catgatgctc ttgatgcaaa atccaaagag tttgcacaga 480
tcatcaagat tggacgtact catactcagg atgctgttcc acttactctt gggcaggaat 540
ttagtggtta tgttcaacaa gtaaaatatg caatgacaag aataa 585

<210> 241
<211> 566
<212> DNA
<213> Homo sapiens

<400> 241
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cgagaagatc aagaactggc agaaggaagc ctttcacaag cagatgatgg gcggcttcaa 120
ggagaccaag gaagctgagg acggctttcg gaaggcacag aagccctggg ccaagaagct 180
gaaagaggta gaagcagcaa agaaagccca ccatgcagcg tgcaaagagg agaagctggc 240
tatctcacga gaagccaaca gcaaggcaga cccatccctc aaccctgaac agctcaagaa 300
attgcaagac aaaatagaaa agtgcaagca agatgttctt aagaccaaag agaagtatga 360
gaagtccctg aaggaactcg accagggcac accccagtac atggagaaca tggagcaggt 420
gtttgagcag tgccagcagt tcgaggagaa acgccttcgc ttcttccggg aggttctgct 480
ggaggttcag aagcacctag acctgtccaa tgtggctggc tacaaagcca tttaccatga 540
cctggagcag agcatcagag cagctg 566

<210> 242
<211> 556
<212> DNA
<213> Homo sapiens

<400> 242
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cgactacaaa cggaacttgc cgcgtcgagg actgtcgggc tacagcatgc tggccatagg 120
gattggaacc ctgatctacg ggcactggag cataatgaag tggaaccgtg agcgcaggcg 180
cctacaaatc gaggacttcg aggctcgcat cgcgctgttg ccactgttac aggcagaaac 240
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cttcatgtgg tacacgtagg ccctgtgccc tccggccacc tggatccctg cccctcccca 480
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aaaaaaaaaa ctcgag 556

<210> 243
<211> 591
<212> DNA
<213> Homo sapiens

<400> 243
gtctatgttt gcagaaatac agatccaaga caaagacagg atgggcactg ctggaaaagt 60
tattaaatgc aaagcagctg tgctttggga gcagaagcaa ccccttctcca ttgaggaaat 120
agaagttgcc ccaccaaaga ctaaagaagt tcgcattaag attttggcca caggaatctg 180
tcgcacagat gaccatgtga taaaaggaac aatggtgtcc aagtttccag tgattgtggg 240
acatgaggca actgggattg tagagagcat tggagaagga gtgactacag tgaaaccagg 300
tgacaaagtc atccctctct ttctgccaca atgtagagaa tgcaatgctt gtcgcaaccc 360
agatggcaac ctttgcatta ggagcgatat tactggtcgt ggagtactgg ctgatggcac 420
caccagattt acatgcaagg gcaaaccagt ccaccacttc atgaacacca gtacatttac 480
cgagtacaca gtggtggatg aatcttctgt tgctaagatt gatgatgcag ctcctcctga 540
gaaagtctgt ttaattggct gtgggttttc cactggatat ggcgctgctg t 591

<210> 244
<211> 594
<212> DNA
<213> Homo sapiens

<400> 244
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aatacagatc caagacaaag acaggatggg cactgctgga aaagttatta aatgcaaagc 120
agctgtgctt tgggagcaga agcaaccctt ctccattgag gaaatagaag ttgccccacc 180
aaagactaaa gaagttcgca ttaagatttt ggccacagga atctgtcgca cagatgacca 240
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gattgtagag agcattggag aaggagtgac tacagtgaaa ccaggtgaca aagtcatccc 360
tctctttctg ccacaatgta gagaatgcaa tgcttgtcgc aacccagatg gcaacctttg 420
cattaggagc gatattactg gtcgtggagt actggctgat ggcaccacca gatttacatg 480
caagggcaaa ccagtccacc acttcatgaa caccagtaca tttaccgagt acacagtggt 540
ggatgaatct tctgttgcta agattgatga tgcagctcct cctgagaaag tctg 594

<210> 245
<211> 615
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (105)
<223> n=A,T,C or G

<400> 245
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cctggagact gcagttctct atccttccac agctctttca ccatnctgga tcacttcctt 120
tgaatgcaga agcttgctgg ccaaaagatg tgggaattgt tgcccttgag atctatttttc 180
cttctcaata tgttgatcaa gcagagttgg aaaaatatga tggtgtagat gctggaaagt 240
ataccattgg cttgggccag gccaagatgg gcttctgcac agatagagaa gatattaact 300

ctctttgcat gactgtggtt cagaatctta tggagagaaa taacctttcc tatgattgca 360
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atttgatgca gctgtttgaa gagtctggga atacagatat agaaggaatc gacacaacta 480
atgcatgcta tggaggcaca gctgctgtct tcaatgcttg ttaactggat tgagtccagc 540
tcttgggatg gacggtatgc cctggtaagt tgcaggagat attgctgtat atgccacagg 600
aaatgctaga cctac 615

<210> 246
<211> 546
<212> DNA
<213> Homo sapiens

<400> 246
gaattcggca ccaggctgcc tcccgctcgc cctgaaccca gtgcctgcag ccatggctcc 60
cggccagctc gccttattta gtgtctctgc aaaaccggcc ttgtgaattt gcaagaaacc 120
tgaccgctct tggtttgaat ctggtcgctt ccggagggac tgcaaaagct ctcagggatg 180
ctggtctggc agtcagagat gtctctgagt tgacgggatt tcctgaaatg ttgggggggac 240
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ataatgctga catggccaga cttgatttca atcttataag agttgttgcc tgcaatctct 360
atccctttgt aaagacagtg gcttctccag gtgtaactgt tgaggaggct gtggagcaaa 420
ttgacattgg tggagtaacc ttactgagag ctgcagccaa aaaccacgct cgagtgacag 480
tggtgtgtga accagaggac tatgtgggtg ggtgtccacg gagatgcaga gctccgagag 540
taagga 546

<210> 247
<211> 564
<212> DNA
<213> Homo sapiens

<400> 247
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tgaatctgaa aagcttcaac aggaaaattc tattttgaga aatgaaatta ctactttaaa 120
tgaagaagat agcatttcta acctgaaatt agggacatta aatggatctc aggaagaaat 180
gtggcaaaaa acggaaactg taaaacaaga aaatgctgca gttcagaaga tggttgaaaa 240
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agaacttagc caaaagaact ctcaaaacca ggaaaaactg caagaactta atcaacgtct 360
aacagaaatg ctatgccaga aggaaaaaga gccaggaaac agtgcattgg aggaacggga 420
acaagagaag tttaatctga aagaagaact ggaacgttgt aaagtgcagt cctccacttt 480
agtgtcttct ctggaggcgg agctctctga agttaaaata cagacccata ttgtgcaaca 540
ggaaaaccac cttctcaaag atga 564

<210> 248
<211> 434
<212> DNA
<213> Homo sapiens

<400> 248
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gactggtaag accatcaccc tcgaggttga gcccagtgac accatcgaga atgtcaaggc 120
aaagatccaa gataaggaag gcatccctcc tgaccagcag aggctgatct ttgctggaaa 180
acagctggaa gatgggcgca ccctgtctga ctacaacatc cagaaagagt ccaccctgca 240
cctggtgctc cgtctcagag gtgggatgca aatcttcgtg aagacactca ctggcaagac 300
catcaccctt gaggtggagc ccagtgacac catcgagaac gtcaaagcaa agatccagga 360
caaggaaggc attcctcctg accagcagag gttgatcttt gccggaaagc cagcctggga 420
agatggggcc gcca 434

5602274.SEQ

<210> 249
<211> 416
<212> DNA
<213> Homo sapiens

<400> 249
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cggacaggac ccgcacagca agcacctgta cacggccgac atgttcacgc acgggatcca 120
gagcgccgcg cacttcgtca tgttcttcgc gccctggtgt ggacactgcc agcggctgca 180
gccgacttgg aatgacctgg gagacaaata caacagcatg gaagatgcca aagtctatgt 240
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ccccaccttа aagcttttca agccaggcca agaagctgtg aagtaccagg gtcctcggga 360
cttccagaca ctggaaaact ggatgctgca gacactgaac gaggagccag tgacac 416

<210> 250
<211> 504
<212> DNA
<213> Homo sapiens

<400> 250
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aggctgagat ggatcctctc agggcccaac agctggctgc ggagctggag gtggagatga 180
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agctgatgaa gagggtgcag cagagctctg ggcctgcatg aggtccctgt cagtatacac 420
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gtgaagactg ccaggcctag ctct 504

<210> 251
<211> 607
<212> DNA
<213> Homo sapiens

<400> 251
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caatgatgtg gaaaagatgg ccgcacacat gcggatggtt cacattgatg aagagatggg 180
acctaaaaca gattctactt tgagttttga tttgacattg cagcagggta gtcacactaa 240
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aacccttttgt cctctttgct tttcaatcct aaaaggaccc atatctgatg cacttgcaca 480
tcacttacga gagaggcacc aagttattca gacggttcat ccagttgaga aaaagctcac 540
ctacaaatgt atccattgcc ttggtgtgta taccagcaac atgaccgcct caactatcac 600
tctgcat 607

<210> 252
<211> 618
<212> DNA
<213> Homo sapiens

<400> 252

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cgctgccact ggggtccctg gccccaccga catggcggcg gtgttgagca agtcctggag 120
cgcacggagc tgaacaagct gcccaagtct gtccagaaca aacttgaaaa gttccttgct 180
gatcagcaat ccgagatcga tggcctgaag gggcggcatg agaaatttaa ggtggagagc 240
gaacaacagt attttgaaat agaaaagagg ttgtcccaca gtcaggagag acttgtgaat 300
gaaacccgag agtgtcaaag cttgcggctt gagctagaga aactcaacaa tcaactgaag 360
gcactaactg agaaaaacaa agaacttgaa attgctcagg atcgcaatat tgccattcag 420
agccaattta caagaacaaa ggaagaatta gaagctgaga aaagagactt aattagaacc 480
aatgagagac tatctcaaga acttgaatac ttaacagagg atgttaaacg tctgaatgaa 540
aaacttaaag aaagcaatac aacaaagggc gaacttcagt taaaattgga tgaacttcaa 600
gcttctgatg tttctgtt 618

<210> 253
<211> 1201
<212> DNA
<213> Homo sapiens

<400> 253
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tgtgagtttg gcatgatttg gtcccctggg attctgcctt agcaagaaag aagttggaaa 120
tacttcctgg aagaaaacta aaacaataca aaagccacag cttattgatt gcatgtcagc 180
cccttacaa atatggacac atttcctagc ctatttccac ctggaggaga tagtaggctg 240
aatcctgagc ctgagttcca aatatgttta attgatgaaa gggtacgctg tgaacatcat 300
aaacataatt atcaggctct gaaaattgaa cacaaaaggt tgcaggaaga atatgtaaaa 360
tcacaaaatg aacttaaacg tgtattaatt gaaaagcaag cagccagga aaaattccaa 420
ctgctccttg aagacttaag gggagaatta gtagagaaag ctagagacat agaaaaaatg 480
aaactgcagg tactaacacc acaaaaattg gaattggtaa aagcccaact acaacaagaa 540
ttagaagctc caatgcgaga acgctttcgg actcttgatg aagaagtgga aaggtacaga 600
gctgagtata acaagctgcg ctacgagtat acatttctca agtcagagtt tgaacaccag 660
aaagaagagt ttactcgggt ttcagaagaa gagaaaatga aatacaagtc agaggctgca 720
cgactggaga aggacaaaga ggagctacat aaccagctgc ttagtgttga tcccacgaga 780
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a 1201

<210> 254
<211> 560
<212> DNA
<213> Homo sapiens

<400> 254
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ctgatgtttt tgcagattac ctcagggaaa cggaggtttg ttgagttaca gacacattaa 120
accaaaggcc gtgggaaaac ccctctccag ctccaggggg ttggtcagga ccacccacta 180
accagtgcct tccttcttaa cattcacttt tagcagcttg tgtttatttt acatgggcag 240
ttttgatggg aaattgccat gaccacaggg gtttggagtt ctgcttttct ttttttcttct 300
tctttttcgg gggactgggg gactcctccc aagatcacat tttagcatct ttctctccta 360
ctccatttag aaaaataagt aacaggtgaa atgtggtctc agtgttaacg ggataattct 420
gctaccggct cctccctgat gattctgaaa tacactactg aacgagctct ggctggtcct 480
ttctatcctg gatgtggttc ttctgtgtag caattccttg atgtccagtt tggaaagatg 540

tactcttctc aacaagaaaa 560

<210> 255
<211> 612
<212> DNA
<213> Homo sapiens

<400> 255
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ctcaaagcca tctggcacgc cttcaccgac tcgaccagga ccacagggca aggtctccaa 120
gtcccagctc aaggtccttt cccataacct gtgcacggtg ctgaaggttc ctcatgaccc 180
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attcaatagg atgtgttgga ccctctgtgt caaaaaaaaa cctcacaaag aatcccctgc 360
tcattacaga agaagatgca tttaaaatat gggttatttt caacttttta tctgaggaca 420
agtatccatt aattattgtg tcagaagaga ttgaatacct gcttaagaag cttacagaag 480
ctatgggagg aggttggcag caagaacaat ttgaacatta taaaatcaac tttgatgaca 540
gtaaaaatgg cctttctgca tgggaactta ttgagcttat tggaaatgga cagtttagca 600
aaggcatgga cc 612

<210> 256
<211> 1132
<212> DNA
<213> Homo sapiens

<400> 256
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ccaaggcccc gccgtccagc ttctaagtgc cagatgatgg aggagcgtgc caacctgatg 120
cacatgatga aactcagcat caaggtgttg ctccagtcgg ctctgagcct gggccgcagc 180
gtggatgcgg accatgcccc cttgcagcag ttctttgtag tgatggagca ctgcctcaaa 240
catgggctga aagttaagaa gagttttatt ggccaaaata aatcattctt tggtcctttg 300
gagctggtgg agaaactttg tccagaagca tcagatatag cgactagtgt cagaaatctt 360
ccagaattaa agacagctgt gggaagaggc cgagcgtggc tttatcttgc actcatgcaa 420
aagaaactgg cagattatct gaaagtgctt atagacaata aacatctctt aagcgagttc 480
tatgagcctg aggctttaat gatggaggaa gaagggatgg tgattgttgg tctgctggtg 540
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ggagtaatag atttttccct ctaccttaag gatgtgcagg atcttgatgg tggcaaggag 660
catgaaagaa ttactgatgt ccttgatcaa aaaaattatg tggaagaact taaccggcac 720
ttgagctgta cagttgggga tcttcaaacc aagatagatg gcttggaaaa gactaactca 780
aagcttcaag aagagctttc agctgcaaca gaccgaattt gctcacttca agaagaacag 840
cagcagttaa gagaacaaaa tgaattaatt cgagaaagaa gtgaaaagag tgtagagata 900
acaaaacagg ataccaaagt tgagctggag acttacaagc aaactcggca aggtctggat 960
gaaatgtaca gtgatgtgtg gaagcagcta aaagaggaga agaaagtccg gttggaactg 1020
gaaaaagaac tggagttaca aattggaatg aaaaccgaaa tggaaattgc aatgaagtta 1080
ctggaaaagg acacccacga gaagcaggac acactagttg ccctccgcca gc 1132

<210> 257
<211> 519
<212> DNA
<213> Homo sapiens

<400> 257
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tctgtacgtg ggggacctgc accccgacgt gaccgaggcg atgctctacg agaagttcag 120
cccggccggg cccatcctct ccatccgggt ctgcagggac atgatcaccc gccgctcctt 180

gggctacgcg tacgtgaact tccagcagcc ggcggacgcg gaacgtgctt tggacaccat 240
gaattttgat gttataaagg gcaagccagt acgcatcatg tggtctcagc gtgatccatc 300
acttcgcaaa agtggagtag gcaacatatt cattaaaaat ttggacaaat ccatcgacaa 360
taaagcacta tatgatacgt tttctgcgtt tggtaacatc ctttcatgta aggtggtttg 420
tgatgaaaat ggctccaagg gctatggatt tgtacacttt gaaacacagg aagcagctga 480
aagagctatt gaaaaaatga atgggatgct tctaaatga 519

<210> 258
<211> 596
<212> DNA
<213> Homo sapiens

<400> 258
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gcagtggagg cactcgccac aggctgccac gagaaatgat ttttgttgga agagatgact 120
gtgagctcat gttgcagtct cgtagtgtgg ataagcaaca cgctgtcatc aactatgatg 180
cgtctacgga tgagcattta gtgaaggatt tgggcagcct caatgggact tttgtgaatg 240
atgtaaggat tccggaacag acttatatca ccttgaaact tgaagataag ctgagatttg 300
gatatgatac aaatcttttc actgtagtac aaggagaaat gagggtccct gaagaagctc 360
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tatccaaatc tgcaagtgcc aaaagcatag attcaaaggt agcagacgct gctactgaag 480
tgcagcacaa aactactgaa gcactgaaat ccgaggaaaa agccatggat atttctgcta 540
tgccccgtgg tactccatta tatgggcagc cgtcatggtg gggggatgat gaggtg 596

<210> 259
<211> 595
<212> DNA
<213> Homo sapiens

<400> 259
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tcggagaatt tcagaattaa gagaggagct gcaaatggac cagcaagcaa agaaacatct 120
tcaggacgag tttgatgcat gtttggagga gaaagatcag tatatcagtg ttctccagac 180
tcaggtttct cttctaaagc agcgattaca gaatggccca atgaatgttg atgctcccaa 240
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cgtcggggaa ccagtgggag gtgggacttc cgctaaaacc ctggaaatgc tccagcaaag 360
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gcagtgcgca ctgctgctga gtgagaagga ggcactgcag gagcagttgg atgaaaggct 480
gcaggagctg gaaaagatga aggggatggt aataaccgag acgaagcggc aaatgcttga 540
gacccctggaa ctgaaagaag atgaaattgc tcagcttcgt agtcatatca aacag 595

<210> 260
<211> 994
<212> DNA
<213> Homo sapiens

<400> 260
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ttttcgcctt ccctgttctt ccctttctca aacaaacaag acatggcaaa ccgcagtcta 120
acccagccct ttgaaattat ccatagtttt acagacagct ccaggccatg agccacaatg 180
tccaaaatta ttcttgagca ctgatataaa ttacttagac cttctttgag ggcagaactc 240
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ccacgagttt actgagtgct tacaggtaaa ggaatgaata taagatgtct ttctgatcag 360
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tctgaaccat tttttaatac ttgttttgtc atggtgaaat tatagcagtt atcccaaaat 480

gttttaatta tcaaaatact gtctttaaa aaaaaaaaa agtaacacct tttaaagcat 540
tagatttcac ttgggtttct tttccaaaaa atgctaggta gacaaggcat tgtaaacatg 600
agtttccttt aagaaccatc agaatataaa tttaacatga agaaaactgc tatatctagt 660
agaaataata tctaaagttt aacaactaaa gtaccctcac agaatagcaa ataccctttct 720
gttctggaca tgggttcaaa tttgaatatg gaaataattt ccttggaagt ccctagaggc 780
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tgcagattta tgccttattt tttagcattt tttaaatgtt gggtctttca aggtgttttt 900
tgcttttttat tagatctata taaataagtt aactagcaat ttagttttgt atttaagcta 960
cacttaatct ttttctttgg tgatatttat ttct 994

<210> 261
<211> 594
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (538)
<223> n=A,T,C or G

<400> 261
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tctcagaggc caggacgacc tgaaagagca gctggccatg gttgagcgca gagccaacct 180
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agtggccgag caagagctac tggatgccag tgagcgcgtg cagctcctcc acacccagaa 300
caccagcctc atcaacacca agaagaagct ggagacagac atttcccaaa tccagggaga 360
gatggaagac atcgtccagg aagcccgcaa cgcagaagag aaggccaaga aagccatcac 420
tgatgccgcc atgatggcgg aggagctgaa gaaggagcag gacaccagcg cccacctgga 480
gcggatgaag aagaacatgg agcagaccgt gaaggacctg cagcaccgtc tggacgangc 540
tgagcagctt ggcgctgaag ggcgggcaag aagcagatcc agaaactgga ggct 594

<210> 262
<211> 594
<212> DNA
<213> Homo sapiens

<400> 262
gaaaaggtgg ctggagccaa aggcatagtc agggttaatg ctccttttc tttatcccaa 60
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tcggcagcaa cctgagacg ctttacagct ctagacccta aaaggtcaaa aggccgtctt 180
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taaatccggc cctcaaaccc cacaacagga cttaattgac ctcaccttca aggtgtagaa 300
taataaaaaa aaaaagttgc aattccttgc ctccgctgtg agacaaaccc cagccacatc 360
tccagcacac aagaacttcc aaacgcctga accacagcag ccaggcgttc ctccagaacc 420
tcctcccccа ggagcttgct acatgtgccg gaaatctggc cactaggcca aggaatgcct 480
gcagcccccgg attcctccta agccgtgtcc catctgtgcg ggaccccact gaaaatcgga 540
ctgttcaact cacctggcag ccactctcag agaccctgga actctggccc aagg 594

<210> 263
<211> 506
<212> DNA
<213> Homo sapiens

<400> 263

gaattcggca cgagcggaaa cttaggggcc acgtgagcca cggccacggc cgcataggca 60
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acttcgacaa ataccaccca ggctactttg ggaaagttgg tatgaagcat taccacttaa 180
agaggaacca gagcttctgc ccaactgtca accttgacaa attgtggact ttggtcagtg 240
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tgcgatcggg ctactataaa gttctgggaa agggaaagct cccaaagcag cctgtcatcg 360
tgaaggccaa attcttcagc agaagagctg aggagaagat taagagtgtt gggggggcct 420
gtgtcctggt ggcttgaagc cacatggagg gagtttcatt aaatgctaac tacttttaa 480
aaaaaaaaaa aaaaaaaaaa ctcgag 506

<210> 264
<211> 600
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (32)
<223> n=A,T,C or G

<400> 264
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ggaccctgtc agcaggcggc tcaggtgctg atccgcgagg tggccgagaa ggagctgctg 240
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tattacagac acttagcacc tgatcacttg ctgcaaatat gtcatcgact aggacctctt 360
cttgaacaag aaattcctca aagtgttcct ggagtacaaa ctttattagg agctggaaga 420
cagtctttac tacgcacaaa taaaagctgc aagcatgttg tgtggaaagg atctgctctg 480
gctgcgttgc actgtggaag accacctgag tcaccagtta actatggtag cccacccagc 540
attgcggata ctctgttttc aaggaagctg aatgggaaat acagacttga gcgacttgtt 600

<210> 265
<211> 534
<212> DNA
<213> Homo sapiens

<400> 265
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gccacggggg agaaagtgct gcgctacgag accttcatca gtgacgtgct gcagcgggac 120
ttgcgaaagg tgctggacca tcgagacaag gtatatgagc agctggccaa ataccttcaa 180
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gatttgggct gtaacttctt cgttgacaca gtggtcccag atacttcacg catctatgtg 300
gccctgggat atggtttttt cctggagttg acactggcag aagctctcaa gttcattgat 360
cgtaagagct ctctcctcac agagctcagc aacagcctca ccaaggactc catgaatatc 420
aaagcccata tccacatgtt gctagagggg cttagagaac tacaaggcct gcagaatttc 480
ccagagaagc ctcaccattg acttcttccc cccatcctca gacattaaag agcc 534

<210> 266
<211> 552
<212> DNA
<213> Homo sapiens

<400> 266
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gccgcctagg atgaatatca tggacttcaa cgtgaagaag ctggcggccg acgcaggcac 120
cttcctcagt cgcgccgtgc agttcacaga agaaaagctt ggccaggctg agaagacaga 180
attggatgct cacttagaga acctccttag caaagctgaa tgtaccaaaa tatggacaga 240
aaaaataatg aaacaaactg aagtgttatt gcagccaaat ccaaatgcca ggatagaaga 300
atttgtttat gagaaactgg atagaaaagc tccaagtcgt ataaacaacc cagaactttt 360
gggacaatat atgattgatg cagggactga gtttggccca ggaacagctt atggtaatgc 420
ccttattaaa tgtggagaaa cccaaaaaag aattggaaca gcagacagag aactgattca 480
aacgtcagcc ttaaattttc ttactccttt aagaaacttt atagaaggag attacaaaac 540
aattgctaaa ga 552

<210> 267
<211> 551
<212> DNA
<213> Homo sapiens

<400> 267
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caggcctgtg atatccatgc aggcccaggc ggccgtggct gggccccgga tgcccagcgt 360
gcagccaccc aggagcatct cacccagcgc tctgcaagac ctgctgcgga ccctgaagtc 420
gcccagctcc cctcagcagc aacagcaggt gctgaacatt ctcaaatcaa acccgcagct 480
aatggcagct ttcatcaaac agcgcacagc caagtacgtg gccaatcagc ccggcatgca 540
gccccagcct g 551

<210> 268
<211> 573
<212> DNA
<213> Homo sapiens

<400> 268
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ccctgccaat ccagcaattt tgtcagaagc ttctgctcct atcccctcacg atggaaatct 180
ctatcccaga ctgtatccag agctctctca atacatgggg ctgagtttaa atgaagaaga 240
aatacgtgca aatgtggccg tggtttctgg tgcaccactt caggggcagt tggtagcaag 300
accttccagt ataaactata tggtggctcc tgtaactggt aatgatgttg gaattcgtag 360
agcagaaatt aagcaaggga ttcgtgaagt cattttgtgt aaggatcaag atggaaaaat 420
tggactcagg cttaaatcaa tagataatgg tatatttgtt cagctagtcc aggctaattc 480
tccagcctca ttggttggtc tgagatttgg ggaccaagta cttcagatca atggtgaaaa 540
ctgtgcagga tggagctctg ataaagcgca caa 573

<210> 269
<211> 500
<212> DNA
<213> Homo sapiens

<400> 269
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atgtgggggga gccatgaaga aactaactaa aggggagcct ttggggacca gggggagaca 120
agtcactatt ttgagggaga aagctctgga ttgattctga caggacactt gagtgtgaac 180
tgtccaagct aagcctctgg gtgtgtagag agagcccttа cagatagata gcacctttgc 240
tttcagagtg gaaggactag ccactaagga ccagaccaag atgcatgtag gtcactgaca 300

agcacctgat gaagaggagg ggtctcctcc aagtttgtgt ttggaactcc tcctgtgttc 360
aatttcctaa aagccataat ccagcaagct gaactcatga gaaggtctgc ttcatgttga 420
gcatggaaga cagaacacag acggaaactg cagtgatggt gtgaagacac cacggatagg 480
ttaggggcag tgaggaggaa 500

<210> 270
<211> 224
<212> DNA
<213> Homo sapiens

<400> 270
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cataactgaa agtagctaag gcaccccagc cggaggaagt gagctctcct ggggcgtggt 120
tgttcgtgat ccttgcatct gttacttagg gtcaaggctt gggtcttgcc ccgcagaccc 180
ttgggacgac ccggccccag cgcagctatg aacctggagc gagt 224

<210> 271
<211> 447
<212> DNA
<213> Homo sapiens

<400> 271
gaattcggca cgaggctggg ccgggcccga gcggatcgcg ggctcgggct gcggggctcc 60
ggctgcgggc gctgggccgc gaggcgcgga gcttgggagc ggagcccagg ccgtgccgcg 120
cggcgccatg aagggcaagg aggagaagga gggcggcgca cggctgggcg ctggcggcgg 180
aagccccgag aagagcccga gcgcgcagga gctcaaggag cagggcaatc gtctgttcgt 240
gggccgaaag tacccggagg cggcggcctg ctacggccgc gcgatcaccc ggaacccgct 300
ggtggccgtg tattacacca accgggcctt gtgctacctg aagatgcagc agcacgagca 360
ggccctggcc gactgccggc gcgccctgga gctggacggg cagtctgtga aggcgcactt 420
cttcctgggg cagtgccagc tggagat 447

<210> 272
<211> 606
<212> DNA
<213> Homo sapiens

<400> 272
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gaggttattg atttgcttaa acctgaccaa gtagaaggga tccagaaatc tgggactaaa 120
aaactgaaga ccgaaactga caaagaaaat gctgaagtga agtttaaaga ttttcttctg 180
tccttgaaga ctatgatgtt ttctgaagat gaggctcttt gtgttgtaga cttgctaaag 240
gagaagtctg gtgtaataca agatgcttta aagaagtcaa gtaagggaga attgactacg 300
cttatacatc agcttcaaga aaaggacaag ttactcgctg ctgtgaagga agatgctgct 360
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tttcaaaaca aaatacatgt cagttatcaa gagactcaac agatgcagat gaagtttcag 540
caagttcgtg agcagatgga ggcagagata gctcacttga agcaggaaaa tgggtatact 600
ggagaa 606

<210> 273
<211> 598
<212> DNA
<213> Homo sapiens

<400> 273

938

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gaagatggtg gaccgcgagc aactggtgca gaaagcccgg ctggccgagc aggcggagcg 240
ctacgacgac atggccgcgg ccatgaagaa cgtyacagag ctgaatgagc cactgtcgaa 300
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tgagatggtc cgtgcgtacc gggagaagat agagaaggag ttggaggctg tgtgccagga 480
tgtgctgagc ctgctggata actacctgat caagaattgc agcgagaccc agtacgagag 540
caaagtgttc tacctgaaga tgaaagggga ctactaccgc tacctggctg aagtggcc 598

<210> 274
<211> 536
<212> DNA
<213> Homo sapiens

<400> 274
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aaagacagaa aatgtcttcg tagatgaacc ccttattcat gcaactactt atattccttt 120
gatggataac gctgactcaa gtcctgtggt agataagaga gaggttattg atttgcttaa 180
acctgaccaa gtagaaggga tccagaaatc tgggactaaa aaactgaaga ccgaaactga 240
caaagaaaat gctgaagtga agtttaaaga ttttcttctg tccttgaaga ctatgatgtt 300
ttctgaagat gaggctcttt gtgttgtaga cttgctaaag gagaagtctg gtgtaataca 360
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aaaggacaag ttactcgctg ctgtgaagga agatgctgct gctacaaagg atcggtgtaa 480
gcagttaacc caggaaatga tgacagagaa agaaagaagc aatgtggtta taacaa 536

<210> 275
<211> 494
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (379)
<223> n=A,T,C or G

<400> 275
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gcagatcttc gtgaagactc tgactggtaa gaccatcacc ctcgaggttg agcccagtga 120
caccatcgag aatgtcaagg caaagatcca agataaggaa ggcatccctc ctgaccagca 180
gaggctgatc tttgctggaa aacagctgga agatgggcgc accctgtctg actacaacat 240
ccagaaagag tccaccctgc acctggtgct ccgtctcaga ggtgggatgc aaatcttcgt 300
gaagacactc actggcaaga ccatcaccct tgaggtggag cccagtgaca ccatcgagaa 360
cgtcaaagca aagatccang acaaggaagg cattcctcct gaccagcaga ggttgatctt 420
tgccggaaag cagctggaag atgggcgcac cctgtctgac tacaacatcc agaaagagtc 480
taccctgcac ctgg 494

<210> 276
<211> 484
<212> DNA
<213> Homo sapiens

<400> 276
ggcttttaac cagaagtcaa acctgttcag acagaaggca gtcacagcag aaaaatcttc 60

939

agacaaaagg cagtcacagg tgtgcaggga gtgtgggcga ggctttagca ggaagtcaca 120
gctcatcata caccagagga cacacacagg agaaaagcct tatgtctgcg gagagtgtgg 180
gcgaggcttt atagttgagt cagtcctccg caaccacctg agtacacact ccgggggaga 240
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tcagaggaca cacacaaggg agaaatcgtt tatgtgcaca gtgtgtgggc gaggctttcg 360
tgaaaagtca gagctcatta agcaccagag aattcacacg ggggataagc cttatgtgtg 420
cagagattga ggccgaggct ttgtaaagga gatcatgtct caacacacac cagaggatta 480
catt 484

<210> 277
<211> 513
<212> DNA
<213> Homo sapiens

<400> 277
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ggaacatgca gcagctttgc gggccctaca agatcaggta tccatccaga gtgcagatgc 120
acaggaacaa gtggaagggc ttttggctga gaacaatgcc ttgaggacta gcctggctgc 180
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tgggctggca gctgagttgc agcagcagca ggctgagtac gaggacctta tgggacagaa 300
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acttcaagaa atagggcagg agaaggagca gttgacccag gaattacagg aggctcggaa 420
gagtgcggag aagcggaagg ccatgcttgg atgagctagc aatggaaacg ctgcaagaga 480
agtcccacac aaggaagagc ttgggagcag ttc 513

<210> 278
<211> 471
<212> DNA
<213> Homo sapiens

<400> 278
gaattcggca ccagccaagg ccctgtccct ggctcgggcc cttgaagagg ccttggaagc 60
caaagaggaa ctcgagcgga ccaacaaaat gctcaaagcc gaaatggaag acctggtcag 120
ctccaaggat gacgtgggca agaacgtcca tgagctggag aagtccaagc gggccctgga 180
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ggatctccaa gcccgggacg agcagaatga ggagaagagg aggcaactgc agagacagct 360
tcacgagtat gagacggaac tggaagacga gcgaaagcaa cgtgccctgg cagctgcagc 420
aaagaagaag ctggaagggg acctgaaaga cctggagctt caggccgact t 471

<210> 279
<211> 497
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (457)
<223> n=A,T,C or G
<221> misc_feature
<222> (471)
<223> n=A,T,C or G

<400> 279
gaattcggca cgaggccaca gaggcggcgg agagatggcc ttcagcggtt cccaggctcc 60

USSN: 09/254,113

ctacctgagt ccagctgtcc ccttttctgg gactattcaa ggaggtctcc aggacggact 120
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tcagactggc ttcagtggaa atgacattgc cttccacttc aaccctcggt ttgaagatgg 240
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tttcaaggtg atggtgaacg ggatcctctt cgtgcagtac ttccaccgcg tgcccttcca 420
ccgtgtggac accatctccg tcaatggctc tgtgcanctg tcctacatca ncttccagac 480
ccagacagtc atccaca 497

<210> 280
<211> 544
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (451)
<223> n=A,T,C or G

<400> 280
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agacgggtga tttctgcatt tccatctgag gtaccgggtt catctcacta gggagtgcca 120
gacagtgggc gcaggccagt gtgtgtgcgc accgtgcgcg agccgaagca gggcgaggca 180
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acggaatctc gctgattgct agcacagcag tcttagatca aactgcaagg ggggcaacga 420
ggctgggggg ggggcgcccg ccattgccca ngcttgctta ggtaaacaaa gcagccggga 480
agcttgaact gggtggagcc caccacagct caaggaggcc tgcctgcctc tgtagctcca 540
cctc 544

<210> 281
<211> 527
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (456)
<223> n=A,T,C or G

<400> 281
gaattcggca cgaggcctcg ctcagctcca acatggcaaa aatctccagc cctacagaga 60
ctgagcggtg catcgagtcc ctgattgctg tcttccagaa gtatgctgga aaggatggtt 120
ataactacac tctctccaag acagagttcc taagcttcat gaatacagaa ctagctgcct 180
tcacaaagaa ccagaaggac cctggtgtcc ttgaccgcat gatgaagaaa ctggacacca 240
acagtgatgg tcagctagat ttctcagaat ttcttaatct gattggtggc ctagctatgg 300
cttgccatga ctccttcctc aaggctgtcc cttcccagaa gcggacctga ggacccctg 360
gccctggcct tcaaacccac ccccttcct tccagcctt ctgtcatcat ctccacagcc 420
cacccatccc ctgagcacac taaccacctc atgcanggcc cccctgccaa tagtaataaa 480
gcaatgtcct tttttaaaac atgaaaaaaa aaaaaaaaaa actcgag 527

<210> 282
<211> 514
<212> DNA

<213> Homo sapiens

<220>
<221> misc_feature
<222> (494)
<223> n=A,T,C or G

<400> 282
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cccggctggt gctgcggggg ccccgggagg ttgaaaacta agcatgggga agagctgcaa 120
ggtggtcgtg tgtggccagg cgtctgtggg caaaacttca atcctggagc agcttctgta 180
tgggaaccat gtagtgggtt cggagatgat cgagacgcag gaggacatct acgtgggctc 240
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agatggggcc gaactgcccc gacactgctt ctcttgcact gatggctacg tcctggtcta 360
tagcacagat agcagagagt cttttcagcg tgtggagctg ctcaagaagg agattgacaa 420
atccaaggac aagaaggagg tcaccatcgt ggtccttggc aacaagtgtg acttacagga 480
gcagcggcgt gtanacccaa atgtggctca acac 514

<210> 283
<211> 484
<212> DNA
<213> Homo sapiens

<400> 283
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ggaccgcgcc gggaagagca cgcagagccg caagctggtg gaagcgctgt gcgccgcggg 120
ccaccgcgcc gaactgctcc ggttcccgga aagatcaact gaaatcggca aacttctgag 180
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ggct 484

<210> 284
<211> 514
<212> DNA
<213> Homo sapiens

<400> 284
gaattcggca cgaggcggag gccgcggagg ctcctcggtc cttcagcacc cctcggcccg 60
acgcacccac gcccctcacc ccccgagagc cgaaaatgga cccaagtggg gtcaaagtgc 120
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aagctgaagt gcaggccaac tcaggagcca ttgttaagct ggatgaaact ggaaacctga 420
tgatctcaga agggcatttt gcatctgaaa ccatacggac ccgtttgatg gagctgcacc 480
gccagtggga attacttttg gagaagatgc gaga 514

<210> 285
<211> 383
<212> DNA
<213> Homo sapiens

621 8912
942

GGCGCT 5823 4150

<400> 285
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gggcccccgc cgcgggcgcg gcgcccgcca tgggcgagga ggactactat ctggagctgt 120
gcgagcggcc ggtgcagttc gagaaggcga accctgtcaa ctgcgtcttc ttcgatgagg 180
ccaacaagca ggtttttgct gttcgatctg gtggagctac tggcgtggta gttaaaggcc 240
cagatgatag gaatcccatc tcatttagaa tggatgacaa aggagaagtg aagtgcatta 300
agttttcctt agaaaataag atattggctg ttcagaggac ctcaaagact gtggattttt 360
gtaattttat ccctgataat tcc 383

<210> 286
<211> 943
<212> DNA
<213> Homo sapiens

<400> 286
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tggtggcatg ctacgctcaa ccttgacacc agcgtcttca tctccacctt cctcggctaq 900
ccaaaacagc tggcaggact gccggtcaca caccagcacg tcc 943

<210> 287
<211> 1143
<212> DNA
<213> Homo sapiens

<400> 287
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gaggaagcaa agaaaatgat atcaggacta caggccttac tgctcaatgg atccttacct 120
gaagatgaac aggagaggcc cttggccctc tgtgaaccag gtgtcaatcc cgaggaacaa 180
ctgattataa tccaaagtcg tctggatcag agtatggagg agaatcagga cttaaagaag 240
gaactgctga aatgtaaaca agaagccaga aacttacagg ggataaagga tgccttgcag 300
cagagattga ctcagcagga cacatctgtt cttcagctca aacaagagct actgagggca 360
aatatggaca aagatgagct gcacaaccag aatgtggatc tgcagaggaa gctagatgag 420
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actattgaca gcttggagca gggcatttct agcctcatgg agcgcctgca tgttatggag 840
acgcagaaga aacaagaaag aaaggttcgg gtcaagtcac ccagaactca agtaggtagt 900
gaataccggg agtcctggcc ccctaactca aagttgcctc actcacagag ctctccaact 960
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gag 1143

<210> 288
<211> 881
<212> DNA
<213> Homo sapiens

<400> 288
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gggctggtgg gaacagccgc ccgaaggaag caccatgatt tcggccgcgc agttgttgga 120
tgagttaatg ggccgggacc gaaacctagc cccggacgag aagcgcagca acgtgcggtg 180
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tcaggttcta acagacaaaa ttgatgtact tctgcaacag attgaagaat tagggtctga 540
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tgaccatttg atgggaaaac aacacatggg ctatgccaaa attaaagcta ctgtagaaga 780
attaaaagaa aagttaagga aaagaaccga agaacctgat cgtgatgagc gtctaaaaaa 840
ggagaagcaa gaaagagaaa aaaaaaaaaa aaaaactcga g 881

<210> 289
<211> 987
<212> DNA
<213> Homo sapiens

<400> 289
gaattcggca cgagggactg tggtttccag gaatggtggc gtctcacgct tcttgtgctt 60
ttttctttgg ggcctccgag cggctggggt tgggggactg ggcaggaggc tccctgtaaa 120
catttggact tgggctgggg cagggggctgg tgttgggcaa agctgggggt ccaggctgga 180
gaagcagggg cccctccaga cgcagccttg ggagactcag catgtgcccc cctccccctca 240
tcacagaaca agacaatggt taaaaaccag aacagatgcc cagaaggggg taccatggcc 300
attaccagca tctcagacaa gggcaggctt caaacaggga ggcctgtggc aacccctccc 360
ctacgtctgg agctgagggg acaggggggag ctgagaacaa agagaggaaa gaggagaaaa 420
gcggcggggg aacaggcggg gagcgtgatc ttcttgcccc catcttcctc aggggttggg 480
gggtacaaag tcggcggtgg cccatcccgc caggccccgc tgcccctcag aagaggccgc 540
agtccttcag gttgttcttg atgatgacat cggtgacggc gtcaaacacg aactgcacgt 600
tcttggtgtc ggtggcgcac gtgaagtgcg tgtagatctc cttggtgtct ttgcgcttat 660
tcaggtcctc aaacttactc tggatgtagc tggctgcctc atcatatttg ttggcccctg 720
tatactcagg gaagcagatg gtcaggggac tgtgtgtgat cttctcctca aacaggtcct 780
tcttgttgag gaagaggatg atggacgtgt ctgtgaacca cttgttgttg cagatgctat 840
cgaatagctt catgctctca tgcatgcggt tcatctcctc gtcctcagct agcaccaagt 900
cataggcgct caaggctacg cagaagatga tggctgtgac gccctcaaag cagtggatcc 960
acttcttccg ctcagaccgc tgaccac 987

<210> 290
<211> 300
<212> DNA
<213> Homo sapien

944

<220>
<221> misc_feature
<222> (1)...(300)
<223> n = A,T,C or G

<400> 290
gattcaagat gtaccccatt gactttgaga aggatgatga cagcaacttt catatggatt 60
tcatcgtggc tgcatccaac ctccgggcag aaaactatga cattccttct gcagaccggc 120
acaagagcaa gctgattgca gggaagatca tcccagccat tgccacgacc acagcagccg 180
tggttggccc tgtgtgtctg gagctgtaca aggttgtgca ggggcaccga cancttgact 240
cctacangaa tgggtgcctc aacttgagcc ctgccttttct ttggtttctc tgaaccccct 300

<210> 291
<211> 352
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(352)
<223> n = A,T,C or G

<400> 291
aaccaagctg ccaccgggggg tggatcggat gcggcttgag aggcatctgt ctgccgagga 60
cttctcaagg gtatttgcca tgtcccctga agagtttggc aagctggctc tgtggaagcg 120
gaatgagctc aagaagaagg cctctctctt ctgatggccc ccacctgctc cgggacggcc 180
cccttacccc tgctgcttca gggtttttcc ccggcgggtt gggaggggca ggaggtgggg 240
tggaaatngg gtgggcncct ttcctcaggt agagngggggg gccaaaacct ctgcngtccc 300
cggagngagc tatggacttt cttcccccctc acaaggntgg gggcctcctg ct 352

<210> 292
<211> 511
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(511)
<223> n = A,T,C or G

<400> 292
cgcggtggct gcgcactcng cctgagaaac tcggcaagcg cgcagtgtcg actccccggt 60
ctatgccagg cgcatctcag ctaatccaaa agtaaatgag aaacttagaa aaagattgcc 120
aattccaaat caacatattt agagaaaatt ggaaaaggag aagcttacta cagctttatt 180
tgaggacttt ttaaagaacg ctgggttcta tctgtgagct gcaaatcttg gagcaaaaac 240
cagagacatt gccagagcaa acaagaacag aaatacaaat ggagaactgg tcaaaagaca 300
taacccacag ttatcttgaa caagaaacta cggggataaa taaaagtacg canccagatg 360
agcaactgac tatgaattct gagaaaagta tgcatcggaa atccactgaa ttagntaatg 420
aaataacatg ngagaacaca gaatggccag gggcagagat caacgaattt tcanatcatc 480
agttcttatc cagatgatga gtctgtttac t 511

<210> 293
<211> 526
<212> DNA

<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(526)
<223> n = A,T,C or G

<400> 293
gataaaaaga actttaatgg aaggcactgt tgtccaaaat cacataaagg gtaagagccc 60
acacggtacc accctgctct cctacttctc aaacccacat ccaccaccca gacaggaggg 120
tgcanacccc acaggaaatt acctcccgga gcactgactg atatttttcc ttaaaacaaa 180
aaaatggctg tctcagacta ataacagaac atcttaagag ctataccagc tattacagcc 240
tggtaatana agcagctttc taanaattcc caagtttata anaggcccaa naaatgcatt 300
tattctgttg tctattaagc ctccatgaca aggagaaagt tatgagtaaa tccttggttc 360
atcaggagtt aagagctgtg ngcctcatga ggagttaana gctgtgtgca taagcaggtt 420
caagaaacaa actcctgttt gttcgcctct ttgatggttc aaaaacattc agctgctttc 480
acctctanga caaaatgctt aaagaattta ctctcatcac cttggg 526

<210> 294
<211> 601
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(601)
<223> n = A,T,C or G

<400> 294
actttaaaag ccaaatatat ttttaaaaga tcatgcttat aataagtaaa ttacncatta 60
aggaaacatc aaaataaagt agatgaataa aaaggcacac tcgaaaaatt tgagcgcaga 120
aaggacagtt ctttttgttt tgtttctaat gtcggaagaa aaagaaagag atatattaaa 180
atcattgttt tcaagtgaag gtttctgtca gttgaagtag ttagcaatgg cttcttttct 240
cccgtgtcca aagcaggctc ttcctgcgct gacttctgag gaggngttca gtcctctgcc 300
atgtataggc gatacatcaa ggcgacggcc actgcagaga tggcagggat cacccagttg 360
gtccaccaac tggaactaga atcaatagta gtgataagag tttccggagg cttgtttaac 420
tttggtctgt catctggatg gagctcccca atgatgaatg ttttggacat ttccctggca 480
tctgtagant gcccgacatc ctcaaagttc tcagtagcng tcacctccac ttgttccctt 540
aaaacttctt ccccaccagg atgctcttcc agaaatttgg gncaaatcgn acaccttgtg 600
g 601

<210> 295
<211> 262
<212> DNA
<213> Homo sapien

<400> 295
cccttagccc caagggccct gggggcagcc accctcccgc ctgtcggccc gtagatttat 60
caagggtgtt atgggcccag ctttgggggg ccagtcccga tgcactttga ggggtgttgg 120
agaggggact cccccactcg cacttaactc aacggctctc gggccctggg gctgttttta 180
ccatgtttgt ttttgaagct caggtgtctc acgtctgggc tgcaccaggc gaagagagaa 240
attaaagatt tgaggttttt cc 262

<210> 296
<211> 598

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305
896
946

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<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(598)
<223> n = A,T,C or G

<400> 296
gttagaacaa ctcagcaaaa taaaattcct gtttattgtt ggacaacatt gtttcacaca 60
tacatcaaac aggccaaaaa aaataaacag caacttcata gacaaaaaag gaaaaaaaaa 120
gaaaccttct atctttggcc tttttaacca tctcatacaa accaactact tatagtacag 180
ctaagtacat acacaaaaaa gttactggaa tgctcggaat aagattgttt ttctgttgtc 240
atttttgctt tttttacaag gnttttttc tcctttgaga ttataatgaa catggncaca 300
ccacaagtaa agccagaagt aggacagana acgctccgaa ggctggtttg gtcatccgan 360
atcattaaaa atggctgacc ctaacaatat gtacaaaaat ataaaatgta aataaaaaat 420
acaaacaaat ttccttttta aagtactttt aagaaaaaaa gcagggcctt ggaagttttg 480
gttctttttt cctcccctgt tgcaaattct catggtttgg gttgggtggn gganancccg 540
tgtcatctgc gggtggcact gccccggngg gcgggcgggc ctctctctcg aangngac 598

<210> 297
<211> 509
<212> DNA
<213> Homo sapien

<400> 297
agaacacagg tgtcgtgaaa actaccccta aaagccaaaa tgggaaagga aaagactcat 60
atcaacattg tcgtcattgg acacgtagat tcgggcaagt ccaccactac tggccatctg 120
atctataaat gcggtggcat cgacaaaaga accattgaaa aatttgagaa ggaggctgct 180
gagatgggaa agggctcctt caagtatgcc tgggtcttgg ataaactgaa agctgagcgt 240
gaacgtggta tcaccattga tatctccttg tggaaatttg agaccagcaa gtactatgtg 300
actatcattg atgccccagg acacagagac tttatcaaaa acatgattac agggacatct 360
caggctgact gtgctgtcct gattgttgct gctggtgttg gtgaatttga agctggtatc 420
tccaagaatg ggcaggaccc gagagcatgc ccttctggct tacacactgg gtgtgaaaca 480
actaattgtc ggtgttaaca aaatggatt 509

<210> 298
<211> 267
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(267)
<223> n = A,T,C or G

<400> 298
gggacggggg aaaggagacg cttcttcctc ttgctgctct tctcgttccc gagatcagcg 60
gcggcggtga ccgcgagtgg gtcggcaccg tctccggctc cgggngcnaa caatgctgac 120
tgatagcgga ggcggnggca cctccttnna ggaggacctg gactctgtgg ctccgcgatc 180
cgccccagct ggggcctcgg agccgcctcc gccgggaggg gtcggtctgg ggatccncac 240
cgngaggctn tttggggagg gcgggcc 267

<210> 299
<211> 121

<212> DNA
<213> Homo sapien

<400> 299
ggcacgaggg ccctcggagc tcgtttccag atcgaggtaa gagggacttt cttaaaggcc 60
tagtctatgg gatggggcgg cggagggaat tttttgagaa ataaaatgaa gctgcagtgt 120
a 121

<210> 300
<211> 533
<212> DNA
<213> Homo sapien

<400> 300
aaggtgcaca gtatttgatg caggctgctg gtcttggtcg tatgaagcca aacacacttg 60
tccttggatt taagaaagat tggttgcaag cagatatgag ggatgtggat atgtatataa 120
acttatttca tgatgctttt gacatacaat atggagtagt ggttattcgc ctaaaagaag 180
gtctggatat atctcatctt caaggacaag aagaattatt gtcatcacaa gagaaatctc 240
ctggcaccaa ggatgtggta gtaagtgtgg aatatagtaa aaagtccgat ttagatactt 300
ccaaaccact cagtgaaaaa ccaattacac acaaagttga ggaagaggat ggcaagactg 360
caactcaacc actgttgaaa aaagaatcca aaggccctat tgtgccttta aatgtagctg 420
accaaaagct tcttgaagct agtacacagt ttcagaaaaa acaaggaaag aatactattg 480
atgtctggtg gctttttgat gatggaggtt tgaccttatt gataccttac ctt 533

<210> 301
<211> 560
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(560)
<223> n = A,T,C or G

<400> 301
ataaatgatc ccttttattg taagtaatgc gcaacactgg cctggctttg cactgcaagc 60
cctcggtcaa gatatagtca aataactatg gctgcaggtt ccacagttcc acaataacca 120
tggctgcacg atccacaatt cagacacaga catagagctg gggtgggtgg aaggggcagg 180
agggtggcag agtgcggact gtccccagcc ctggcctctc catgcanagt tggcccaggc 240
agacacaccc catggaatga tgagaaagtg acggcacggc cccttcccac agcaagcctg 300
gggctgccag gaactgccct tcanaacctt tgggcccagg tcnccctgaa ncccccacaac 360
tttttatctg gaataagtat taaaaaacaa taaattaagc aaacaacntg gnccttgaag 420
gatgttgacc nacatggtcc acagtttttg gcncaaaaaa ataagggctg gtttgctttt 480
tttggaaggc agggtttgtg gnttggcttt caaatnattt tcaaaccatt ccccagggag 540
gganaacccc cgggggggaa 560

<210> 302
<211> 599
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(599)
<223> n = A,T,C or G

<400> 302
gcaaagttac aaatttattg gtctggaaat aaatacaaat atctcattaa naaactcctc 60
tggaaagact tgtgcacaat agtttcccat ccgtactcag cctctcttgc cccgatcccc 120
gacttttcta ctcaaggcca gggaaggcct ccaaggngat gggcggcagg taacgagtca 180
ttgcctctca cgccacctgg aaggctggac tacttcctcc tcccaactgc ggggtcccan 240
aaatcctcgg gtcccagngg ctgacttaca atattcaatt cactctgacc aaacttccta 300
tganaaaatc cacggngagc caaaatgaaa agtacaaggc agtagtacag gaacctggca 360
gccgcactgg ccgcccanaa acgtcagtgg ngctgcccca ttcggcgaaa ggttagggag 420
caggaaaaga ggaagcagga gagggaagga aagtcccatg gaatatgtat tccanaatcc 480
ttacattttc tcagccaccg ctccccacgt gagttcccac ccccaccccg acaagaagca 540
aagagttctg aggatccaag aacgtgaccg ggtcanacan gttcagctac tgagttcac 599

<210> 303
<211> 591
<212> DNA
<213> Homo sapien

<400> 303
cggagttgta acgctccact gactgataga gcgaccggcc gaccatggcg cccggagtgg 60
cccgcgggcc gacgccgtac tggaggttgc gcctcggtgg cgccgcgctg ctcctgctgc 120
tcatcccggt ggccgccgcg caggagcctc ccggagctgc ttgttctcag aacacaaaca 180
aaacctgtga agagtgcctg aagaacgtct cctgtctttg gtgcaacact aacaaggctt 240
gtctggacta cccagttaca agcgtcttgc cacccggcttc cctttgtaaa ttgagctctg 300
cacgctgggg agtttgttgg gtgaactttg aggcgctgat catcaccatg tcggtagtcg 360
ggggaaccct cctcctgggc attgccatct gctgctgctg ctgctgcagg aggaagagga 420
gccggaagcc ggacaggagt gaggagaagg ccatgcgtga gcgggaggag aggcggatac 480
ggcaggagga acggagagca gagatgaaga caagacatga tgaaatcaga aaaaaatatg 540
gcctgtttaa agaagaaaac ccgtatgcta gatttgaaaa caactaaagc g 591

<210> 304
<211> 441
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(441)
<223> n = A,T,C or G

<400> 304
gctggacgga gacctgctgg aggaggagga gctggaggaa gcagaggagg aggaccggtc 60
gtcgctgctg ctgctgtcgc cgcccgcggc caccgcctct cagacccagc agatcccagg 120
cgggtccctg gggtctgtgc tgctgccagc cgccaggttc gatgcccggg aggcggcggc 180
ggcggcgggg gtgctgtacg gaggggacga tgcccagggc atgatggcgg cgatgctgtc 240
ccacgcctac ggccccggcg gttgtgtggggc ggcggcggcc gccctgaacg gggagcaggc 300
ggccctgctc cggagaaaga gcgtcaacac caccgagtgc gtcccggtgc ccagctccga 360
gcacgtcgcc gagatcgtcg gccgccaggg ttgtaaaatt aaagcactga nagccaagac 420
aaacacgtat atcaagactc c 441

<210> 305
<211> 491
<212> DNA
<213> Homo sapien

949

<400> 305
tcgccatgcc cccttcttag cactgcaccg ccaggtccat gctgctgcca ccccagacct 60
gggctttgcc tgccacctct gtgggcagag cttccgaggc tgggtggccc tggttctgca 120
tctgcgggcc cattcagctg caaagcggcc catcgcttgt cccaaatgcg agagacgctt 180
ctggcgacga aagcagcttc gagctcatct gcggcggtgc caccctcccg ccccggaggc 240
ccggcccttc atatgcggca actgtggccg gagctttgcc cagtgggacc agctagttgc 300
ccacaagcgg gtgcacgtag ctgaggccct ggaggaggcc gcagccaagg ctctggggcc 360
ccggccccagg ggccgccccg cggtgaccgc cccccggccc ggtggagatg ccgtcgaccg 420
ccccttccag tgtgcctgtt gtggcaagcg cttccggcac aagcccaact tgatcgctca 480
cccgcgcgtg c 491

<210> 306
<211> 547
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(547)
<223> n = A,T,C or G

<400> 306
tctctttctt ttaagacagg aatgtaagcc acaacattta caaatacaat gttttaactc 60
cctacatgta ggaagccaac ctgctccttt ttgatcttct tctttggcac aacctcagtg 120
gatttctctg attcagaacg agttctaatt gatcttctct gttgcttctt ttctactgag 180
cctgtagaac cagatgttgc ttcaggagat gatacactct gcgttggcct ttcatttctc 240
tggtttggtg tagaaattat aagcctgtct tgccccctga cacttatttc tgttttgtta 300
ccaattccct ttgttgaata aacaaattga tcgataaatt tcccatcccc tgtagcattc 360
tgaagagcaa acacttgttc aattttcaca actggagaca tgttacactt ctgcaaatcc 420
aggctccctt tgtgcatccg taatggaagc tggtaaggat ttccttgctg ccgcagtttt 480
ccaggctatt ttaacaggcg gnggctcttc ctctttccgc acttgtgtgc cgcctctggc 540
tatgtct 547

<210> 307
<211> 571
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(571)
<223> n = A,T,C or G

<400> 307
cgctgcatgt gataatgtca tcatttattt ttaaatggtt ctaaattgca natttaagtt 60
gatttcaaat caacctatt tttaaattac ttttaatagg aanaaatgaa gcaaggacat 120
acataatcta ctatatttga aggactcaaa caaatacatg tttggctgtg aattctgtac 180
tctcaccaaa acagagataa aaatccacct aaaatacact ttccttcatt tagtgcttgt 240
gggaaaaggt caagtattgc actttaaaat tactttcatc taacatttgc cccaactttc 300
cccctgaatt cactatatgt tttcagcaaa catgatttta taaatttttaa gtataaaagc 360
aactaggttt tctaattcaa ctttggaagg tttactttac tctacanagc tatttttgta 420
aaacggcata tttacttaca aaattganag ataggggcat ccagctgagg tacatttcct 480
cccttggcgt tgagtttctg gacttgggtc gggggcacag gcttgtgtga ctgccccgtg 540
gcccgataca tggcctggac cccaggatgc g 571

<210> 308
<211> 591
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(591)
<223> n = A,T,C or G

<400> 308
ctccttatgt gtctgcctac ttcattcttc ggcatttcct gcttatccaa gttcaccatt 60
tcaggtcacc actggatatc agttgcctgt atataattat caggcatttc ctgcttatcc 120
aagttcacca tttcaggtca ccactggata tcagttgcct gtatataatt atcaggcatt 180
tcctgcttat ccaagttcac catttcaggt caccactgga tatcagttgc ctgtatataa 240
ttatcaggca tttcctgctt atccaagttc accatttcag gtcaccactg gatatcagtt 300
gcctgtatat aattatcagg catttcctgc ttatccaagt tcaccatttc aggtcaccac 360
tggatatcag ttgcctgtat ataattatca ggcatttcct gcttatccaa gttcaccatt 420
tcaggtcacc actggatatc agttgcctgt atataattat caggcatttc ctgcttatcc 480
aaattcagca gttcaggtca ccactggata tcagttccat gtatacaatt accagatgcc 540
accgcagtgc cctgttgggg gagcaaagga gaaatntgtg gaccgaagca t 591

<210> 309
<211> 591
<212> DNA
<213> Homo sapien

<400> 309
aggggtgcca cgtactccca actgtggtcg cgctctcacc ccttctgctg ctctcgtggc 60
cccctcgcga tggcgggcat cctgtttgag gatatttccy atgtgaagga tattgacccg 120
gagggcaaga agtttgaccg aggtaagtaa gtgtctcgac tgcattgtga gagtgaatct 180
ttcaagatgg atctaatctt agatgtaaac attcaaatct accctgtaga cttgggtgac 240
aagtttcggt tggtcatagc tagtaccttg tatgaagatg gtaccctgga tgatggtgaa 300
tacaacccca ctgatgatag gccttccagg gctgaccagt ttgagtatgt aatgtatgga 360
aaagtgtaca ggattgaggg agatgaaact tctactgaag cagcaacacg cctgctgaga 420
ttgagagctg ctgagtggca gtgctccaga atcacgggat ggggccttct gtttcagctc 480
tgcgtacgtg tcctatgggg gcctgctcat gaggctgcag ggggatgcca acaacctgca 540
tggattcgag gtggactcca gagtttatct cctgatgaag aagctagcct t 591

<210> 310
<211> 488
<212> DNA
<213> Homo sapien

<400> 310
tggtctcaag cctgaagagg ctccgcccac aagctggccc atgaagttag caatgcctgt 60
ggcttcagtc aattgtcttg agactgtgaa gaggctgaaa gacaccttcc cgggtggaag 120
aaggagttca ctgaaaactt atcttaaact gacccttccc tttgagtgag tcttcattcc 180
tctcccatgt gggaacccag cctccgatgc cccggggact aggggaaaca gttggaggtc 240
cgtgccgtcc ccagcctgcc acgggtgcga ggacagccaa gtcctgagtg actcaagatg 300
cttcacttac atggaagaaa cttctaaaac tctaccgagt ggtttttgta tatactaaag 360
ttctatttag agctttttctg ttttgggcaa gttcgctgct ccttctattt gggcactttg 420
gtttttgtac tgtctttttgt gacggcattg attgaacatt ttttactagt agtcttatga 480
cttttgta 488

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951

<210> 311
<211> 511
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(511)
<223> n = A,T,C or G

<400> 311
cccgtttntg nagcaaaana gggggaagat ttataggtag aggcgacaaa cctaccgagc 60
ctggtgatag ctggttgtcc aagatagaat cttagttcaa ctttaaattt gcccacagaa 120
ccctctaaat ccccttgtaa atttaactgt tagtccaaag aggaacagct ctttggacac 180
taggaaaaaa ccttgtagag agagtaaaaa atttaacacc catagtaggc ctaaaagcag 240
ccaccaatta agaaagcgtt caagctcaac acccactacc taaaaaatcc caaacatata 300
actgaacccc tcacacccaa ttggaccaat ctatcaccct atagaagaac taatgttagt 360
ataagtaaca tgaaaacatt ctcctccgca taagcctgcg tcagattaaa acactgaact 420
gacaattaac agcccaatat ctacaatcaa ccaacaagtc attattaccc tcactgtcaa 480
cccaacacag gcatgctcat aaggaaaggt t 511

<210> 312
<211> 591
<212> DNA
<213> Homo sapien

<400> 312
gaacttgcgt tgaaggaagc agaaactgat gaaataaaaa ttttgctgga agaaagcaga 60
gcccagcaga aggagacctt gaaatctctt cttgaacaag agacagaaaa tttgagaaca 120
gaaattagta aactcaacca aaagattcag gataataatg aaaattatca ggtgggctta 180
gcagagctaa gaactttaat gacaattgaa aaagatcagt gtatttccga gttaattagt 240
agacatgaag aagaatctaa tatacttaaa gctgaattaa acaaagtaac atctttgcat 300
aaccaagcat ttgaaataga aaaaaacctа aaagaacaaa taattgaact gcagagtaaa 360
ttggattcag aattgagtgc tcttgaaaga caaaaagatg aaaaaattac ccaacaagaa 420
gagaaatacg aagctattat ccagaacctt gagaaagaca gacaaaaatt ggtcagcagc 480
caggagcaag acagagaaca gttaattcag aagcttaatt gtgaaaaaga tgaagctatt 540
cagactgccc taaaagaatt taaattggag agagaagttg ttgagaaaga g 591

<210> 313
<211> 373
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(373)
<223> n = A,T,C or G

<400> 313
ttgattttta ttctgnattt tattactgaa atangttgtc ctantnatcc caccccacaa 60
taaaaatntn acccangccc cccntttctt tncctnatnc cctnttccac cacaccatcc 120
cggaacaagt gctccaggat tccctgccca ctggccattt tggagtgtgn ccattgggta 180
gcaatgtgga aaccaccaag gcctttgtgg anaaaatgga gggggttgag ggagncccan 240
gaggggctna tttgagggcc tttgccactt gctcataggc gagctcnatc tcctcntnat 300
ctgnacangt ggaagcaaat tcttcccggg cgtnggnant gctnaagnac cgatgcactc 360

cccggaaggn ctn 373

<210> 314
<211> 591
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(591)
<223> n = A,T,C or G

<400> 314
cccgtgccgc cgccgcctcc tgggaagaga ggaagcggga gaggagccca cgtcgcctgt 60
cacccaatat ctccagccgc gcagtcccga agagtgtaag atgttcgcct gcgccaagct 120
cgcctgcacc ccctctctga tccgagctgg atccagagtt gcatacagac caattttctgc 180
atcagtgtta tctcgaccag aggctagtag gactggagag ggctctacgg tatttaatgg 240
ggcccagaat ggtgtgtctc agctaatcca aagggagttt cagaccagtg caatcagcag 300
agacattgat actgctgcca aatttattgg tgcaggtgct gcaacagtag gagtggctgg 360
ttctggtgct ggtattggaa cagtctttgg cagccttatc attggttatg ccagaaaccc 420
ttcgctgaag cagcagctgt tctcatatgc tatcctggga tttgccttgt ctgaagctat 480
gggtctcttt tgtttgatgg ttgctttctt gattttgttt gccatgtaac aaattactgc 540
ttgacatgtt ggcattcata ttaattacng atgtaattct gtgtatctta c 591

<210> 315
<211> 591
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(591)
<223> n = A,T,C or G

<400> 315
aagcccttca ccaacaaaga tgcctatact tgtgcaaatt gcagtgcttt tgtccacaaa 60
ggctgccgag aaagtctagc ctcctgtgca aaggtcaaaa tgaagcagcc caaagggagc 120
cttcaggcac atgacacatc atcactgccc acggtcatta tgagaaacaa gccctcacag 180
cccaaggagc gtcctcggtc cgcagtcctc ctggtggatg aaaccgctac caccccaata 240
tttgccaata gacgatccca gcagagtgtc tcgctctcca aaagtgtctc catacagaac 300
atcactggag ctggcaatga tgagaacatg tcaaacacct ggaaattcct gtctcattca 360
acagactcac taaataaaat cagcaaggtc aatgagtcaa cagaatcact tactgatgag 420
ggtacagaca tgaatgaagg acaactactg ggagactttg agattgagtc caaacagctg 480
gaagcagagt cttggagtcg gataatagac agcaagtttc taaaacagcc aaaagaaaga 540
tgtgggtcaa acngcgagaa gtaatatatg agttggatgc agacagagtt t 591

<210> 316
<211> 591
<212> DNA
<213> Homo sapien

<400> 316
gtttttataa gaataaaatt ccattcaagc cagatggtgt ttacattgaa gaagttctaa 60
gtaaatggaa aggagattat gaaaaactgg agcacaacca cacttacatt caatggcttt 120
tccccctgag agaacaaggc ttgaacttct atgccaaaga actaactaca tatgaaattg 180

aggaattcaa aaaaacaaaa gaagcaatta gaagattcct cctggcttat aaaatgatgc 240
tagaattttt tggaataaaa ctgactgata aaactggaaa tgttgctcgg gctgttaact 300
ggcaggaaag atttcagcat ctgaatgagt cccagcacaa ctatttaaga atcactcgta 360
ttcttaaaag ccttggtgag cttggatatg aaagttttaa atctcctctt gtaaaattta 420
ttcttcatga agctcttgtg gagaatacta ttcccaatat taagcagagt gctctagagt 480
attttgttta tacaattaga gacagaagag aaaggagaaa gctcctgcgg ttcgcccaga 540
aacactacac gccttcagag aactttatct ggggacccgc ctcgaaaaga a 591

<210> 317
<211> 323
<212> DNA
<213> Homo sapien

<400> 317
ccaagctacg gaagcaagtg gaagagattt ttaatttgaa atttgctcaa gctcttggac 60
tcaccgaggc agtaaaagta ccatatcctg tgtttgaatc aaacccggag ttcttccatg 120
tggaaggctt gccagagggg attcccttcc gaagccctac ctggtttgga attccacgac 180
ttgaaaggat cgtccacggg agtaataaaa tcaagttcgt tgttaaaaaa cctgaactag 240
ttatttccta cttgcctcct gggatggcta gtaaaataaa cactaaagct ttgcagtccc 300
ccaaaagacc acgaagtcct ggg 323

<210> 318
<211> 591
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(591)
<223> n = A,T,C or G

<400> 318
gatggcgtac ttggcttgga gactggcgcg gcgttcgtgt ccgagttctc tgcaggtcac 60
tagtttcccg gtagttcagc tgcacatgaa tagaacagca atgagagcca gtcagaagga 120
ctttgaaaat tcaatgaatc aagtgaaact cttgaaaaag gatccaggaa acgaagtgaa 180
gctaaaactc tacgcgctat ataagcaggc cactgaagga ccttgtaaca tgcccaaacc 240
aggtgtattt gacttgatca acaaggccaa atgggacgca tggaatgccc ttggcagcct 300
gcccaaggaa gctgccaggc agaactatgt ggatttggtg tccagtttga gtccttcatt 360
ggaatcctct agtcaggtgg agcctggaac agacaggaaa tcaactgggt ttgaaactct 420
ggtggtgacc tccgaagatg gcatcacaaa gatcatgttc aaccggccca aaaagaaaaa 480
tgccataaac actgagatgt atcatgaaat tatgcgtgca cttaaagctg ccagcaanga 540
tgactcaatc atcacttgtt ttaacaggaa atggtgacta ttacagtagn g 591

<210> 319
<211> 591
<212> DNA
<213> Homo sapien

<400> 319
gaattcggca cgaggttgct gctaagcgaa cgcccctttgg agcttacgga ggccttctga 60
aagacttcac tgctactgac ttgtctgaat ttgctgccaa ggctgccttg tctgctggca 120
aagtctcacc tgaaacagtt gacagtgtga ttatgggcaa tgtcctgcag agttcttcag 180
atgctatata tttggcaagg catgttggtt tgcgtgtggg aatcccaaag gagacccccag 240
ctctcacgat taataggctc tgtggttctg gttttcagtc cattgtgaat ggatgtcagg 300
aaatttgtgt taaagaagct gaagttgttt tatgtggagg aaccgaaagc atgagccaag 360

ctccctactg tgtcagaaat gtgcgttttg gaaccaagct tggatcagat atcaagctgg 420
aagattcttt atgggtatca ttaacagatc agcatgtcca gctccccatg gcaatgactg 480
cagagaatct tgctgtaaaa cacaaaataa gcagagaaga atgtgacaaa tatgccctgc 540
agtcacagca gagatggaaa gctgctaatg atgctggcta ctttaatgat g 591

<210> 320
<211> 591
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(591)
<223> n = A,T,C or G

<400> 320
ggctccggcg tctgcagggg tcgccgagct aacccgtggc taggcgagtg gggcggggcg 60
gccggcacca tgtcgaggca ggcgaaccgt ggcaccgaga gcaagaaaat gagctctgag 120
ctcttcaccc tgacctatgg tgccctggtc acccagctat gtaaggacta tgaaaatgat 180
gaagatgtga ataaacagct ggacaaaatg ggctttaaca ttggagtccg gctgattgaa 240
gatttcttgg ctcggtcaaa tgttgggagg tgccatgact ttcgggaaac tgcggatgtc 300
attgccaagg tggcgttcaa gatgtacttg ggcatcactc caagcattac taattggagc 360
ccagctggtg atgaattctc cctcattttg gaaaataacc ccttggtgga ctttgtggaa 420
cttcctgata accactcatc ccttatttat tccaatctct tgtgtggggt gttgcgggga 480
gctttggaga tggtccagat ggctngngga ggcccaagtt tgtccaggac accctnaaag 540
gagacgggng tgacagaaat ccggatgaga ttcatcaggc ggattganga c 591

<210> 321
<211> 260
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(260)
<223> n = A,T,C or G

<400> 321
ctgcttggct ccacacgtgg gccgccgtag gtattccgac cggtaattcc tcctattggt 60
gtgcagcagc cacattgaag gatagagtgg cagcagaggc caaggatcgt gagttgatgg 120
agtttgctgc tgaaaatgaa gggaagtctg ggggaggtct ccacagcgta gctgaggggg 180
tgcggctaag tccagagcct ggcagggagg gagtaaggga cttagcaggg gcggaggagt 240
tctgcggngg anaggagggg 260

<210> 322
<211> 559
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(559)
<223> n = A,T,C or G

<400> 322

ttccacatga catggagtgt gaagctggat gagcacatca ttccactggg aagcatggca 60
nttaacagca tctcaaaact gactnanctc acccagtctt ccatgtattc acttcctaat 120
gcacccactc tggcanacct gnaggacnat acacatgaag ncantgatga tcagccagan 180
aancctcact ttgactctcg canngtgata tttgagctgg attcatgcaa tggnagtggg 240
aaagtttgcc ttgtctacaa aagtgggaaa ccagnattag cagaanacac tgagatctgg 300
ttcctgnaca nancgttata ctggcatttt ctcacanaca cctttactgc ctattaccgc 360
ctgctcatca cccacctggg cctgccccag tggcaatatg ccttcccagc tatggcatta 420
gcccacaggc caagcaatgg ttcagcatgt ataaacctat cacctacaac acaaacctgc 480
tcacagaaga naccgactcc tttgtgaata agctagatcc canctnagtg tttaagagca 540
agaacaagat cgttatccc 559

<210> 323
<211> 492
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(492)
<223> n = A,T,C or G

<400> 323
cctgtcctccc agccgtacca gcgagggctc ggccggcagc gccgggctgg gyggcggcgg 60
cgccggcgcc ggagccgggg tgggtgcagg cggcggcggg ggcagcggcg cgagcagcgg 120
cggcgggggcc ggggggctgc aacccagcag ccgcgctggc ggcggccggc cctccagccc 180
cagcccgtcg gtggtgagcg agaaggagaa ggaagagttg gagcggctgc agaaagagga 240
ggaggagagg aagaagaggc tgcagctgta tgtgttcgtg atgcgctgca tcgcctaccc 300
ctttaatgcc aagcagccca ccgacatggc tcgccggcag cagaagatca gcaaacagca 360
gctgcagaca gtcaaggacc ggtttcaggc tttcctcaat ggggaaaccc anatcatggc 420
tgacgaagcc ttcatgaacr gctgtngcag agttactatg aggtgttcct gaagaccacc 480
cgtgtggccg ca 492

<210> 324
<211> 474
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(474)
<223> n = A,T,C or G

<400> 324
aatttcagca acatacttct caatttcttc aggatttaaa atcttgaggg attgatctcg 60
cctcatgaca gcaagttcaa tgtttttgcc acctgactga accacttcca ggagtgcctt 120
gatcaccagc ttaatggtca natcatctgt ttcaatggct tcgtcagtat agttcttctc 180
cagnaactca cgcactgact tggcaccccg gcctatggca ttggccttcc aggcatggta 240
tgtgcccgag gggtcagtct gatagagcct aggagtgcca tcaaagtcga aacccacgat 300
gagggcagag atgccaaacg gcctgcgccc attgctctgc gtataacgct gcttcanact 360
ggcgatgtag cgggtgatgt actccacagt gaccgggtcc tccacagtca gccggtggct 420
ctggcactcc acccgggccc tgttgatgac tatccttgca tcggcggtga ggcc 474

<210> 325
<211> 532
<212> DNA

635
906
956

<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(532)
<223> n = A,T,C or G

<400> 325
gaggagacag gacagagcgt ctggagaggc aggaggacac cgagttcccc gtgttggcct 60
ccaggtcctg tgcttgcgga gccgtccggc ggctgggatc gagccccgac aatgggcaac 120
gcgcaggagc ggccgtcaga gactatcgac cgcgagcgga aacgcctggt cgagacgctg 180
caggcggact cgggactgct gttggacgcg ctgctggcgc ggggcgtgct caccgggcca 240
gagtacgagg cattggatgc actgcctgat gccgagcgca gggtgcgccg cctactgctg 300
ctggtgcagg gcaagggcga ggccgcctgc caggagctgc tacgctgtgc ccagcgtacc 360
gcgggcgcgc cggaccccgc ttgggactgg cagcacgtgg gtccgggcta ccgggaccgc 420
agctatgacc ctccatgccc aggccactgg acgccggagg cacccggctc ggggaccaca 480
tgccccgggt tgcccagact tcagaccctg acgaggncgg gggccctgag gg 532

<210> 326
<211> 322
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(322)
<223> n = A,T,C or G

<400> 326
caaaattaac atttttatta aatcaagtta aaaaaaatgt tcagtgtana aaagtcaaca 60
agggttttaa caaaaccaaa atataccttt ttatacaata tatgtatata ttagcagcaa 120
actacttctg anattctctt tcttttatgt tcttctagtt attttaaaga aagcataaac 180
aatgtacatt agtatggaat gtcagcaaat ccactcttag tcctttattc tgtgatttgg 240
gccttctaca aaatactttg tgattctcac taatgaatat taagaacata cccaatttta 300
actaaaaagt agtgaaacag tg 322

<210> 327
<211> 387
<212> DNA
<213> Homo sapien

<400> 327
aaaaccgtgt actattagcc atggtcaacc ccaccgtgtt cttcgacatt gccgtcgacg 60
gcgagccctt gggccgcgtc tcctttgagc tgtttgcaga caaggtccca aagacagcag 120
aaaattttcg tgctctgagc actggagaga aaggatttgg ttataagggt tcctgctttc 180
acagaattat tccagggttt atgtgtcagg gtggtgactt cacacgccat aatggcactg 240
gtggcaagtc catctatggg gagaaatttg aagatgagaa cttcatccta aagcatacgg 300
gtcctggcat cttgtccatg gcaaatgctg gacccaacac aaatggttcc cagtttttca 360
tctgcactgc caagactgag tggttgg 387

<210> 328
<211> 502
<212> DNA
<213> Homo sapien

C96
9/05
957

09172235 - 022027

<220>
<221> misc_feature
<222> (1)...(502)
<223> n = A,T,C or G

<400> 328
agcagcccgg cgcggccgcc gcgccggcgg gcggcaaggc tccgggccag catgggggct 60
tcgtggtgac tgtcaagcaa gagcgcggcg agggtccacg cgcgggcgag aggggtcccc 120
acgaggagga gccggtgaag aaacgcggct ggcccaaggg caagaagcgg aagaagattc 180
tgccgaatgg gcccaaggca ccggtcacgg gctacgtgcg cttcctgaac gagcggcgcg 240
agcagatccg cacgcgccac ccggatctgc cctttcccga gatcaccaag atgctgggcg 300
ccgagtggag caagctgcag ccaacggaaa agcagcggta cctggatgag gccnagagag 360
agaagcagca gtacatgaag gagctgcggg cgtaccagca gtctgaagcc tataagatgt 420
gcacggagaa gatccaggag aagaagatca agaaagaaga ctcgagctct gggctcatga 480
acactcttct gaatggacac aa 502

<210> 329
<211> 463
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(463)
<223> n = A,T,C or G

<400> 329
caagttgcac attttaattt acaattttta ccaataaaaa ggattagttt acaaaaaggg 60
aagtccttta tacaaaataa ggacaatttg taaaganaat ccactgtcat gttttgcctt 120
gtcaagtcaa aacccaaata gcttgttttg gtaaaattat tccagaaaca taatccagac 180
aaaatcaata acgtcatcag cttcctaacc atgtttaana ggaataactt catgaacatt 240
ttgccctgaa ctgaanagtt ctaaatactt gtaaaccttt aggaaaaaat gactgctcgc 300
aggcagcttg actggtaaga gggtacacca nagactccgg gtcactcact gtcagaatat 360
tcttatacat acaatgagtc tccacgcctg tacaatgagt gtcgtgcaac ataattggag 420
taatggcctc taaaatttta caagtaaact ttattgnggc ccc 463

<210> 330
<211> 500
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(500)
<223> n = A,T,C or G

<400> 330
taattataga tctacaaaat atgaaatgta ttccaagaat gcagaaaaac catctagaag 60
caaaaggact ataaaacaaa aacagagaag aaaattcatg gctaaaccag ctgaagaaca 120
gcttgatgtg ggacagtcta aagatgaaaa catacataca tcacatatta cccaagacga 180
atttcaaaga aattcagaca gaaatatgga agagcatgaa gagatgggaa atgattgtgt 240
ttccaaaaaa acagatgcca cctgtgggaa gcaagaaaag tagcactaga aaagataagg 300
aagaatctaa aaagaagcgc ttttccagtg agtccaagaa caaacttgtn cctgaagaag 360
tgacttcaac tgtcacgaaa agtcgaanaa tttccangcg tccatctgat tggtgggtgg 420
taaaancaga ggagagtcct gtttatagca attcttcagt aagaaatgaa ttaccaantg 480

C37
958
958

catcacaatn ntgcccggaa 500

<210> 331
<211> 494
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(494)
<223> n = A,T,C or G

<400> 331
tctctctctc tctcaaaatt acagtgttca ttgtcattga cctcagcagc aaatttgact 60
tgaattcact taggatcgca ggaatcaggg gaaagtgatt ttaaaggtgg tttctccagc 120
acattttaag aaaagggacc aaaagttatt ttagcttcct caatagattg catgttgctt 180
attaggataa taaattaata ttaaatgcaa tatatgtctt gnctttatta tggcatctat 240
ttaggagttg ttcaaatcac tgcagtaggg ctctgcaaat aaaataatgn aacctattat 300
catggatcta atgnactgna actttatcag tgaaaggnaa aatctcaaat aacaagtaca 360
aacattggac aattacctat aaagatttgt aaaaggaaaa tttttccata gatttcattc 420
ttggcatttt gtaaagacga ccctgcagnc ccctgtttgn aacttttta ataaaataga 480
catctgttta cttg 494

<210> 332
<211> 538
<212> DNA
<213> Homo sapien

<400> 332
aaagaacaaa tggaacgcga tggttgttct gaacaagagt ctcaaccgtg tgcatttatt 60
gggataggaa atagtgacca agaaatgcag cagctaaact tggaaggaaa gaactattgc 120
acagccaaaa cattgtatat atctgactca gacaagcgaa agcacttcat gttgtctgta 180
aagatgttct atggcaacag tgatgacatt ggtgtgttcc tcagcaagcg gataaaagtc 240
atctccaaac cttccaaaaa gaagcagtca ttgaaaaatg ctgacttatg cattgcctca 300
ggaacaaagg tggctctgtt taatcgacta cgatcccaga cagttagtac cagatacttg 360
catgtagaag gaggtaattt tcatgccagt tcacagcagt ggggagcctt ttttattcat 420
ctcttggatg atgatgaatc agaaggagaa gaattcacag tccgagatgg ctacatccat 480
tatggacaaa cagtcaaact tgtgtgctca gttactggca tggcactccc aagattga 538

<210> 333
<211> 499
<212> DNA
<213> Homo sapien

<400> 333
ctcagcctgc gggactgctc ggctcggctt ctaggcggtt ttgatgaaca cctggcttta 60
ttcttgcaat gaagaaaggt tctcaacaaa aaatattctc caaagcaaag ataccatcat 120
catctcactc tcctatccca tcatctatgt ccaatatgag atctaggtca ctttcacctt 180
tgattggatc agagactcta ccttttcatt ctggaggaca gtggtgtgag caagttgaga 240
ttgcagatga aaacaatatg cttttggact atcaagacca taaaggagct gattcacatg 300
caggagttag atatattaca gaggccctca ttaaaaaact tactaaacag gataatttgg 360
ctttgataaa atctctgaac ctttcacttt ctaaagacgg tggcaagaaa tttaagtata 420
ttgagaattt ggaaaaatgt gttaaacttg aagtactgaa tctcagctat aatctaatag 480
ggaagattga aaagtcgga 499

959

<210> 334
<211> 561
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(561)
<223> n = A,T,C or G

<400> 334
ttcccggtag ttcagctgca catgaataga acagcaatga gagccagtca gaaggacttt 60
gaaaattcaa tgaatcaagt gaaactcttg aaaaaggatc caggaaacga agtgaagcta 120
aaactctacg cgctatataa gcaggccact gaaggacctt gtaacatgcc caaaccaggt 180
gtatttgact tgatcaacaa ggccaaatgg gacgcatgga atgcccttgg cagcctgccc 240
aaggaagctg ccaggcagaa ctatgtggat ttggtgtcca gtttgagtcc ttcattggaa 300
tcctctagtc aggtggagcc tggaacagac aggaaatcaa ctgggtttga aactctggtg 360
gtgacctccg aagatggcat cacaaagatc atgttcaacc cggcccaaaa agaaaaatgc 420
cataaacact gagatgtatc atgaaattat gcgtgcactt aaagctgcca gcaaggatga 480
ctcaatcatc actgttttaa cangaaatgg tgactattac agtagtggga atgatctgac 540
taacttcnct gatattcccc c 561

<210> 335
<211> 551
<212> DNA
<213> Homo sapien

<400> 335
aagctggtca tggctgggga gaccaccaac tcccgcggcc agcggctgcc ccagaaggga 60
gacgtggaga tgctgtgcgg cgggccgccc tgccagggct tcagcggcat gaaccgcttc 120
aattcgcgca cctactccaa gttcaaaaac tctctggtgg tttccttcct cagctactgc 180
gactactacc ggccccggtt cttcctcctg gagaatgtca ggaactttgt ctccttcaag 240
cgctccatgg tcctgaagct caccctccgc tgcctggtcc gcatgggcta tcagtgcacc 300
ttcggcgtgc tgcaggccgg tcagtacggc gtggcccaga ctaggaggcg ggccatcatc 360
ctggccgcgg cccctggaga gaagctccct ctgttcccgg agccactgca cgtgtttgct 420
ccccgggcct gccagctgag cgtggtgggt ggatgacaag aagtttgtga gcaacataac 480
caggttgagc tcgggtcctt tccggaccat acggtgcgag aaacgatgtc cgacctgccg 540
gaagtgcgga a 551

<210> 336
<211> 540
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(540)
<223> n = A,T,C or G

<400> 336
aggtctatgt ctactgaagg caataaacga ggaatgatcc agcttattgt tgcaaggaga 60
ataagcaagt gcaatgagct gaagtcacct gggagccccc ctggacctga gctgcccatt 120
gaaacagcgt tggatgatag agaacgaaga atttcccatt ccctctacag tgggattgag 180
gggcttgatg aatcgcccag cagaaatgct gccctcagta ggataatggg taaataccag 240
ctgtcccctа cagtgaatat gccccaagat gacactgtca ttatagaaga tgacaggttg 300

ccagtgcttc ctccacatct ctctgaccag tcctcttcca gctcccatga tgatgtgggg 360
tttgtgacgg cagatgctgg tacttgggcc aaggctgcaa tcagtgattc agccgactgc 420
tctttgagtc cagatgttga tccagttctt gcttttcaac gaaaaaggat ttggacgtca 480
gaagtatgtc agaaaaacgc accaaagcaa ttttcanatg ccagtcaatt ggatttcgtt 540

<210> 337
<211> 422
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(422)
<223> n = A,T,C or G

<400> 337
gcagcaggaa cagttacagc agcagcagca acagcagctg ttgcaacagc agcaggaaca 60
attgcagcag caacaactgc agcctcctcc cctggagccc gaggaggagg aagaggtgga 120
gctggagctc atgccggtgg acctggggtc agagcaggag ctggagcagc agcggcagga 180
gttggagcgg cagcaggagc tggaacggca gcaggagcag cggcagctgc agctcaaact 240
gcaggaggag ctgcagcagc tggagcaaca gctggagcag cagcagcagc agctggagca 300
gcaggaggtg cagctggagc tgaccccggt ggagctaggc gcccagcagc aggaggtgca 360
gctggagctg acccccgtgc agccggagct gcagctggaa ctggtgccan cccagggggc 420
gg 422

<210> 338
<211> 601
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(601)
<223> n = A,T,C or G

<400> 338
catcttacga acgctctatg atgtcttatg agcggtctat gatgtccccc atggctgaac 60
gctctatgat gtcagcctac gagcgctcta tgatgtcagc ctacgagcgc tctatgatgt 120
cccctatggc tgagcgctct atgatgtcag cttatgaacg ctccatgatg tcagcttatg 180
aacgctccat gatgtcccca atggctgatc gatctatgat gtccatgggt gctgaccggt 240
ctatgatgtc gtcatactct gctgctgacc ggtctatgat gtcatcgtac tctgcagctg 300
accgatctat gatgtcatct tatactgctg atcgttcaat gatgtctatg gctgctgatt 360
cttacaccga ttcttacact gacacatata cagaggcata tatggtgcca cctttgcctc 420
ctgaagagcc cccaacaatg ccaccgttgc cacctgagga gccaccaatg acaccaccat 480
tgcctnctga ggaaccaccc agaggggtcca gcattgccca cttgagcagt cagcattaac 540
cagcttgaaa atacttggcc ctacanangg tgccatcatt accatctgaa gagctgtatc 600
g 601

<210> 339
<211> 440
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature

<222> (1)...(440)
<223> n = A,T,C or G

<400> 339
agagggagga ggcccaactg gtgatgctgc tgctgctgct gctgccgccg ccgccgcctc 60
tattgctgat actctagtgg ggctggaagg gtggttccta ttcgcaccat cgccaaccag 120
agacagaggg aaaaaaaaaa ccggcagcca ctgctgatgt tgggttcgga ggctgcatcc 180
gactcggtca caaggaaaat ggattcagtt tgcatctctc cctcctttaa acagcttctc 240
cgggtctcag catggtatca aagcttgaaa gagagaagac tcaagaagcg aagaggattc 300
gtgagctgga gcagcgcaag cacacggtgc tggtgacaga actcaaagcc aagctccatg 360
aggagaagat gaaggagctg caggctgtga gggagaacct tatcaagcag cacgacagga 420
aatgtcaang acggtgaagg 440

<210> 340
<211> 450
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(450)
<223> n = A,T,C or G

<400> 340
gatttccagg ggcggatatt gagtgtcgac ccagaggaag aaagggagga gggcccgcct 60
aggattcctc aggccgacca gtggaagtct tcaaacaaga gcctggtgga ggctctgggg 120
ctggaagccg agggtgcagt tcctgagaca cagactttga ccggatggag taaggggttc 180
attggcatgc acagggaaat gcaagtcaac cccatttcaa agcggatggg gcccatgact 240
gtggtcagga tggacgcttc agtccagcca ggccctttte ggaccctgct ccagtttcct 300
tatacgggac aactggatga aaaggaaaag gatttggtgg gcctggctca gatcgcagag 360
gtcctcgaga tgttcgattt gaggatgatg gtggaaaaca tcatgaacaa ggaagccttc 420
atgaaccagg agattacgaa nnccttccac 450

<210> 341
<211> 451
<212> DNA
<213> Homo sapien

<400> 341
aacagctatt aaaacagaaa atggatgaac ttcataagaa gttgcatcag gtggtggaga 60
catcccatga ggatctgccc gcttcccagg aaaggtccga ggttaatcca gcacgtatgg 120
ggccaagtgt aggctcccag caggaactga gagcgccatg tcttccagta acctatcagc 180
agacaccagt gaacatggaa aagaacccaa gagaggcacc tcctgttgtt cctcctttgg 240
caaatgctat ttctgcagct ttggtgtccc cagccaccag ccagagcatt gctcctcctg 300
ttcctttgaa agcccagaca gtaacagact ccatgtttgc agtggccagc aaagatgctg 360
gatgtgtgaa taagagtact catgaattca agccacagag tggagcagag atcaaagaag 420
ggtgtgaaac acataaggtt gccaacacaa g 451

<210> 342
<211> 498
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature

647
962
962

09624-052301.60

<222> (1)...(498)
<223> n = A,T,C or G

<400> 342
ctcaagcagg ctattgaaga ggaaggaggc gatccagata atattgaatt aactgtttca 60
actgatactc caaacaagaa accaactaaa ggcaaaggta aaaaacatga agcagatgag 120
ttgagtggag atgcttctgt gggaagatga tgcttttatc aaggactgtg aattggagaa 180
tcaagaggca catgagcaag atggaaatga tgaactaaag gactctgaag aatttggtga 240
aaatgaagaa gaaaaatgtgc attccaagga gttactctct gcagaagaaa acaagagagc 300
tcatgaatta atagaggcag aaggaataga agatatagaa aaagaggaca tcgaaagtca 360
ggaaattgaa gctcaagaag gtgaagatga taccttttcta acagcccaag atggtgagga 420
agaagaaaat gagaaagata tagcagggtt ctggtgatgg cncacaagaa gtatntaaac 480
ctcttccttc aaaaaggg 498

<210> 343
<211> 491
<212> DNA
<213> Homo sapien

<400> 343
ccgaccccta ctcggcggcg caactccaca accagtacgg ccccatgaat atgaacatgg 60
gtatgaacat ggcagcagcc gcggcccacc accaccacca ccaccaccac caccccggtg 120
ccttttccg ctatatgcgg cagcagtgca tcaagcagga gctaatctgc aagtggatcg 180
accccgagca actgagcaat cccaagaaga gctgcaacaa aactttcagc accatgcacg 240
agctggtgac acacgtctcg gtggagcacg tcggcggccc ggagcagagc aaccacgtct 300
gcttctggga ggagtgtccg cgcgagggca agcccttcaa ggccaaatac aaactggtca 360
accacatccg cgtgcacaca ggcgagaaac ccttccctgc ccttccgggt gtggcaaagt 420
cttcgcgcgc tccgagaacc tcaagatcca caaaaggacc acacagggga gaagccgtcc 480
agtggagttg a 491

<210> 344
<211> 412
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(412)
<223> n = A,T,C or G

<400> 344
gtgcgctgtc ttcccgcttg cgtcagggac ctgcccgact cagtggccgc catggcatca 60
gatgaaggca aacttttttgt tggagggctg agttttgaca ccaatgagca gtcgctggag 120
caggtcttct caaagtacgg acagatctct gaagtggtgg ttgtgaaaga cagggagacc 180
cagagatctc ggggatttgg gtttgtcacc tttgagaaca ttgacgacgc taaggatgcc 240
atgatggcca tgaatgggaa gtctgtagat ggacggcaga tccgagtaga ccaggcaggc 300
aagtcgtcan acaaccgatc ccgtgggtac cgtggtggct ctgccggggg ccggggcttc 360
ttccgtgggg gcccgangac ggggcccgtg ggttctctaa aagaagaggg ga 412

<210> 345
<211> 498
<212> DNA
<213> Homo sapien

<400> 345

aactagtctc gggccatcct ttctgcgcac ccggtgtcgc tgggctgcac cccgggcggg 60
gacgtccgcc gggcacggga gggggccaag atgccgatca ataaatcaga gaagccagaa 120
agctgcgata atgtgaaggt tgttgttagg tgccggcccc tcaatgagag agagaaatca 180
atgtgctaca aacaggctgt cagtgtggat gagatgaggg gaactatcac tgtacataag 240
actgattctt ccaatgaacc tccaaagaca tttacttttg atactgtttt tggaccagag 300
agtaaacaac ttgatgttta taacttaact gcaagaccta ttattgattc tgtacttgaa 360
ggctacaatg ggactatttt tgcatatgga caaaccggaa caggcaaaac ttttaccatg 420
gaaaggtgtc gagctattcc tgaacttaga ggaataattc cccaatttct ttgctcacaa 480
tatttgggcc atatttgc 498

<210> 346
<211> 427
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(427)
<223> n = A,T,C or G

<400> 346
agatggcggt cgccgtgaga actttgcagg aacagctgga aaaggccaaa gagagtctta 60
agaacgtgga tgagaacatt cgcaagctca ccgggcggga tccgaatgac gtgaggccca 120
tccaagccag attgctggcc ctttctggtc ctggtggagg tagaggacgt ggtagtttat 180
tactgaggcg tggattctca gatagtggag gaggacccgc agccaaacag agagaccttg 240
aaggggcagt cagtaggctg ggcggggagc gtcggaccag aagagaatca cgccaggaaa 300
gcgacccgga ggatgatgat gttaaaaagc cagcattgca gtctccannt gtagctacct 360
cccaaagagc gccccacgta gagaccttat ccagggatca aaattttgga tgaaaaaggg 420
gaaagcc 427

<210> 347
<211> 280
<212> DNA
<213> Homo sapien

<400> 347
cacagaaagt tctccgctcc cagacatggg tccctcggct tcctgcctcg gaagcgcagc 60
agcaggcatc gtgggaaggt gaagagcttc cctaaggatg acccgtccaa gccggtccac 120
ctcacagcct tcctgggata caaggctggc atgactcaca tcgtgcggga agtcgacagg 180
ccgggatcca aggtgaacaa gaaggaggtg gtggaggctg tgaccattgt agagacacca 240
cccatggtgg ttgtgggcat tgtgggctac gtggaaaccc 280

<210> 348
<211> 411
<212> DNA
<213> Homo sapien

<400> 348
caactatgat gtgcctgaaa aatgggcacg attctatact gcagaagtag ttcttgcatt 60
ggatgcaatc cattccatgg gttttattca cagagatgtg aagcctgata acatgctgct 120
ggataaatct ggacatttga agttagcaga ttttggtact tgtatgaaga tgaataagga 180
aggcatggta cgatgtgata cagcggttgg aacacctgat tatatttccc ctgaagtatt 240
aaaatcccaa ggtggtgatg gttattatgg aagagaatgt gactggtggt cggttggggt 300
atttttatac gaaatgcttg taggtgatac acctttttat gcagattctt tggttggaac 360
ttacagtaaa attatgaacc attaaaaatt cacttacctt tcctgatgat a 411

6942 963

964

<210> 349
<211> 408
<212> DNA
<213> Homo sapien

<400> 349
gatgggcatc tctcgggaca actggcacaa gcgccgcaaa accgggggca agagaaagcc 60
ctaccacaag aagcggaagt atgagttggg gcgcccagct gccaacacca agattggccc 120
ccgccgcatc cacacagtcc gtgtgcgggg aggtaacaag aaataccgtg ccctgaggtt 180
ggacgtgggg aatttctcct ggggctcaga gtgttgtact cgtaaaacaa ggatcatcga 240
tgttgtctac aatgcatcta ataacgagct ggttcgtacc aagaccctgg tgaagaattg 300
catcgtgctc atcgacagca caccgtaccg acagtggtac gagtcccact atgcgctgcc 360
cctgggccgc aagaagggag ccaaactgac ttctgaggaa gaagaaaa 408

<210> 350
<211> 409
<212> DNA
<213> Homo sapien

<400> 350
ggttccccca gctctgggta cccggctctg catcgcgtcg ccatgatggg ccatcgtcca 60
gtgctcgtgc tcagccagaa cacaaagcgt gaatccggaa gaaaagttca atctggaaac 120
atcaatgctg ccaagactat tgcagatatc atccgaacat gtttgggacc caagtccatg 180
atgaagatgc ttttggaccc aatgggaggc attgtgatga ccaatgatgg caatgccatt 240
cttcgagaga ttcaagtcca gcatccagcg gccaagtcca tgatcgaaat tagccggacc 300
caggatgaag aggttggaga tgggaccaca tcagtaatta ttcttgcagg ggaaatgctg 360
tctgtagctg agcacttcct ggagcagcag atgcacccaa caggtgggg 409

<210> 351
<211> 226
<212> DNA
<213> Homo sapien

<400> 351
aatcccaaac atataactga actcctcaca cccaattgga ccaatctatc accctataga 60
agaactaatg ttagtataag taacatgaaa acattctcct ccgcataagc ctgcgtcaga 120
ttaaaacact gaactgacaa ttaacagccc aatatctaca atcaaccaac aagtcattat 180
taccctcact gtcaacccaa cacaggcatg ctcataagga aaggtt 226

<210> 352
<211> 410
<212> DNA
<213> Homo sapien

<400> 352
gcggaggggc tggctgggca ggaggggttg gcggggcagc agggccgcgg ccatggggag 60
cttgaaggag gagctgctca aagccatctg gcacgccttc accgcactcg accaggacca 120
cagcggcaag gtctccaagt cccagctcaa ggtcctttcc cataacctgt gcacggtgct 180
gaaggttcct catgacccag ttgcccttga agagcacttc agggatgatg atgagggtcc 240
agtgtccaac cagggctaca tgccttattt aaacaggttc attttggaaa aggtccaaga 300
caactttgac aagattgaat tcaataggat gtgttggacc ctctgtgtca aaaaaaacct 360
cacaaagaat cccctgctca ttacagaaga agatgcattt aaaatatggg 410

<210> 353

644
P/5
965

09/782,150

<211> 380
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(380)
<223> n = A,T,C or G

<400> 353
gagtttattt agaaagtatc atagtgtaaa caaacaaatt gtaccacttt gattttcttg 60
gaatacaaga ctcgtgatgc aaagctgaag ttgtgtgtac aagactcttg acagttgtgc 120
ttctctagga ggntgggttt ttttaaaaaa agaattatct gngaaccata cgtgattaat 180
aaagatttcc tttaaggcan aggctggtcn agatgctgct gttatcttct gcctcagaca 240
gacagtataa gnggtcttgt ttctaagatt cctaccacca gttactttgg gccaagtatc 300
cacatcccct tgcgtatggg aggnggggtga anagtgttgg atgcaaagng gttattatgg 360
gaagnagctc natggtaaaa 380

<210> 354
<211> 379
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(375)
<223> n = A,T,C or G

<400> 354
caacacatct ttattaaaca cctgaagtta ctgggaggag gccatgatgc tggacacact 60
gtcaaagtca atcttctcca caatgttctt gggtttaatg ctctcttctt ggctacagan 120
gaanatctgc cccgactngt cggcactcca gccgtatttg ctcatccaca cctttagctg 180
gctgtccgac agancccccga gcatntcggc cagcagccan cggncaatgt gctggtaagt 240
gatacccaca acatggcaga taaactttcg gacanagtct tcaaagccag ttataccttc 300
caagaggtcc atgttttcat ccagggcttg ccansagcct ggaaatggca ggtctccaac 360
aggtccccca ggtacaaaa 379

<210> 355
<211> 499
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(499)
<223> n = A,T,C or G

<400> 355
gtccagagct gctggtgctc ccgttcccca gaccctaccc ctatccccag tggagccgga 60
gtgcgggcgc gccccaccac cgccctcacc atggtgctgt tggcagcagc ggtctgcaca 120
aaagcaggaa aggctattgt ttctcgacag tttgtggaaa tgacccgaac tcggattgag 180
ggcttattag cagcttttcc aaagctcatg aacactggaa aacaacatac gtttgttgaa 240
acagagagtg taagatatgt ctaccagcct atggagaaac tgtatatggt actgatcact 300
accaaaaaca gcaacatttt agaagatttg gagaccctaa ggctcttctc aagagtgatc 360
cctgaatatt gcgagcctta gaagagaatg aaatatctga gcactgnttt gatttgattt 420

ttgcttttga tgaaaatgtc gcactgggat acccgggang aatgttaact tggcacagat 480
canaaccttt cacagaaaa 499

<210> 356
<211> 511
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(511)
<223> n = A,T,C or G

<400> 356
gggcttctgc tgaggggca ggcggagctt gaggaaaccg cagataagtt tttttctctt 60
tgaaagatag agatteatac aactacttaa aaaatatagt caataggtta ctaagatatt 120
gcttagcgtt aagtttttaa cgtaatttta atagcttaag attttaagag aaaatatgaa 180
gacttagaag agtagcatga ggaaggaaaa gataaaaggt ttctaaaaca tgacggaggt 240
tgagatgaag cttcttcatg gagtaaaaaa tgtatttaaa agaaaattga gagaaaggac 300
tacagagccc cgaattaata ccaatagaag ggcaatgctt ttagattaaa atgaaggtga 360
cttaaacagc ttaaagttta ntttaaaagt tgtaggtgat taaaataatt tgaaggcgat 420
cttttaaaaa gagattaaac ccgaaggtga ttaaaagacc ttgaaatcca tgacgccagg 480
gagaattgcc gtcatttaaa gcctagttaa c 511

<210> 357
<211> 511
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(511)
<223> n = A,T,C or G

<400> 357
gatacttcac atttccctag ggacgggagc ccgaggggtc cgttcggccc tcttcctctc 60
gctgggccga caccccgctg taggaccgta acccttagtc ccaatgcctc cgtaagcgga 120
gttgagtggg tgcctgtggt tggagctgtg gaggtgtccc cggtggcgag cgcggccaga 180
actgcggtca cttaagtttt ccgtgtgcgg gttgcaagga grgtgcgtgc gtctggtata 240
atttggcttc ctgagattct gcttacaaga aaggagtggg aaataccctt ggaaagaaaa 300
ctaaaacagt aagaaaacca aaacttattt ttacatggnt gtcagcacat ttaccgatat 360
ggacactttt cccaataatt tcctcctggt ggagacagtg gattgacagg ttctcagtcg 420
gaattccaga aaaatgttaa ttgatgaaaa gggtacnatg tgagcatcat aaagntaatt 480
attaanacac tgaaggctga acacacaagg g 511

<210> 358
<211> 401
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

967

<400> 358
acggatgaag atgatgacct tcaagaaaat gaagacaata aacaacataa agaaagcttg 60
aaaagagtga cctttgcttt accagatgat gcggaaactg aagatacagg tgttttaaat 120
gtaaagaaaa attctgatga agttaaatcc tcctttgaaa aaagacagga aaagatgaat 180
gaaaaaattg catctttaga aaaagagttg ttagaaaaaa agcccgtggc agcttcaggg 240
ggaagtgaca gcacagaaga ggccagagaa cacctcctgg aggagaccct acctttgcca 300
tctgcccgat ggccctgtga ttacagagga acccccttca ctggagattt ctttaacnga 360
ngatagagat cngnttggga tatgtntcct taagaaaacc t 401

<210> 359
<211> 511
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(511)
<223> n = A,T,C or G

<400> 359
gcgatgcccg cgcgcccagg acgcctcctc ccgctgctgg cccggccggc ggccctgact 60
gcgctgctgc tgctgctgct gggccatggc ggcggcgggc gctggggcgc ccgggcccag 120
gaggcggcgg cggcggcggc ggacgggccc cccgcggcag acggcgagga cggacaggac 180
ccgcacagca agcacctgta cacggccgac atgttccacgc acgggatcca gagcgcccgc 240
gcacttcgtc atgttcttcg cgccctggtg tggacacttg ccagcggctt gcagccgant 300
ttggaatgac cttgggangа acaaatacaa cagcatggaa agaatgccaa aagtctatgt 360
ggnttaaagt ggacttgcac nggccacttc gactngtgct cccccaaggg gnggggaagat 420
acccacctta aaacttttca accaagccaa aaactttgaa aaccaggtct cggattcaaa 480
atggaaaact gatgttcaac ctgaacaaga a 511

<210> 360
<211> 511
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(511)
<223> n = A,T,C or G

<400> 360
tactgggaga ctttgagatt gagtccaaac agctggaagc agagtcttgg agtcggataa 60
tagacagcaa gtttctaaaa cagcaaaaga aagatgtggt caaacggcaa gaagtaatat 120
atgagttgat gcagacagag tttcatcatg tcccgactct caagatcatg agtggtgtgt 180
cnagccnggg gatgatggcg gatctgnttt ttgagcanca gatggtagaa aaagctggtt 240
ccctgtttgg atgagcttga tcagtatccc atacccattc tttccagagg attcttggag 300
ccggaaagaa nggagtcttc ttggtgggat aaaaagtgaa aaagaacttt ctcttcaana 360
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647
968

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cttgcggagg ctgcagctta acgcggaccc tgagaagcct ggcgcttncn gctggaactt 240
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gcccaccaca cgactaagct cacaagaagg ctgaactnnc tgattctnaa cctagaanta 360
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cctcccgtct ttggctcgtt ggctgccgcc gccggggctt cgccagcctt caagtcgaga 180
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agggtgacaa tgaccaaaag tgacactgga gaatttttat agcaacctta tcgctcacat 360
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aantttcttt cgtttgaaan aaaaacaaan a 511

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that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10*:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

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In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

BINDING AGENTS

The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to a lung tumor protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to a lung tumor protein if it reacts at a detectable level (within, for example, an ELISA) with a lung tumor protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a

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complex is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10^3 L/mol. The binding constant may be determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as lung cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a lung tumor protein will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (*e.g.*, blood, sera, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

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Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of

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mammals (*e.g.*, mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol. 6*:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention

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may be used in the purification process in, for example, an affinity chromatography step.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988) and digested by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ^{90}Y, ^{123}I, ^{125}I, ^{131}I, ^{186}Re, ^{188}Re, ^{211}At, and ^{212}Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

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It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler et al.).

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It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small

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molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

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T CELLS

Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for a lung tumor protein. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the ISOLEX™ system, available from Nexell Therapeutics Inc., Irvine, CA (see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a lung tumor polypeptide, polynucleotide encoding a lung tumor polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, a lung tumor polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a lung tumor polypeptide if the T cells kill

target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., *Cancer Res. 54*:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (*e.g.*, by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a lung tumor polypeptide (100 ng/ml - 100 μg/ml, preferably 200 ng/ml - 25 μg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (*e.g.*, TNF or IFN-γ) is indicative of T cell activation (*see* Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a lung tumor polypeptide, polynucleotide or polypeptide-expressing APC may be $CD4^-$ and/or $CD8^+$. Lung tumor protein-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from either a patient or a related, or unrelated, donor and are administered to the patient following stimulation and expansion.

For therapeutic purposes, $CD4^+$ or $CD8^+$ T cells that proliferate in response to a lung tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a lung tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a lung tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of a lung tumor protein can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

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PHARMACEUTICAL COMPOSITIONS AND VACCINES

Within certain aspects, polypeptides, polynucleotides, T cells and/or binding agents disclosed herein may be incorporated into pharmaceutical compositions or immunogenic compositions (*i.e.*, vaccines). Pharmaceutical compositions comprise one or more such compounds and a physiologically acceptable carrier. Vaccines may comprise one or more such compounds and an immunostimulant. An immunostimulant may be any substance that enhances or potentiates an immune response to an exogenous antigen. Examples of immunostimulants include adjuvants, biodegradable microspheres (*e.g.*, polylactic galactide) and liposomes (into which the compound is incorporated; *see e.g.*, Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and vaccines within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound, within the composition or vaccine.

A pharmaceutical composition or vaccine may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems 15*:143-198, 1998, and references cited therein. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope. In a preferred embodiment, the DNA may be introduced using a viral expression system (*e.g.*, vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-

pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., *Proc. Natl. Acad. Sci. USA 86*:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci. 569*:86-103, 1989; Flexner et al., *Vaccine 8*:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques 6*:616-627, 1988; Rosenfeld et al., *Science 252*:431-434, 1991; Kolls et al., *Proc. Natl. Acad. Sci. USA 91*:215-219, 1994; Kass-Eisler et al., *Proc. Natl. Acad. Sci. USA 90*:11498-11502, 1993; Guzman et al., *Circulation 88*:2838-2848, 1993; and Guzman et al., *Clr. Res. 73*:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., *Science 259*:1745-1749, 1993 and reviewed by Cohen, *Science 259*:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (*e.g.*, polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Such compositions may also comprise buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione, adjuvants (*e.g.*, aluminum hydroxide) and/or preservatives.

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Alternatively, compositions of the present invention may be formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of immunostimulants may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bortadella pertussis* or *Mycobacterium tuberculosis* derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

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Within the vaccines provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (*e.g.*, IFN-γ, TNFα, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (*e.g.*, IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, *Ann. Rev. Immunol.* 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Ribi ImmunoChem Research Inc. (Hamilton, MT) (*see* US Patent Nos. 4,436,727;

4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555. Another preferred adjuvant is a saponin, preferably QS21, which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprises an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210. Any vaccine provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient.

The compositions described herein may be administered as part of a sustained release formulation (*i.e.*, a formulation such as a capsule, sponge or gel (composed of polysaccharides, for example) that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and vaccines to facilitate production of an antigen-specific immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient

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APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med. 50*:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency, and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (*see* Zitvogel et al., *Nature Med. 4*:594-600, 1998).

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Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFα, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce maturation and proliferation of dendritic cells.

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Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcγ receptor, mannose receptor and DEC-205 marker. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (*e.g.*, CD54 and CD11) and costimulatory molecules (*e.g.*, CD40, CD80, CD86 and 4-1BB).

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APCs may generally be transfected with a polynucleotide encoding a lung tumor protein (or portion or other variant thereof) such that the lung tumor polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place *ex vivo*, and a composition or vaccine comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs *in vivo*. *In vivo* and *ex vivo* transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., *Immunology and cell Biology* 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the lung tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (*e.g.*, vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (*e.g.*, a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

CANCER THERAPY

In further aspects of the present invention, the compositions described herein may

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be used for immunotherapy of cancer, such as lung cancer. Within such methods, pharmaceutical compositions and vaccines are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and vaccines may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. A cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs.

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Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides disclosed herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as $CD8^+$ cytotoxic T lymphocytes and $CD4^+$ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition

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in vivo are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (*see*, for example, Cheever et al., *Immunological Reviews 157*:177, 1997).

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Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions disclosed herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (*i.e.*, untreated) level. Such response can be monitored by

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measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells *in vitro*. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 μg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a lung tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

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METHODS FOR DETECTING CANCER

In general, a cancer may be detected in a patient based on the presence of one or more lung tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as lung cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a lung tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

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There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length lung tumor proteins and portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present

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invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 μg, and preferably about 100 ng to about 1 μg, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see*, *e.g.*, Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or

Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with lung cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as lung cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to

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a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result.

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In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1μg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use lung tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such lung tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a lung tumor protein in a biological sample. Within certain methods, a biological sample comprising $CD4^+$ and/or $CD8^+$ T cells isolated from a patient is incubated with a lung tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated *in vitro* for 2-9 days (typically 4 days) at 37°C with polypeptide (*e.g.*, 5 - 25 μg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of lung tumor polypeptide to serve as a control. For $CD4^+$ T cells, activation is preferably detected by evaluating proliferation of the T cells. For $CD8^+$ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

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As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a lung tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a lung tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the lung tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a lung tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a lung tumor protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes will hybridize to a polynucleotide encoding a polypeptide disclosed herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence recited in SEQ ID NOS: 1-31, 49-55, 63,64, 66, 68-72, 78-80, 84-92 and 217-389. Techniques for both PCR based assays and hybridization assays are well known in the art (*see*, for example, Mullis et al., *Cold Spring Harbor Symp. Quant. Biol.*, *51*:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken

from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the disclosed compositions may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple lung tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

DIAGNOSTIC KITS

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for

performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a lung tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a lung tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a lung tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a lung tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1

PREPARATION OF LUNG TUMOR-SPECIFIC cDNA SEQUENCES USING DIFFERENTIAL DISPLAY RT-PCR

This example illustrates the preparation of cDNA molecules encoding lung tumor-specific polypeptides using a differential display screen.

Tissue samples were prepared from lung tumor and normal tissue of a patient with lung cancer that was confirmed by pathology after removal of samples from the patient. Normal RNA and tumor RNA was extracted from the samples and mRNA was isolated and converted into cDNA using a $(dT)_{12}AG$ (SEQ ID NO: 47) anchored 3' primer. Differential display PCR

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was then executed using a randomly chosen primer (SEQ ID NO: 48). Amplification conditions were standard buffer containing 1.5 mM $MgCl_2$, 20 pmol of primer, 500 pmol dNTP and 1 unit of Taq DNA polymerase (Perkin-Elmer, Branchburg, NJ). Forty cycles of amplification were performed using 94 °C denaturation for 30 seconds, 42 °C annealing for 1 minute and 72 °C extension for 30 seconds. Bands that were repeatedly observed to be specific to the RNA fingerprint pattern of the tumor were cut out of a silver stained gel, subcloned into the pGEM-T vector (Promega, Madison, WI) and sequenced. The isolated 3' sequences are provided in SEQ ID NO: 1-16.

Comparison of these sequences to those in the public databases using the BLASTN program, revealed no significant homologies to the sequences provided in SEQ ID NO: 1-11. To the best of the inventors' knowledge, none of the isolated DNA sequences have previously been shown to be expressed at a greater level in human lung tumor tissue than in normal lung tissue.

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Example 2

USE OF PATIENT SERA TO IDENTIFY DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by expression screening of lung tumor samples with autologous patient sera.

A human lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a late SCID mouse passaged human squamous epithelial lung carcinoma and poly A+ RNA was isolated using the Message Maker kit (Gibco BRL, Gaithersburg, MD). The resulting library was screened using *E. coli*-absorbed autologous patient serum, as described in Sambrook et al., (*Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989), with the secondary antibody being goat anti-human IgG-A-M (H + L) conjugated with alkaline phosphatase, developed with NBT/BCIP (Gibco BRL). Positive plaques expressing immunoreactive antigens were purified. Phagemid from the plaques was rescued and the nucleotide sequences of the clones was determined.

Fifteen clones were isolated, referred to hereinafter as LT86-1 – LT86-15. The isolated cDNA sequences for LT86-1 – LT86-8 and LT86-10 - LT86-15 are provided in SEQ ID NO: 17-24 and 26-31, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 32-39 and 41-46, respectively. The determined cDNA sequence for LT86-9 is provided in SEQ ID NO: 25, with the corresponding predicted amino acid sequences from the 3' and 5' ends being provided in SEQ ID NO: 40 and 65, respectively. These sequences were compared to those in the gene bank as described above. Clones LT86-3, LT86-6 – LT86-9, LT86-11 – LT86-13 and LT86-15 (SEQ ID NO: 19, 22-25, 27-29 and 31, respectively) were found to show some homology to previously identified expressed sequence tags (ESTs), with clones LT86-6, LT86-8, LT86-11, LT86-12 and LT86-15 appearing to be similar or identical to each other. Clone LT86-3 was found to show some homology with a human transcription

repressor. Clones LT86-6, 8, 9, 11, 12 and 15 were found to show some homology to a yeast RNA Pol II transcription regulation mediator. Clone LT86-13 was found to show some homology with a *C. elegans* leucine aminopeptidase. Clone LT86-9 appears to contain two inserts, with the 5' sequence showing homology to the previously identified antisense sequence of interferon alpha-induced P27, and the 3' sequence being similar to LT86-6. Clone LT86-14 (SEQ ID NO: 30) was found to show some homology to the trithorax gene and has an "RGD" cell attachment sequence and a beta-Lactamase A site which functions in hydrolysis of penicillin. Clones LT86-1, LT86-2, LT86-4, LT86-5 and LT86-10 (SEQ ID NOS: 17, 18, 20, 21 and 26, respectively) were found to show homology to previously identified genes. A subsequently determined extended cDNA sequence for LT86-4 is provided in SEQ ID NO: 66, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 67.

Subsequent studies led to the isolation of five additional clones, referred to as LT86-20, LT86-21, LT86-22, LT86-26 and LT86-27. The determined 5' cDNA sequences for LT86-20, LT86-22, LT86-26 and LT86-27 are provided in SEQ ID NO: 68 and 70-72, respectively, with the determined 3' cDNA sequences for LT86-21 being provided in SEQ ID NO: 69. The corresponding predicted amino acid sequences for LT86-20, LT86-21, LT86-22, LT86-26 and LT86-27 are provided in SEQ ID NO: 73-77, respectively. LT86-22 and LT86-27 were found to be highly similar to each other. Comparison of these sequences to those in the gene bank as described above, revealed no significant homologies to LT86-22 and LT86-27. LT86-20, LT86-21 and LT86-26 were found to show homology to previously identified genes.

In further studies, a cDNA expression library was prepared using mRNA from a lung small cell carcinoma cell line in the lambda ZAP Express expression vector (Stratagene), and screened as described above, with a pool of two lung small cell carcinoma patient sera. The sera pool was adsorbed with *E. coli* lysate and human PBMC lysate was added to the serum to block antibody to proteins found in normal tissue. Seventy-three clones were isolated. The determined cDNA sequences of these clones are provided in SEQ ID NO: 290-362. The sequences of SEQ ID NO: 289-292, 294, 296-297, 300, 302, 303, 305, 307-315, 317-320, 322-325, 327-332, 334, 335, 338-341, 343-352, 354-358, 360 and 362 were found to show some

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homology to previously isolated genes. The sequences of SEQ ID NO: 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 and 361 were found to show some homology to previously identified ESTs.

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Example 3

USE OF MOUSE ANTISERA TO IDENTIFY DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by screening of lung tumor cDNA libraries with mouse anti-tumor sera.

A directional cDNA lung tumor expression library was prepared as described above in Example 2. Sera was obtained from SCID mice containing late passaged human squamous cell and adenocarcinoma tumors. These sera were pooled and injected into normal mice to produce anti-lung tumor serum. Approximately 200,000 PFUs were screened from the unamplified library using this antiserum. Using a goat anti-mouse IgG-A-M (H+L) alkaline phosphatase second antibody developed with NBT/BCIP (BRL Labs.), approximately 40 positive plaques were identified. Phage was purified and phagemid excised for 9 clones with inserts in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined cDNA sequences for 7 of the isolated clones (hereinafter referred to as L86S-3, L86S-12, L86S-16, L86S-25, L86S-36, L86S-40 and L86S-46) are provided in SEQ ID NO: 49-55, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 56-62, respectively. The 5' cDNA sequences for the remaining 2 clones (hereinafter referred to as L86S-30 and L86S-41) are provided in SEQ ID NO: 63 and 64. L86S-36 and L86S-46 were subsequently determined to represent the same gene. Comparison of these sequences with those in the public database as described above, revealed no significant homologies to clones L86S-30, L86S-36 and L86S-46 (SEQ ID NO: 63, 53 and 55, respectively). L86S-16 (SEQ ID NO: 51) was found to show some homology to an EST previously identified in fetal lung and germ cell tumor. The remaining clones were found to show at least some degree of homology to previously identified human genes. Subsequently determined extended cDNA sequences for L86S-12, L86S-36 and L86S-46 are provided in SEQ ID NO: 78-80, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 81-83.

Subsequent studies led to the determination of 5' cDNA sequences for an

additional nine clones, referred to as L86S-6, L86S-11, L86S-14, L86S-29, L86S-34, L86S-39, L86S-47, L86S-49 and L86S-51 (SEQ ID NO: 84-92, respectively). The corresponding predicted amino acid sequences are provided in SEQ ID NO: 93-101, respectively. L86S-30, L86S-39 and L86S-47 were found to be similar to each other. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to L86S-14. L86S-29 was found to show some homology to a previously identified EST. L86S-6, L86S-11, L86S-34, L86S-39, L86S-47, L86S-49 and L86S-51 were found to show some homology to previously identified genes.

In further studies, a directional cDNA library was constructed using a Stratagene kit with a Lambda Zap Express vector. Total RNA for the library was isolated from two primary squamous lung tumors and poly A+ RNA was isolated using an oligo dT column. Antiserum was developed in normal mice using a pool of sera from three SCID mice implanted with human squamous lung carcinomas. Approximately 700,000 PFUs were screened from the unamplified library with *E. coli* absorbed mouse anti-SCID tumor serum. Positive plaques were identified as described above. Phage was purified and phagemid excised for 180 clones with inserts in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined cDNA sequences for 23 of the isolated clones are provided in SEQ ID NO: 126-148. Comparison of these sequences with those in the public database as described above revealed no significant homologies to the sequences of SEQ ID NO: 139 and 143-148. The sequences of SEQ ID NO: 126-138 and 140-142 were found to show homology to previously identified human polynucleotide sequences.

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Example 4

USE OF MOUSE ANTISERA TO SCREEN LUNG TUMOR LIBRARIES PREPARED FROM SCID MICE

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by screening of lung tumor cDNA libraries prepared from SCID mice with mouse anti-tumor sera.

A directional cDNA lung tumor expression library was prepared using a Stratagene kit with a Lambda Zap Express vector. Total RNA for the library was taken from a late passaged lung adenocarcinoma grown in SCID mice. Poly A+ RNA was isolated using a Message Maker Kit (Gibco BRL). Sera was obtained from two SCID mice implanted with lung adenocarcinomas. These sera were pooled and injected into normal mice to produce anti-lung tumor serum. Approximately 700,000 PFUs were screened from the unamplified library with *E. coli*-absorbed mouse anti-SCID tumor serum. Positive plaques were identified with a goat anti-mouse IgG-A-M (H+L) alkaline phosphatase second antibody developed with NBT/BCIP (Gibco BRL). Phage was purified and phagemid excised for 100 clones with insert in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

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The determined 5' cDNA sequences for 33 of the isolated clones are provided in SEQ ID NO: 149-181. The corresponding predicted amino acid sequences for SEQ ID NO: 149, 150, 152-154, 156-158 and 160-181 are provided in SEQ ID NO: 182, 183, 186, 188-193 and 194-215, respectively. The clone of SEQ ID NO: 151 (referred to as SAL-25) was found to contain two open reading frames (ORFs). The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 184 and 185. The clone of SEQ ID NO: 153 (referred to as SAL-50) was found to contain two open reading frames encoding the predicted amino acid sequences of SEQ ID NO: 187 and 216. Similarly, the clone of SEQ ID NO: 155 (referred to as SAL-66) was found to contain two open reading frames encoding the predicted amino acid sequences of SEQ ID NO: 189 and 190. Comparison of the isolated sequences with those in the public database revealed no significant homologies to the sequences of SEQ ID NO: 151, 153

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and 154. The sequences of SEQ ID NO: 149, 152, 156, 157 and 158 were found to show some homology to previously isolated expressed sequence tags (ESTs). The sequences of SEQ ID NO: 150, 155 and 159-181 were found to show homology to sequences previously identified in humans.

Using the procedures described above, two directional cDNA libraries (referred to as LT46-90 and LT86-21) were prepared from two late passaged lung squamous carcinomas grown in SCID mice and screened with sera obtained from SCID mice implanted with human squamous lung carcinomas. The determined cDNA sequences for the isolated clones are provided in SEQ ID NO: 217-237 and 286-289. SEQ ID NO: 286 was found to be a longer sequence of LT4690-71 (SEQ ID NO: 237). Comparison of these sequences with those in the public databases revealed no known homologies to the sequences of SEQ ID NO: 219, 220, 225, 226, 287 and 288. The sequences of SEQ ID NO: 218, 221, 222 and 224 were found to show some homology to previously identified sequences of unknown function. The sequence of SEQ ID NO: 236 was found to show homology to a known mouse mRNA sequence. The sequences of SEQ ID NO: 217, 223, 227-237, 286 and 289 showed some homology to known human DNA and/or RNA sequences.

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In further studies using the techniques described above, one of the cDNA libraries described above (LT86-21) was screened with *E. coli*-absorbed mouse anti-SCID tumor serum. This serum was obtained from normal mice immunized with a pool of 3 sera taken from SCID mice implanted with human squamous lung carcinomas. The determined cDNA sequences for the isolated clones are provided in SEQ ID NO: 238-285. Comparison of these sequences with those in the public databases revealed no significant homologies to the sequences of SEQ ID NO: 253, 260, 277 and 285. The sequences of SEQ ID NO: 249, 250, 256, 266, 276 and 282 were found to show some homology to previously isolated expressed sequence tags (ESTs). The sequences of SEQ ID NO: 238-248, 251, 252, 254, 255, 257-259, 261-263, 265, 267-275, 278-281, 283 and 284 were found to show some homology to previously identified DNA or RNA sequences.

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Example 5

DETERMINATION OF TISSUE SPECIFICITY OF LUNG TUMOR POLYPEPTIDES

Using gene specific primers, mRNA expression levels for representative lung tumor polypeptides were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent. First strand synthesis was carried out using 2 μg of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42 °C for one hour. The cDNA was then amplified by PCR with gene-specific primers. To ensure the semi-quantitative nature of the RT-PCR, β-actin was used as an internal control for each of the tissues examined. 1 μl of 1:30 dilution of cDNA was employed to enable the linear range amplification of the β-actin template and was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the β-actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in five different types of tumor tissue (lung squamous tumor from 3 patients, lung adenocarcinoma, prostate tumor, colon tumor and lung tumor), and different normal tissues, including lung from four patients, prostate, brain, kidney, liver, ovary, skeletal muscle, skin, small intestine, myocardium, retina and testes. L86S-46 was found to be expressed at high levels in lung squamous tumor, colon tumor and prostate tumor, and was undetectable in the other tissues examined. L86S-5 was found to be expressed in the lung tumor samples and in 2 out of 4 normal lung samples, but not in the other normal or tumor tissues tested. L86S-16 was found to be expressed in all tissues except normal liver and normal stomach. Using real-time PCR, L86S-46 was found to be over-expressed in lung squamous tissue and normal tonsil, with expression being low or undetectable in all other tissues examined.

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Example 6

ISOLATION OF DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

DNA sequences encoding antigens potentially involved in squamous cell lung tumor formation were isolated as follows.

A lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a pool of two human squamous epithelial lung carcinomas and poly A+ RNA was isolated using oligo-dT cellulose (Gibco BRL, Gaithersburg, MD). Phagemid were rescued at random and the cDNA sequences of isolated clones were determined.

The determined cDNA sequence for the clone SLT-T1 is provided in SEQ ID NO: 102, with the determined 5' cDNA sequences for the clones SLT-T2, SLT-T3, SLT-T5, SLT-T7, SLT-T9, SLT-T10, SLT-T11 and SLT-T12 being provided in SEQ ID NO: 103-110, respectively. The corresponding predicted amino acid sequence for SLT-T1, SLT-T2, SLT-T3, SLT-T10 and SLT-T12 are provided in SEQ ID NO: 111-115, respectively. Comparison of the sequences for SLT-T2, SLT-T3, SLT-T5, SLT-T7, SLT-T9 and SLT-T11 with those in the public databases as described above, revealed no significant homologies. The sequences for SLT-T10 and SLT-T12 were found to show some homology to sequences previously identified in humans.

The sequence of SLT-T1 was determined to show some homology to a PAC clone of unknown protein function. The cDNA sequence of SLT-T1 (SEQ ID NO: 102) was found to contain a mutator (MUTT) domain. Such domains are known to function in removal of damaged guanine from DNA that can cause A to G transversions (see, for example, el-Deiry, W.S., 1997 *Curr. Opin. Oncol.* 9:79-87; Okamoto, K. et al. 1996 *Int. J. Cancer* 65:437-41; Wu, C. et al. 1995 *Biochem. Biophys. Res. Commun.* 214:1239-45; Porter, D.W. et al. 1996 *Chem. Res. Toxicol.* 9:1375-81). SLT-T1 may thus be of use in the treatment, by gene therapy, of lung cancers caused by, or associated with, a disruption in DNA repair.

In further studies, DNA sequences encoding antigens potentially involved in

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adenocarcinoma lung tumor formation were isolated as follows. A human lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a late SCID mouse passaged human adenocarcinoma and poly A+ RNA was isolated using the Message Maker kit (Gibco BRL, Gaithersburg, MD). Phagemid were rescued at random and the cDNA sequences of isolated clones were determined.

The determined 5' cDNA sequences for five isolated clones (referred to as SALT-T3, SALT-T4, SALT-T7, SALT-T8, and SALT-T9) are provided in SEQ ID NO: 116-120, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 121-125. SALT-T3 was found to show 98% identity to the previously identified human transducin-like enhancer protein TLE2. SALT-T4 appears to be the human homologue of the mouse H beta 58 gene. SALT-T7 was found to have 97% identity to human 3-mercaptopyruvate sulfurtransferase and SALT-T8 was found to show homology to human interferon-inducible protein 1-8U. SALT-T9 shows approximately 90% identity to human mucin MUC 5B.

cDNA sequences encoding antigens potentially involved in small cell lung carcinoma development were isolated as follows. cDNA expression libraries were constructed with mRNA from the small cell lung carcinoma cell lines NCIH69, NCIH128 and DMS79 (all available from the American Type Culture Collection, Manassas, VA) employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Phagemid were rescued at random and the cDNA sequences of 27 isolated clones were determined. Comparison of the determined cDNA sequences revealed no significant homologies to the sequences of SEQ ID NO: 372 and 373. The sequences of SEQ ID NO: 364, 369, 377, 379 and 386 showed some homology to previously isolated ESTs. The sequences of the remaining 20 clones showed some homology to previously identified genes. The cDNA sequences of these clones are provided in SEQ ID NO: 363, 365-368, 370, 371, 374-376, 378, 380-385 and 387-389, wherein SEQ ID NO: 363, 366-368, 370, 375, 376, 378, 380-382, 384 and 385 are full-length sequences.

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Example 7

SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

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Example 8

ISOLATION AND CHARACTERIZATION OF DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS BY T-CELL EXPRESSION CLONING

Lung tumor antigens may also be identified by T cell expression cloning. One source of tumor specific T cells is from surgically excised tumors from human patients.

A non-small cell lung carcinoma was minced and enzymatically digested for several hours to release tumor cells and infiltrating lymphocytes (tumor infiltrating T cells, or TILs). The cells were washed in HBSS buffer and passed over a Ficoll (100%/75%/HBSS) discontinuous gradient to separate tumor cells and lymphocytes from non-viable cells. Two bands were harvested from the interfaces; the upper band at the 75%/HBSS interface contained

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predominantly tumor cells, while the lower band at the 100%/75%/HBSS interface contained a majority of lymphocytes. The TILs were expanded in culture, either in 24-well plates with culture media supplemented with 10 ng/ml IL-7 and 100 U/ml IL-2, or alternatively, 24-well plates that have been pre-coated with the anti-CD3 monoclonal antibody OKT3. The resulting TIL cultures were analyzed by FACS to confirm that a high percentage were CD8+ T cells (>90% of gated population) with only a small percentage of CD4+ cells.

In addition, non-small cell lung carcinoma cells were expanded in culture using standard techniques to establish a tumor cell line, which was later confirmed to be a lung carcinoma cell line by immunohistochemical analysis. This tumor cell line was transduced with a retroviral vector to express human CD80, and characterized by FACS analysis to confirm high expression levels of CD80, and class I and II MHC molecules.

The specificity of the TIL lines to lung tumor was confirmed by INF-γ and/or TNF-α cytokine release assays. TIL cells from day 21 cultures were co-cultured with either autologous or allogeneic tumor cells, EBV-immortalized LCL, or control cell lines Daudi and K562, and the culture supernatant monitored by ELISA for the presence of cytokines. The TIL specifically recognized autologous tumor but not allogeneic tumor. In addition, there was no recognition of EBV-immortalized LCL or the control cell lines, indicating that the TIL lines are tumor specific and are potentially recognizing a tumor antigen presented by autologous MHC molecules.

The characterized tumor-specific TIL lines were expanded to suitable numbers for T cell expression cloning using soluble anti-CD3 antibody in culture with irradiated EBV transformed LCLs and PBL feeder cells in the presence of 20 U/ml IL-2. Clones from the expanded TIL lines were generated by standard limiting dilution techniques. Specifically, TIL cells were seeded at 0.5 cells/well in a 96-well U bottom plate and stimulated with CD-80-transduced autologous tumor cells, EBV transformed LCL, and PBL feeder cells in the presence of 50 U/ml IL-2. These clones were further analyzed for tumor specificity by ^{51}Cr microcytotoxicity and IFN-γ bioassays. The MHC restriction element recognized by the TIL clones may be determined by antibody blocking studies.

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CTL lines or clones prepared as described above may be employed to identify tumor specific antigens. For example, autologous fibroblasts or LCL from a patient may be transfected or transduced with polynucleotide fragments derived from a lung tumor cDNA library to generate target cells expressing tumor polypeptides. The target cells expressing tumor polypeptides in the context of MHC will be recognized by the CTL line or clone, resulting in T-cell activation which can be monitored by cytokine detection assays. The tumor gene being expressed by the target cell and recognized by the tumor-specific CTL may then be isolated.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

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Claims

1. An isolated polypeptide, comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NOs: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168, 170-182, 184, 189, 191-193, 196, 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303, 310-313, 315, 317, 320, 322, 324, 332-335, 345, 347, 356, 358, 361, 362, 366, 369, 371-378, 380-404, 406, 409-417, 419-423, 425, 427-429, 433-436, 438-441, 443, 446-451, 454, 455, 457-461, 476, 477, 479, 483, 488, 491, 492, 497, 498, 500, 510, 519, 527, 528, 543, 545, 547, 553, 556, 559, 561, 564, 565, 568, 569, 574-577, 579, 580, 584, 585, 587, 592, 595, 598, 603, 608, 610, 613, 621-623, 626, 642, 648 and 668;

(b) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168, 170-182, 184, 189, 191-193, 196, 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303, 310-313, 315, 317, 320, 322, 324, 332-335, 345, 347, 356, 358, 361, 362, 366, 369, 371-378, 380-404, 406, 409-417, 419-423, 425, 427-429, 433-436, 438-441, 443, 446-451, 454, 455, 457-461, 476, 477, 479, 483, 488, 491, 492, 497, 498, 500, 510, 519, 527, 528, 543, 545, 547, 553, 556, 559, 561, 564, 565, 568, 569, 574-577, 579, 580, 584, 585, 587, 592, 595, 598, 603, 608, 610, 613, 621-623, 626, 642, 648 and 668 under moderately stringent

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conditions; and

(c) complements of sequences of (a) or (b).

2. An isolated polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379 and 386, or a complement of any of the foregoing polynucleotide sequences.

3. An isolated polynucleotide encoding at least 15 amino acid residues of a lung tumor protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID Nos: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379 and 386, or a complement of any of the foregoing sequences.

4. An isolated polynucleotide encoding a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379 and 386, or a complement of any of the foregoing sequences.

5. An isolated polynucleotide, comprising a sequence recited in any one of SEQ ID NOs: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377,

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379 and 386.

6. An isolated polynucleotide, comprising a sequence that hybridizes to a sequence recited in any one of SEQ ID NOs:_ 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379 and 386 under moderately stringent conditions.

7. An isolated polynucleotide complementary to a polynucleotide according to any one of claims 3-6.

8. An expression vector, comprising a polynucleotide according to any one of claims 3-8.

9. A host cell transformed or transfected with an expression vector according to claim 8.

10. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a lung tumor protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:_ 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379 and 386, or a complement of any of the foregoing polynucleotide sequences.

11. A fusion protein, comprising at least one polypeptide according to claim 1.

12. A fusion protein according to claim 11, wherein the fusion protein comprises an expression enhancer that increases expression of the fusion protein in a host cell transfected with a polynucleotide encoding the fusion protein.

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13. A fusion protein according to claim 11, wherein the fusion protein comprises a T helper epitope that is not present within the polypeptide of claim 1.

14. A fusion protein according to claim 11, wherein the fusion protein comprises an affinity tag.

15. An isolated polynucleotide encoding a fusion protein according to claim 11.

16. A pharmaceutical composition, comprising a physiologically acceptable carrier and at least one component selected from the group consisting of:

(a) a polypeptide according to claim 1;

(b) a polynucleotide according to claim 3;

(c) an antibody according to claim 10;

(d) a fusion protein according to claim 11; and

(e) a polynucleotide according to claim 15.

17. A vaccine comprising an immunostimulant and at least one component selected from the group consisting of:

(a) a polypeptide according to claim 1;

(b) a polynucleotide according to claim 3;

(c) an antibody according to claim 10;

(d) a fusion protein according to claim 11; and

(e) a polynucleotide according to claim 15.

18. A vaccine according to claim 17, wherein the immunostimulant is an adjuvant.

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19. A vaccine according to any claim 17, wherein the immunostimulant induces a predominantly Type I response.

20. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 16.

21. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a vaccine according to claim 17.

22. A pharmaceutical composition comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a pharmaceutically acceptable carrier or excipient.

23. A pharmaceutical composition according to claim 22, wherein the antigen presenting cell is a dendritic cell or a macrophage.

24. A vaccine comprising an antigen-presenting cell that expresses a polypeptide comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NOs: 217-389;

(b) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 217-389 under moderately stringent conditions; and

(c) complements of sequences of (i) or (ii);

in combination with an immunostimulant.

25. A vaccine according to claim 24, wherein the immunostimulant is an adjuvant.

26. A vaccine according to claim 24, wherein the immunostimulant induces a predominantly Type I response.

27. A vaccine according to claim 24, wherein the antigen-presenting cell is a dendritic cell.

28. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antigen-presenting cell that expresses a polypeptide comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(a) sequences recited in SEQ ID NOs: 217-389;

(b) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 217-389 under moderately stringent conditions; and

(c) complements of sequences of (i) or (ii)encoded by a polynucleotide recited in any one of SEQ ID NOs: 217-389;

and thereby inhibiting the development of a cancer in the patient.

29. A method according to claim 28, wherein the antigen-presenting cell is a dendritic cell.

30. A method according to any one of claims 20, 21 and 28, wherein the cancer is lung cancer.

31. A method for removing tumor cells from a biological sample, comprising

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contacting a biological sample with T cells that specifically react with a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) polynucleotides recited in any one of SEQ ID NOs: 217-389; and

(ii) complements of the foregoing polynucleotides;

wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the antigen from the sample.

32. A method according to claim 31, wherein the biological sample is blood or a fraction thereof.

33. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated according to the method of claim 31.

34. A method for stimulating and/or expanding T cells specific for a lung tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:

(a) polypeptides comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(i) sequences recited in SEQ ID NOs: 217-389;

(ii) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 217-389 under moderately stringent conditions; and

(iii) complements of sequences of (i) or (ii);

(b) polynucleotides encoding a polypeptide of (a); and

(c) antigen presenting cells that express a polypeptide of (a);

under conditions and for a time sufficient to permit the stimulation and/or

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expansion of T cells.

35. An isolated T cell population, comprising T cells prepared according to the method of claim 34.

36. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population according to claim 35.

37. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating $CD4^+$ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:

(i) polypeptides comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(1) sequences recited in SEQ ID NOs: 217-389;

(2) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 217-389 under moderately stringent conditions; and

(3) complements of sequences of (1) or (2);

(ii) polynucleotides encoding a polypeptide of (i); and

(iii) antigen presenting cells that expresses a polypeptide of (i);

such that T cells proliferate; and

(b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.

38. A method for inhibiting the development of a cancer in a patient,

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comprising the steps of:

(a) incubating $CD4^+$ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:

(i) polypeptides comprising at least an immunogenic portion of a lung tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:

(1) sequences recited in SEQ ID NOs: 217-389;

(2) sequences that hybridize to a sequence recited in any one of SEQ ID NOs: 217-389 under moderately stringent conditions; and

(3) complements of sequences of (1) or (2);

(ii) polynucleotides encoding a polypeptide of (i); and

(iii) antigen presenting cells that express a polypeptide of (i);

such that T cells proliferate;

(b) cloning at least one proliferated cell to provide cloned T cells; and

(c) administering to the patient an effective amount of the cloned T cells, and thereby inhibiting the development of a cancer in the patient.

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39. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with a binding agent that binds to a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 217-389 or a complement of any of the foregoing polynucleotide sequences;

(b) detecting in the sample an amount of polypeptide that binds to the binding agent; and

(c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

40. A method according to claim 39, wherein the binding agent is an antibody.

41. A method according to claim 42, wherein the antibody is a monoclonal antibody.

42. A method according to claim 39, wherein the cancer is lung cancer.

43. A method for monitoring the progression of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 217-389 or a complement of any of the foregoing polynucleotide sequences;

(b) detecting in the sample an amount of polypeptide that binds to the binding agent;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polypeptide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

44. A method according to claim 43, wherein the binding agent is an antibody.

45. A method according to claim 44, wherein the antibody is a monoclonal antibody.

46. A method according to claim 43, wherein the cancer is a lung cancer.

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47. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 217-389 or a complement of any of the foregoing polynucleotide sequences;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and

(c) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

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48. A method according to claim 47, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

49. A method according to claim 47, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.

50. A method for monitoring the progression of a cancer in a patient, comprising the steps of:

(a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a lung tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs: 217-389 or a complement of any of the foregoing polynucleotide sequences;

(b) detecting in the sample an amount of a polynucleotide that hybridizes to

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the oligonucleotide;

(c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and

(d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

51. A method according to claim 50, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

52. A method according to claim 50, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.

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53. A diagnostic kit, comprising:

(a) one or more antibodies according to claim 10; and

(b) a detection reagent comprising a reporter group.

54. A kit according to claim 53, wherein the antibodies are immobilized on a solid support.

55. A kit according to claim 53, wherein the detection reagent comprises an anti-immunoglobulin, protein G, protein A or lectin.

56. A kit according to claim 53, wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.

57. An oligonucleotide comprising 10 to 40 contiguous nucleotides that hybridize under moderately stringent conditions to a polynucleotide that encodes a lung tumor

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protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:_ 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379 and 386, or a complement of any of the foregoing polynucleotides.

58. A oligonucleotide according to claim 57, wherein the oligonucleotide comprises 10-40 contiguous nucleotides recited in any one of SEQ ID NOs:_ 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379 and 386.

59. A diagnostic kit, comprising:

(a) an oligonucleotide according to claim 58; and

(b) a diagnostic reagent for use in a polymerase chain reaction or hybridization assay.

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COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE

Abstract of the Disclosure

Compositions and methods for the therapy and diagnosis of cancer, such as lung cancer, are disclosed. Compositions may comprise one or more lung tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a lung tumor protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as lung cancer. Diagnostic methods based on detecting a lung tumor protein, or mRNA encoding such a protein, in a sample are also provided.

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SEQUENCE LISTING

<110> Reed, Steven G.
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Secrist, Heather

<120> COMPOUNDS FOR THERAPY AND DIAGNOSIS OF LUNG CANCER AND METHODS FOR THEIR USE

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<212> DNA
<213> Homo sapien

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<212> DNA
<213> Homo sapien

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<212> DNA
<213> Homo sapien

<220>
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<211> 449
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<213> Homo sapien

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ggtacgggag gaaacactgg gctnacccag atnctggact tgagtcttgc ctctgctgct 300
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caaatagagg gcctgggcaa aaaaaaaaa 449

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<211> 538

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<212> DNA
<213> Homo sapien

<220>
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<210> 11
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<213> Homo sapien

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ggcaagacca taggtggggt gctgggaatc ctcggggccg gctggcaccc actcctggtg 180
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1026

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<213> Homo sapien

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<213> Homo sapien

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<211> 633
<212> DNA
<213> Homo sapien

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<211> 1328
<212> DNA
<213> Homo sapien

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<212> DNA
<213> Homo sapien

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<211> 493
<212> DNA
<213> Homo sapien

<400> 26

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<211> 1331
<212> DNA
<213> Homo sapien

<400> 27

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<211> 1333
<212> DNA
<213> Homo sapien

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<400> 28

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<400> 29

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<211> 1316
<212> DNA
<213> Homo sapien

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<400> 30

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<212> DNA
<213> Homo sapien

<400> 31

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agaaggagac cacaaagaat gtacaacaga cagtgagtgc taaaggcccc cctgaaaaac 720
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atcatacctc agtactgtgg ctcttgagct ttgaagtact ttattgtaac cttcttattt 840
gtatggaatg cgcttatttt ttgaaaggat attaggccgg atgtggtggc tcacgcctgt 900
aatcccagca ctttgggagg ccatggcggg tggatcactt gaggtcagaa gttcaagacc 960
agcctgacca atatggtgaa accccgtctc tactaaaaat acaaaaatta gccgggcgtg 1020
gtggcgggcg cccatagtcc cagctacteg ggaggctgag acaggagact tgcttgaacc 1080
cgggaggtgg aggttgccct gagctgatta tcatgctgtt gcactccagc ttgggcgaca 1140
gaacgagact ttgtctcaaa aaaagaagaa aagatattat tcccatcatg atttcttgtg 1200
aatatttgtt atatgtcttc tggtaacctt tcctctcccg gacttgaagc aacctcacac 1260

760
1040
1035

09518 09.03200

actcacatgt ttactggtag atatgtttta aaagcaaaat aaaggtattt gtttttccaa 1320
aaaaaaaaaa aaaaaaaaaa aaaaaaaaac tcgag 1355

<210> 32
<211> 80
<212> PRT
<213> Homo sapien

<400> 32

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

<210> 33
<211> 130
<212> PRT
<213> Homo sapien

<400> 33

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

<210> 34
<211> 506
<212> PRT
<213> Homo sapien

<400> 34

1036

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```
Asn Ser Glu Lys Glu Ile Pro Val Leu Asn Glu Leu Pro Val Pro Met
 1               5                  10                  15
Val Ala Arg Tyr Ile Arg Ile Asn Pro Gln Ser Trp Phe Asp Asn Gly
            20                  25                  30
Ser Ile Cys Met Arg Met Glu Ile Leu Gly Cys Pro Leu Pro Asp Pro
        35                  40                  45
Asn Asn Tyr Tyr His Arg Arg Asn Glu Met Thr Thr Thr Asp Asp Leu
    50                  55                  60
Asp Phe Lys His His Asn Tyr Lys Glu Met Arg Gln Leu Met Lys Val
65                  70                  75                  80
Val Asn Glu Met Cys Pro Asn Ile Thr Arg Ile Tyr Asn Ile Gly Lys
                85                  90                  95
Ser His Gln Gly Leu Lys Leu Tyr Ala Val Glu Ile Ser Asp His Pro
            100                 105                 110
Gly Glu His Glu Val Gly Glu Pro Glu Phe His Tyr Ile Ala Gly Ala
        115                 120                 125
His Gly Asn Glu Val Leu Gly Arg Glu Leu Leu Leu Leu Leu Leu His
    130                 135                 140
Phe Leu Cys Gln Glu Tyr Ser Ala Gln Asn Ala Arg Ile Val Arg Leu
145                 150                 155                 160
Val Glu Glu Thr Arg Ile His Ile Leu Pro Ser Leu Asn Pro Asp Gly
                165                 170                 175
Tyr Glu Lys Ala Tyr Glu Gly Gly Ser Glu Leu Gly Gly Trp Ser Leu
            180                 185                 190
Gly Arg Trp Thr His Asp Gly Ile Asp Ile Asn Asn Asn Phe Pro Asp
        195                 200                 205
Leu Asn Ser Leu Leu Trp Glu Ala Glu Asp Gln Gln Asn Ala Pro Arg
    210                 215                 220
Lys Val Pro Asn His Tyr Ile Ala Ile Pro Glu Trp Phe Leu Ser Glu
225                 230                 235                 240
Asn Ala Thr Val Ala Thr Glu Thr Arg Ala Val Ile Ala Trp Met Glu
                245                 250                 255
Lys Ile Pro Phe Val Leu Gly Gly Asn Leu Gln Gly Gly Glu Leu Val
            260                 265                 270
Val Ala Tyr Pro Tyr Asp Met Val Arg Ser Leu Trp Lys Thr Gln Glu
        275                 280                 285
His Thr Pro Thr Pro Asp Asp His Val Phe Arg Trp Leu Ala Tyr Ser
    290                 295                 300
Tyr Ala Ser Thr His Arg Leu Met Thr Asp Ala Arg Arg Arg Val Cys
305                 310                 315                 320
His Thr Glu Asp Phe Gln Lys Glu Glu Gly Thr Val Asn Gly Ala Ser
                325                 330                 335
Trp His Thr Val Ala Gly Ser Leu Asn Asp Phe Ser Tyr Leu His Thr
            340                 345                 350
Asn Cys Phe Glu Leu Ser Ile Tyr Val Gly Cys Asp Lys Tyr Pro His
        355                 360                 365
Glu Ser Glu Leu Pro Glu Glu Trp Glu Asn Asn Arg Glu Ser Leu Ile
    370                 375                 380
Val Phe Met Glu Gln Val His Arg Gly Ile Lys Gly Ile Val Arg Asp
385                 390                 395                 400
Leu Gln Gly Lys Gly Ile Ser Asn Ala Val Ile Ser Val Glu Gly Val
```

09518809.03 300

370
1992
1037

405 410 415
Asn His Asp Ile Arg Thr Ala Ser Asp Gly Asp Tyr Trp Arg Leu Leu
420 425 430
Asn Pro Gly Glu Tyr Val Val Thr Ala Lys Ala Glu Gly Phe Ile Thr
435 440 445
Ser Thr Lys Asn Cys Met Val Gly Tyr Asp Met Gly Ala Thr Arg Cys
450 455 460
Asp Phe Thr Leu Thr Lys Thr Asn Leu Ala Arg Ile Arg Glu Ile Met
465 470 475 480
Glu Thr Phe Gly Lys Gln Pro Val Ser Leu Pro Ser Arg Arg Leu Lys
485 490 495
Leu Arg Gly Arg Lys Arg Arg Gln Arg Gly
500 505

<210> 35
<211> 96
<212> PRT
<213> Homo sapien

<400> 35
Met Asn Gly Glu Ala Asp Cys Pro Thr Asp Leu Glu Met Ala Ala Pro
1 5 10 15
Arg Gly Gln Asp Arg Trp Ser Gln Glu Asp Met Leu Thr Leu Leu Glu
20 25 30
Cys Met Lys Asn Asn Leu Pro Ser Asn Asp Ser Ser Gln Phe Lys Thr
35 40 45
Thr Gln Thr His Met Asp Arg Glu Lys Val Ala Leu Lys Asp Phe Ser
50 55 60
Gly Asp Met Cys Lys Leu Lys Trp Val Glu Ile Ser Asn Glu Val Arg
65 70 75 80
Lys Phe Arg Thr Leu Thr Glu Leu Ile Leu Asp Thr Gln Glu His Val
85 90 95

<210> 36
<211> 129
<212> PRT
<213> Homo sapien

<400> 36
Gly Ile Val Val Phe Ser Leu Gly Ser Met Val Ser Glu Ile Pro Glu
1 5 10 15
Lys Lys Ala Val Ala Ile Ala Asp Ala Leu Gly Lys Ile Pro Gln Thr
20 25 30
Val Leu Trp Arg Tyr Thr Gly Thr Arg Pro Ser Asn Leu Ala Asn Asn
35 40 45
Thr Ile Leu Val Gln Trp Leu Pro Gln Asn Asp Leu Leu Gly His Pro
50 55 60
Met Thr Arg Ala Phe Ile Thr His Ala Ser Ser His Gly Val Asn Glu
65 70 75 80
Ser Ile Cys Asn Gly Val Pro Met Val Met Ile Pro Leu Phe Gly Asp
85 90 95

771
1/3
1038

0951 80S 030300

Gln Met Asp Asn Ala Lys Arg Arg Glu Thr Lys Gly Ala Gly Val Thr
100 105 110
Leu Asn Val Leu Glu Met Thr Ser Glu Asp Leu Glu Asp Ala Leu Lys
115 120 125
Ser

<210> 37
<211> 238
<212> PRT
<213> Homo sapien

<400> 37
Asn Leu Leu Gly Ile Ser Trp Val Asp Ser Ser Trp Ile Pro Ile Leu
1 5 10 15
Asn Ser Gly Ser Val Leu Asp Tyr Phe Ser Glu Arg Ser Asn Pro Phe
20 25 30
Tyr Asp Arg Thr Cys Asn Asn Glu Val Val Lys Met Gln Arg Leu Thr
35 40 45
Leu Glu His Leu Asn Gln Met Val Gly Ile Glu Tyr Ile Leu Leu His
50 55 60
Ala Gln Glu Pro Ile Leu Phe Ile Ile Arg Lys Gln Gln Arg Gln Ser
65 70 75 80
Pro Ala Gln Val Ile Pro Leu Ala Asp Tyr Tyr Ile Ile Ala Gly Val
85 90 95
Ile Tyr Gln Ala Pro Asp Leu Gly Ser Val Ile Asn Ser Arg Val Leu
100 105 110
Thr Ala Val His Gly Ile Gln Ser Ala Phe Asp Glu Ala Met Ser Tyr
115 120 125
Cys Arg Tyr His Pro Ser Lys Gly Tyr Trp Trp His Phe Lys Asp His
130 135 140
Glu Glu Gln Asp Lys Val Arg Pro Lys Ala Lys Arg Lys Glu Glu Pro
145 150 155 160
Ser Ser Ile Phe Gln Arg Gln Arg Val Asp Ala Leu Leu Leu Asp Leu
165 170 175
Arg Gln Lys Phe Pro Pro Lys Phe Val Gln Leu Lys Pro Gly Glu Lys
180 185 190
Pro Val Pro Val Asp Gln Thr Lys Lys Glu Ala Glu Pro Ile Pro Glu
195 200 205
Thr Val Lys Pro Glu Glu Lys Glu Thr Thr Lys Asn Val Gln Gln Thr
210 215 220
Val Ser Ala Lys Gly Pro Pro Glu Lys Arg Met Arg Leu Gln
225 230 235

<210> 38
<211> 202
<212> PRT
<213> Homo sapien

<400> 38
Lys Gly Ser Glu Gly Glu Asn Pro Leu Thr Val Pro Gly Arg Glu Lys

772
1944
1039

0951 809.030300

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

<210> 39
<211> 243
<212> PRT
<213> Homo sapien

<400> 39

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

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

<210> 40
<211> 245
<212> PRT
<213> Homo sapien

<400> 40

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

104!

245

<210> 41
<211> 163
<212> PRT
<213> Homo sapien

<400> 41

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

<210> 42
<211> 243
<212> PRT
<213> Homo sapien

<400> 42

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

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1042

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```
Asn Ser Arg Val Leu Thr Ala Val His Gly Ile Gln Ser Ala Phe Asp
        115                 120                 125
Glu Ala Met Ser Tyr Cys Arg Tyr His Pro Ser Lys Gly Tyr Trp Trp
    130                 135                 140
His Phe Lys Asp His Glu Glu Gln Asp Lys Val Arg Pro Lys Ala Lys
145                 150                 155                 160
Arg Lys Glu Glu Pro Ser Ser Ile Phe Gln Arg Gln Arg Val Asp Ala
                165                 170                 175
Leu Leu Leu Asp Leu Arg Gln Lys Phe Pro Pro Lys Phe Val Gln Leu
            180                 185                 190
Lys Pro Gly Glu Lys Pro Val Pro Val Asp Gln Thr Lys Lys Glu Ala
        195                 200                 205
Glu Pro Ile Pro Glu Thr Val Lys Pro Glu Glu Lys Glu Thr Thr Lys
    210                 215                 220
Asn Val Gln Gln Thr Val Ser Ala Lys Gly Pro Pro Glu Lys Arg Met
225                 230                 235                 240
Arg Leu Gln
```

<210> 43
<211> 244
<212> PRT
<213> Homo sapien

<400> 43

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

1043

Ala Glu Pro Ile Pro Glu Thr Val Lys Pro Glu Glu Lys Glu Thr Thr
210 215 220
Lys Asn Val Gln Gln Thr Val Ser Ala Lys Gly Pro Pro Glu Lys Arg
225 230 235 240
Met Arg Leu Gln

<210> 44
<211> 109
<212> PRT
<213> Homo sapien

<400> 44
Glu Leu His Phe Ser Glu Phe Thr Ser Ala Val Ala Asp Met Lys Asn
1 5 10 15
Ser Val Ala Asp Arg Asp Asn Ser Pro Ser Ser Cys Ala Gly Leu Phe
20 25 30
Ile Ala Ser His Ile Gly Phe Asp Trp Pro Gly Val Trp Val His Leu
35 40 45
Asp Ile Ala Ala Pro Val His Ala Gly Glu Arg Ala Thr Gly Phe Gly
50 55 60
Val Ala Leu Leu Leu Ala Leu Phe Gly Arg Ala Ser Glu Asp Pro Leu
65 70 75 80
Leu Asn Leu Val Ser Pro Leu Asp Cys Glu Val Asp Ala Gln Glu Gly
85 90 95
Asp Asn Met Gly Arg Asp Ser Lys Arg Arg Arg Leu Val
100 105

<210> 45
<211> 324
<212> PRT
<213> Homo sapien

<400> 45
Arg Arg Pro Val Met Ala Gln Glu Thr Ala Pro Pro Cys Gly Pro Val
1 5 10 15
Ser Arg Gly Asp Ser Pro Ile Ile Glu Lys Met Glu Lys Arg Thr Cys
20 25 30
Ala Leu Cys Pro Glu Gly His Glu Trp Ser Gln Ile Tyr Phe Ser Pro
35 40 45
Ser Gly Asn Ile Val Ala His Glu Asn Cys Leu Leu Tyr Ser Ser Gly
50 55 60
Leu Val Glu Cys Glu Thr Leu Asp Leu Arg Asn Thr Ile Arg Asn Phe
65 70 75 80
Asp Val Lys Ser Val Lys Lys Glu Ile Trp Arg Gly Arg Arg Leu Lys
85 90 95
Cys Ser Phe Cys Asn Lys Gly Gly Ala Thr Val Gly Cys Asp Leu Trp
100 105 110
Phe Cys Lys Lys Ser Tyr His Tyr Val Cys Ala Lys Lys Asp Gln Ala
115 120 125
Ile Leu Gln Val Asp Gly Asn His Gly Thr Tyr Lys Leu Phe Cys Pro

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777
1045
1044

0951880 .030300

```
    130                 135                 140
Glu His Ser Pro Glu Gln Glu Glu Ala Thr Glu Ser Ala Asp Asp Pro
145                 150                 155                 160
Ser Met Lys Lys Lys Arg Gly Lys Asn Lys Arg Leu Ser Ser Gly Pro
                165                 170                 175
Pro Ala Gln Pro Lys Thr Met Lys Cys Ser Asn Ala Lys Arg His Met
            180                 185                 190
Thr Glu Glu Pro His Gly His Thr Asp Ala Ala Val Lys Ser Pro Phe
        195                 200                 205
Leu Lys Lys Cys Gln Glu Ala Gly Leu Leu Thr Glu Leu Phe Glu His
    210                 215                 220
Ile Leu Glu Asn Met Asp Ser Val His Gly Arg Leu Val Asp Glu Thr
225                 230                 235                 240
Ala Ser Glu Ser Asp Tyr Glu Gly Ile Glu Thr Leu Leu Phe Asp Cys
                245                 250                 255
Gly Leu Phe Lys Asp Thr Leu Arg Lys Phe Gln Glu Val Ile Lys Ser
            260                 265                 270
Lys Ala Cys Glu Trp Glu Glu Arg Gln Arg Gln Met Lys Gln Gln Leu
        275                 280                 285
Glu Ala Leu Ala Asp Leu Gln Gln Ser Leu Cys Ser Phe Gln Glu Asn
    290                 295                 300
Gly Asp Leu Asp Cys Ser Ser Ser Thr Ser Gly Ser Leu Leu Pro Pro
305                 310                 315                 320
Glu Asp His Gln
```

<210> 46
<211> 244
<212> PRT
<213> Homo sapien

<400> 46

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

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

<210> 47
<211> 14
<212> DNA
<213> Homo sapien

<400> 47
tttttttttt ttag 14

<210> 48
<211> 10
<212> DNA
<213> Homo sapien

<400> 48
cttcaacctc 10

<210> 49
<211> 496
<212> DNA
<213> Homo sapien

<400> 49
gcaccatgta ccgagcactt cggctcctcg cgcgctcgcg tcccctcgtg cgggctccag 60
ccgcagcctt agcttcggct cccggcttgg gtggcgcggc cgtgccctcg ttttggcctc 120
cgaacgcggc tcgaatggca agccaaaatt ccttccggat agaatatgat acctttggtg 180
aactaaaggt gccaaatgat aagtattatg gcgccccagac cgtgagatct acgatgaact 240
ttaagattgg aggtgtgaca gaacgcatgc caacccccagt tattaaagct tttggcatct 300
tgaagcgagc ggccgctgaa gtaaaccagg attatggtct tgatccaaag attgctaatg 360
caataatgaa ggcagcagat gaggtagctg aaggtaaatt aaatgatcat tttcctctcg 420
tggtatggca gactggatca ggaactcaga caaatatgaa tgtaaatgaa gtcattagcc 480
aatagagcaa ttgaaa 496

<210> 50
<211> 499
<212> DNA
<213> Homo sapien

329
10/25/
1045

<400> 50
agaaaaagtc tatgtttgca gaaatacaga tccaagacaa agacaggatg ggcactgctg 60
gaaaagttat taaatgcaaa gcagctgtgc tttgggagca gaagcaaccc ttctccattg 120
aggaaataga agttgcccca ccaaagacta aagaagttcg cattaagatt ttggccacag 180
gaatctgtcg cacagatgac catgtgataa aaggaacaat ggtgtccaag tttccagtga 240
ttgtgggaca tgaggcaact gggattgtag agagcattgg agaaggagtg actacagtga 300
aaccaggtga caaagtcatc cctctctttc tgccacaatg tagagaatgc aatgcttgtc 360
gcaacccaga tggcaacctt tgcattagga gcgatattac tggtcgtgga gtactggctg 420
atggcaccac cagatttaca tgcaagggcg aaccagtcca ccacttcatg aacaccagta 480
catttaccga gtacacagt 499

<210> 51
<211> 887
<212> DNA
<213> Homo sapien

<400> 51
gagtctgagc agaaaggaaa agcagccttg gcagccacgt tagaggaata caaagccaca 60
gtggccagtg accagataga gatgaatcgc ctgaaggctc agctggagaa tgaaaagcag 120
aaagtggcag agctgtattc tatccataac tctggagaca aatctgatat tcaggacctc 180
ctggagagtg tcaggctgga caaagaaaaa gcagagactt tggctagtag cttgcaggaa 240
gatctggctc atacccgaaa tgatgccaat cgattacagg atgccattgc taaggtagag 300
gatgaatacc gagccttcca agaagaagct aagaaacaaa ttgaagattt gaatatgacg 360
ttagaaaaat taagatcaga cctggatgaa aaagaaacag aaaggagtga catgaaagaa 420
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<210> 52
<211> 491
<212> DNA
<213> Homo sapien

<400> 52
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cctgctatag ctcagttttc agttcagaaa gtcactcctc agtctgatgg ctccagttca 180
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cagacaccag gcagaaaata aggcagagtc tgaagaaatg gagacctctc aagctggatc 420
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<210> 53
<211> 787

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<212> DNA
<213> Homo sapien

<400> 53
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caggggtagt gatcctggca gtcaccatag ctctacttgt ttacttttta gcttttgatc 180
aaaaatctta cttttatagg agcagttttc aactcctaaa tgttgaatat aatagtcagt 240
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ggctcaataa tgcccaccac tgtggaggca gcctgatcaa taacatgtgg atcctgacag 720
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ccacaac 787

<210> 54
<211> 386
<212> DNA
<213> Homo sapien

<400> 54
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gaaatggaga cctctcaagc tggatccaag gataaaaaga tggaccaacc accccaagcc 240
aagaaggcaa aagtgaagac cagtactgtg gacctgccaa tcgagaatca gctattatgg 300
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<210> 55
<211> 1462
<212> DNA
<213> Homo sapien

<400> 55
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760
1992
1047

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aaaaaaaaaa aaaaaactcg ag 1462

<210> 56
<211> 159
<212> PRT
<213> Homo sapien

<400> 56

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

<210> 57
<211> 165
<212> PRT
<213> Homo sapien

<400> 57

Lys	Lys	Ser	Met	Phe	Ala	Glu	Ile	Gln	Ile	Gln	Asp	Lys	Asp	Arg	Met
1				5				10					15		
Gly	Thr	Ala	Gly	Lys	Val	Ile	Lys	Cys	Lys	Ala	Ala	Val	Leu	Trp	Glu
			20					25					30		

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```
Gln Lys Gln Pro Phe Ser Ile Glu Glu Ile Glu Val Ala Pro Pro Lys
        35                  40                  45
Thr Lys Glu Val Arg Ile Lys Ile Leu Ala Thr Gly Ile Cys Arg Thr
    50                  55                  60
Asp Asp His Val Ile Lys Gly Thr Met Val Ser Lys Phe Pro Val Ile
65                  70                  75                  80
Val Gly His Glu Ala Thr Gly Ile Val Glu Ser Ile Gly Glu Gly Val
                85                  90                  95
Thr Thr Val Lys Pro Gly Asp Lys Val Ile Pro Leu Phe Leu Pro Gln
            100                 105                 110
Cys Arg Glu Cys Asn Ala Cys Arg Asn Pro Asp Gly Asn Leu Cys Ile
        115                 120                 125
Arg Ser Asp Ile Thr Gly Arg Gly Val Leu Ala Asp Gly Thr Thr Arg
    130                 135                 140
Phe Thr Cys Lys Gly Glu Pro Val His His Phe Met Asn Thr Ser Thr
145                 150                 155                 160
Phe Thr Glu Tyr Thr
                165

      <210> 58
      <211> 259
      <212> PRT
      <213> Homo sapien

      <400> 58
Glu Ser Glu Gln Lys Gly Lys Ala Ala Leu Ala Ala Thr Leu Glu Glu
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Tyr Lys Ala Thr Val Ala Ser Asp Gln Ile Glu Met Asn Arg Leu Lys
            20                  25                  30
Ala Gln Leu Glu Asn Glu Lys Gln Lys Val Ala Glu Leu Tyr Ser Ile
        35                  40                  45
His Asn Ser Gly Asp Lys Ser Asp Ile Gln Asp Leu Leu Glu Ser Val
    50                  55                  60
Arg Leu Asp Lys Glu Lys Ala Glu Thr Leu Ala Ser Ser Leu Gln Glu
65                  70                  75                  80
Asp Leu Ala His Thr Arg Asn Asp Ala Asn Arg Leu Gln Asp Ala Ile
                85                  90                  95
Ala Lys Val Glu Asp Glu Tyr Arg Ala Phe Gln Glu Glu Ala Lys Lys
            100                 105                 110
Gln Ile Glu Asp Leu Asn Met Thr Leu Glu Lys Leu Arg Ser Asp Leu
        115                 120                 125
Asp Glu Lys Glu Thr Glu Arg Ser Asp Met Lys Glu Thr Ile Phe Glu
    130                 135                 140
Leu Glu Asp Glu Val Glu Gln His Arg Ala Val Lys Leu His Asp Asn
145                 150                 155                 160
Leu Ile Ile Ser Asp Leu Glu Asn Thr Val Lys Lys Leu Gln Asp Gln
                165                 170                 175
Lys His Asp Met Glu Arg Glu Ile Lys Thr Leu His Arg Arg Leu Arg
            180                 185                 190
Glu Glu Ser Ala Glu Trp Arg Gln Phe Gln Ala Asp Leu Gln Thr Ala
        195                 200                 205
```

Val Val Ile Ala Asn Asp Ile Lys Ser Glu Ala Gln Glu Glu Ile Gly
210 215 220
Asp Leu Lys Arg Arg Leu His Glu Ala Gln Glu Lys Asn Glu Lys Leu
225 230 235 240
Thr Lys Glu Leu Glu Glu Ile Lys Ser Arg Lys Gln Glu Glu Glu Arg
245 250 255
Gly Gly Tyr

<210> 59
<211> 125
<212> PRT
<213> Homo sapien

<400> 59
Gly Thr Ser Phe Ser Lys Asn His Ala Ala Pro Phe Ser Lys Val Leu
1 5 10 15
Thr Phe Tyr Arg Lys Glu Pro Phe Thr Leu Glu Ala Tyr Tyr Ser Ser
20 25 30
Pro Gln Asp Leu Pro Tyr Pro Asp Pro Ala Ile Ala Gln Phe Ser Val
35 40 45
Gln Lys Val Thr Pro Gln Ser Asp Gly Ser Ser Ser Lys Val Lys Val
50 55 60
Lys Val Arg Val Asn Val His Gly Ile Phe Ser Val Ser Ser Ala Ser
65 70 75 80
Leu Val Glu Val His Lys Ser Glu Glu Asn Glu Glu Pro Met Glu Thr
85 90 95
Asp Gln Asn Ala Lys Glu Glu Glu Lys Met Gln Val Asp Gln Glu Glu
100 105 110
Pro His Val Glu Glu Gln Gln Gln Gln Thr Pro Gly Arg
115 120 125

<210> 60
<211> 246
<212> PRT
<213> Homo sapien

<400> 60
Met Tyr Arg Pro Ala Arg Val Thr Ser Thr Ser Arg Phe Leu Asn Pro
1 5 10 15
Tyr Val Val Cys Phe Ile Val Val Ala Gly Val Val Ile Leu Ala Val
20 25 30
Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
35 40 45
Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
50 55 60
Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65 70 75 80
Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
85 90 95
Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val

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```
            100                 105                 110
Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
        115                 120                 125
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
    130                 135                 140
Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145                 150                 155                 160
Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
                165                 170                 175
Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
            180                 185                 190
Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
        195                 200                 205
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
    210                 215                 220
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225                 230                 235                 240
Thr Ser Gly Ile Ser Thr
                245
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<210> 61
<211> 128
<212> PRT
<213> Homo sapien

<400> 61

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

<210> 62
<211> 418
<212> PRT
<213> Homo sapien

<400> 62

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Met Tyr Arg Pro Ala Arg Val Thr Ser Thr Ser Arg Phe Leu Asn Pro
 1               5                  10                  15
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780
1052
1052

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```
Tyr Val Val Cys Phe Ile Val Val Ala Gly Val Val Ile Leu Ala Val
            20                  25                  30
Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
        35                  40                  45
Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
    50                  55                  60
Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65                  70                  75                  80
Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
                85                  90                  95
Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
            100                 105                 110
Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
        115                 120                 125
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
    130                 135                 140
Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145                 150                 155                 160
Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
                165                 170                 175
Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
            180                 185                 190
Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
        195                 200                 205
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
    210                 215                 220
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225                 230                 235                 240
Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
                245                 250                 255
Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
            260                 265                 270
Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
        275                 280                 285
His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
    290                 295                 300
Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
305                 310                 315                 320
Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
                325                 330                 335
Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
            340                 345                 350
Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
        355                 360                 365
Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
    370                 375                 380
Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
385                 390                 395                 400
Val Tyr Thr Arg Val Thr Ala Tyr Ile Asp Trp Ile Arg Gln Gln Thr
                405                 410                 415
Gly Ile
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786
1058
1053

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<210> 63
<211> 776
<212> DNA
<213> Homo sapien

<400> 63
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aacagaaatt acaggagcag ccagcaacag atggaggctc aagataagag tcgcaaggaa 180
aactagccaa ctgaaggaga agctgcagat ggagagagaa cacctactga gagagcagat 240
tatgatgttg gagcacacgc agaaggtcca aaatgattgg cttcatgaag gatttaagaa 300
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<210> 64
<211> 160
<212> DNA
<213> Homo sapien

<400> 64
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<210> 65
<211> 72
<212> PRT
<213> Homo sapien

<400> 65
Leu Ser Ala Met Gly Phe Thr Ala Ala Gly Ile Ala Ser Ser Ser Ile
1 5 10 15
Ala Ala Lys Met Met Ser Ala Ala Ala Ile Ala Asn Gly Gly Gly Val
20 25 30
Ala Ser Gly Ser Leu Val Ala Thr Leu Gln Ser Leu Gly Ala Thr Gly
35 40 45
Leu Ser Gly Leu Thr Lys Phe Ile Leu Gly Ser Ile Gly Ser Ala Ile
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Ala Ala Val Ile Ala Arg Phe Tyr
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<210> 66
<211> 2581

1054

09518860 '6 03300

<212> DNA
<213> Homo sapien

<400> 66

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gaagaagaag atgaaatata ttcaggactt ccagagagag aaacaggagt tcgagcgaaa 660
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<210> 67
<211> 764

1055

09S1 T560 030300

<212> PRT
<213> Homo sapien

<400> 67

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Met Asn Gly Glu Ala Asp Cys Pro Thr Asp Leu Glu Met Ala Ala Pro
 1               5                  10                  15
Lys Gly Gln Asp Arg Trp Ser Gln Glu Asp Met Leu Thr Leu Leu Glu
            20                  25                  30
Cys Met Lys Asn Asn Leu Pro Ser Asn Asp Ser Ser Lys Phe Lys Thr
        35                  40                  45
Thr Glu Ser His Met Asp Trp Glu Lys Val Ala Phe Lys Asp Phe Ser
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Gly Asp Met Cys Lys Leu Lys Trp Val Glu Ile Ser Asn Glu Val Arg
65                  70                  75                  80
Lys Phe Arg Thr Leu Thr Glu Leu Ile Leu Asp Ala Gln Glu His Val
                85                  90                  95
Lys Asn Pro Tyr Lys Gly Lys Lys Leu Lys Lys His Pro Asp Phe Pro
            100                 105                 110
Lys Lys Pro Leu Thr Pro Tyr Phe Arg Phe Phe Met Glu Lys Arg Ala
        115                 120                 125
Lys Tyr Ala Lys Leu His Pro Glu Met Ser Asn Leu Asp Leu Thr Lys
    130                 135                 140
Ile Leu Ser Lys Lys Tyr Lys Glu Leu Pro Glu Lys Lys Lys Met Lys
145                 150                 155                 160
Tyr Ile Gln Asp Phe Gln Arg Glu Lys Gln Glu Phe Glu Arg Asn Leu
                165                 170                 175
Ala Arg Phe Arg Glu Asp His Pro Asp Leu Ile Gln Asn Ala Lys Lys
            180                 185                 190
Ser Asp Ile Pro Glu Lys Pro Lys Thr Pro Gln Gln Leu Trp Tyr Thr
        195                 200                 205
His Glu Lys Lys Val Tyr Leu Lys Val Arg Pro Asp Ala Thr Thr Lys
    210                 215                 220
Glu Val Lys Asp Ser Leu Gly Lys Gln Trp Ser Gln Leu Ser Asp Lys
225                 230                 235                 240
Lys Arg Leu Lys Trp Ile His Lys Ala Leu Glu Gln Arg Lys Glu Tyr
                245                 250                 255
Glu Glu Ile Met Arg Asp Tyr Ile Gln Lys His Pro Glu Leu Asn Ile
            260                 265                 270
Ser Glu Glu Gly Ile Thr Lys Ser Thr Leu Thr Lys Ala Glu Arg Gln
        275                 280                 285
Leu Lys Asp Lys Phe Asp Gly Arg Pro Thr Lys Pro Pro Pro Asn Ser
    290                 295                 300
Tyr Ser Leu Tyr Cys Ala Glu Leu Met Ala Asn Met Lys Asp Val Pro
305                 310                 315                 320
Ser Thr Glu Arg Met Val Leu Cys Ser Gln Gln Trp Lys Leu Leu Ser
                325                 330                 335
Gln Lys Glu Lys Asp Ala Tyr His Lys Lys Cys Asp Gln Lys Lys Lys
            340                 345                 350
Asp Tyr Glu Val Glu Leu Leu Arg Phe Leu Glu Ser Leu Pro Glu Glu
        355                 360                 365
Glu Gln Gln Arg Val Leu Gly Glu Glu Lys Met Leu Asn Ile Asn Lys
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Lys Gln Ala Thr Ser Pro Ala Ser Lys Lys Pro Ala Gln Glu Gly Gly
385                 390                 395                 400
Lys Gly Gly Ser Glu Lys Pro Lys Arg Pro Val Ser Ala Met Phe Ile
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Phe Ser Glu Glu Lys Arg Arg Gln Leu Gln Glu Glu Arg Pro Glu Leu
            420                 425                 430
Ser Glu Ser Glu Leu Thr Arg Leu Leu Ala Arg Met Trp Asn Asp Leu
        435                 440                 445
Ser Glu Lys Lys Lys Ala Lys Tyr Lys Ala Arg Glu Ala Ala Leu Lys
    450                 455                 460
Ala Gln Ser Glu Arg Lys Pro Gly Gly Glu Arg Glu Glu Arg Gly Lys
465                 470                 475                 480
Leu Pro Glu Ser Pro Lys Arg Ala Glu Glu Ile Trp Gln Gln Ser Val
                485                 490                 495
Ile Gly Asp Tyr Leu Ala Arg Phe Lys Asn Asp Arg Val Lys Ala Leu
            500                 505                 510
Lys Ala Met Glu Met Thr Trp Asn Asn Met Glu Lys Lys Glu Lys Leu
        515                 520                 525
Met Trp Ile Lys Lys Ala Ala Glu Asp Gln Lys Arg Tyr Glu Arg Glu
    530                 535                 540
Leu Ser Glu Met Arg Ala Pro Pro Ala Ala Thr Asn Ser Ser Lys Lys
545                 550                 555                 560
Met Lys Phe Gln Gly Glu Pro Lys Lys Pro Pro Met Asn Gly Tyr Gln
                565                 570                 575
Lys Phe Ser Gln Glu Leu Leu Ser Asn Gly Glu Leu Asn His Leu Pro
            580                 585                 590
Leu Lys Glu Arg Met Val Glu Ile Gly Ser Arg Trp Gln Arg Ile Ser
        595                 600                 605
Gln Ser Gln Lys Glu His Tyr Lys Lys Leu Ala Glu Glu Gln Gln Lys
    610                 615                 620
Gln Tyr Lys Val His Leu Asp Leu Trp Val Lys Ser Leu Ser Pro Gln
625                 630                 635                 640
Asp Arg Ala Ala Tyr Lys Glu Tyr Ile Ser Asn Lys Arg Lys Ser Met
                645                 650                 655
Thr Lys Leu Arg Gly Pro Asn Pro Lys Ser Ser Arg Thr Thr Leu Gln
            660                 665                 670
Ser Lys Ser Glu Ser Glu Glu Asp Asp Glu Glu Asp Glu Asp Asp Glu
        675                 680                 685
Asp Glu Asp Glu Glu Glu Glu Asp Asp Glu Asn Gly Asp Ser Ser Glu
    690                 695                 700
Asp Gly Gly Asp Ser Ser Glu Ser Ser Ser Glu Asp Glu Ser Glu Asp
705                 710                 715                 720
Gly Asp Glu Asn Glu Glu Asp Asp Glu Asp Glu Asp Asp Asp Glu Asp
                725                 730                 735
Asp Asp Glu Asp Glu Asp Asn Glu Ser Glu Gly Ser Ser Ser Ser Ser
            740                 745                 750
Ser Ser Leu Gly Asp Ser Ser Asp Phe Asp Ser Asn
        755                 760
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<210> 68

<211> 434
<212> DNA
<213> Homo sapien

<400> 68
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ccaatcgcat ctgcaaagtg ttggcggtca atcaagagaa cgagcagctt atggaagact 180
atgagaagct ggccagtgat ctgttggagt ggatccgccg caccatccca tggctggaga 240
atcgggtgcc tgagaacacc atgcatgcca tgcagcagaa gctggaggac ttccgagact 300
atagacgcct gcacaagccg cccaaggtgc aggagaagtg ccagctggag atcaacttta 360
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ggatggtctc ggat 434

<210> 69
<211> 244
<212> DNA
<213> Homo sapien

<400> 69
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ttatgtgctg accttccctc cactattgtc ctgtgaccct gccaaatccc cctttgtgag 180
aaacacccaa gaatgatcaa taaaaaatna attaatttag gaaaaaaaaa aaaaaaaact 240
cgag 244

<210> 70
<211> 437
<212> DNA
<213> Homo sapien

<400> 70
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ccaggcagtg ggaccccgcg agctgcacgt ccctgggcac ggacaagtgt gaggcactgt 180
tggggctgtg ccaggtgcgg ggtgggctgc ccccttctc agaaccttcc agcctggtgc 240
cgtggccccc aggccggagt cttcctaagg ctgtgaggcc accccctgtcc tggcctccgt 300
tctcgcagca gcagaccttg cccgtgatga gcggggaggc ccttggctgg ctgggccagg 360
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tggcgcagga agccggg 437

<210> 71
<211> 271
<212> DNA
<213> Homo sapien

<400> 71
gcgcagagtt ctgtcgtcca ccatcgagtg aggaagagag cattggttcc cctgagatag 60
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gaccaatcca aggagggctg caggagggac ttcaggtgac cctccagggg actaccgaga 180
gttttgcaca aaagtttgtg gtgaactttt cagaacagct tcaatggaga tgacttggcc 240

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<210> 72
<211> 290
<212> DNA
<213> Homo sapien

<400> 72
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ctggtgccct ctcctgctgc gaggactcgg cccagggctc gggcccgccc aaggccccta 120
cggtggccga gggtcccagc tcctgccttc ggcggaacgt gatcagcgag agggagcgca 180
ggaagcggat gtcgttgagc tgtgagcgtc tgcgggccct gctgccccag ttcgatggcc 240
ggcgggagga catggcctcg gtcctggaga tgtctgttgc aattcctgcg 290

<210> 73
<211> 144
<212> PRT
<213> Homo sapien

<400> 73
Lys Met Leu Asp Ala Glu Asp Ile Val Gly Thr Ala Arg Pro Asp Glu
1 5 10 15
Lys Ala Ile Met Thr Tyr Val Ser Ser Phe Tyr His Ala Phe Ser Gly
20 25 30
Ala Gln Lys Ala Glu Thr Ala Ala Asn Arg Ile Cys Lys Val Leu Ala
35 40 45
Val Asn Gln Glu Asn Glu Gln Leu Met Glu Asp Tyr Glu Lys Leu Ala
50 55 60
Ser Asp Leu Leu Glu Trp Ile Arg Arg Thr Ile Pro Trp Leu Glu Asn
65 70 75 80
Arg Val Pro Glu Asn Thr Met His Ala Met Gln Gln Lys Leu Glu Asp
85 90 95
Phe Arg Asp Tyr Arg Arg Leu His Lys Pro Pro Lys Val Gln Glu Lys
100 105 110
Cys Gln Leu Glu Ile Asn Phe Asn Thr Leu Gln Thr Lys Leu Arg Leu
115 120 125
Ser Asn Arg Pro Ala Phe Met Pro Ser Glu Gly Arg Met Val Ser Asp
130 135 140

<210> 74
<211> 64
<212> PRT
<213> Homo sapien

<400> 74
Gly Ser Met Leu Val Glu Ser His His His Ser Leu Ile Ser Ser Thr
1 5 10 15
Gln Gly His Lys His Cys Gly Arg Pro Gln Gly Pro Leu Pro Arg Lys
20 25 30
Thr Arg Asp Leu Cys Ser Leu Val Tyr Val Leu Thr Phe Pro Pro Leu
35 40 45

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Leu Ser Cys Asp Pro Ala Lys Ser Pro Phe Val Arg Asn Thr Gln Glu
50 55 60

<210> 75
<211> 145
<212> PRT
<213> Homo sapien

<400> 75
Gly Thr Gly Ala Ser Ser Gly Thr Arg Thr Pro Asp Val Lys Ala Phe
1 5 10 15
Leu Glu Ser Pro Trp Ser Leu Asp Pro Ala Ser Ala Ser Pro Glu Pro
20 25 30
Val Pro His Ile Leu Ala Ser Ser Arg Gln Trp Asp Pro Ala Ser Cys
35 40 45
Thr Ser Leu Gly Thr Asp Lys Cys Glu Ala Leu Leu Gly Leu Cys Gln
50 55 60
Val Arg Gly Gly Leu Pro Pro Phe Ser Glu Pro Ser Ser Leu Val Pro
65 70 75 80
Trp Pro Pro Gly Arg Ser Leu Pro Lys Ala Val Arg Pro Pro Leu Ser
85 90 95
Trp Pro Pro Phe Ser Gln Gln Gln Thr Leu Pro Val Met Ser Gly Glu
100 105 110
Ala Leu Gly Trp Leu Gly Gln Ala Gly Ser Leu Ala Met Gly Ala Ala
115 120 125
Pro Leu Gly Glu Pro Ala Lys Glu Asp Pro Met Leu Ala Gln Glu Ala
130 135 140
Gly
145

<210> 76
<211> 69
<212> PRT
<213> Homo sapien

<400> 76
Ala Glu Phe Cys Arg Pro Pro Ser Ser Glu Glu Glu Ser Ile Gly Ser
1 5 10 15
Pro Glu Ile Glu Glu Met Ala Leu Phe Ser Ala Gln Ser Pro Tyr Ile
20 25 30
Asn Pro Ile Ile Pro Phe Thr Gly Pro Ile Gln Gly Gly Leu Gln Glu
35 40 45
Gly Leu Gln Val Thr Leu Gln Gly Thr Thr Glu Ser Phe Ala Gln Lys
50 55 60
Phe Val Val Asn Phe
65

<210> 77
<211> 96
<212> PRT
<213> Homo sapien

1060

<400> 77

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

<210> 78
<211> 2076
<212> DNA
<213> Homo sapien

<400> 78

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aggaaataga agttgcccca ccaaagacta aagaagttcg cattaagatt ttggccacag 180
gaatctgtcg cacagatgac catgtgataa aaggaacaat ggtgtccaag tttccagtga 240
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gcaacccaga tggcaacctt tgcattagga gcgatattac tggtcgtgga gtactggctg 420
atggcaccac cagatttaca tgcaagggca aaccagtcca ccacttcatg aacaccagta 480
catttaccga gtacacagtg gtggatgaat cttctgttgc taagattgat gatgcagctc 540
ctcctgagaa agtctgttta attggctgtg ggttttccac tggatatggc gctgctgtta 600
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tagaatcata ttatcatact tatcataatg ttcaatttga tacagtagaa ttgcaagtcc 1920
ttaagtccct attcactgtg cttagtagtg actccattta ataaaaagtg tttttagttt 1980
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<210> 79
<211> 2790
<212> DNA
<213> Homo sapien

<400> 79
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caggggtagt gatcctggca gtcaccatag ctctacttgt ttacttttta gcttttgatc 180
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<210> 80
<211> 1460
<212> DNA
<213> Homo sapien

<400> 80
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acaaaaaaaa aaaaaaaaaa 1460

<210> 81
<211> 386
<212> PRT
<213> Homo sapien.

<400> 81
Met Phe Ala Glu Ile Gln Ile Gln Asp Lys Asp Arg Met Gly Thr Ala
 1   5   10   15
Gly Lys Val Ile Lys Cys Lys Ala Ala Val Leu Trp Glu Gln Lys Gln
            20   25   30

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Pro Phe Ser Ile Glu Glu Ile Glu Val Ala Pro Pro Lys Thr Lys Glu
        35                  40                  45
Val Arg Ile Lys Ile Leu Ala Thr Gly Ile Cys Arg Thr Asp Asp His
    50                  55                  60
Val Ile Lys Gly Thr Met Val Ser Lys Phe Pro Val Ile Val Gly His
65                  70                  75                  80
Glu Ala Thr Gly Ile Val Glu Ser Ile Gly Glu Gly Val Thr Thr Val
                85                  90                  95
Lys Pro Gly Asp Lys Val Ile Pro Leu Phe Leu Pro Gln Cys Arg Glu
            100                 105                 110
Cys Asn Ala Cys Arg Asn Pro Asp Gly Asn Leu Cys Ile Arg Ser Asp
        115                 120                 125
Ile Thr Gly Arg Gly Val Leu Ala Asp Gly Thr Thr Arg Phe Thr Cys
    130                 135                 140
Lys Gly Lys Pro Val His His Phe Met Asn Thr Ser Thr Phe Thr Glu
145                 150                 155                 160
Tyr Thr Val Val Asp Glu Ser Ser Val Ala Lys Ile Asp Asp Ala Ala
                165                 170                 175
Pro Pro Glu Lys Val Cys Leu Ile Gly Cys Gly Phe Ser Thr Gly Tyr
            180                 185                 190
Gly Ala Ala Val Lys Thr Gly Lys Val Lys Pro Gly Ser Thr Cys Val
        195                 200                 205
Val Phe Gly Leu Arg Gly Val Gly Leu Ser Val Ile Met Gly Cys Lys
    210                 215                 220
Ser Ala Gly Ala Ser Arg Ile Ile Gly Ile Asp Leu Asn Lys Asp Lys
225                 230                 235                 240
Phe Glu Lys Ala Met Ala Val Gly Ala Thr Glu Cys Ile Ser Pro Lys
                245                 250                 255
Asp Ser Thr Lys Pro Ile Ser Glu Val Leu Ser Glu Met Thr Gly Asn
            260                 265                 270
Asn Val Gly Tyr Thr Phe Glu Val Ile Gly His Leu Glu Thr Met Ile
        275                 280                 285
Asp Ala Leu Ala Ser Cys His Met Asn Tyr Gly Thr Ser Val Val Val
    290                 295                 300
Gly Val Pro Pro Ser Ala Lys Met Leu Thr Tyr Asp Pro Met Leu Leu
305                 310                 315                 320
Phe Thr Gly Arg Thr Trp Lys Gly Cys Val Phe Gly Gly Leu Lys Ser
                325                 330                 335
Arg Asp Asp Val Pro Lys Leu Val Thr Glu Phe Leu Ala Lys Lys Phe
            340                 345                 350
Asp Leu Asp Gln Leu Ile Thr His Val Leu Pro Phe Lys Lys Ile Ser
        355                 360                 365
Glu Gly Phe Glu Leu Leu Asn Ser Gly Gln Ser Ile Arg Thr Val Leu
    370                 375                 380
Thr Phe
385
```

<210> 82
<211> 418
<212> PRT
<213> Homo sapien

799
1064

9518809 030300

<400> 82

```
Met Tyr Arg Pro Ala Arg Val Thr Ser Thr Ser Arg Phe Leu Asn Pro
 1               5                  10                  15
Tyr Val Val Cys Phe Ile Val Val Ala Gly Val Val Ile Leu Ala Val
            20                  25                  30
Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
        35                  40                  45
Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
    50                  55                  60
Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65                  70                  75                  80
Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
                85                  90                  95
Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
            100                 105                 110
Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
        115                 120                 125
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
    130                 135                 140
Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145                 150                 155                 160
Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
                165                 170                 175
Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
            180                 185                 190
Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
        195                 200                 205
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
    210                 215                 220
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225                 230                 235                 240
Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
                245                 250                 255
Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
            260                 265                 270
Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
        275                 280                 285
His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
    290                 295                 300
Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
305                 310                 315                 320
Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
                325                 330                 335
Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
            340                 345                 350
Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
        355                 360                 365
Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
    370                 375                 380
Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
```

1076
1065

385 390 395 400
Val Tyr Thr Arg Val Thr Ala Tyr Leu Asp Trp Ile Arg Gln Gln Thr
405 410 415
Gly Ile

<210> 83
<211> 418
<212> PRT
<213> Homo sapien

<400> 83
Met Tyr Arg Pro Ala Arg Val Thr Ser Thr Ser Arg Phe Leu Asn Pro
1 5 10 15
Tyr Val Val Cys Phe Ile Val Val Ala Gly Val Val Ile Leu Ala Val
20 25 30
Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
35 40 45
Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
50 55 60
Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65 70 75 80
Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
85 90 95
Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
100 105 110
Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
115 120 125
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
130 135 140
Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145 150 155 160
Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
165 170 175
Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
180 185 190
Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
195 200 205
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
210 215 220
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225 230 235 240
Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
245 250 255
Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
260 265 270
Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
275 280 285
His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
290 295 300
Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr

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1066

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```
305                 310                 315                 320
Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
                325                 330                 335
Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
            340                 345                 350
Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
        355                 360                 365
Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
    370                 375                 380
Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
385                 390                 395                 400
Val Tyr Thr Arg Val Thr Ala Tyr Leu Asp Trp Ile Arg Gln Gln Thr
                405                 410                 415
Gly Ile
```

<210> 84
<211> 489
<212> DNA
<213> Homo sapien

<400> 84

```
aaaagggtaa gcttgatgat taccaggaac gaatgaacaa aggggaaagg cttaatcaag      60
atcagctgga tgccgtttct aagtaccagg aagtcacaaa taatttggag tttgcaaaag     120
aattacagag gagtttcatg gcactaagtc aagatattca gaaaacaata aagaagacag     180
cacgtcggga gcagcttatg agagaagaag ctgaacagaa acgtttaaaa actgtacttg     240
agctacagta tgttttggac aaattgggag atgatgaagt gcggactgac ctgaaacaag     300
gtttgaatgg agtgccaata ttgtccgaag aggagttgtc attgttggat gaattctata     360
agctagtaga ccctgaacgg gacatgagct tgaggttgaa tgaacagtat gaacatgcct     420
ccattcacct gtgggacctg ctggaaggga aggaaaaacc tgtatgtgga accacctata     480
aagttctaa                                                             489
```

<210> 85
<211> 304
<212> DNA
<213> Homo sapien

<400> 85

```
gggacctgga ggaggccacg ctgcagcatg aagccacagc agccaccctg aggaagaagc      60
acgcggacag cgtggccgag ctcggggagc agatcgacaa cctgcagcgg gtgaagcaga     120
agctggagaa ggagaagagc gagatgaaga tggagatcga tgacctcgct tgtaacatgg     180
aggtcatctc caaatctaag ggaaaccttg agaagatgtg ccgcacactg gaggaccaag     240
tgagtgagct gaagacccag gaggaggaac agcagcggct gatcaatgaa ctgactgcgc     300
agag                                                                  304
```

<210> 86
<211> 296
<212> DNA
<213> Homo sapien

<400> 86

1067

gaaaatcctt cctttgaatg ggaatctcca agcagttgaa ttgggcgaaa aaagaacctc 60
ttccttaagg attaaaatgt ttagggcaac acgtgttact tccacttcca gatttctgaa 120
tccatatgtt gtatgtttcc ttgtcctccc aggggttgtg atcctggcag tccccatagc 180
tctacttgtt tacttttttag cttttgatca aaaatcttac ttttattgga gcaatttttcc 240
actcccaaat gttgaatata atagtccgtt taattccccc gcttcaccgg gaattc 296

<210> 87
<211> 904
<212> DNA
<213> Homo sapien

<400> 87
gtgtccagga aacgattcat gaacataaca agcttgctgc aaattcagat catctcatgc 60
agattcaaaa atgtgagttg gtcttgatcc acacctaccc agttggtgaa gacagccttg 120
tatctgatcg ttctaaaaaa gagttgtccc cggttttaac cagtgaagtt catagtgttc 180
gtgcaggacg gcatcttgct accaaattga atattttagt acagcaacat tttgacttgg 240
cttcaactac tattacaaat attccaatga aggaagaaca gcatgctaac acatctgcca 300
attatgatgt ggagctactt catcacaaag atgcacatgt agatttcctg aaaagtggtg 360
attcgcatct aggtggcggc agtcgagaag gctcgtttaa agaaacaata acattaaagt 420
ggtgtacacc aaggacaaat aacattgaat tacactattg tactggagct tatcggattt 480
cacctgtaga tgtaaatagt agaccttcct cctgccttac taatttttctt ctaaatggtc 540
gttctgtttt attggaacaa ccacgaaagt caggttctaa agtcattagt catatgctta 600
gtagccatgg aggagagatt tttttgcacg tccttagcag ttctcgatcc attctagaag 660
atccaccttc aattagtgaa ggatgtggag gaagagttac agactaccgg attacagatt 720
ttggtgaatt tatgagggga aaacagatta actccttttc tacaccccag atataaaatc 780
gatggaagtc ttgaggtccc tttggaaccg agccaaaaga tcagttaaaa aaacataccc 840
gttactggcc tatgatttca aaaacccacc atttttaaca tgcaagcggt agttccgtta 900
acca 904

<210> 88
<211> 387
<212> DNA
<213> Homo sapien

<400> 88
cgtctctccc ccagtttgcc gttcacccgg agcgctcggg acttgccgat agtggtgacg 60
gcggcaacat gtctgtggct ttcgcggccc cgaggcagcg aggcaagggg gagatcactc 120
ccgctgcgat tcagaagatg ttggatgaca ataaccatct tattcagtgt ataatggact 180
ctcagaataa aggaaagacc tcagagtgtt ctcagtatca gcagatgttg cacacaaact 240
tggtatacct tgctacaata gcagattcta atcaaaatat gcagtctctt ttaccagcac 300
cacccacaca gaatatgcct atgggtcctg gagggatgaa tcagagcggg cctcccccac 360
ctccacgctc tcacaacatg ccttcaa 387

<210> 89
<211> 481
<212> DNA
<213> Homo sapien

<400> 89
tgttcttgga cctgcggtgc tatagagcag gctcttctag gttggcagtt gccatggaat 60
ctggacccaa aatgttggcc cccgtttgcc tggtggaaaa taacaatgag cagctattgg 120

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-82
10/73
1068

003 30.09 81560

tgaaccagca agctatacag attcttgaaa agatttctca gccagtggtg gtggtggcca 180
ttgtaggact gtaccgtaca gggaaatcct acttgatgaa ccatctggca ggacagaatc 240
atggcttccc tctgggctcc acggtgcagt ctgaaaccaa gggcatctgg atgtggtgcg 300
tgccccaccc atccaagcca aaccacaccc tggtccttct ggacaccgaa ggtctgggcg 360
atgtggaaaa gggtgaccct aagaatgact cctggatctt tgccctggct gtgctcctgt 420
gcagcacctt tgtctacaac agcatgagca ccatcaacca ccaggccctg gagcagctgc 480
a 481

<210> 90
<211> 491
<212> DNA
<213> Homo sapien

<400> 90
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gacccaaaat gttggccccc gtttgcctgg tggaaaataa caatgagcag ctattggtga 120
accagcaagc tatacagatt cttgaaaaga tttctcagcc agtggtggtg gtggccattg 180
taggactgta ccgtacaggg aaatcctact tgatgaacca tctggcagga cagaatcatg 240
gcttccctct gggctccacg gtgcagtctg aaaccaaggg catctggatg tggtgcgtgc 300
cccacccatc caagccaaac cacaccctgg tccttctgga caccgaaggt ctgggcgatg 360
tggaaaaggg tgaccctaag aatgactcct ggatctttgc cctggctgtg ctcctgtgca 420
gcacctttgt ctacaacagc atgagcacca tcaaccacca agccctggag cagctgcatt 480
atgtgacgga c 491

<210> 91
<211> 488
<212> DNA
<213> Homo sapien

<400> 91
ttcgacagtc agccgcatct tcttttgcgt cgccagccga gccacatcgc tcagacacca 60
tggggaaggt gaaggtcgga gtcaacggat ttggtcgtat tgggcgcctg gtcaccaggg 120
ctgcttttaa ctctggtaaa gtggatattg ttgccatcaa tgaccccttc attgacctca 180
actacatggt ttacatgttc caatatgatt ccacccatgg caaattccat ggcaccgtcg 240
aggctgagaa cgggaagctt gtcatcaatg gaaatcccat caccatcttc caggagcgag 300
atcctccaaa aatcaagtgg ggcgatgctg gcgctgagta cgtcgtggag tccactggcg 360
tcttcaccac catggagaag gctggggctc atttgcaggg gggagccaaa agggtcatca 420
tctctgcccc tctgctgatg ccccatgttc gtcatgggtg tgaaccatga gaagtatgac 480
acagcctc 488

<210> 92
<211> 384
<212> DNA
<213> Homo sapien

<400> 92
gacagtcagc cgcatcttct tttgcgtcgc cagccgagcc acatcgctca gacaccatgg 60
ggaaggtgaa ggtcggagtc aacggatttg gtcgtattgg gcgcctggtc accagggctg 120
cttttaactc tggtaaagtg gatattgttg ccatcaatga ccccttcatt gacctcaact 180
acatggttta catgttccaa tatgattcca cccatggcaa attccatggc accgtcgagg 240
ctgagaacgg gaagcttgtc atcaatggaa atcccatcac catcttccag gagcgagatc 300

1069

cctccaaaat caagtggggc gatactggcg ctgagtacgt cgtggagtcc actggcgtct 360
tcaccaccat ggagaaggct gggg 384

<210> 93
<211> 162
<212> PRT
<213> Homo sapien

<400> 93

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

<210> 94
<211> 100
<212> PRT
<213> Homo sapien

<400> 94

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

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1070

100

<210> 95
<211> 99
<212> PRT
<213> Homo sapien

<400> 95

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

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<210> 96
<211> 257
<212> PRT
<213> Homo sapien

<400> 96

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

0205
1996
1071

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```
Leu Asn Gly Arg Ser Val Leu Leu Glu Gln Pro Arg Lys Ser Gly Ser
            180                 185                 190
Lys Val Ile Ser His Met Leu Ser Ser His Gly Gly Glu Ile Phe Leu
        195                 200                 205
His Val Leu Ser Ser Ser Arg Ser Ile Leu Glu Asp Pro Pro Ser Ile
    210                 215                 220
Ser Glu Gly Cys Gly Gly Arg Val Thr Asp Tyr Arg Ile Thr Asp Phe
225                 230                 235                 240
Gly Glu Phe Met Arg Gly Lys Gln Ile Asn Ser Phe Ser Thr Pro Gln
                245                 250                 255
Ile
```

<210> 97
<211> 128
<212> PRT
<213> Homo sapien

<400> 97

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

<210> 98
<211> 159
<212> PRT
<213> Homo sapien

<400> 98

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

1072

65 70 75 80
Gly Phe Pro Leu Gly Ser Thr Val Gln Ser Glu Thr Lys Gly Ile Trp
85 90 95
Met Trp Cys Val Pro His Pro Ser Lys Pro Asn His Thr Leu Val Leu
100 105 110
Leu Asp Thr Glu Gly Leu Gly Asp Val Glu Lys Gly Asp Pro Lys Asn
115 120 125
Asp Ser Trp Ile Phe Ala Leu Ala Val Leu Leu Cys Ser Thr Phe Val
130 135 140
Tyr Asn Ser Met Ser Thr Ile Asn His Gln Ala Leu Glu Gln Leu
145 150 155

<210> 99
<211> 147
<212> PRT
<213> Homo sapien

<400> 99
Met Glu Ser Gly Pro Lys Met Leu Ala Pro Val Cys Leu Val Glu Asn
1 5 10 15
Asn Asn Glu Gln Leu Leu Val Asn Gln Gln Ala Ile Gln Ile Leu Glu
20 25 30
Lys Ile Ser Gln Pro Val Val Val Val Ala Ile Val Gly Leu Tyr Arg
35 40 45
Thr Gly Lys Ser Tyr Leu Met Asn His Leu Ala Gly Gln Asn His Gly
50 55 60
Phe Pro Leu Gly Ser Thr Val Gln Ser Glu Thr Lys Gly Ile Trp Met
65 70 75 80
Trp Cys Val Pro His Pro Ser Lys Pro Asn His Thr Leu Val Leu Leu
85 90 95
Asp Thr Glu Gly Leu Gly Asp Val Glu Lys Gly Asp Pro Lys Asn Asp
100 105 110
Ser Trp Ile Phe Ala Leu Ala Val Leu Leu Cys Ser Thr Phe Val Tyr
115 120 125
Asn Ser Met Ser Thr Ile Asn His Gln Ala Leu Glu Gln Leu His Tyr
130 135 140
Val Thr Asp
145

<210> 100
<211> 124
<212> PRT
<213> Homo sapien

<400> 100
Met Gly Lys Val Lys Val Gly Val Asn Gly Phe Gly Arg Ile Gly Arg
1 5 10 15
Leu Val Thr Arg Ala Ala Phe Asn Ser Gly Lys Val Asp Ile Val Ala
20 25 30
Ile Asn Asp Pro Phe Ile Asp Leu Asn Tyr Met Val Tyr Met Phe Gln
35 40 45

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1078
1073

0951880 030300

```
Tyr Asp Ser Thr His Gly Lys Phe His Gly Thr Val Glu Ala Glu Asn
    50                  55                  60
Gly Lys Leu Val Ile Asn Gly Asn Pro Ile Thr Ile Phe Gln Glu Arg
65                  70                  75                  80
Asp Pro Ser Lys Ile Lys Trp Gly Asp Ala Gly Ala Glu Tyr Val Val
                85                  90                  95
Glu Ser Thr Gly Val Phe Thr Thr Met Glu Lys Ala Gly Ala His Leu
            100                 105                 110
Gln Gly Gly Ala Lys Arg Val Ile Ile Ser Ala Pro
        115                 120
```

<210> 101
<211> 127
<212> PRT
<213> Homo sapien

<400> 101

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

<210> 102
<211> 1225
<212> DNA
<213> Homo sapien

<400> 102

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gcggagacgg cagccgtgac ggtggcagcg gcggcgcggg acctgggcct gggggaatga     120
ggcggccgcg gcgggccagc ggcggagccg tgtagcggag aagctccccc tccctgcttc     180
ccttggccga gccgggggcg cgcgcgcacg cggccgtcca gagcgggctc cccacccctc     240
gactcctgcg acccgcaccg cacccccacc cgggcccgga ggatgatgaa gctcaagtcg     300
aaccagaccc gcacctacga cggcgacggc tacaagaagc gggccgcatg cctgtgtttc     360
cgcagcgaga gcgaggagga ggtgctactc gtgagcagta gtcgccatcc agacagatgg     420
attgtccctg gaggaggcat ggagcccgag gaggagccaa gtgtggcagc agttcgtgaa     480
gtctgtgagg aggctggagt aaaagggaca ttgggaagat tagttggaat ttttgagaac     540
caggagagga agcacaggac gtatgtctat gtgctcattg tcactgaagt gctggaagac     600
tgggaagatt cagttaacat tggaaggaag agggaatggt ttaaaataga agacgccata     660
```

aaagtgctgc agtatcacaa acccgtgcag gcatcatatt ttgaaacatt gaggcaaggc 720
tactcagcca acaatggcac cccagtcgtg gccaccacat actcggtttc tgctcagagc 780
tcgatgtcag gcatcagatg actgaagact tcctgtaaga gaaatggaaa ttggaaacta 840
gactgaagtg caaatcttcc ctctcaccct ggctctttcc acttctcaca ggctcctct 900
ttcaaataag gcatggtggg cagcaaagaa agggtgtatt gataatgttg ctgtttggtg 960
ttaagtgatg gggctttttc ttctgttttt attgagggtg ggggttgggt gtgtaatttg 1020
taagtacttt tgtgcatgat ctgtccctcc ctcttcccac ccctgcagtc ctctgaagag 1080
aggccaacag ccttcccctg ccttggattc tgaagtgttc ctgtttgtct tatcctggcc 1140
ctggccagac gttttctttg atttttaatt ttttttttt attaaaagat accagtatga 1200
gaaaaaaaaa aaaaaaaaac tcgag 1225

<210> 103
<211> 741
<212> DNA
<213> Homo sapien

<400> 103
agaaacctca atcggattca gcaaaggaat ggtgttatta tcactacata ccaaatgtta 60
atcaataact ggcagcaact ttcaagcttt aggggccaag agtttgtgtg ggactatgtc 120
atcctcgatg aagcacataa aataaaaacc tcatctacta agtcagcaat atgtgctcgt 180
gctattcctg caagtaatcg cctcctcctc acaggaaccc caatccagaa taatttacaa 240
gaactatggt ccctatttga ttttgcttgt caagggtccc tgctgggaac attaaaaact 300
tttaagatgg agtatgaaaa tcctattact agagcaagag agaaggatgc taccccagga 360
gaaaaagcct tgggatttaa aatatctgaa aacttaatgg caatcataaa accctatttt 420
ctcaggaggc ctaaagaaga cgtacagaag aaaaagtcaa gcaacccaga ggccagactt 480
aatgaaaaga atccagatgt tgatgccatt tgtgaaatgc cttccctttc caggagaaat 540
gatttaatta tttggatacg acttgtgcct ttacaagaag aaatatacag gaaatttgtg 600
tctttagatc atatcaagga gttgctaatg gagacgcgct caccttggc tgagctaggt 660
gtcttaaaga agctgtgtga tcatcctagg ctgctgtctg cacgggcttg ttgtttgcta 720
aatcttggga cattctctgc t 741

<210> 104
<211> 321
<212> DNA
<213> Homo sapien

<400> 104
ttgctctgcg tcatcaaaga caccaaactg ctgtgctata aaagttccaa ggaccagcag 60
cctcagatgg aactgccact ccaaggctgt aacattacgt acatcccgaa agacagcaaa 120
aagaagaagc acgagctgaa gattactcag cagggcacgg acccgcttgt tctcgccgtc 180
cagagcaagg aacaggccga gcagtggctg aaggtgatca aagaagccta cagtggttgt 240
agtggccccg tggattcaga gtgtcctcct ccaccaagct ccccggtgca caaggcagaa 300
ctggagaaga aactgtcttc a 321

<210> 105
<211> 389
<212> DNA
<213> Homo sapien

<400> 105
cagcactggc cacactataa aattcaggtt cagaaaaaca gggtaagtca cagacagcaa 60

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cgcttccagc atttattttc tttgcaccca tgggcaattt gagaaaattt acctttagaa 120
cgaactctgt taaaggtaca gacagtacaa tacttttttat tcagaaggtt tctgcataaa 180
ggtgatagtc ttttgactta atatattatt gtctcctgcc ttgtgtttct ggaatgaatg 240
aaggtcatta tttagaagat aatctgggtt gtatttgtgt cgtcagattg aattttcatt 300
gcacatgcta cttaatgtct ttaccaaata ataacaaagg gaaagaaaac caaatataga 360
tgtataataa ggaaaagctg gcctataga 389

<210> 106
<211> 446
<212> DNA
<213> Homo sapien

<400> 106
gccacatttg ccctggtcat agtttaaaca ccaggtcctg tgtcacatct ttttggtgcc 60
acaagtatca ctccattgtt cagagagtaa tgtattagtt ctgcccaatt cattcttcac 120
ttttatttct tccatttcat tagcatttat atcagctcaa gaagttaagg ttagaaaatt 180
ttccacttca aattttcagt acagaaatgt gctgtgatgt ttgacaagac tatttcatag 240
taagtgagtt aatgtttatt ggcctctgct ctcctctgtg tcagacctag gaagcctgag 300
gattacttag ttgttctgtc tctgggtcca caggcagaat ttggcccatc caaagactgg 360
ccaagtgcca aaaaaaggcc tgattaggcc ctgaaattca gtgaaattct gcctgaagaa 420
acctcttatt gaatttgaaa accata 446

<210> 107
<211> 467
<212> DNA
<213> Homo sapien

<400> 107
ccgccgctgc cgtcgccttc ctgggattgg agtctcgagc tttcttcgtt cgttcgccgg 60
cgggttcgcg ccctttctcgc gcctcggggc tgcgaggctg gggaaggggt tggaggggcc 120
tgttgatcgc cgcgtttaag ttgcgctcgg ggcggccatg tcggccggcg aggtcgagcg 180
cctagtgtcg gagctgagcg gcgggaccgg aggggatgag gaggaagagt ggctctatgg 240
cgatgaagat gaagttgaaa ggccagaaga agaaaatgcc agtgctaatc ctccatctgg 300
aattgaagat gaaactgctg aaaatggtgt accaaaaccg aaagtgactg agaccgaaga 360
tgatagtgat agtgacagcg atgatgatga agatgatgtg catgtcacta taggagacat 420
taaaacggga gcaccacagt atgggagtta tggtacagca cctgtaa 467

<210> 108
<211> 491
<212> DNA
<213> Homo sapien

<400> 108
gaaagataca acttccccaa cccaaacccg tttgtggagg acgacatgga taagaatgaa 60
atcgcctctg ttgcgtaccg ttaccgcagg tggaagcttg gagatgatat tgaccttatt 120
gtccgttgtg agcacgatgg cgtcatgact ggagccaacg gggaagtgtc cttcatcaac 180
atcaagacac tcaatgagtg ggattccagg cactgtaatg gcgttgactg gcgtcagaag 240
ctggactctc agcgaggggc tgtcattgcc acggagctga agaacaacag ctacaagttg 300
gcccggtgga cctgctgtgc tttgctggct ggatctgagt acctcaagct tggttatgtg 360
tctcggtacc acgtgaaaga ctcctcacgc cacgtcatcc taggcaccca gcagttcaag 420
cctaatgagt ttgccagcca gatcaacctg agcgtggaga atgcctgagg cattttacgc 480

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tgcgtcattg a 491

<210> 109
<211> 489
<212> DNA
<213> Homo sapien

<400> 109
ctcagatagt actgaaccct ttatcaacta tgtttttca gtctgacaac caaggcggct 60
actaagtgac taaggggcag gtagtataca gtgtggataa gcaggacaaa ggggtgattc 120
acatcccagg caggacagag caggagatca tgagatttca tcactcagga tggcttgtga 180
tttattttat tttattcttt ttttttttg agatggagtc tcactcttgc ccaggctgga 240
gtgcagtggt gcgatcttgg ctcactgcaa cctctgcctc ctgggttcaa gcagttctcc 300
tgcctcagcc tcccaagtag ctgggattac aggcgtccgc caccatgccc agccaatttt 360
tgtactttta gtagagatgg ggtttcacca tgttggccag gctggtctcg aactcctgac 420
ctcaggtgat ccactcgcct cggcctccca aagtgctggg attataggca tgcgccacca 480
tgcccgggc 489

<210> 110
<211> 391
<212> DNA
<213> Homo sapien

<400> 110
gcggagtccg ctggctgacc cgagcgctgg tctccgccgg gaaccctggg gcatggagag 60
gtctgagtac ctcggccgcg gcgcacgctg catcgcggag ccaggctgcc gctgtcccag 120
tggagttcca ggagcaccac ctgagtgagg tgcagaatat ggcatctgag gagaagctgg 180
agcaggtgct gagttccatg aaggagaaca aagtggccat cattggaaag attcataccc 240
cgatggagta taaggggggag ctagcctcct atgatatgcg gctgaggcgt aagttggact 300
tatttgccaa cgtaatccat gtgaagtcac ttcctgggta tatgactcgg cacaacaatc 360
tagacctggt gatcattcga gagcagacag a 391

<210> 111
<211> 172
<212> PRT
<213> Homo sapien

<400> 111
Met Met Lys Leu Lys Ser Asn Gln Thr Arg Thr Tyr Asp Gly Asp Gly
1 5 10 15
Tyr Lys Lys Arg Ala Ala Cys Leu Cys Phe Arg Ser Glu Ser Glu Glu
20 25 30
Glu Val Leu Leu Val Ser Ser Ser Arg His Pro Asp Arg Trp Ile Val
35 40 45
Pro Gly Gly Gly Met Glu Pro Glu Glu Glu Pro Ser Val Ala Ala Val
50 55 60
Arg Glu Val Cys Glu Glu Ala Gly Val Lys Gly Thr Leu Gly Arg Leu
65 70 75 80
Val Gly Ile Phe Glu Asn Gln Glu Arg Lys His Arg Thr Tyr Val Tyr
85 90 95
Val Leu Ile Val Thr Glu Val Leu Glu Asp Trp Glu Asp Ser Val Asn

1077

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```
            100                 105                 110
Ile Gly Arg Lys Arg Glu Trp Phe Lys Ile Glu Asp Ala Ile Lys Val
        115                 120                 125
Leu Gln Tyr His Lys Pro Val Gln Ala Ser Tyr Phe Glu Thr Leu Arg
    130                 135                 140
Gln Gly Tyr Ser Ala Asn Asn Gly Thr Pro Val Val Ala Thr Thr Tyr
145                 150                 155                 160
Ser Val Ser Ala Gln Ser Ser Met Ser Gly Ile Arg
                165                 170

      <210> 112
      <211> 247
      <212> PRT
      <213> Homo sapien

      <400> 112
Arg Asn Leu Asn Arg Ile Gln Gln Arg Asn Gly Val Ile Ile Thr Thr
 1               5                  10                  15
Tyr Gln Met Leu Ile Asn Asn Trp Gln Gln Leu Ser Ser Phe Arg Gly
            20                  25                  30
Gln Glu Phe Val Trp Asp Tyr Val Ile Leu Asp Glu Ala His Lys Ile
        35                  40                  45
Lys Thr Ser Ser Thr Lys Ser Ala Ile Cys Ala Arg Ala Ile Pro Ala
    50                  55                  60
Ser Asn Arg Leu Leu Leu Thr Gly Thr Pro Ile Gln Asn Asn Leu Gln
65                  70                  75                  80
Glu Leu Trp Ser Leu Phe Asp Phe Ala Cys Gln Gly Ser Leu Leu Gly
                85                  90                  95
Thr Leu Lys Thr Phe Lys Met Glu Tyr Glu Asn Pro Ile Thr Arg Ala
            100                 105                 110
Arg Glu Lys Asp Ala Thr Pro Gly Glu Lys Ala Leu Gly Phe Lys Ile
        115                 120                 125
Ser Glu Asn Leu Met Ala Ile Ile Lys Pro Tyr Phe Leu Arg Arg Thr
    130                 135                 140
Lys Glu Asp Val Gln Lys Lys Lys Ser Ser Asn Pro Glu Ala Arg Leu
145                 150                 155                 160
Asn Glu Lys Asn Pro Asp Val Asp Ala Ile Cys Glu Met Pro Ser Leu
                165                 170                 175
Ser Arg Arg Asn Asp Leu Ile Ile Trp Ile Arg Leu Val Pro Leu Gln
            180                 185                 190
Glu Glu Ile Tyr Arg Lys Phe Val Ser Leu Asp His Ile Lys Glu Leu
        195                 200                 205
Leu Met Glu Thr Arg Ser Pro Leu Ala Glu Leu Gly Val Leu Lys Lys
    210                 215                 220
Leu Cys Asp His Pro Arg Leu Leu Ser Ala Arg Ala Cys Cys Leu Leu
225                 230                 235                 240
Asn Leu Gly Thr Phe Ser Ala
                245

      <210> 113
      <211> 107
```

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1983
1078

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<212> PRT
<213> Homo sapien

<400> 113

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

<210> 114
<211> 155
<212> PRT
<213> Homo sapien

<400> 114

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

<210> 115
<211> 129
<212> PRT
<213> Homo sapien

-83
1084
1079

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<400> 115

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

<210> 116
<211> 550
<212> DNA
<213> Homo sapien

<400> 116

```
gaattcggca ccagcctcag agccccccag cccggctacc acccccctgcg gaaaggtacc      60
catctgcatt cctgcccgtc gggacctggt ggacagtcca gcctccttgg cctctagcct     120
tggctcaccg ctgcctagag ccaaggagct catcctgaat gaccttcccg ccagcactcc     180
tgcctccaaa tcctgtgact cctccccgcc ccaggacgct tccacccccca ggcccagctc    240
ggccagtcac ctctgccagc ttgctgccaa gccagcacct tccacggaca gcgtcgccct     300
gaggagcccc ctgactctgt ccagtccctt caccacgtcc ttcagcctgg gctcccacag     360
cactctcaac ggagacctct ccgtgcccag ctcctacgtc agcctccacc tgtccccccа     420
ggtcagcagc tctgtggtgt acggacgctc ccccgtgatg gcatttgagt ctcatcccca     480
tctccgaggg tcatccgtct cttcctccct acccagcatc cctgggggaa agccggccta     540
ctccttccac                                                           550
```

<210> 117
<211> 154
<212> DNA
<213> Homo sapien

<400> 117

```
ttctgaggga aagccgagtg gagtgggcga cccggcggcg gtgacaatga gttttcttgg      60
aggctttttt ggtcccattt gtgagattga tgttgccctt aatgatgggg aaaccaggaa     120
aatggcagaa atgaaaactg aggatggcaa agta                                 154
```

<210> 118
<211> 449
<212> DNA
<213> Homo sapien

BTH 1080

1080

<400> 118
gaattcggca ccagggcccg cagcccgagt gtcgccgcca tggcttcgcc gcagctctgc 60
cgcgcgctgg tgtcggcgca atgggtggcg gaggcgctgc gggccccgcg cgctgggcag 120
cctctgcagc tgctggacgc ctcctggtac ctgccgaagc tggggcgcga cgcgcgacgc 180
gagttcgagg agcgccacat cccgggcgcc gctttcttcg acatcgacca gtgcagcgac 240
cgcacctcgc cctacgacca catgctgccc ggggccgagc atttcgcgga gtacgcaggc 300
cgcctgggcg tgggcgcggc cacccacgtc gtgatctacg acgccagcga ccagggcctc 360
tactccgccc cgcgcgtctg gtggatgttc cgcgccttcg gccaccacgc cgtgtcactg 420
cttgatggcg gcctccgcca ctggctgcg 449

<210> 119
<211> 642
<212> DNA
<213> Homo sapien

<400> 119
gaattcggca cgagcagtaa cccgaccgcc gctggtcttc gctggacacc atgaatcaca 60
ctgtccaaac cttcttctct cctgtcaaca gtggccagcc ccccaactat gagatgctca 120
aggaggagca cgaggtggct gtgctggggg cgccccacaa ccctgctccc ccgacgtcca 180
ccgtgatcca catccgcagc gagacctccg tgcccgacca tgtcgtctgg tccctgttca 240
acaccctctt catgaacccc tgctgcctgg gcttcatagc attcgcctac tccgtgaagt 300
ctagggacag gaagatggtt ggcgacgtga ccggggccca ggcctatgcc tccaccgcca 360
agtgcctgaa catctgggcc ctgattctgg gcatcctcat gaccattctg ctcatcgtca 420
tcccagtgct gatcttccag gcctatggat agatcaggag gcatcactga ggccaggagc 480
tctgcccatg acctgtatcc cacgtactcc aacttccatt cctcgccctg ccccggagc 540
cgagtcctgt atcagccctt tatcctcaca cgcttttcta caatggcatt caataaagtg 600
cacgtgtttc tggtgaaaaa aaaaaaaaaa aaaaaactcg ag 642

<210> 120
<211> 603
<212> DNA
<213> Homo sapien

<400> 120
gaattcggca cgagccacaa cagccactac gactgcatcc actggatcca cggccacccc 60
gtcctccacc ccgggaacag ctccccctcc caaagtgctg accagcccgg ccaccacacc 120
catgtccacc atgtccacaa tccacacctc ctctactcca gagaccaccc acacctccac 180
agtgctgacc accacagcca ccatgacaag ggccaccaat tccacggcca caccctcctc 240
cactctgggg acgacccgga tcctcactga gctgaccaca acagccacta caactgcagc 300
cactggatcc acggccaccc tgtcctccac cccagggacc acctggatcc tcacagagcc 360
gagcactata gccaccgtga tggtgcccac cggttccacg gccaccgcct cctccactct 420
gggaacagct cacaccccca aagtggtgac caccatggcc actatgcccc cagccactgc 480
ctccacggtt cccagctcgt ccaccgtggg gaccacccgc acccctgcag tgctccccag 540
cagcctgcca accttcagcg tgtccactgt gtcctcctca gtcctcacca ccctgagacc 600
cac 603

<210> 121
<211> 178
<212> PRT
<213> Homo sapien

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<400> 121
Ser Glu Pro Pro Ser Pro Ala Thr Thr Pro Cys Gly Lys Val Pro Ile
1 5 10 15
Cys Ile Pro Ala Arg Arg Asp Leu Val Asp Ser Pro Ala Ser Leu Ala
20 25 30
Ser Ser Leu Gly Ser Pro Leu Pro Arg Ala Lys Glu Leu Ile Leu Asn
35 40 45
Asp Leu Pro Ala Ser Thr Pro Ala Ser Lys Ser Cys Asp Ser Ser Pro
50 55 60
Pro Gln Asp Ala Ser Thr Pro Arg Pro Ser Ser Ala Ser His Leu Cys
65 70 75 80
Gln Leu Ala Ala Lys Pro Ala Pro Ser Thr Asp Ser Val Ala Leu Arg
85 90 95
Ser Pro Leu Thr Leu Ser Ser Pro Phe Thr Thr Ser Phe Ser Leu Gly
100 105 110
Ser His Ser Thr Leu Asn Gly Asp Leu Ser Val Pro Ser Ser Tyr Val
115 120 125
Ser Leu His Leu Ser Pro Gln Val Ser Ser Ser Val Val Tyr Gly Arg
130 135 140
Ser Pro Val Met Ala Phe Glu Ser His Pro His Leu Arg Gly Ser Ser
145 150 155 160
Val Ser Ser Ser Leu Pro Ser Ile Pro Gly Gly Lys Pro Ala Tyr Ser
165 170 175
Phe His

<210> 122
<211> 36
<212> PRT
<213> Homo sapien

<400> 122
Met Ser Phe Leu Gly Gly Phe Phe Gly Pro Ile Cys Glu Ile Asp Val
1 5 10 15
Ala Leu Asn Asp Gly Glu Thr Arg Lys Met Ala Glu Met Lys Thr Glu
20 25 30
Asp Gly Lys Val
35

<210> 123
<211> 136
<212> PRT
<213> Homo sapien

<400> 123
Met Ala Ser Pro Gln Leu Cys Arg Ala Leu Val Ser Ala Gln Trp Val
1 5 10 15
Ala Glu Ala Leu Arg Ala Pro Arg Ala Gly Gln Pro Leu Gln Leu Leu
20 25 30
Asp Ala Ser Trp Tyr Leu Pro Lys Leu Gly Arg Asp Ala Arg Arg Glu

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618
1087
1082

```
        35                  40                  45
Phe Glu Glu Arg His Ile Pro Gly Ala Ala Phe Phe Asp Ile Asp Gln
    50                  55                  60
Cys Ser Asp Arg Thr Ser Pro Tyr Asp His Met Leu Pro Gly Ala Glu
65                  70                  75                  80
His Phe Ala Glu Tyr Ala Gly Arg Leu Gly Val Gly Ala Ala Thr His
                85                  90                  95
Val Val Ile Tyr Asp Ala Ser Asp Gln Gly Leu Tyr Ser Ala Pro Arg
            100                 105                 110
Val Trp Trp Met Phe Arg Ala Phe Gly His His Ala Val Ser Leu Leu
        115                 120                 125
Asp Gly Gly Leu Arg His Trp Leu
    130                 135

      <210> 124
      <211> 133
      <212> PRT
      <213> Homo sapien

      <400> 124
Met Asn His Thr Val Gln Thr Phe Phe Ser Pro Val Asn Ser Gly Gln
 1               5                  10                  15
Pro Pro Asn Tyr Glu Met Leu Lys Glu Glu His Glu Val Ala Val Leu
            20                  25                  30
Gly Ala Pro His Asn Pro Ala Pro Pro Thr Ser Thr Val Ile His Ile
        35                  40                  45
Arg Ser Glu Thr Ser Val Pro Asp His Val Val Trp Ser Leu Phe Asn
    50                  55                  60
Thr Leu Phe Met Asn Pro Cys Cys Leu Gly Phe Ile Ala Phe Ala Tyr
65                  70                  75                  80
Ser Val Lys Ser Arg Asp Arg Lys Met Val Gly Asp Val Thr Gly Ala
                85                  90                  95
Gln Ala Tyr Ala Ser Thr Ala Lys Cys Leu Asn Ile Trp Ala Leu Ile
            100                 105                 110
Leu Gly Ile Leu Met Thr Ile Leu Leu Ile Val Ile Pro Val Leu Ile
        115                 120                 125
Phe Gln Ala Tyr Gly
    130

      <210> 125
      <211> 195
      <212> PRT
      <213> Homo sapien

      <400> 125
Thr Thr Ala Thr Thr Thr Ala Ser Thr Gly Ser Thr Ala Thr Pro Ser
 1               5                  10                  15
Ser Thr Pro Gly Thr Ala Pro Pro Pro Lys Val Leu Thr Ser Pro Ala
            20                  25                  30
Thr Thr Pro Met Ser Thr Met Ser Thr Ile His Thr Ser Ser Thr Pro
        35                  40                  45
```

1083

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```
Glu Thr Thr His Thr Ser Thr Val Leu Thr Thr Thr Ala Thr Met Thr
    50                  55                  60
Arg Ala Thr Asn Ser Thr Ala Thr Pro Ser Ser Thr Leu Gly Thr Thr
65                  70                  75                  80
Arg Ile Leu Thr Glu Leu Thr Thr Thr Ala Thr Thr Thr Ala Ala Thr
                85                  90                  95
Gly Ser Thr Ala Thr Leu Ser Ser Thr Pro Gly Thr Thr Trp Ile Leu
            100                 105                 110
Thr Glu Pro Ser Thr Ile Ala Thr Val Met Val Pro Thr Gly Ser Thr
        115                 120                 125
Ala Thr Ala Ser Ser Thr Leu Gly Thr Ala His Thr Pro Lys Val Val
    130                 135                 140
Thr Thr Met Ala Thr Met Pro Thr Ala Thr Ala Ser Thr Val Pro Ser
145                 150                 155                 160
Ser Ser Thr Val Gly Thr Thr Arg Thr Pro Ala Val Leu Pro Ser Ser
                165                 170                 175
Leu Pro Thr Phe Ser Val Ser Thr Val Ser Ser Ser Val Leu Thr Thr
            180                 185                 190
Leu Arg Pro
        195
```

<210> 126
<211> 509
<212> DNA
<213> Homo sapien

<400> 126

```
gaattcggca cgagccaagt acccccctgag gaatctgcag cctgcatctg agtacaccgt      60
atcccctcgtg gccataaagg gcaaccaaga gagccccaaa gccactggag tctttaccac     120
actgcagcct gggagctcta ttccaccttа caacaccgag gtgactgaga ccaccattgt     180
gatcacatgg acgcctgctc caagaattgg ttttaagctg ggtgtacgac caagccaggg     240
aggagaggca ccacgagaag tgacttcaga ctcaggaagc atcgttgtgt ccggcttgac     300
tccaggagta gaatacgtct acaccatcca agtcctgaga gatggacagg aaagagatgc     360
gccaattgta aacaaagtgg tgacaccatt gtctccacca acaaacttgc atctggaggc     420
aaaccctgac actggagtgc tcacagtctc ctggagagga gcaccacccc agacattact     480
gggtatagaa ttaccacaac ccctacaaa                                       509
```

<210> 127
<211> 500
<212> DNA
<213> Homo sapien

<400> 127

```
gaattcggca cgagccactg atgtccgggg agtcagccag gagcttgggg aagggaagcg      60
cgccccggg gccggtcccg gagggctcga tccgcatcta cagcatgagg ttctgcccgt      120
ttgctgagag gacgcgtcta gtcctgaagg ccaagggaat caggcatgaa gtcatcaata      180
tcaacctgaa aaataagcct gagtggttct ttaagaaaaa tcccctttggt ctggtgccag     240
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<212> DNA
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<211> 497
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<210> 130
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<212> DNA
<213> Homo sapien

<400> 130
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<210> 131
<211> 509
<212> DNA

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<213> Homo sapien

<400> 131
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<211> 357
<212> DNA
<213> Homo sapien

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<210> 133
<211> 468
<212> DNA
<213> Homo sapien

<400> 133
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<210> 134
<211> 214
<212> DNA
<213> Homo sapien

<400> 134
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WO 00/03030 PCT/US99/15560

<210> 135
<211> 355
<212> DNA
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<400> 135
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<210> 136
<211> 242
<212> DNA
<213> Homo sapien

<400> 136
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gt 242

<210> 137
<211> 424
<212> DNA
<213> Homo sapien

<400> 137
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<211> 448
<212> DNA
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<400> 138
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<211> 510
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<210> 140
<211> 360
<212> DNA
<213> Homo sapien

<400> 140
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<210> 141
<211> 483
<212> DNA
<213> Homo sapien

<400> 141
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tga 483

<210> 142

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<211> 500
<212> DNA
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<211> 400
<212> DNA
<213> Homo sapien

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<210> 144
<211> 243
<212> DNA
<213> Homo sapien

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ctg 243

<210> 145
<211> 450
<212> DNA
<213> Homo sapien

<400> 145
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<212> DNA
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<210> 148
<211> 503
<212> DNA
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<210> 149

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<211> 1061
<212> DNA
<213> Homo sapien

<400> 149
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<212> DNA
<213> Homo sapien

<400> 151

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cttagaatga aaaaaaaaaa aaaaaaactc gag 2313

<210> 158
<211> 2114
<212> DNA
<213> Homo sapien

<400> 158
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gagaataaca gaaatgtcca tttggagcac tcagagcaga atcctggttc atcagcaggt 120
gacacctcag cagcgcacca ggtggtttta ggagaaaact tgatagccac agccctttgt 180
ctttctggca gtgggtctca gtctgatttg aaggatgtgg ccagcacagc aggagaggag 240
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catactaagc agcttgcctc caggaattgc tctgaagaga aatccccaca aacctccatc 360
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ggggttgaag gagtccgagt ggatcaggat gatgatcaag atagctcttc cctgaagctt 480
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B37
1/02
1097

09S1 T560
00E0E0'60 03020D

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cagcttcagc aaaggagaga agaggaaatg aagaatcacc aggagatatt aaaggctatt 720
caggatgtga caataaagcg ggaagaaaca aagaagaaga tagagaaaga gaagaaggag 780
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cgggagtact tcta 2114

<210> 159
<211> 278
<212> DNA
<213> Homo sapien

<400> 159
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tgcagaatga gaatcactcc taaaataggt aatggtaaaa attaaattga caattacctc 180
tctctatgca gaaggaaata tcacctatat gacatcatca tcatctattg atacttgctg 240
gcagtgctaa taatggtttt aatgccaatt tgtaagaa 278

<210> 160
<211> 848
<212> DNA
<213> Homo sapien

<400> 160
gaattcggca cgagccccag aggagctcgg cctgcgctgc gccacgatgt ccggggagtc 60
agccaggagc ttggggaagg gaagcgcgcc cccggggccg gtcccggagg gctcgatccg 120
catctacagc atgaggttct gcccgtttgc tgagaggacg cgtctagtcc tgaaggccaa 180
gggaatcagg catgaagtca tcaatatcaa cctgaaaaat aagcctgagt ggttctttaa 240
gaaaaatccc tttggtctgg tgccagttct ggaaaacagt cagggtcagc tgatctacga 300

832
1105
1098

gtctgccatc acctgtgagt acctggatga agcataccca gggaagaagc tgttgccgga 360
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atttcgtaaa gaatttacca agctagagga ggttctgact aataagaaga cgacctttctt 540
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catgaaggaa gatcccacag tctcagccct gcttactagt gagaaagact ggcaaggttt 720
cctagagctc tacttacaga acagccctga ggcctgtgac tatgggctct gaaggggca 780
ggagtcagca ataaagctat gtctgatatt ttccttcact aaaaaaaaaa aaaaaaaaaa 840
aactcgag 848

<210> 161
<211> 432
<212> DNA
<213> Homo sapien

<400> 161
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cttgagagag cgaggccggg agctgaccac tcagaggcag ctgatgcagg aacgggcaga 120
ggaagggaag ggcccaagta aagcacagcg cgggagccta gagcacatga agctgatcct 180
gcgtgataag gagaaggagg tggaatgtca gcaggagcat atccatgaac tccaggagct 240
caaagaccag ctggagcagc agctccaggg cctgcacagg aaggtaggtg agaccagcct 300
cctcctgtcc cagcgagagc aggaaatagt ggtcctgcag cagcaactgc aggaagccag 360
ggaacaaggg gagctgaagg agcagtcact tcagagtcaa ctggatgagg cccagagagc 420
cctagcccag ag 432

<210> 162
<211> 433
<212> DNA
<213> Homo sapien

<400> 162
gattcggcac gagccggagc tgggttgctc ctgctcccgt ctccaagtcc tggtacctcc 60
ttcaagctgg gagagggctc tagtccctgg ttctgaacac tctggggttc tcgggtgcag 120
gccgccatga gcaaacggaa ggcgccgcag gagactctca acgggggaat caccgacatg 180
ctcacagaac tcgcaaactt tgagaagaac gtgagccaag ctatccacaa gtacaatgct 240
tacagaaaag cagcatctgt tatagcaaaa tacccacaca aaataaagag tggagctgaa 300
gctaagaaat tgcctggagt aggaacaaaa attgctgaaa agattgatga gtttttagca 360
actggaaaat tacgtaaact ggaaaagatt cggcaggatg atacgagttc atccatcaat 420
ttcctgactc gag 433

<210> 163
<211> 432
<212> DNA
<213> Homo sapien

<400> 163
gaattcggca ccagatgagg ccaacgaggt gacggacagc gcgtacatgg gctccgagag 60
cacctacagt gagtgtgaga ccttcacgga cgaggacacc agcaccctgg tgcaccctga 120
gctgcaacct gaaggggacg cagacagtgc cggcggctcg gccgtgccct ctgagtgcct 180
ggacgccatg gaggagcccg accatggtgc cctgctgctg ctcccaggca ggcctcaccc 240

09518809.030300

1099

ccatggccag tctgtcatca cggtgatcgg gggcgaggag cactttgagg actacggtga 300
aggcagtgag gcggagctgt ccccagagac cctatgcaac gggcagctgg gctgcagtga 360
ccccgctttc ctcacgccca gtccgacaaa gcggctctcc agcaagaagg tggcaaggta 420
cctgcaccag tc 432

<210> 164
<211> 395
<212> DNA
<213> Homo sapien

<400> 164
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atgaccccat cctatgaaat tagagcagtg gggaacaaaa acaggcagaa attcatgtgt 120
gaggttcagg tggaaggtta taattacact ggcatgggaa attccaccaa taaaaaagat 180
gcacaaagca atgctgccag agactttgtt aactatttgg ttcgaataaa tgaaataaag 240
agtgaagaag ttccagcttt tggggtagca tctccgcccc cacttactga tactcctgac 300
actacagcaa atgctgaagg catcttgttg acatcgaata tgactttgat aataaatacc 360
ggttcctgaa aaaaaaaaaa aaaaaaaaac tcgag 395

<210> 165
<211> 503
<212> DNA
<213> Homo sapien

<400> 165
gaattcggca ccaggaacgc tcggtgagag gcggaggagc ggtaactacc ccggttgcgc 60
acagctcggc gctccttccc gctccctcac acaccggcct cagcccgcac cggcagtaga 120
agatggtgaa agaaacaact tactacgatg ttttgggggt caaacccaat gctactcagg 180
aagaattgaa aaaggcttat aggaaactgg ccttgaagta ccatcctgat aagaacccaa 240
atgaaggaga gaagtttaaa cagatttctc aagcttacga agttctctct gatgcaaaga 300
aaagggaatt atatgacaaa ggaggagaac aggcaattaa agagggtgga gcaggtggcg 360
gttttggctc ccccatggac atctttgata tgtttttttgg aggaggagga aggatgcaga 420
gagaaaggag aggtaaaaat gttgtacatc agctctcagt aaccctagaa gacttatata 480
atggtgcaac aagaaaactg gct 503

<210> 166
<211> 893
<212> DNA
<213> Homo sapien

<400> 166
gaattcggca cgagaggaac ttctcttgac gagaagagag accaaggagg ccaagcaggg 60
gctgggccag aggtgccaac atggggaaac tgaggctcgg ctcggaaggg tgagagtgag 120
actacatctc aaaaaaaaaa aaaaaaaaaa aaaagaaaga aaagaaaaga aaaaagaaag 180
aacggaagta gttgtaggta gtggtatggt ggtatgagtc tgttttctgt tacttataac 240
aacaacaaca acaaaaaacg ctgaaactgg gtaatttata aagaaaagga aaaaaagcag 300
aaaaaaatca ggaagaagag aaaggaaaag aagacaaata aatgaaattt atgtattaca 360
gttctgaagg ctgagacatc ccaggtcaag ggtccacact tggcgagggc tttcttgctg 420
gtggagactc tttgtggagt cctgggacag tgcagaagga tcacgcctcc ctaccgctcc 480
aagcccagcc ctcagccatg gcatgccccc tggatcaggc cattggcctc ctcgtggcca 540
tcttccacaa gtactccggc agggagggtg acaagcacac cctgagcaag aaggagctga 600

0 5188809 030300

aggagctgat ccagaaggag ctcaccattg gctcgaagct gcaggatgct gaaattgcaa 660
ggctgatgga agacttggac cggaacaagg accaggaggt gaacttccag gagtatgtca 720
ccttcctggg ggccttggct ttgatctaca atgaagccct caagggctga aaataaatag 780
ggaagatgga gacaccctct gggggtcctc tctgagtcaa atccagtggt gggtaattgt 840
acaataaatt ttttttggtc aaatttaaaa aaaaaaaaaa aaaaaaactc gag 893

<210> 167
<211> 549
<212> DNA
<213> Homo sapien

<400> 167
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gccaggagca agccgagagc cagccggccg gcgcactccg actccgagca gtctctgtcc 120
ttcgacccga gccccgcgcc ctttccggga cccctgcccc gcgggcagcg ctgccaacct 180
gccggccatg gagaccccgt cccagcggcg cgccacccgc agcggggcgc aggccagctc 240
cactccgctg tcgccccacc gcatcacccg gctgcaggag aaggaggacc tgcaggagct 300
caatgatcgc ttggcggtct acatcgaccg tgtgcgctcg ctggaaacgg agaacgcagg 360
gctgcgcctt cgcatcaccg agtctgaaga ggtggtcagc cgcgaggtgt ccggcatcaa 420
ggccgcctac gaggccgagc tcggggatgc ccgcaagacc cttgactcag tagccaagga 480
gcgcgcccgc ctgcagctgg agctgagcaa agtgcgtgaa gagtttaagg agctgaaagc 540
gcgcaatac 549

<210> 168
<211> 547
<212> DNA
<213> Homo sapien

<400> 168
gaattcggca cgagatggcg gcaggggtcg aagcggcggc ggaggtggcg gcgacggaga 60
tcaaaatgga ggaagagagc ggcgcgcccg gcgtgccgag cggcaacggg gctccgggcc 120
ctaagggtga aggagaacga cctgctcaga atgagaagag gaaggagaaa aacataaaaa 180
gaggaggcaa tcgctttgag ccatatgcca atccaactaa aagatacaga gccttcatta 240
caaacatacc ttttgatgtg aaatggcagt cacttaaaga cctggttaaa gaaaaagttg 300
gtgaggtaac atacgtggag ctcttaatgg acgctgaagg aaagtcaagg ggatgtgctg 360
ttgttgaatt caagatggaa gagagcatga aaaaagctgc ggaagtccta aacaagcata 420
gtctgagcgg aagaccactg aaagtcaaag aagatcctga tggtgaacat gccaggagag 480
caatgcaaaa ggctggaaga cttggaagca cagtatttgt agcaaatctg gattataaag 540
ttggctg 547

<210> 169
<211> 547
<212> DNA
<213> Homo sapien

<400> 169
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aaaactgtga gatggtgtgc agtgtcggag catgaggcca ctaagtgcca gagtttccgc 180
gaccatatga aaagcgtcat tccatccgat ggtcccagtg ttgcttgtgt gaagaaagcc 240
tcctaccttg attgcatcag ggccattgcg gcaaacgaag cggatgctgt gacactggat 300

09518809 030300

gcaggtttgg tgtatgatgc ttacctggct cccaataacc tgaagcctgt ggtggcagag 360
ttctatgggt caaaagagga tccacagact ttctattatg ctgttgctgt ggtgaagaag 420
gatagtggct tccagatgaa ccagcttcga ggcaagaagt cctgccacac gggtctaggc 480
aggtccgctg ggtggaacat ccccataggc ttactttact gtgacttacc tgagccacgt 540
aaaccctc 547

<210> 170
<211> 838
<212> DNA
<213> Homo sapien

<400> 170
gaattcggca ccagaggagc tcggcctgcg ctgcgccacg atgtccgggg agtcagccag 60
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cagcatgagg ttctgcccgt ttgctgagag gacgcgtcta gtcctgaagg ccaagggaat 180
caggcatgaa gtcatcaata tcaacctgaa aaataagcct gagtggttct ttaagaaaaa 240
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catcacctgt gagtacctgg atgaagcata cccagggaag aagctgttgc cggatgaccc 360
ctatgagaaa gcttgccaga agatgatctt agagttgttt tctaaggtgc catccttggt 420
aggaagcttt attagaagcc aaaataaaga agactatgat ggcctaaaag aagaatttcg 480
taaagaattt accaagctag aggaggttct gactaataag aagacgacct tctttggtgg 540
caattctatc tctatgattg attacctcat ctggccctgg tttgaacggc tggaagcaat 600
gaagttaaat gagtgtgtag accacactcc aaaactgaaa ctgtggatgg cagccatgaa 660
ggaagatccc acagtctcag ccctgcttac tagtgagaaa gactggcaag gtttcctaga 720
gctctactta cagaacagcc ctgaggcctg tgactatggg ctctgaaggg ggcaggagtc 780
agcaataaag ctatgtctga tattttcctt cactaaaaaa aaaaaaaaaa aactcgag 838

<210> 171
<211> 547
<212> DNA
<213> Homo sapien

<400> 171
gaattcggca ccagcgggat ttgggtcgca gttcttgttt gtggattgct gtgatcgtca 60
cttgacaatg cagatcttcg tgaagactct gactggtaag accatcaccc tcgaggttga 120
gcccagtgac accatcgaga atgtcaaggc aaagatccaa gataaggaag gcatccctcc 180
tgaccagcag aggctgatct ttgctggaaa acagctggaa gatgggcgca ccctgtctga 240
ctacaacatc cagaaagagt ccaccctgca cctggtgctc cgtctcagag gtgggatgca 300
aatcttcgtg aagacactca ctggcaagac catcaccctt gaggtcgagc ccagtgacac 360
catcgagaac gtcaaagcaa agatccagga caaggaaggc attcctcctg accagcagag 420
gttgatcttt gccggaaagc agctggaaga tgggcgcacc ctgtctgact acaacatcca 480
gaaagagtct accctgcacc tggtgctccg tctcagaggt gggatgcaga tcttcgtgaa 540
gaccctg 547

<210> 172
<211> 608
<212> DNA
<213> Homo sapien

<400> 172
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0 518 09-030300

856
1107
1102

09518 09.03030

caccctcatc tacaatggtg ccctgccatg tcagtgcaac cctcaaggtt cactgagttc 120
tgagtgcaac cctcatggtg gtcagtgcct gtgcaagcct ggagtggttg ggcgccgctg 180
tgacctctgt gcccctggct actatggctt tggccccaca ggctgtcaag gcgcttgcct 240
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gagccaacgg cactttgcta cttcttgcca ccaggatgaa tattcccagc agattgtgtg 420
ccactgccgg gcaggctata cggggctgcg atgtgaagct tgtgcccctg ggcactttgg 480
ggacccatca aggccaggtg gccggtgcca actgtgtgag tgcagtggga acattgaccc 540
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agagggtc 608

<210> 173
<211> 543
<212> DNA
<213> Homo sapien

<400> 173
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gctccgggag ggcaccagga gcctccgtga ggctctcgag gcggagtccg cctggtgcta 180
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ggcacaggca gccacaggct tcctgctgga cccggtgaag ggggaacggc tgactgtgga 360
tgaagctgtg cggaagggcc tcgtggggcc cgaactgcac gaccgcctgc tctcggctga 420
gcgggcggtc accggctacc gtgacccctа caccgagcag accatctcgc tcttccaggc 480
catgaagaag gaactgatcc ctactgagga ggccctgcgg ctgtggatgc ccagctggcc 540
acc 543

<210> 174
<211> 548
<212> DNA
<213> Homo sapien

<400> 174
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ccctaagggt gaaggagaac gacctgctca gaatgagaag aggaaggaga aaaacataaa 180
aagaggaggc aatcgctttg agccatatgc caatccaact aaaagataca gagccttcat 240
tacaaacata ccttttgatg tgaaatggca gtcacttaaa gacctggtta aagaaaaagt 300
tggtgaggta acatacgtgg agctcttaat ggacgctgaa ggaaagtcaa ggggatgtgc 360
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agcaatgcaa aaggtgatgg ctacgactgg tgggatgggt atgggaccag gtggcccagg 540
aatgatta 548

<210> 175
<211> 604
<212> DNA
<213> Homo sapien

<400> 175

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cgaggccatc ctggccatcc acaaggaggc ccagaggatc gctgagagca accacatcaa 180
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ggacctgctg gagcagcagc accagcttat ccaggaggcc ctcatcttcg acaacaagca 540
caccaactat accatggagc acatccgcgt gggctgggag cagctgctca ccaccattgc 600
ccgg 604

<210> 176
<211> 486
<212> DNA
<213> Homo sapien

<400> 176
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aggcgaaaga gtggatggca acagtctaat tgtaggatat gtaataggaa ctcaacaagc 180
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ctccagcaac aactccaacc ccgtggagga caaggatgct gtggccttca cctgtgaacc 420
tgaggttcag aacacaacct acctgtggtg ggtaaatggt cagagcctcc cggtcagtcc 480
caaggc 486

<210> 177
<211> 387
<212> DNA
<213> Homo sapien

<400> 177
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ctcggccccc ccccacagat ggtgcatccc ctggcagagg ctcctgctca cagcctcact 180
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tgtcgcagag gggaaggagg tgcttctact tgtccacaat ctgccccagc atcttttgg 300
ctacagctgg tacaaaggtg aaagagtgga tggcaaccgt caaattatag gatatgtaat 360
aggaactcaa caagctaccc cagggcc 387

<210> 178
<211> 440
<212> DNA
<213> Homo sapien

<400> 178
gaattcggca cgaggagaag cagaaaaaca aggaatttag ccagacttta gaaaatgaga 60
aaaatacctt actgagtcag atatcaacaa aggatggtga actaaaaatg cttcaggagg 120
aagtaaccaa aatgaacctg ttaaatccagc aaatccaaga agaactctct agagttacca 180

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aactaaagga gacagcagaa gaagagaaag atgatttgga agagaggctt atgaatcaat 240
tagcagaact taatggaagc attgggaatt actgtcagga tgttacagat gcccaaataa 300
aaaatgagct attggaatct gaaatgaaga accttaaaaa gtgtgtgagt gaattggaag 360
aagaaaagca gcagttagtc aaggaaaaaa ctaaggtgga atcagaaata cgaaaggaat 420
atttggagaa aatacaaggt 440

<210> 179
<211> 443
<212> DNA
<213> Homo sapien

<400> 179
gaattcggca ccagcggggg gctacggcgg cggctacggc ggcgtcctga ccgcgtccga 60
cgggctgctg gcgggcaacg agaagctaac catgcagaac ctcaacgacc gcctggcctc 120
ctacctggac aaggtgcgcg ccctggaggc ggccaacggc gagctagagg tgaagatccg 180
cgactggtac cagaagcagg ggcctgggcc ctcccgcgac tacagccact actacacgac 240
catccaggac ctgcgggaca agattcttgg tgccaccatt gagaactcca ggattgtcct 300
gcagatcgac aacgcccgtc tggctgcaga tgacttccga accaagtttg agacggaaca 360
ggctctgcgc atgagcgtgg aggccgacat caacggcctg cgcagggtgc tggatgagct 420
gaccctggcc aggaccgacc tgg 443

<210> 180
<211> 403
<212> DNA
<213> Homo sapien

<400> 180
gaattcggca cgaggttatg agagtcgact tcaatgttcc tatgaagaac aaccagataa 60
caaacaacca gaggattaag gctgctgtcc caagcatcaa attctgcttg gacaatggag 120
ccaagtcggt agtccttatg agccacctag gccggcctga tggtgtgccc atgcctgaca 180
agtactcctt agagccagtt gctgtagaac tcagatctct gctgggcaag gatgttctgt 240
tcttgaagga ctgtgtaggc ccagaagtgg agaaagcctg tgccaaccca gctgctgggt 300
ctgtcatcct gctggagaac ctccgctttc atgtggagga agaagggaag ggaaaagatg 360
cttctgggaa caaggttaaa gccgagccag ccaaaatagg agc 403

<210> 181
<211> 493
<212> DNA
<213> Homo sapien

<400> 181
gaattcggca ccagcagagg tctccagagc cttctcttct ctgtgcaaaa tggcaactct 60
taaggaaaaa ctcattgcac cagttgcgga agaagaggca acagttccaa acaataagat 120
cactgtagtg ggtgttggac aagttggtat ggcgtgtgct atcagcattc tgggaaagtc 180
tctggctgat gaacttgctc ttgtggatgt tttggaagat aagcttaaag gagaaatgat 240
ggatctgcag catgggagct tatttcttca gacacctaaa attgtggcag ataaagatta 300
ttctgtgacc gccaattcta agattgtagt ggtaactgca ggagtccgtc agcaagaagg 360
ggagagtcgg ctcaatctgg tgcagagaaa tgttaatgtc ttcaaattca ttattcctca 420
gatcgtcaag tacagtcctg attgcatcat aattgtggtt tccaacccag tggacattct 480
tacgtatgtt acc 493

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<210> 182
<211> 209
<212> PRT
<213> Homo sapien

<400> 182

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

<210> 183
<211> 255
<212> PRT
<213> Homo sapien

<400> 183

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

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Val Lys Trp Gln Ser Leu Lys Asp Leu Val Lys Glu Lys Val Gly Glu
85 90 95
Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg Gly
100 105 110
Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala Ala
115 120 125
Glu Val Leu Asn Lys His Ser Leu Ser Gly Arg Pro Leu Lys Val Lys
130 135 140
Glu Asp Pro Asp Gly Glu His Ala Arg Arg Ala Met Gln Lys Ala Gly
145 150 155 160
Arg Leu Gly Ser Thr Val Phe Val Ala Asn Leu Asp Tyr Lys Val Gly
165 170 175
Trp Lys Lys Leu Lys Glu Val Phe Ser Met Ala Gly Val Val Val Arg
180 185 190
Ala Asp Ile Leu Glu Asp Lys Asp Gly Lys Ser Arg Gly Ile Gly Ile
195 200 205
Val Thr Phe Glu Gln Ser Ile Glu Ala Val Gln Ala Ile Ser Met Phe
210 215 220
Asn Gly Gln Leu Leu Phe Asp Arg Pro Met His Val Lys Met Asp Glu
225 230 235 240
Arg Ala Leu Pro Lys Gly Asp Phe Phe Pro Pro Glu Arg His Ser
245 250 255

<210> 184
<211> 188
<212> PRT
<213> Homo sapien

<400> 184
Leu Ser Gly Ser Cys Ile Arg Arg Glu Gln Thr Pro Glu Lys Glu Lys
1 5 10 15
Gln Val Val Leu Phe Glu Glu Ala Ser Trp Thr Cys Thr Pro Ala Cys
20 25 30
Gly Asp Glu Pro Arg Thr Val Ile Leu Leu Ser Ser Met Leu Ala Asp
35 40 45
His Arg Leu Lys Leu Glu Asp Tyr Lys Asp Arg Leu Lys Ser Gly Glu
50 55 60
His Leu Asn Pro Asp Gln Leu Glu Ala Val Glu Lys Tyr Glu Glu Val
65 70 75 80
Leu His Asn Leu Glu Phe Ala Lys Glu Leu Gln Lys Thr Phe Ser Gly
85 90 95
Leu Ser Leu Asp Leu Leu Lys Ala Gln Lys Lys Ala Gln Arg Arg Glu
100 105 110
His Met Leu Lys Leu Glu Ala Glu Lys Lys Lys Leu Arg Thr Ile Leu
115 120 125
Gln Val Gln Tyr Val Leu Gln Asn Leu Thr Gln Glu His Val Gln Lys
130 135 140
Asp Phe Lys Gly Gly Leu Asn Gly Ala Val Tyr Leu Pro Ser Lys Glu
145 150 155 160
Leu Asp Tyr Leu Ile Lys Phe Ser Lys Leu Thr Cys Pro Glu Arg Asn
165 170 175

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1112
1107

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Glu Ser Leu Arg Gln Thr Leu Glu Gly Ser Thr Val
180 185

<210> 185
<211> 746
<212> PRT
<213> Homo sapien

<400> 185

```
Asp Lys His Leu Lys Asp Leu Leu Ser Lys Leu Leu Asn Ser Gly Tyr
 1               5                  10                  15
Phe Glu Ser Ile Pro Val Pro Lys Asn Ala Lys Glu Lys Glu Val Pro
            20                  25                  30
Leu Glu Glu Glu Met Leu Ile Gln Ser Glu Lys Lys Thr Gln Leu Ser
        35                  40                  45
Lys Thr Glu Ser Val Lys Glu Ser Glu Ser Leu Met Glu Phe Ala Gln
    50                  55                  60
Pro Glu Ile Gln Pro Gln Glu Phe Leu Asn Arg Arg Tyr Met Thr Glu
65                  70                  75                  80
Val Asp Tyr Ser Asn Lys Gln Gly Glu Glu Gln Pro Trp Glu Ala Asp
                85                  90                  95
Tyr Ala Arg Lys Pro Asn Leu Pro Lys Arg Trp Asp Met Leu Thr Glu
            100                 105                 110
Pro Asp Gly Gln Glu Lys Lys Gln Glu Ser Phe Lys Ser Trp Glu Ala
        115                 120                 125
Ser Gly Lys His Gln Glu Val Ser Lys Pro Ala Val Ser Leu Glu Gln
    130                 135                 140
Arg Lys Gln Asp Thr Ser Lys Leu Arg Ser Thr Leu Pro Glu Glu Gln
145                 150                 155                 160
Lys Lys Gln Glu Ile Ser Lys Ser Lys Pro Ser Pro Ser Gln Trp Lys
                165                 170                 175
Gln Asp Thr Pro Lys Ser Lys Ala Gly Tyr Val Gln Glu Glu Gln Lys
            180                 185                 190
Lys Gln Glu Thr Pro Lys Leu Trp Pro Val Gln Leu Gln Lys Glu Gln
        195                 200                 205
Asp Pro Lys Lys Gln Thr Pro Lys Ser Trp Thr Pro Ser Met Gln Ser
    210                 215                 220
Glu Gln Asn Thr Thr Lys Ser Trp Thr Thr Pro Met Cys Glu Glu Gln
225                 230                 235                 240
Asp Ser Lys Gln Pro Glu Thr Pro Lys Ser Trp Glu Asn Asn Val Glu
                245                 250                 255
Ser Gln Lys His Ser Leu Thr Ser Gln Ser Gln Ile Ser Pro Lys Ser
            260                 265                 270
Trp Gly Val Ala Thr Ala Ser Leu Ile Pro Asn Asp Gln Leu Leu Pro
        275                 280                 285
Arg Lys Leu Asn Thr Glu Pro Lys Asp Val Pro Lys Pro Val His Gln
    290                 295                 300
Pro Val Gly Ser Ser Ser Thr Leu Pro Lys Asp Pro Val Leu Arg Lys
305                 310                 315                 320
Glu Lys Leu Gln Asp Leu Met Thr Gln Ile Gln Gly Thr Cys Asn Phe
                325                 330                 335
```

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```
Met Gln Glu Ser Val Leu Asp Phe Asp Lys Pro Ser Ser Ala Ile Pro
            340                 345                 350
Thr Ser Gln Pro Pro Ser Ala Thr Pro Gly Ser Pro Val Ala Ser Lys
        355                 360                 365
Glu Gln Asn Leu Ser Ser Gln Ser Asp Phe Leu Gln Glu Pro Leu Gln
    370                 375                 380
Val Phe Asn Val Asn Ala Pro Leu Pro Pro Arg Lys Glu Gln Glu Ile
385                 390                 395                 400
Lys Glu Ser Pro Tyr Ser Pro Gly Tyr Asn Gln Ser Phe Thr Thr Ala
                405                 410                 415
Ser Thr Gln Thr Pro Pro Gln Cys Gln Leu Pro Ser Ile His Val Glu
            420                 425                 430
Gln Thr Val His Ser Gln Glu Thr Ala Ala Asn Tyr His Pro Asp Gly
        435                 440                 445
Thr Ile Gln Val Ser Asn Gly Ser Leu Ala Phe Tyr Pro Ala Gln Thr
    450                 455                 460
Asn Val Phe Pro Arg Pro Thr Gln Pro Phe Val Asn Ser Arg Gly Ser
465                 470                 475                 480
Val Arg Gly Cys Thr Arg Gly Gly Arg Leu Ile Thr Asn Ser Tyr Arg
                485                 490                 495
Ser Pro Gly Gly Tyr Lys Gly Phe Asp Thr Tyr Arg Gly Leu Pro Ser
            500                 505                 510
Ile Ser Asn Gly Asn Tyr Ser Gln Leu Gln Phe Gln Ala Arg Glu Tyr
        515                 520                 525
Ser Gly Ala Pro Tyr Ser Gln Arg Asp Asn Phe Gln Gln Cys Tyr Lys
    530                 535                 540
Arg Gly Gly Thr Ser Gly Gly Pro Arg Ala Asn Ser Arg Ala Gly Trp
545                 550                 555                 560
Ser Asp Ser Ser Gln Val Ser Ser Pro Glu Arg Asp Asn Glu Thr Phe
                565                 570                 575
Asn Ser Gly Asp Ser Gly Gln Gly Asp Ser Arg Ser Met Thr Pro Val
            580                 585                 590
Asp Val Pro Val Thr Asn Pro Ala Ala Thr Ile Leu Pro Val His Val
        595                 600                 605
Tyr Pro Leu Pro Gln Gln Met Arg Val Ala Phe Ser Ala Ala Arg Thr
    610                 615                 620
Ser Asn Leu Ala Pro Gly Thr Leu Asp Gln Pro Ile Val Phe Asp Leu
625                 630                 635                 640
Leu Leu Asn Asn Leu Gly Glu Thr Phe Asp Leu Gln Leu Gly Arg Phe
                645                 650                 655
Asn Cys Pro Val Asn Gly Thr Tyr Val Phe Ile Phe His Met Leu Lys
            660                 665                 670
Leu Ala Val Asn Val Pro Leu Tyr Val Asn Leu Met Lys Asn Glu Glu
        675                 680                 685
Val Leu Val Ser Ala Tyr Ala Asn Asp Gly Ala Pro Asp His Glu Thr
    690                 695                 700
Ala Ser Asn His Ala Ile Leu Gln Leu Phe Gln Gly Asp Gln Ile Trp
705                 710                 715                 720
Leu Arg Leu His Arg Gly Ala Ile Tyr Gly Ser Ser Trp Lys Tyr Ser
                725                 730                 735
Thr Phe Ser Gly Tyr Leu Leu Tyr Gln Asp
```

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740 745

<210> 186
<211> 705
<212> PRT
<213> Homo sapien

<400> 186

Ala Leu Leu Asn Val Arg Gln Pro Pro Ser Thr Thr Thr Phe Val Leu
1 5 10 15
Asn Gln Ile Asn His Leu Pro Pro Leu Gly Ser Thr Ile Val Met Thr
20 25 30
Lys Thr Pro Pro Val Thr Thr Asn Arg Gln Thr Ile Thr Leu Thr Lys
35 40 45
Phe Ile Gln Thr Thr Ala Ser Thr Arg Pro Ser Val Ser Ala Pro Thr
50 55 60
Val Arg Asn Ala Met Thr Ser Ala Pro Ser Lys Asp Gln Val Gln Leu
65 70 75 80
Lys Asp Leu Leu Lys Asn Asn Ser Leu Asn Glu Leu Met Lys Leu Lys
85 90 95
Pro Pro Ala Asn Ile Ala Gln Pro Val Ala Thr Ala Ala Thr Asp Val
100 105 110
Ser Asn Gly Thr Val Lys Lys Glu Ser Ser Asn Lys Glu Gly Ala Arg
115 120 125
Met Trp Ile Asn Asp Met Lys Met Arg Ser Phe Ser Pro Thr Met Lys
130 135 140
Val Pro Val Val Lys Glu Asp Asp Glu Pro Glu Glu Glu Asp Glu Glu
145 150 155 160
Glu Met Gly His Ala Glu Thr Tyr Ala Glu Tyr Met Pro Ile Lys Leu
165 170 175
Lys Ile Gly Leu Arg His Pro Asp Ala Val Val Glu Thr Ser Ser Leu
180 185 190
Ser Ser Val Thr Pro Pro Asp Val Trp Tyr Lys Thr Ser Ile Ser Glu
195 200 205
Glu Thr Ile Asp Asn Gly Trp Leu Ser Ala Leu Gln Leu Glu Ala Ile
210 215 220
Thr Tyr Ala Ala Gln Gln His Glu Thr Phe Leu Pro Asn Gly Asp Arg
225 230 235 240
Ala Gly Phe Leu Ile Gly Asp Gly Ala Gly Val Gly Lys Gly Arg Thr
245 250 255
Ile Ala Gly Ile Ile Tyr Glu Asn Tyr Leu Leu Ser Arg Lys Arg Ala
260 265 270
Leu Trp Phe Ser Val Ser Asn Asp Leu Lys Tyr Asp Ala Glu Arg Asp
275 280 285
Leu Arg Asp Ile Gly Ala Lys Asn Ile Leu Val His Ser Leu Asn Lys
290 295 300
Phe Lys Tyr Gly Lys Ile Ser Ser Lys His Asn Gly Ser Val Lys Lys
305 310 315 320
Gly Val Ile Phe Ala Thr Tyr Ser Ser Leu Ile Gly Glu Ser Gln Ser
325 330 335
Gly Gly Lys Tyr Lys Thr Arg Leu Lys Gln Leu Leu His Trp Cys Gly

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```
            340                 345                 350
Asp Asp Phe Asp Gly Val Ile Val Phe Asp Glu Cys His Lys Ala Lys
        355                 360                 365
Asn Leu Cys Pro Val Gly Ser Ser Lys Pro Thr Lys Thr Gly Leu Ala
    370                 375                 380
Val Leu Glu Leu Gln Asn Lys Leu Pro Lys Ala Arg Val Val Tyr Ala
385                 390                 395                 400
Ser Ala Thr Gly Ala Ser Glu Pro Arg Asn Met Ala Tyr Met Asn Arg
                405                 410                 415
Leu Gly Ile Trp Gly Glu Gly Thr Pro Phe Arg Glu Phe Ser Asp Phe
            420                 425                 430
Ile Gln Ala Val Glu Arg Arg Gly Val Gly Ala Met Glu Ile Val Ala
        435                 440                 445
Met Asp Met Lys Leu Arg Gly Met Tyr Ile Ala Arg Gln Leu Ser Phe
    450                 455                 460
Thr Gly Val Thr Phe Lys Ile Glu Glu Val Leu Leu Ser Gln Ser Tyr
465                 470                 475                 480
Val Lys Met Tyr Asn Lys Ala Val Lys Leu Trp Val Ile Ala Arg Glu
                485                 490                 495
Arg Phe Gln Gln Ala Ala Asp Leu Ile Asp Ala Glu Gln Arg Met Lys
            500                 505                 510
Lys Ser Met Trp Gly Gln Phe Trp Ser Ala His Gln Arg Phe Phe Lys
        515                 520                 525
Tyr Leu Cys Ile Ala Ser Lys Val Lys Arg Val Val Gln Leu Ala Arg
    530                 535                 540
Glu Glu Ile Lys Asn Gly Lys Cys Val Val Ile Gly Leu Gln Ser Thr
545                 550                 555                 560
Gly Glu Ala Arg Thr Leu Glu Ala Leu Glu Glu Gly Gly Gly Glu Leu
                565                 570                 575
Asn Asp Phe Val Ser Thr Ala Lys Gly Val Leu Gln Ser Leu Ile Glu
            580                 585                 590
Lys His Phe Pro Ala Pro Asp Arg Lys Lys Leu Tyr Ser Leu Leu Gly
        595                 600                 605
Ile Asp Leu Thr Ala Pro Ser Asn Asn Ser Ser Pro Arg Asp Ser Pro
    610                 615                 620
Cys Lys Glu Asn Lys Ile Lys Lys Arg Lys Gly Glu Glu Ile Thr Arg
625                 630                 635                 640
Glu Ala Lys Lys Ala Arg Lys Val Gly Gly Leu Thr Gly Ser Ser Ser
                645                 650                 655
Asp Asp Ser Gly Ser Glu Ser Asp Ala Ser Asp Asn Glu Glu Ser Asp
            660                 665                 670
Tyr Glu Ser Ser Lys Asn Met Ser Ser Gly Asp Asp Asp Asp Phe Asn
        675                 680                 685
Pro Phe Leu Asp Glu Ser Asn Glu Asp Asp Glu Asn Asp Pro Trp Leu
    690                 695                 700
Ile
705
```

<210> 187
<211> 595
<212> PRT

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<213> Homo sapien

<400> 187

```
Glu Ser Pro Arg His Arg Gly Glu Gly Gly Gly Glu Trp Gly Pro Gly
 1               5                  10                  15
Val Pro Arg Glu Arg Arg Glu Ser Ala Gly Glu Trp Gly Ala Asp Thr
            20                  25                  30
Pro Lys Glu Gly Gly Glu Ser Ala Gly Glu Trp Gly Ala Glu Val Pro
        35                  40                  45
Arg Gly Arg Gly Glu Gly Ala Gly Glu Trp Gly Pro Asp Thr Pro Lys
    50                  55                  60
Glu Arg Gly Gln Gly Val Arg Glu Trp Gly Pro Glu Ile Pro Gln Glu
65                  70                  75                  80
His Gly Glu Ala Thr Arg Asp Trp Ala Leu Glu Ser Pro Arg Ala Leu
                85                  90                  95
Gly Glu Asp Ala Arg Glu Leu Gly Ser Ser Pro His Asp Arg Gly Ala
            100                 105                 110
Ser Pro Arg Asp Leu Ser Gly Glu Ser Pro Cys Thr Gln Arg Ser Gly
        115                 120                 125
Leu Leu Pro Glu Arg Arg Gly Asp Ser Pro Trp Pro Pro Trp Pro Ser
    130                 135                 140
Pro Gln Glu Arg Asp Ala Gly Thr Arg Asp Arg Glu Glu Ser Pro Arg
145                 150                 155                 160
Asp Trp Gly Gly Ala Glu Ser Pro Arg Gly Trp Glu Ala Gly Pro Arg
                165                 170                 175
Glu Trp Gly Pro Ser Pro Ser Gly His Gly Asp Gly Pro Arg Arg Arg
            180                 185                 190
Pro Arg Lys Arg Arg Gly Arg Lys Gly Arg Met Gly Arg Gln His Glu
        195                 200                 205
Ala Ala Ala Thr Ala Ala Thr Ala Ala Thr Ala Thr Gly Gly Thr Ala
    210                 215                 220
Glu Glu Ala Gly Ala Ser Ala Pro Glu Ser Gln Ala Gly Gly Gly Pro
225                 230                 235                 240
Arg Gly Arg Ala Arg Gly Pro Arg Gln Gln Gly Arg Arg Arg His Gly
                245                 250                 255
Thr Gln Arg Arg Arg Gly Pro Pro Gln Ala Arg Glu Glu Gly Pro Arg
            260                 265                 270
Asp Ala Thr Thr Ile Leu Gly Leu Gly Thr Pro Ser Gly Glu Gln Arg
        275                 280                 285
Ala Asp Gln Ser Gln Ala Leu Pro Ala Leu Ala Gly Ala Ala Ala Ala
    290                 295                 300
His Ala His Ala Ile Pro Gly Ala Gly Pro Ala Ala Ala Pro Val Gly
305                 310                 315                 320
Gly Arg Gly Arg Arg Gly Gly Trp Arg Gly Gly Arg Arg Gly Gly Ser
                325                 330                 335
Ala Gly Ala Gly Gly Gly Gly Arg Gly Gly Arg Gly Arg Gly Arg Gly
            340                 345                 350
Gly Gly Arg Gly Gly Gly Gly Ala Gly Arg Gly Gly Gly Ala Ala Gly
        355                 360                 365
Pro Arg Glu Gly Ala Ser Ser Pro Gly Ala Arg Arg Gly Glu Gln Arg
    370                 375                 380
```

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```
Arg Arg Gly Arg Gly Pro Pro Ala Ala Gly Ala Ala Gln Val Ser Ala
385                 390                 395                 400
Arg Gly Arg Arg Ala Arg Gly Gln Arg Ala Gly Glu Glu Ala Gln Asp
                405                 410                 415
Gly Leu Leu Pro Arg Gly Arg Asp Arg Leu Pro Leu Arg Pro Gly Asp
            420                 425                 430
Ala Asn Gln Arg Ala Glu Arg Pro Gly Pro Pro Arg Gly Gly His Gly
        435                 440                 445
Pro Val Asn Ala Ser Ser Ala Pro Asp Thr Ser Pro Pro Arg His Pro
    450                 455                 460
Arg Arg Trp Val Ser Gln Gln Arg Gln Arg Leu Trp Arg Gln Phe Arg
465                 470                 475                 480
Val Gly Gly Gly Phe Pro Pro Pro Pro Pro Ser Arg Pro Pro Ala Val
                485                 490                 495
Leu Leu Pro Leu Leu Arg Leu Ala Cys Ala Gly Asp Pro Gly Ala Thr
            500                 505                 510
Arg Pro Gly Pro Arg Arg Pro Ala Arg Arg Pro Arg Gly Glu Leu Ile
        515                 520                 525
Pro Arg Arg Pro Asp Pro Ala Ala Pro Ser Glu Glu Gly Leu Arg Met
    530                 535                 540
Glu Ser Ser Val Asp Asp Gly Ala Thr Ala Thr Thr Ala Asp Ala Ala
545                 550                 555                 560
Ser Gly Glu Ala Pro Glu Ala Gly Pro Ser Pro Ser His Ser Pro Thr
                565                 570                 575
Met Cys Gln Thr Gly Gly Pro Gly Pro Pro Pro Pro Gln Pro Pro Arg
            580                 585                 590
Trp Leu Pro
        595

      <210> 188
      <211> 376
      <212> PRT
      <213> Homo sapien

      <400> 188
Glu Met Arg Lys Phe Asp Val Pro Ser Met Glu Ser Thr Leu Asn Gln
 1                5                  10                  15
Pro Ala Met Leu Glu Thr Leu Tyr Ser Asp Pro His Tyr Arg Ala His
            20                  25                  30
Phe Pro Asn Pro Arg Pro Asp Thr Asn Lys Asp Val Tyr Lys Val Leu
        35                  40                  45
Pro Glu Ser Lys Lys Ala Pro Gly Ser Gly Ala Val Phe Glu Arg Asn
    50                  55                  60
Gly Pro His Ala Ser Ser Ser Gly Val Leu Pro Leu Gly Leu Gln Pro
65                  70                  75                  80
Ala Pro Gly Leu Ser Lys Ser Leu Ser Ser Gln Val Trp Gln Pro Ser
                85                  90                  95
Pro Asp Pro Trp His Pro Gly Glu Gln Ser Cys Glu Leu Ser Thr Cys
            100                 105                 110
Arg Gln Gln Leu Glu Leu Ile Arg Leu Gln Met Glu Gln Met Gln Leu
        115                 120                 125
```

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Gln Asn Gly Ala Met Cys His His Pro Ala Ala Phe Ala Pro Leu Leu
130 135 140
Pro Thr Leu Glu Pro Ala Gln Trp Leu Ser Ile Leu Asn Ser Asn Glu
145 150 155 160
His Leu Leu Lys Glu Lys Glu Leu Leu Ile Asp Lys Gln Arg Lys His
165 170 175
Ile Ser Gln Leu Glu Gln Lys Val Arg Glu Ser Glu Leu Gln Val His
180 185 190
Ser Ala Leu Leu Gly Arg Pro Ala Pro Phe Gly Asp Val Cys Leu Leu
195 200 205
Arg Leu Gln Glu Leu Gln Arg Glu Asn Thr Phe Leu Arg Ala Gln Phe
210 215 220
Ala Gln Lys Thr Glu Ala Leu Ser Lys Glu Lys Met Glu Leu Glu Lys
225 230 235 240
Lys Leu Ser Ala Ser Glu Val Glu Ile Gln Leu Ile Arg Glu Ser Leu
245 250 255
Lys Val Thr Leu Gln Lys His Ser Glu Glu Gly Lys Lys Gln Glu Glu
260 265 270
Arg Val Lys Gly Arg Asp Lys His Ile Asn Asn Leu Lys Lys Lys Cys
275 280 285
Gln Lys Glu Ser Glu Gln Asn Arg Glu Lys Gln Gln Arg Ile Glu Thr
290 295 300
Leu Glu Arg Tyr Leu Ala Asp Leu Pro Thr Leu Glu Asp His Gln Lys
305 310 315 320
Gln Thr Glu Gln Leu Lys Asp Ala Glu Leu Lys Asn Thr Glu Leu Gln
325 330 335
Glu Arg Val Ala Glu Leu Glu Thr Leu Leu Glu Asp Thr Gln Ala Thr
340 345 350
Cys Arg Glu Lys Glu Val Gln Leu Glu Ser Leu Arg Gln Arg Glu Ala
355 360 365
Asp Leu Ser Ser Ala Arg His Arg
370 375

<210> 189
<211> 160
<212> PRT
<213> Homo sapien

<400> 189
Met Leu Glu Ala His Arg Arg Gln Arg His Pro Phe Leu Leu Leu Gly
1 5 10 15
Thr Thr Ala Asn Arg Thr Gln Ser Leu Asn Tyr Gly Cys Ile Val Glu
20 25 30
Asn Pro Gln Thr His Glu Val Leu His Tyr Val Glu Lys Pro Ser Thr
35 40 45
Phe Ile Ser Asp Ile Ile Asn Cys Gly Ile Tyr Leu Phe Ser Pro Glu
50 55 60
Ala Leu Lys Pro Leu Arg Asp Val Phe Gln Arg Asn Gln Gln Asp Gly
65 70 75 80
Gln Leu Glu Asp Ser Pro Gly Leu Trp Pro Gly Ala Gly Thr Ile Arg
85 90 95

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Leu Glu Gln Asp Val Phe Ser Ala Leu Ala Gly Gln Gly Gln Ile Tyr
100 105 110
Val His Leu Thr Asp Gly Ile Trp Ser Gln Ile Lys Ser Ala Gly Ser
115 120 125
Ala Leu Tyr Ala Ser Arg Leu Tyr Leu Ser Arg Tyr Gln Asp Thr His
130 135 140
Pro Glu Arg Leu Ala Lys His Thr Pro Gly Gly Pro Trp Ile Arg Gly
145 150 155 160

<210> 190
<211> 146
<212> PRT
<213> Homo sapien

<400> 190
Met Asp Pro Arg Ala Ser Leu Leu Leu Leu Gly Asn Val Tyr Ile His
1 5 10 15
Pro Thr Ala Lys Val Ala Pro Ser Ala Val Leu Gly Pro Asn Val Ser
20 25 30
Ile Gly Lys Gly Val Thr Val Gly Glu Gly Val Arg Leu Arg Glu Ser
35 40 45
Ile Val Leu His Gly Ala Thr Leu Gln Glu His Thr Cys Val Leu His
50 55 60
Ser Ile Val Gly Trp Gly Ser Thr Val Gly Arg Trp Ala Arg Val Glu
65 70 75 80
Gly Thr Pro Ser Asp Pro Asn Pro Asn Asp Pro Arg Ala Arg Met Asp
85 90 95
Ser Glu Ser Leu Phe Lys Asp Gly Lys Leu Leu Pro Ala Ile Thr Ile
100 105 110
Leu Gly Cys Arg Val Arg Ile Pro Ala Glu Val Leu Ile Leu Asn Ser
115 120 125
Ile Val Leu Pro His Lys Glu Leu Ser Arg Ser Phe Thr Asn Gln Ile
130 135 140
Ile Leu
145

<210> 191
<211> 704
<212> PRT
<213> Homo sapien

<400> 191
Glu Gly Gly Cys Ala Ala Gly Arg Gly Arg Glu Leu Glu Pro Glu Leu
1 5 10 15
Glu Pro Gly Pro Gly Pro Gly Ser Ala Leu Glu Pro Gly Glu Glu Phe
20 25 30
Glu Ile Val Asp Arg Ser Gln Leu Pro Gly Pro Gly Asp Leu Arg Ser
35 40 45
Ala Thr Arg Pro Arg Ala Ala Glu Gly Trp Ser Ala Pro Ile Leu Thr
50 55 60
Leu Ala Arg Arg Ala Thr Gly Asn Leu Ser Ala Ser Cys Gly Ser Ala

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```
65                  70                  75                  80
Leu Arg Ala Ala Ala Gly Leu Gly Gly Gly Asp Ser Gly Asp Gly Thr
                85                  90                  95
Ala Arg Ala Ala Ser Lys Cys Gln Met Met Glu Glu Arg Ala Asn Leu
            100                 105                 110
Met His Met Met Lys Leu Ser Ile Lys Val Leu Leu Gln Ser Ala Leu
        115                 120                 125
Ser Leu Gly Arg Ser Leu Asp Ala Asp His Ala Pro Leu Gln Gln Phe
    130                 135                 140
Phe Val Val Met Glu His Cys Leu Lys His Gly Leu Lys Val Lys Lys
145                 150                 155                 160
Ser Phe Ile Gly Gln Asn Lys Ser Phe Phe Gly Pro Leu Glu Leu Val
                165                 170                 175
Glu Lys Leu Cys Pro Glu Ala Ser Asp Ile Ala Thr Ser Val Arg Asn
            180                 185                 190
Leu Pro Glu Leu Lys Thr Ala Val Gly Arg Gly Arg Ala Trp Leu Tyr
        195                 200                 205
Leu Ala Leu Met Gln Lys Lys Leu Ala Asp Tyr Leu Lys Val Leu Ile
    210                 215                 220
Asp Asn Lys His Leu Leu Ser Glu Phe Tyr Glu Pro Glu Ala Leu Met
225                 230                 235                 240
Met Glu Glu Glu Gly Met Val Ile Val Gly Leu Leu Val Gly Leu Asn
                245                 250                 255
Val Leu Asp Ala Asn Leu Cys Leu Lys Gly Glu Asp Leu Asp Ser Gln
            260                 265                 270
Val Gly Val Ile Asp Phe Ser Leu Tyr Leu Lys Asp Val Gln Asp Leu
        275                 280                 285
Asp Gly Gly Lys Glu His Glu Arg Ile Thr Asp Val Leu Asp Gln Lys
    290                 295                 300
Asn Tyr Val Glu Glu Leu Asn Arg His Leu Ser Cys Thr Val Gly Asp
305                 310                 315                 320
Leu Gln Thr Lys Ile Asp Gly Leu Glu Lys Thr Asn Ser Lys Leu Gln
                325                 330                 335
Glu Glu Leu Ser Ala Ala Thr Asp Arg Ile Cys Ser Leu Gln Glu Glu
            340                 345                 350
Gln Gln Gln Leu Arg Glu Gln Asn Glu Leu Ile Arg Glu Arg Ser Glu
        355                 360                 365
Lys Ser Val Glu Ile Thr Lys Gln Asp Thr Lys Val Glu Leu Glu Thr
    370                 375                 380
Tyr Lys Gln Thr Arg Gln Gly Leu Asp Glu Met Tyr Ser Asp Val Trp
385                 390                 395                 400
Lys Gln Leu Lys Glu Glu Lys Lys Val Arg Leu Glu Leu Glu Lys Glu
                405                 410                 415
Leu Glu Leu Gln Ile Gly Met Lys Thr Glu Met Glu Ile Ala Met Lys
            420                 425                 430
Leu Leu Glu Lys Asp Thr His Glu Lys Gln Asp Thr Leu Val Ala Leu
        435                 440                 445
Arg Gln Gln Leu Glu Glu Val Lys Ala Ile Asn Leu Gln Met Phe His
    450                 455                 460
Lys Ala Gln Asn Ala Glu Ser Ser Leu Gln Gln Lys Asn Glu Ala Ile
465                 470                 475                 480
```

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1116
1116

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```
Thr Ser Phe Glu Gly Lys Thr Asn Gln Val Met Ser Ser Met Lys Gln
                485                 490                 495
Met Glu Glu Arg Leu Gln His Ser Glu Arg Ala Arg Gln Gly Ala Glu
            500                 505                 510
Glu Arg Ser His Lys Leu Gln Gln Glu Leu Gly Gly Arg Ile Gly Ala
        515                 520                 525
Leu Gln Leu Gln Leu Ser Gln Leu His Glu Gln Cys Ser Ser Leu Glu
    530                 535                 540
Lys Glu Leu Lys Ser Glu Lys Glu Gln Arg Gln Ala Leu Gln Arg Glu
545                 550                 555                 560
Leu Gln His Glu Lys Asp Thr Ser Ser Leu Leu Arg Met Glu Leu Gln
                565                 570                 575
Gln Val Glu Gly Leu Lys Lys Glu Leu Arg Glu Leu Gln Asp Glu Lys
            580                 585                 590
Ala Glu Leu Gln Lys Ile Cys Glu Glu Gln Glu Gln Ala Leu Gln Glu
        595                 600                 605
Met Gly Leu His Leu Ser Gln Ser Lys Leu Lys Met Glu Asp Ile Lys
    610                 615                 620
Glu Val Asn Gln Ala Leu Lys Gly His Ala Trp Leu Lys Asp Asp Glu
625                 630                 635                 640
Ala Thr His Cys Arg Gln Cys Glu Lys Glu Phe Ser Ile Ser Arg Arg
                645                 650                 655
Lys His His Cys Arg Asn Cys Gly His Ile Phe Cys Asn Thr Cys Ser
            660                 665                 670
Ser Asn Glu Leu Ala Leu Pro Ser Tyr Pro Lys Pro Val Arg Val Cys
        675                 680                 685
Asp Ser Cys His Thr Leu Leu Leu Gln Arg Cys Ser Ser Thr Ala Ser
    690                 695                 700

      <210> 192
      <211> 331
      <212> PRT
      <213> Homo sapien

      <400> 192
Arg Ala Gly Ala Ser Ala Met Ala Leu Arg Lys Glu Leu Leu Lys Ser
 1               5                  10                  15
Ile Trp Tyr Ala Phe Thr Ala Leu Asp Val Glu Lys Ser Gly Lys Val
            20                  25                  30
Ser Lys Ser Gln Leu Lys Val Leu Ser His Asn Leu Tyr Thr Val Leu
        35                  40                  45
His Ile Pro His Asp Pro Val Ala Leu Glu Glu His Phe Arg Asp Asp
    50                  55                  60
Asp Asp Gly Pro Val Ser Ser Gln Gly Tyr Met Pro Tyr Leu Asn Lys
65                  70                  75                  80
Tyr Ile Leu Asp Lys Val Glu Glu Gly Ala Phe Val Lys Glu His Phe
                85                  90                  95
Asp Glu Leu Cys Trp Thr Leu Thr Ala Lys Lys Asn Tyr Arg Ala Asp
            100                 105                 110
Ser Asn Gly Asn Ser Met Leu Ser Asn Gln Asp Ala Phe Arg Leu Trp
        115                 120                 125
```

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Cys Leu Phe Asn Phe Leu Ser Glu Asp Lys Tyr Pro Leu Ile Met Val
130 135 140
Pro Asp Glu Val Glu Tyr Leu Leu Lys Lys Val Leu Ser Ser Met Ser
145 150 155 160
Leu Glu Val Ser Leu Gly Glu Leu Glu Glu Leu Leu Ala Gln Glu Ala
165 170 175
Gln Val Ala Gln Thr Thr Gly Gly Leu Ser Val Trp Gln Phe Leu Glu
180 185 190
Leu Phe Asn Ser Gly Arg Cys Leu Arg Gly Val Gly Arg Asp Thr Leu
195 200 205
Ser Met Ala Ile His Glu Val Tyr Gln Glu Leu Ile Gln Asp Val Leu
210 215 220
Lys Gln Gly Tyr Leu Trp Lys Arg Gly His Leu Arg Arg Asn Trp Ala
225 230 235 240
Glu Arg Trp Phe Gln Leu Gln Pro Ser Cys Leu Cys Tyr Phe Gly Ser
245 250 255
Glu Glu Cys Lys Glu Lys Arg Gly Ile Ile Pro Leu Asp Ala His Cys
260 265 270
Cys Val Glu Val Leu Pro Asp Arg Asp Gly Lys Arg Cys Met Phe Cys
275 280 285
Val Lys Thr Ala Thr Arg Thr Tyr Glu Met Ser Ala Ser Asp Thr Arg
290 295 300
Gln Arg Gln Glu Trp Thr Ala Ala Ile Gln Met Ala Ile Arg Leu Gln
305 310 315 320
Ala Glu Gly Lys Thr Ser Leu His Lys Asp Leu
325 330

<210> 193
<211> 475
<212> PRT
<213> Homo sapien

<400> 193
Lys Asn Ser Pro Leu Leu Ser Val Ser Ser Gln Thr Ile Thr Lys Glu
1 5 10 15
Asn Asn Arg Asn Val His Leu Glu His Ser Glu Gln Asn Pro Gly Ser
20 25 30
Ser Ala Gly Asp Thr Ser Ala Ala His Gln Val Val Leu Gly Glu Asn
35 40 45
Leu Ile Ala Thr Ala Leu Cys Leu Ser Gly Ser Gly Ser Gln Ser Asp
50 55 60
Leu Lys Asp Val Ala Ser Thr Ala Gly Glu Glu Gly Asp Thr Ser Leu
65 70 75 80
Arg Glu Ser Leu His Pro Val Thr Arg Ser Leu Lys Ala Gly Cys His
85 90 95
Thr Lys Gln Leu Ala Ser Arg Asn Cys Ser Glu Glu Lys Ser Pro Gln
100 105 110
Thr Ser Ile Leu Lys Glu Gly Asn Arg Asp Thr Ser Leu Asp Phe Arg
115 120 125
Pro Val Val Ser Pro Ala Asn Gly Val Glu Gly Val Arg Val Asp Gln
130 135 140

0952
1123
1118

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

<210> 194
<211> 241
<212> PRT
<213> Homo sapien

<400> 194
Met Ser Gly Glu Ser Ala Arg Ser Leu Gly Lys Gly Ser Ala Pro Pro
1 5 10 15

853
1124
1119

09518 03030D

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

<210> 195
<211> 138
<212> PRT
<213> Homo sapien

<400> 195

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

Glu Ala Arg Glu Gln Gly Glu Leu Lys Glu Gln Ser Leu Gln Ser Gln
115 120 125
Leu Asp Glu Ala Gln Arg Ala Leu Ala Gln
130 135

<210> 196
<211> 102
<212> PRT
<213> Homo sapien

<400> 196
Met Ser Lys Arg Lys Ala Pro Gln Glu Thr Leu Asn Gly Gly Ile Thr
1 5 10 15
Asp Met Leu Thr Glu Leu Ala Asn Phe Glu Lys Asn Val Ser Gln Ala
20 25 30
Ile His Lys Tyr Asn Ala Tyr Arg Lys Ala Ala Ser Val Ile Ala Lys
35 40 45
Tyr Pro His Lys Ile Lys Ser Gly Ala Glu Ala Lys Lys Leu Pro Gly
50 55 60
Val Gly Thr Lys Ile Ala Glu Lys Ile Asp Glu Phe Leu Ala Thr Gly
65 70 75 80
Lys Leu Arg Lys Leu Glu Lys Ile Arg Gln Asp Asp Thr Ser Ser Ser
85 90 95
Ile Asn Phe Leu Thr Arg
100

<210> 197
<211> 138
<212> PRT
<213> Homo sapien

<400> 197
Glu Ala Asn Glu Val Thr Asp Ser Ala Tyr Met Gly Ser Glu Ser Thr
1 5 10 15
Tyr Ser Glu Cys Glu Thr Phe Thr Asp Glu Asp Thr Ser Thr Leu Val
20 25 30
His Pro Glu Leu Gln Pro Glu Gly Asp Ala Asp Ser Ala Gly Gly Ser
35 40 45
Ala Val Pro Ser Glu Cys Leu Asp Ala Met Glu Glu Pro Asp His Gly
50 55 60
Ala Leu Leu Leu Leu Pro Gly Arg Pro His Pro His Gly Gln Ser Val
65 70 75 80
Ile Thr Val Ile Gly Gly Glu Glu His Phe Glu Asp Tyr Gly Glu Gly
85 90 95
Ser Glu Ala Glu Leu Ser Pro Glu Thr Leu Cys Asn Gly Gln Leu Gly
100 105 110
Cys Ser Asp Pro Ala Phe Leu Thr Pro Ser Pro Thr Lys Arg Leu Ser
115 120 125
Ser Lys Lys Val Ala Arg Tyr Leu His Gln
130 135

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1121

<210> 198
<211> 100
<212> PRT
<213> Homo sapien

<400> 198
Met Gly Asp Val Lys Asn Phe Leu Tyr Ala Trp Cys Gly Lys Arg Lys
1 5 10 15
Met Thr Pro Ser Tyr Glu Ile Arg Ala Val Gly Asn Lys Asn Arg Gln
20 25 30
Lys Phe Met Cys Glu Val Gln Val Glu Gly Tyr Asn Tyr Thr Gly Met
35 40 45
Gly Asn Ser Thr Asn Lys Lys Asp Ala Gln Ser Asn Ala Ala Arg Asp
50 55 60
Phe Val Asn Tyr Leu Val Arg Ile Asn Glu Ile Lys Ser Glu Glu Val
65 70 75 80
Pro Ala Phe Gly Val Ala Ser Pro Pro Pro Leu Thr Asp Thr Pro Asp
85 90 95
Thr Thr Ala Asn
100

<210> 199
<211> 127
<212> PRT
<213> Homo sapien

<400> 199
Met Val Lys Glu Thr Thr Tyr Tyr Asp Val Leu Gly Val Lys Pro Asn
1 5 10 15
Ala Thr Gln Glu Glu Leu Lys Lys Ala Tyr Arg Lys Leu Ala Leu Lys
20 25 30
Tyr His Pro Asp Lys Asn Pro Asn Glu Gly Glu Lys Phe Lys Gln Ile
35 40 45
Ser Gln Ala Tyr Glu Val Leu Ser Asp Ala Lys Lys Arg Glu Leu Tyr
50 55 60
Asp Lys Gly Gly Glu Gln Ala Ile Lys Glu Gly Gly Ala Gly Gly Gly
65 70 75 80
Phe Gly Ser Pro Met Asp Ile Phe Asp Met Phe Phe Gly Gly Gly Gly
85 90 95
Arg Met Gln Arg Glu Arg Arg Gly Lys Asn Val Val His Gln Leu Ser
100 105 110
Val Thr Leu Glu Asp Leu Tyr Asn Gly Ala Thr Arg Lys Leu Ala
115 120 125

<210> 200
<211> 90
<212> PRT
<213> Homo sapien

<400> 200
Met Ala Cys Pro Leu Asp Gln Ala Ile Gly Leu Leu Val Ala Ile Phe

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

<210> 201
<211> 120
<212> PRT
<213> Homo sapien

<400> 201

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

<210> 202
<211> 177
<212> PRT
<213> Homo sapien

<400> 202

```
Met Ala Ala Gly Val Glu Ala Ala Ala Glu Val Ala Ala Thr Glu Ile
 1               5                  10                  15
Lys Met Glu Glu Glu Ser Gly Ala Pro Gly Val Pro Ser Gly Asn Gly
            20                  25                  30
Ala Pro Gly Pro Lys Gly Glu Gly Glu Arg Pro Ala Gln Asn Glu Lys
        35                  40                  45
Arg Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr
    50                  55                  60
Ala Asn Pro Thr Lys Arg Tyr Arg Ala Phe Ile Thr Asn Ile Pro Phe
65                  70                  75                  80
```

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Asp Val Lys Trp Gln Ser Leu Lys Asp Leu Val Lys Glu Lys Val Gly
85 90 95
Glu Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg
100 105 110
Gly Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala
115 120 125
Ala Glu Val Leu Asn Lys His Ser Leu Ser Gly Arg Pro Leu Lys Val
130 135 140
Lys Glu Asp Pro Asp Gly Glu His Ala Arg Arg Ala Met Gln Lys Ala
145 150 155 160
Gly Arg Leu Gly Ser Thr Val Phe Val Ala Asn Leu Asp Tyr Lys Val
165 170 175
Gly.

<210> 203
<211> 164
<212> PRT
<213> Homo sapien

<400> 203
Met Arg Leu Ala Val Gly Ala Leu Leu Val Cys Ala Val Leu Gly Leu
1 5 10 15
Cys Leu Ala Val Pro Asp Lys Thr Val Arg Trp Cys Ala Val Ser Glu
20 25 30
His Glu Ala Thr Lys Cys Gln Ser Phe Arg Asp His Met Lys Ser Val
35 40 45
Ile Pro Ser Asp Gly Pro Ser Val Ala Cys Val Lys Lys Ala Ser Tyr
50 55 60
Leu Asp Cys Ile Arg Ala Ile Ala Ala Asn Glu Ala Asp Ala Val Thr
65 70 75 80
Leu Asp Ala Gly Leu Val Tyr Asp Ala Tyr Leu Ala Pro Asn Asn Leu
85 90 95
Lys Pro Val Val Ala Glu Phe Tyr Gly Ser Lys Glu Asp Pro Gln Thr
100 105 110
Phe Tyr Tyr Ala Val Ala Val Val Lys Lys Asp Ser Gly Phe Gln Met
115 120 125
Asn Gln Leu Arg Gly Lys Lys Ser Cys His Thr Gly Leu Gly Arg Ser
130 135 140
Ala Gly Trp Asn Ile Pro Ile Gly Leu Leu Tyr Cys Asp Leu Pro Glu
145 150 155 160
Pro Arg Lys Pro

<210> 204
<211> 241
<212> PRT
<213> Homo sapien

<400> 204
Met Ser Gly Glu Ser Ala Arg Ser Leu Gly Lys Gly Ser Ala Pro Pro

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1129
1124

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

<210> 205
<211> 160
<212> PRT
<213> Homo sapien

<400> 205

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

859
1120
1125

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```
            100                 105                 110
Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu Glu Asp
        115                 120                 125
Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu Ser Thr Leu His
    130                 135                 140
Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe Val Lys Thr Leu
145                 150                 155                 160
```

<210> 206
<211> 197
<212> PRT
<213> Homo sapien

<400> 206

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

<210> 207
<211> 175
<212> PRT
<213> Homo sapien

<400> 207

```
Ile Ile Arg Gln Gln Gly Leu Ala Ser Tyr Asp Tyr Val Arg Arg Arg
 1               5                  10                  15
Leu Thr Ala Glu Asp Leu Phe Glu Ala Arg Ile Ile Ser Leu Glu Thr
            20                  25                  30
```

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

      <210> 208
      <211> 177
      <212> PRT
      <213> Homo sapien

      <400> 208
Met Ala Ala Gly Val Glu Ala Ala Ala Glu Val Ala Ala Thr Glu Ile
 1               5                  10                  15
Lys Met Glu Glu Glu Ser Gly Ala Pro Gly Val Pro Ser Gly Asn Gly
            20                  25                  30
Ala Pro Gly Pro Lys Gly Glu Gly Glu Arg Pro Ala Gln Asn Glu Lys
        35                  40                  45
Arg Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr
    50                  55                  60
Ala Asn Pro Thr Lys Arg Tyr Arg Ala Phe Ile Thr Asn Ile Pro Phe
65                  70                  75                  80
Asp Val Lys Trp Gln Ser Leu Lys Asp Leu Val Lys Glu Lys Val Gly
                85                  90                  95
Glu Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg
            100                 105                 110
Gly Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala
        115                 120                 125
Ala Glu Val Leu Asn Lys His Ser Leu Ser Gly Arg Pro Leu Lys Val
    130                 135                 140
Lys Glu Asp Pro Asp Gly Glu His Ala Arg Arg Ala Met Gln Lys Val
145                 150                 155                 160
Met Ala Thr Thr Gly Gly Met Gly Met Gly Pro Gly Gly Pro Gly Met
                165                 170                 175
Ile

      <210> 209
```

89
1122
1127

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<211> 196
<212> PRT
<213> Homo sapien

<400> 209

```
Asp Leu Gln Asp Met Phe Ile Val His Thr Ile Glu Glu Ile Glu Gly
 1               5                  10                  15
Leu Ile Ser Ala His Asp Gln Phe Lys Ser Thr Leu Pro Asp Ala Asp
            20                  25                  30
Arg Glu Arg Glu Ala Ile Leu Ala Ile His Lys Glu Ala Gln Arg Ile
        35                  40                  45
Ala Glu Ser Asn His Ile Lys Leu Ser Gly Ser Asn Pro Tyr Thr Thr
    50                  55                  60
Val Thr Pro Gln Ile Ile Asn Ser Lys Trp Glu Lys Val Gln Gln Leu
65                  70                  75                  80
Val Pro Lys Arg Asp His Ala Leu Leu Glu Glu Gln Ser Lys Gln Gln
                85                  90                  95
Ser Asn Glu His Leu Arg Arg Gln Phe Ala Ser Gln Ala Asn Val Val
            100                 105                 110
Gly Pro Trp Ile Gln Thr Lys Met Glu Glu Ile Gly Arg Ile Ser Ile
        115                 120                 125
Glu Met Asn Gly Thr Leu Glu Asp Gln Leu Ser His Leu Lys Gln Tyr
    130                 135                 140
Glu Arg Ser Ile Val Asp Tyr Lys Pro Asn Leu Asp Leu Leu Glu Gln
145                 150                 155                 160
Gln His Gln Leu Ile Gln Glu Ala Leu Ile Phe Asp Asn Lys His Thr
                165                 170                 175
Asn Tyr Thr Met Glu His Ile Arg Val Gly Trp Glu Gln Leu Leu Thr
            180                 185                 190
Thr Ile Ala Arg
        195
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<210> 210
<211> 156
<212> PRT
<213> Homo sapien

<400> 210

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

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            100                 105                 110
Pro Ser Ile Ser Ser Asn Asn Ser Asn Pro Val Glu Asp Lys Asp Ala
        115                 120                 125
Val Ala Phe Thr Cys Glu Pro Glu Val Gln Asn Thr Thr Tyr Leu Trp
    130                 135                 140
Trp Val Asn Gly Gln Ser Leu Pro Val Ser Pro Lys
145                 150                 155

      <210> 211
      <211> 92
      <212> PRT
      <213> Homo sapien

      <400> 211
Met Glu Ser Pro Ser Ala Pro Pro His Arg Trp Cys Ile Pro Trp Gln
 1               5                  10                  15
Arg Leu Leu Leu Thr Ala Ser Leu Leu Thr Phe Trp Asn Pro Pro Thr
            20                  25                  30
Thr Ala Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly
        35                  40                  45
Lys Glu Val Leu Leu Leu Val His Asn Leu Pro Gln His Leu Phe Gly
    50                  55                  60
Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Arg Gln Ile Ile
65                  70                  75                  80
Gly Tyr Val Ile Gly Thr Gln Gln Ala Thr Pro Gly
                85                  90

      <210> 212
      <211> 142
      <212> PRT
      <213> Homo sapien

      <400> 212
Glu Lys Gln Lys Asn Lys Glu Phe Ser Gln Thr Leu Glu Asn Glu Lys
 1               5                  10                  15
Asn Thr Leu Leu Ser Gln Ile Ser Thr Lys Asp Gly Glu Leu Lys Met
            20                  25                  30
Leu Gln Glu Glu Val Thr Lys Met Asn Leu Leu Asn Gln Gln Ile Gln
        35                  40                  45
Glu Glu Leu Ser Arg Val Thr Lys Leu Lys Glu Thr Ala Glu Glu Glu
    50                  55                  60
Lys Asp Asp Leu Glu Glu Arg Leu Met Asn Gln Leu Ala Glu Leu Asn
65                  70                  75                  80
Gly Ser Ile Gly Asn Tyr Cys Gln Asp Val Thr Asp Ala Gln Ile Lys
                85                  90                  95
Asn Glu Leu Leu Glu Ser Glu Met Lys Asn Leu Lys Lys Cys Val Ser
            100                 105                 110
Glu Leu Glu Glu Glu Lys Gln Gln Leu Val Lys Glu Lys Thr Lys Val
        115                 120                 125
Glu Ser Glu Ile Arg Lys Glu Tyr Leu Glu Lys Ile Gln Gly
    130                 135                 140
```

-663
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<210> 213
<211> 142
<212> PRT
<213> Homo sapien

<400> 213

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

<210> 214
<211> 129
<212> PRT
<213> Homo sapien

<400> 214

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

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<210> 215
<211> 148
<212> PRT
<213> Homo sapien

<400> 215

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

<210> 216
<211> 527
<212> PRT
<213> Homo sapien

<400> 216

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

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```
Ala Pro Lys Asn Gly Thr Leu Glu Pro Gly Thr Glu Arg Arg Ala Pro
145                 150                 155                 160
Glu Thr Gly Gly Ala Pro Arg Ala Pro Gly Ala Gly Arg Leu Asp Leu
                165                 170                 175
Gly Ser Gly Gly Arg Ala Pro Val Gly Thr Gly Thr Ala Pro Gly Gly
            180                 185                 190
Gly Pro Gly Ser Gly Val Asp Ala Lys Ala Gly Trp Val Asp Asn Thr
        195                 200                 205
Arg Pro Gln Pro Pro Pro Pro Pro Leu Pro Pro Pro Pro Glu Ala Gln
    210                 215                 220
Pro Arg Arg Leu Glu Pro Ala Pro Pro Arg Ala Arg Pro Glu Val Ala
225                 230                 235                 240
Pro Glu Gly Glu Pro Gly Ala Pro Asp Ser Arg Ala Gly Gly Asp Thr
                245                 250                 255
Ala Leu Ser Gly Asp Gly Asp Pro Pro Lys Pro Glu Arg Lys Gly Pro
            260                 265                 270
Glu Met Pro Arg Leu Phe Leu Asp Leu Gly Pro Pro Gln Gly Asn Ser
        275                 280                 285
Glu Gln Ile Lys Ala Arg Leu Ser Arg Leu Ser Leu Ala Leu Pro Pro
    290                 295                 300
Leu Thr Leu Thr Pro Phe Pro Gly Pro Gly Pro Arg Arg Pro Pro Trp
305                 310                 315                 320
Glu Gly Ala Asp Ala Gly Ala Ala Gly Gly Glu Ala Gly Gly Ala Gly
                325                 330                 335
Ala Pro Gly Pro Ala Glu Glu Asp Gly Glu Asp Glu Asp Glu Asp Glu
            340                 345                 350
Glu Glu Asp Glu Glu Ala Ala Ala Pro Gly Ala Ala Ala Gly Pro Arg
        355                 360                 365
Gly Pro Gly Arg Ala Arg Ala Ala Pro Val Pro Val Val Val Ser Ser
    370                 375                 380
Ala Asp Ala Asp Ala Ala Arg Pro Leu Arg Gly Leu Leu Lys Ser Pro
385                 390                 395                 400
Arg Gly Ala Asp Glu Pro Glu Asp Ser Glu Leu Glu Arg Lys Arg Lys
                405                 410                 415
Met Val Ser Phe His Gly Asp Val Thr Val Tyr Leu Phe Asp Gln Glu
            420                 425                 430
Thr Pro Thr Asn Glu Leu Ser Val Gln Ala Pro Pro Glu Gly Asp Thr
        435                 440                 445
Asp Pro Ser Thr Pro Pro Ala Pro Pro Thr Pro Pro His Pro Ala Thr
    450                 455                 460
Pro Gly Asp Gly Phe Pro Ser Asn Asp Ser Gly Phe Gly Gly Ser Phe
465                 470                 475                 480
Glu Trp Ala Glu Asp Phe Pro Leu Leu Pro Pro Pro Gly Pro Pro Leu
                485                 490                 495
Cys Phe Ser Arg Phe Ser Val Ser Pro Ala Leu Glu Thr Pro Gly Pro
            500                 505                 510
Pro Ala Arg Ala Pro Asp Ala Arg Pro Ala Gly Pro Val Glu Asn
        515                 520                 525
```

<210> 217
<211> 466

<212> DNA
<213> Homo sapien

<400> 217
gaatggtgcc tgtcctgctg tctctgctgc tgcttctggg tcctgctgtc ccccaggaga 60
accaagatgg tcgttactct ctgacctata tctacactgg gctgtccaag catgttgaag 120
acgtccccgc gtttcaggcc cttggctcac tcaatgacct ccagttcttt agatacaaca 180
gtaaagacag gaagtctcag cccatgggac tctggagaca ggtggaagga atggaggatt 240
ggaagcagga cagccaactt cagaaggcca gggaggacat ctttatggag accctgaaag 300
acatcgtgga gtattacaac gacagtaacg ggtctcacgt attgcaggga aggtttggtt 360
gtgagatcga gaataacaga agcagcggag cattctggaa atattactat gatggaaagg 420
actacattga attcaacaaa gaaatcccag cctgggtccc cttcga 466

<210> 218
<211> 381
<212> DNA
<213> Homo sapien

<400> 218
gagtttcctt cgcaagttca tgtggggtac cttcccaggc tgcctggctg accagctggt 60
tttaaagcgc cggggtaacc agttggagat ctgtgccgtg gtcctgaggc agttgtctcc 120
acacaagtac tacttcctcg tgggctacag tgaaactttg ctgtcctact tttacaaatg 180
tcctgtgcga ctccacctcc aaactgtgcc ctcaaaggtt gtgtataagt acctctagaa 240
caatcccctt ttttccatca agctgtagcc tgcagagaat ggaaacgtgg gaaaggaatg 300
gtatgtgggg gaaatgcatc ccctcagagg actgaggcat agtctctcat ctgctattga 360
atcaagacct tctatcttgt a 381

<210> 219
<211> 1293
<212> DNA
<213> Homo sapien

<400> 219
gaggggaggc gcatggcggg gatggcgctg gcgcgggcct ggaagcagat gtcctggttc 60
tactaccagt acctgctggt cacggcgctc tacatgctgg agccctggga gcggacggtg 120
ttcaattcca tgctggtttc cattgtgggg atggcactat acacaggata cgtcttcatg 180
ccccagcaca tcatggcgat attgcactac tttgaaatcg tacaatgacc aagatgcgac 240
caggatcaga ggttccttgg ggaagaccca ccctacgaag ttggaatgag accatcagat 300
gtgataagaa actcttctag atgtcaacat aaccaacctt ataaagacta aaattcatga 360
gtagaacagg aaaatcatcc tgactcatgt gttgtgttct ttatttttaa ttttcaaaga 420
ggctcttgta tagcagtttt tgtctatttt aacattgtag tcatttgtac tttgatatca 480
gtattttctt aaccctttgtg actgtttcaa tattaccccc gtgaaagctt ttcttaatgt 540
aactttgagt acattttaat tgccttctat ttttaaaact caaaatcatt agttgggctt 600
tactgttctt gctattgtat ggcatataca tctgcctgga tatatttcta ctcttgacca 660
aagttttgta aagaacaata taagatttcg ggtaggggta tggggaggga agatatttta 720
ttgagaacta cttaacaaaa gatttatctg taagcttgaa ctcaggagta cagttttagc 780
tatctagact ctaacagctt ttgctttaaa attattaaag tgtttcttaa tgaaaaagaa 840
aagatcttgc taaagttaaa ataaggaaca tttcaccttt taaatattta attcttatgt 900
ggacttattt ccagaaaact ttggtgataa ttcttgagac aaaaggtggt taagtagcat 960
tattatgtaa tgcttatata ccatagagtt tttaatagaa gagaaatcca tttcctccga 1020
gggtcactat taacaatgta cttccttaaa tttagtttaa tgattgtaat gggtgctgca 1080

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tttgcacatt gcattaagtt atgatgagac gaattgttgt taaaaattat agcaaaaaga 1140
aatgtaaact tggttaaaat cctttcactc tttgtattgt ttttttaag gtttttattc 1200
cttaaatgta aaatgactac ctaatttttt gatgtaaata cattaaattc aaagagaaaa 1260
aaaatcaaaa aaaaaaaaaa aaaaaaactc gag 1293

<210> 220
<211> 983
<212> DNA
<213> Homo sapien

<400> 220
caggttattc tgatcctgcc gcctgtcttc cctgtaagag tggagcctcg aggtgtacct 60
taaagtgacc ggaatgttag agatgcaatt tgcagagctg gggcaaggaa gggctccttg 120
tcactgtagt tactttcctt gcagtggcca aatgcccaat aagaaggaat acatgaccac 180
tgctgtgggg agtcagcagg tgcgtgatgc agctggccac actccatcca cggccatgac 240
ataaaacaga caagaagtaa ggctggactg taacacctca aggcctgctc cagtgaccca 300
ctttcttcag agaggctcta ccacacacac aaccaccttc caaatttaca ctcagatcac 360
tacaccatgt ctcccaagtt aaaacatgta tccacctaga ctttaaatgt gctttgtaac 420
tgttgatggc actgtacaga gggccaaagt atttcccatc agatagcatt tttctgaacc 480
catgcctctt gggacgagat cacaggactt gacccatcat caaataggac caggtgacct 540
acagagacat cacaatgatg gcttcctaca gtcaagtcca tttccaataa tgctctcatc 600
taagagaacc catgaacctt atttgaatcc tggttcaaac aaaaacctta aattatttat 660
gagacaatta taaacttgat agattttgat gtgtgaaggt atttatgaat atttttagtc 720
agtgatggta tactgttaag gaaaaggttc atattttagg gacaaaggct gaaacattta 780
tggacagagt gatatgatat ctgggatttg ttttaggatg aagtgggagg gaggaaatga 840
atggaaatag tgttgaaaca gtattggcca cgagtcagct attgtgtgct aagacgctcc 900
tcacaccagt ctactctgta tgtgtttgaa tatctctgta ataaacttaa caaggaaaaa 960
aaaaaaaaaa aaaaaaactc gag 983

<210> 221
<211> 373
<212> DNA
<213> Homo sapien

<400> 221
cattttatgg gttaattttt tattaaatag caataagata cttttataac tcaataaaat 60
tattcaatga tacattcgga aaataaatgt ataaaatatg aaaaagtact aaaaagcatt 120
tttcagtact tttaggtaag attaatccaa ctaaacacta gcatatgtta tacagtaata 180
ataaggggaa aatacaataa tgttgagaaa gcaaactcaa agcatagatc aatgaaaaaa 240
ttgagaaatg gacataaatg atttagtatt tttaaagaga gtgaaaaatc attatttcat 300
gcttttgtgt agcgttagat gaattaaata acatatgcac atatagcttt gcgatacaaa 360
tttccagacc ata 373

<210> 222
<211> 544
<212> DNA
<213> Homo sapien

<400> 222
cagagatgct gctgctacaa aggatcggtg taagcagtta acccaggaaa tgatgacaga 60
gaaagaaaga agcaatgtgg ttataacaag gatgaaagat cgaattggaa cattagaaaa 120

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ggaacataat gtatttcaaa acaaaataca tgtcagttat caagagactc aacagatgca 180
gatgaagttt cagcaagttc gtgagcagat ggaggcagag atagctcact tgaagcagga 240
aaatggtata ctgagagatg cagtcagcaa cactacaaat caactggaaa gcaagcagtc 300
tgcagaacta aataaactac gccaggatta tgctaggttg gtgaatgagc tgactgagaa 360
aacaggaaag ctacagcaag aggaagtcca aaagaagaat gctgagcaag cagctactca 420
gttgaaggtt caactacaag aagctgagag aaggtgggaa gaagttcaga gctacatcag 480
gaagagaaca gcggaacatg aggcagcaca gctagattta cagagtaaat ttgtggccaa 540
agaa 544

<210> 223
<211> 316
<212> DNA
<213> Homo sapien

<400> 223
gaggcaaggg atatgcttta gtgcctatta tagttaattc ttcaactcca aagtctaaaa 60
cagttgaatc tgctgaagga aaatctgaag aagtaaatga aacattagtt atacccactg 120
aggaagcaga aatggaagaa agtggacgaa gtgcaactcc tgttaactgt gaacagcctg 180
atatcttggt ttcttctaca ccaataaatg aaggacagac tgtgttagac aaggtggctg 240
agcagtgtga acctgctgaa agtcagccag aagcacttct gagaggaaga tgtttgcaag 300
gtaactctaa cagttg 316

<210> 224
<211> 1583
<212> DNA
<213> Homo sapien

<400> 224
cagaccacgt ctgccctcgc cgctctagcc ctgcgcccca gcccggccgc ggcacctccg 60
cctcgccgcc gctaggtcgg ccggctccgc ccggctgccg cctaggatga atatcatgga 120
cttcaacgtg aagaagctgg cggccgacgc aggcaccttc ctcagtcgcg ccgtgcagtt 180
cacagaagaa aagcttggcc aggctgagaa gacagaattg gatgctcact tagagaacct 240
ccttagcaaa gctgaatgta ccaaaatatg gacagaaaaa ataatgaaac aaactgaagt 300
gttattgcag ccaaatccaa atgccaggat agaagaattt gtttatgaga aactggatag 360
aaaagctcca agtcgtataa acaacccaga acttttggga caatatatga ttgatgcagg 420
gactgagttt ggcccaggaa cagcttatgg taatgccctt attaaatgtg gagaaaccca 480
aaaaagaatt ggaacagcag acagagaact gattcaaacg tcagccttaa attttcttac 540
tccctttaaga aactttatag aaggagatta caaaacaatt gctaaagaaa ggaaactatt 600
gcaaaataag agactggatt tggatgctgc aaaaacgaga ctaaaaaagg caaaagctgc 660
agaaactaga aattcatctg aacaggaatt aagaataact caaagtgaat ttgatcgtca 720
agcagagatt accagacttc tgctagaggg aatcagcagt acacatgccc atcaccttcg 780
ctgtctgaat gactttgtag aagcccagat gacttactat gcacagtgtt accagtatat 840
gttggacctc cagaaacaac tgggaagttt tccatccaat tatcttagta acaacaatca 900
gacttctgtg acacctgtac catcagtttt accaaatgcg attggttctt ctgccatggc 960
ttcaacaagt ggcctagtaa tcacctctcc ttccaacctc agtgacctta aggagtgtag 1020
tggcagcaga aaggccaggg ttctctatga ttatgatgca gcaaacagta ctgaattatc 1080
acttctggca gatgaggtga tcactgtgtt cagtgttgtt ggaatggatt cagactggct 1140
aatgggggaa aggggaaacc agaagggcaa ggtgccaatt acctacttag aactgctcaa 1200
ttaagtaggt ggactatgga aaggttgccc atcatgactt tgtatttata tacaattaac 1260
tctaaataaa gcaggttaag tatcttccat gttaatgtgt taagagactg aaaataccag 1320
ccatcagaaa ctggcctttt tgccaataaa gttgcatggt aaatatttca ttacagaatt 1380

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tatgttagag ctttcatgcc aagaatgttt tcttacaaaa ttctcttttt attgaggttt 1440
cactaataag cagcttctac ttttgagcct caacttaaag cagaactgtt ttttactgga 1500
tttttcatta acagcaagct ttttttttta tgtaaaataa atctattgtg aattgaaaaa 1560
aaaaaaaaaa aaaaaaactc gag 1583

<210> 225
<211> 491
<212> DNA
<213> Homo sapien

<400> 225
gaacaacatc atcttgaatc actagataga ctcttgacgg aaagcaaagg ggaaatgaaa 60
aaggaaaata tgaagaaaga tgaagcttta aaagcattac agaaccaagt atctgaagaa 120
acaatcaagg ttaggcaact agattcagca ttggaaattt gtaaggaaga acttgtcttg 180
catttgaatc aattggaagg aaataaggaa aagtttgaaa aacagttaaa gaagaaatct 240
gaagaggtat attgtttaca gaaagagcta aagataaaaa atcacagtct tcaagagact 300
tctgagcaaa acgttattct acagcatact cttcagcaac agcagcaaat gttacaacaa 360
gagacaatta gaaatggaga gctagaagat actcaaacta aacttgaaaa acaggtgtca 420
aaactggaac aagaacttca aaaacaaagg gaaagttcag ctgaaaagtt gagaaaaatg 480
gaggagaaat g 491

<210> 226
<211> 483
<212> DNA
<213> Homo sapien

<400> 226
cagccgcacg ccgcggagca ggggctcgga ggtcccggga ttacggtgct cgagcacgct 60
ggtgggaaag gacccgggac ttgaacagtg ttgtgcggcg ccatgcaggt ctccagcctc 120
aatgaggtga agatttacag cctcagctgc ggcaagtccc ttcctgagtg gctttctgat 180
aggaagaaga gagcgctaca gaagaaagat gtagatgtcc gtaggagaat tgaacttatt 240
caggactttg aaatgcctac tgtgtgtacc actattaagg tgtcaaaaga tggacagtac 300
attttagcaa ctggaacata taaacctcgg gttcgatgtt atgacaccta tcaattatcc 360
ttgaagtttg aaaggtgttt agattcagaa gttgtcacct ttgaaatttt gtctgatgac 420
tactcaaaga ttgtcttctt acataatgat agatacattg aatttcattc gcaatcaggt 480
ttt 483

<210> 227
<211> 486
<212> DNA
<213> Homo sapien

<400> 227
gagcctcgct aagctccgac tctgggcggc accgggcgtc ccacgatgcc gaagaacaag 60
aagcggaaca ctccccaccg cggtagcagt gctggcggcg gcgggtcagg agcagccgca 120
gcgacggcgg cgacagcagg tggccagcat cgaaatgttc agccttttag tgatgaagat 180
gcatcaattg aaacagtgag ccattgcagt ggttatagcg atccttccag ttttgctgaa 240
gatggaccag aagtccttga tgaggaagga actcaagaag acctagagta caagttgaag 300
ggattaattg acctaaccct ggataagagt gcgaagacaa ggcaagcagc tcttgaaggt 360
attaaaaatg cactggcttc aaaaatgctg tatgaattta ttctggaaag gagaatgact 420
ttaactgata gcattgaacg ctgcctgaaa aaaggtaaga gtgatgagca acgtgcagct 480

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gcagcg 486

<210> 228
<211> 494
<212> DNA
<213> Homo sapien

<400> 228
gaggccagga ctccgggaat gcgagcaggc cccttattct cccagtggcc tcggtctgtc 60
cccacagcgg cccggtcagg gttgcccgag ccccaaggcg gggggcggca ccggggtgct 120
gaaagggaca gaatgctttg acctccaagc tgttttaaat ctagtagata agccagatcc 180
tgtgttgcca taagcccttg gcccacattt aagtgggaat gcagctagct tggatgtctg 240
aaactttgta agcgccttct gtctgaatcc tgaacacagg caccaagact actgaagaag 300
ctcgtcattc ttgtgcaggg atagccacac aagcaaacat gtttgcaaaa cttgaaagaa 360
agaaaattgc agaaagaaga cttgctgttc ttaagaggcc caggaaggtg ctacttagga 420
atcccaccgg cttgtgaagc aagggaatca agtttgcctt caatggggaa cttgacttca 480
ggaaaatgaa cttt 494

<210> 229
<211> 465
<212> DNA
<213> Homo sapien

<400> 229
gtcagagagc tggtataacc tcctgttgga catgcagaac cgactcaata aggtcatcaa 60
aagcgtgggc aagattgagc actccttctg gagatccttt cacactgagc gaaagacaga 120
accagccaca ggcttcatcg atggtgatct gattgaaagt ttcctagata tcagccgccc 180
taagatgcag gaggttgtgg caaacttgca gtatgatgat ggcagtggta tgaagcggga 240
ggcaactgca gatgacctca tcaaagtcgt ggaggaacta actcggatcc attagccaag 300
gacaggatct cttttcctga ccctcctaaa ggcgttgccc tcctatcctc ccttccttgc 360
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gtgaccttgt gtggaaacag ggtttttttt acttaaaaca gttca 465

<210> 230
<211> 495
<212> DNA
<213> Homo sapien

<400> 230
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accagcgcct agggctggac tacgaggaac gagtgttgcc gtccattgtc aacgaggtgc 180
tcaagagtgt ggtggccaag ttcaatgcct cacagctgat cacccagcgg gcccaggtat 240
ccctgttgat ccgccgggag ctgacagaaa gggccaaagg acttcagcct catcctggat 300
gatgtggcca tcacagactt gagctttagc cgagaagtac acaagctgcc tgtaagaaac 360
ccaaccaagt ggggtgaatt ccaaaaaccc gtgggggtga agggcttctt aagaatgcaa 420
ggaaggagga aaagaattcc atgggggggg ggttccttaa cccaggaaca ggggtttccc 480
ttgaattttt ttcca 495

<210> 231
<211> 498

00E0E0*608 T560

871
1142
1137

<212> DNA
<213> Homo sapien

<400> 231
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tgggccgggg gtcgcttttc gcgcgcccag cattcacggg ggctccggcg gccgcggcgt 180
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cggcggcgtc ctgaccgcgt ccgacgggct gctggcgggc aacgagaagc taaccatgca 300
gaacctcaac gaccgcctgc ctcctacctg gacaaagtgc gcgccctgga agcgggcaac 360
ggcgaactta gaggtgaaag aatcccgcga actggtacca aaaacaaggg gcctggggcc 420
ttccgcgact tacagccaac ttactacacc gaacattcaa gaacttgcgg gaacaaaaat 480
ttttggtgcc acccattt 498

<210> 232
<211> 465
<212> DNA
<213> Homo sapien

<400> 232
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ttaggaattg ttttctcact taccttcttt aaaagaagaa tgtggccatt agccttcggt 180
tctggcatgg gattaggaat ggcttattcc aactgtcagc atgatttcca ggctccatat 240
cttctacatg gaaaatatgt caaagagcag gagcagtgac ttcacctgag aacatcccag 300
cgggaggaca agagaaaatc atgtttattc ctcaggaata cttgaagtgc cctggagtaa 360
actgccattc ttctgtaaca atggtatcag taatgcttta aactccagca cctggttatg 420
catttgaaac ccaagtctgg ttcttggttt ggattttctc tctgg 465

<210> 233
<211> 366
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(366)
<223> n = A,T,C or G

<400> 233
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aatcacaaca aaatatacac taacttaaaa aacaaaagat tatagtgaca taaaatgtta 180
tattctcttt ttaagtgggt aaaagtattt tgtttgcttc tacataaatt tctattcatg 240
ananaataac aaatattaaa atacagtgat agtttgcatt tcttctatag aatgaacata 300
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ttatca 366

<210> 234
<211> 379
<212> DNA

09518 00E030'60

<213> Homo sapien

<400> 234
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acccagtgcc tgcagccatg gctcccggcc agctcgcctt atttagtgtc tctgacaaaa 120
ccggccttgt ggaatttgca agaaacctga ccgctcttgg tttgaatctg gtcgcttccg 180
gagggactgc aaaagctctc agggatgctg gtctggcagt cacagatgtc tctgagttga 240
cgggatttct gaaatgttgg ggggacgtgt gaaaactttg catcctgcac gatcccatgc 300
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tcttataaca attgttgcc 379

<210> 235
<211> 406
<212> DNA
<213> Homo sapien

<400> 235
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actgggaggt gggacccctt tcattttcag ttttgctcat ctagggaaaa taaggctttg 120
gtttccagtt taattgtttt tgaccttcta aaatgttttt atgttagcac tgatagttgg 180
cattactgtt gttaagcact gtgttccaga ccgtgtctga cttagtgtaa cctaggagat 240
tttatagttt tattttaatg aaaccctgat tgacgcacag cagtggggag aacagcgtct 300
tttacctgtc accgaagcca ggaagccccg tttgtaagcg tgtgttgtgg tgctttattg 360
tacatcctcc agtggcgttc tttttactct aatgttcttt tggttt 406

<210> 236
<211> 278
<212> DNA
<213> Homo sapien

<400> 236
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tcttaagcta attctgcaaa atcacatatt gaaagtaaaa gttggcctta gcgacctcta 120
caatggacag atactggaaa ccattggagg caaacaactc cgagtctttg tgtatcggac 180
ggctatctgc atagaaaact catgcatggt gagaggaagc aagcagggaa ggaacggtgc 240
cattcacata ttccgagaga tcatccaacc agcagaat 278

<210> 237
<211> 322
<212> DNA
<213> Homo sapien

<400> 237
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ggagttcgtg cagcagtacg tgcgcccctg atcgcggagg tcgcgtcctg ttcaccggcc 120
cgtctgcccc gaccgcccaa ggccgccttc ccctgacctc gcgcgcacgc gtggggctgg 180
ggcggcgagg ctggcggtcc ggcctggccg cgactctgcc cttctttcca gaggttccgg 240
gccctgtgct cccgcgacag gttgctggct tcgtttgggg acagagtggt ccggtgagca 300
ccgccaacac ctactcctac ct 322

09518809 030300

823
1145
1139

<210> 238
<211> 613
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (399)
<223> n=A,T,C or G

<400> 238
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agacaaatct cccacacctc ctaatttacc tagcgataaa atctaccctc cttctgggtc 180
ccccgaagag aataccagca cagccaccat gacttacatg acaactactc cagcaacagc 240
ccaaatgagc accaaggaag ccagctggga tgtggctgaa caacccacca ctgctgattt 300
tgctgctgcc acacttcagc gcacgcacag aactaatcgt ccccttcccc ctccgccttc 360
ccagagatct gcagagcagc caccagttgt ggggcaggna caagcagcaa ccaatatagg 420
attaaataat tcccacaagg ttcaaggagt agttccagtt ccagagaggc cacctgaacc 480
tcgagccatg gatgacccctg cgtctgcctt catcagtgac agtggtgctg ctgctgctca 540
gtgtcccatg gctacagctg tccagccagg cctgcctgag aaagtgcggg acggtgcccg 600
ggtcccgctg ctg 613

<210> 239
<211> 613
<212> DNA
<213> Homo sapiens

<400> 239
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cctgccagaa gctaggactc ctgtctcacc agggagcccg cagccccagc cacccgtggc 480
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taagatcact gta 613

<210> 240
<211> 585
<212> DNA
<213> Homo sapiens

<400> 240
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tgccaacccc agttattaaa gcttttggca tcttgaagcg agcggccgct gaagtaaacc 120
aggattatgg tcttgatcca aagattgcta atgcaataat gaaggcagca gatgaggtag 180
ctgaaggtaa attaaatgat cattttcctc tcgtggtatg gcagactgga tcaggaactc 240

09SL 8092'6030300

234
1145
1140

agacaaatat gaatgtaaat gaagtcatta gcaatagagc aattgaaatg ttaggaggtg 300
aacttggcag caagatacct gtgcatccca acgatcatgt taataaaagc cagagctcaa 360
atgatacttt tcccacagca atgcacattg ctgctgcaat agaagttcat gaagtactgt 420
taccaggact acagaagtta catgatgctc ttgatgcaaa atccaaagag tttgcacaga 480
tcatcaagat tggacgtact catactcagg atgctgttcc acttactctt gggcaggaat 540
ttagtggtta tgttcaacaa gtaaaatatg caatgacaag aataa 585

<210> 241
<211> 566
<212> DNA
<213> Homo sapiens

<400> 241
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cgagaagatc aagaactggc agaaggaagc ctttcacaag cagatgatgg gcggcttcaa 120
ggagaccaag gaagctgagg acggctttcg gaaggcacag aagccctggg ccaagaagct 180
gaaagaggta gaagcagcaa agaaagccca ccatgcagcg tgcaaagagg agaagctggc 240
tatctcacga gaagccaaca gcaaggcaga cccatccctc aaccctgaac agctcaagaa 300
attgcaagac aaaatagaaa agtgcaagca agatgttctt aagaccaaag agaagtatga 360
gaagtccctg aaggaactcg accagggcac accccagtac atggagaaca tggagcaggt 420
gtttgagcag tgccagcagt tcgaggagaa acgccttcgc ttcttccggg aggttctgct 480
ggaggttcag aagcacctag acctgtccaa tgtggctggc tacaaagcca tttaccatga 540
cctggagcag agcatcagag cagctg 566

<210> 242
<211> 556
<212> DNA
<213> Homo sapiens

<400> 242
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cgactacaaa cggaacttgc cgcgtcgagg actgtcgggc tacagcatgc tggccatagg 120
gattggaacc ctgatctacg ggcactggag cataatgaag tggaaccgtg agcgcaggcg 180
cctacaaatc gaggacttcg aggctcgcat cgcgctgttg ccactgttac aggcagaaac 240
cgaccggagg accttgcaga tgcttcggga gaacctggag gaggaggcca tcatcatgaa 300
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cttcatgtgg tacacgtagg ccctgtgccc tccggccacc tggatccctg cccctcccca 480
ctgggacgga ataaatgctc tgcagacctg gaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 540
aaaaaaaaaa ctcgag 556

<210> 243
<211> 591
<212> DNA
<213> Homo sapiens

<400> 243
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tattaaatgc aaagcagctg tgctttggga gcagaagcaa cccttctcca ttgaggaaat 120
agaagttgcc ccaccaaaga ctaaagaagt tcgcattaag attttggcca caggaatctg 180
tcgcacagat gaccatgtga taaaaggaac aatggtgtcc aagtttccag tgattgtggg 240

09518 09.03030D

835
7/46
1141

acatgaggca actgggattg tagagagcat tggagaagga gtgactacag tgaaaccagg 300
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agatggcaac ctttgcatta ggagcgatat tactggtcgt ggagtactgg ctgatggcac 420
caccagattt acatgcaagg gcaaaccagt ccaccacttc atgaacacca gtacatttac 480
cgagtacaca gtggtggatg aatcttctgt tgctaagatt gatgatgcag ctcctcctga 540
gaaagtctgt ttaattggct gtgggttttc cactggatat ggcgctgctg t 591

<210> 244
<211> 594
<212> DNA
<213> Homo sapiens

<400> 244
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aatacagatc caagacaaag acaggatggg cactgctgga aaagttatta aatgcaaagc 120
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aaagactaaa gaagttcgca ttaagatttt ggccacagga atctgtcgca cagatgacca 240
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gattgtagag agcattggag aaggagtgac tacagtgaaa ccaggtgaca aagtcatccc 360
tctctttctg ccacaatgta gagaatgcaa tgcttgtcgc aacccagatg gcaacctttg 420
cattaggagc gatattactg gtcgtggagt actggctgat ggcaccacca gatttacatg 480
caagggcaaa ccagtccacc acttcatgaa caccagtaca tttaccgagt acacagtggt 540
ggatgaatct tctgttgcta agattgatga tgcagctcct cctgagaaag tctg 594

<210> 245
<211> 615
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (105)
<223> n=A,T,C or G

<400> 245
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atttgatgca gctgtttgaa gagtctggga atacagatat agaaggaatc gacacaacta 480
atgcatgcta tggaggcaca gctgctgtct tcaatgcttg ttaactggat tgagtccagc 540
tcttgggatg gacggtatgc cctggtaagt tgcaggagat attgctgtat atgccacagg 600
aaatgctaga cctac 615

<210> 246
<211> 546
<212> DNA
<213> Homo sapiens

5188809.030300

1142

09518809 030300

<400> 246
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taagga 546

<210> 247
<211> 564
<212> DNA
<213> Homo sapiens

<400> 247
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ggaaaaccac cttctcaaag atga 564

<210> 248
<211> 434
<212> DNA
<213> Homo sapiens

<400> 248
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gactggtaag accatcaccc tcgaggttga gcccagtgac accatcgaga atgtcaaggc 120
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agatggggcc gcca 434

<210> 249
<211> 416
<212> DNA
<213> Homo sapiens

<400> 249

1148
1143

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gagcgccgcg cacttcgtca tgttcttcgc gccctggtgt ggacactgcc agcggctgca 180
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ggctaaagtg gactgcacgg cccactccga cgtgtgctcc gcccaggggg tgcgaggata 300
ccccacctta aagcttttca agccaggcca agaagctgtg aagtaccagg gtcctcggga 360
cttccagaca ctggaaaact ggatgctgca gacactgaac gaggagccag tgacac 416

<210> 250
<211> 504
<212> DNA
<213> Homo sapiens

<400> 250
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gtgaagactg ccaggcctag ctct 504

<210> 251
<211> 607
<212> DNA
<213> Homo sapiens

<400> 251
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caatgatgtg gaaaagatgg ccgcacacat gcggatggtt cacattgatg aagagatggg 180
acctaaaaca gattctactt tgagttttga tttgacattg cagcagggta gtcacactaa 240
catccatctc ctggtaacta catacaatct gagggatgcc ccagctgaat ctgttgctta 300
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ctacaaatgt atccattgcc ttggtgtgta taccagcaac atgaccgcct caactatcac 600
tctgcat 607

<210> 252
<211> 618
<212> DNA
<213> Homo sapiens

<400> 252
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cgctgccact ggggtccctg gccccaccga catggcggcg gtgttgagca agtcctggag 120
cgcacggagc tgaacaagct gccccaagtct gtccagaaca aacttgaaaa gttccttgct 180

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gatcagcaat ccgagatcga tggcctgaag gggcggcatg agaaatttaa ggtggagagc 240
gaacaacagt attttgaaat agaaaagagg ttgtcccaca gtcaggagag acttgtgaat 300
gaaacccgag agtgtcaaag cttgcggctt gagctagaga aactcaacaa tcaactgaag 360
gcactaactg agaaaaacaa agaacttgaa attgctcagg atcgcaatat tgccattcag 420
agccaattta caagaacaaa ggaagaatta gaagctgaga aaagagactt aattagaacc 480
aatgagagac tatctcaaga acttgaatac ttaacagagg atgttaaacg tctgaatgaa 540
aaacttaaag aaagcaatac aacaaagggt gaacttcagt taaaattgga tgaacttcaa 600
gcttctgatg tttctgtt 618

<210> 253
<211> 1201
<212> DNA
<213> Homo sapiens

<400> 253
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<211> 560
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<213> Homo sapiens

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gctaccggct cctccctgat gattctgaaa tacactactg aacgagctct ggctggtcct 480

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ttctatcctg gatgtggttc ttctgtgtag caattccttg atgtccagtt tggaaagatg 540
tactcttctc aacaagaaaa 560

<210> 255
<211> 612
<212> DNA
<213> Homo sapiens

<400> 255
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aaggcatgga cc 612

<210> 256
<211> 1132
<212> DNA
<213> Homo sapiens

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<210> 257
<211> 519
<212> DNA
<213> Homo sapiens

09518 09.03030D

1146

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aagagctatt gaaaaaatga atgggatgct tctaaatga 519

<210> 258
<211> 596
<212> DNA
<213> Homo sapiens

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<210> 259
<211> 595
<212> DNA
<213> Homo sapiens

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tcaggacgag tttgatgcat gtttggagga gaaagatcag tatatcagtg ttctccagac 180
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gcaggagctg gaaaagatga aggggatggt aataaccgag acgaagcggc aaatgcttga 540
gaccctggaa ctgaaagaag atgaaattgc tcagcttcgt agtcatatca aacag 595

<210> 260
<211> 994
<212> DNA
<213> Homo sapiens

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B4
1152
1147

0951 T560
9.0303 0

<400> 260
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<211> 594
<212> DNA
<213> Homo sapiens

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caccagcctc atcaacacca agaagaagct ggagacagac atttcccaaa tccagggaga 360
gatggaagac atcgtccagg aagcccgcaa cgcagaagag aaggccaaga aagccatcac 420
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gcggatgaag aagaacatgg agcagaccgt gaaggacctg cagcaccgtc tggacgangc 540
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<210> 262
<211> 594
<212> DNA
<213> Homo sapiens

<400> 262
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tcggcagcaa ccctgagacg ctttacagct ctagacccta aaaggtcaaa aggccgtctt 180
atgctcaata tacatttttat tacccaatct gccccggaca ttaaataaaa ctccaaaaat 240

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taataaaaaa aaaaagttgc aattccttgc ctccgctgtg agacaaaccc cagccacatc 360
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tcctccccca ggagcttgct acatgtgccg gaaatctggc cactaggcca aggaatgcct 480
gcagcccccgg attcctccta agccgtgtcc catctgtgcg ggacccccact gaaaatcgga 540
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<210> 263
<211> 506
<212> DNA
<213> Homo sapiens

<400> 263
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agcaccggaa gcaccccggc ggccgcggta atgctggtgg tctgcatcac caccggatca 120
acttcgacaa ataccaccca ggctactttg ggaaagttgg tatgaagcat taccacttaa 180
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aacagacacg ggtgaatgct gctaaaaaca agactggggc tgctcccatc attgatgtgg 300
tgcgatcggg ctactataaa gttctgggaa agggaaagct cccaaagcag cctgtcatcg 360
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gtgtcctggt ggcttgaagc cacatggagg gagtttcatt aaatgctaac tacttttaa 480
aaaaaaaaaa aaaaaaaaaa ctcgag 506

<210> 264
<211> 600
<212> DNA
<213> Homo sapiens

<220>
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<222> (32)
<223> n=A,T,C or G

<400> 264
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<210> 265
<211> 534
<212> DNA
<213> Homo sapiens

<400> 265

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1149

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<211> 552
<212> DNA
<213> Homo sapiens

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ccttattaaa tgtggagaaa cccaaaaaag aattggaaca gcagacagag aactgattca 480
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aattgctaaa ga 552

<210> 267
<211> 551
<212> DNA
<213> Homo sapiens

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gccccagcct g 551

<210> 268
<211> 573
<212> DNA
<213> Homo sapiens

<400> 268
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09518 030300

1150

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ctatcccaga ctgtatccag agctctctca atacatgggg ctgagtttaa atgaagaaga 240
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<210> 269
<211> 500
<212> DNA
<213> Homo sapiens

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<210> 270
<211> 224
<212> DNA
<213> Homo sapiens

<400> 270
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<210> 271
<211> 447
<212> DNA
<213> Homo sapiens

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<210> 273
<211> 598
<212> DNA
<213> Homo sapiens

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tgaggaacga aaccttctgt ctgtggccta caagaacgtt gtgggggcac gccgctcttc 360
ctggagggtc atcagtagca ttgagcagaa gacatctgca gacggcaatg agaagaagat 420
tgagatggtc cgtgcgtacc gggagaagat agagaaggag ttggaggctg tgtgccagga 480
tgtgctgagc ctgctggata actacctgat caagaattgc agcgagaccc agtacgagag 540
caaagtgttc tacctgaaga tgaaagggga ctactaccgc tacctggctg aagtggcc 598

<210> 274
<211> 536
<212> DNA
<213> Homo sapiens

<400> 274
gcaccaagag actaaacaag aaagtggatc agggaagaag aaagcttcat caaagaaaca 60
aaagacagaa aatgtcttcg tagatgaacc ccttattcat gcaactactt atattccttt 120
gatggataat gctgactcaa gtcctgtggt agataagaga gaggttattg atttgcttaa 180
acctgaccaa gtagaaggga tccagaaatc tgggactaaa aaactgaaga ccgaaactga 240
caaagaaaat gctgaagtga agtttaaaga ttttcttctg tccttgaaga ctatgatgtt 300
ttctgaagat gaggctcttt gtgttgtaga cttgctaaag gagaagtctg gtgtaataca 360
agatgcttta aagaagtcaa gtaagggaga attgactacg cttatacatc agcttcaaga 420
aaaggacaag ttactcgctg ctgtgaagga agatgctgct gctacaaagg atcggtgtaa 480
gcagttaacc caggaaatga tgacagagaa agaaagaagc aatgtggtta taacaa 536

1152

0030300 0 81560

<210> 275
<211> 494
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (379)
<223> n=A,T,C or G

<400> 275
gaattcggca ccagggtcgc ggttcttgtt tgtggatcgc tgtgatcgtc acttgacaat 60
gcagatcttc gtgaagactc tgactggtaa gaccatcacc ctcgaggttg agcccagtga 120
caccatcgag aatgtcaagg caaagatcca agataaggaa ggcatccctc ctgaccagca 180
gaggctgatc tttgctggaa aacagctgga agatgggcgc accctgtctg actacaacat 240
ccagaaagag tccaccctgc acctggtgct ccgtctcaga ggtgggatgc aaatcttcgt 300
gaagacactc actggcaaga ccatcaccct tgaggtggag cccagtgaca ccatcgagaa 360
cgtcaaagca aagatccang acaaggaagg cattcctcct gaccagcaga ggttgatctt 420
tgccggaaag cagctggaag atgggcgcac cctgtctgac tacaacatcc agaaagagtc 480
taccctgcac ctgg 494

<210> 276
<211> 484
<212> DNA
<213> Homo sapiens

<400> 276
ggcttttaac cagaagtcaa acctgttcag acagaaggca gtcacagcag aaaaatcttc 60
agacaaaagg cagtcacagg tgtgcaggga gtgtgggcga ggctttagca ggaagtcaca 120
gctcatcata caccagagga cacacacagg agaaaagcct tatgtctgcg gagagtgtgg 180
gcgaggcttt atagttgagt cagtcctccg caaccacctg agtacacact ccggggagaa 240
accttatgtg tgcagccatt gtgggcgagg ctttagctgc aagccatacc tcatcagaca 300
tcagaggaca cacacaaggg agaaatcgtt tatgtgcaca gtgtgtgggc gaggctttcg 360
tgaaaagtca gagctcatta agcaccagag aattcacacg ggggataagc cttatgtgtg 420
cagagattga ggccgaggct ttgtaaagga gatcatgtct caacacacac cagaggatta 480
catt 484

<210> 277
<211> 513
<212> DNA
<213> Homo sapiens

<400> 277
gcttgaggct gccaatcaga gcttggcaga gctgagagat cagcggcagg gggagcgcct 60
ggaacatgca gcagctttgc gggccctaca agatcaggta tccatccaga gtgcagatgc 120
acaggaacaa gtggaagggc ttttggctga gaacaatgcc ttgaggacta gcctggctgc 180
cctggagcag atccaaacag caaagaccca agaactgaat atgctccggg aacagaccac 240
tgggctggca gctgagttgc agcagcagca ggctgagtac gaggacctta tgggacagaa 300
agatgacctc aactcccagc tccaggagtc attacgggcc aatagtcgac tgctggaaca 360
acttcaagaa atagggcagg agaaggagca gttgacccag gaattacagg aggctcggaa 420

gagtgcggag aagcggaagg ccatgcttgg atgagctagc aatggaaacg ctgcaagaga 480
agtcccacac aaggaagagc ttgggagcag ttc 513

<210> 278
<211> 471
<212> DNA
<213> Homo sapiens

<400> 278
gaattcggca ccagccaagg ccctgtccct ggctcgggcc cttgaagagg ccttggaagc 60
caaagaggaa ctcgagcgga ccaacaaaat gctcaaagcc gaaatggaag acctggtcag 120
ctccaaggat gacgtgggca agaacgtcca tgagctggag aagtccaagc gggccctgga 180
gacccagatg gaggagatga agacgcagct ggaagagctg gaggacgagc tgcaagccac 240
ggaggacgcc aaactgcggc tggaagtcaa catgcaggcg ctcaagggcc agttcgaaag 300
ggatctccaa gcccgggacg agcagaatga ggagaagagg aggcaactgc agagacagct 360
tcacgagtat gagacggaac tggaagacga gcgaaagcaa cgtgccctgg cagctgcagc 420
aaagaagaag ctggaagggg acctgaaaga cctggagctt caggccgact t 471

<210> 279
<211> 497
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (457)
<223> n=A,T,C or G
<221> misc_feature
<222> (471)
<223> n=A,T,C or G

<400> 279
gaattcggca cgaggccaca gaggcggcgg agagatggcc ttcagcggtt cccaggctcc 60
ctacctgagt ccagctgtcc ccttttctgg gactattcaa ggaggtctcc aggacggact 120
tcagatcact gtcaatggga ccgttctcag ctccagtgga accaggtttg ctgtgaactt 180
tcagactggc ttcagtggaa atgacattgc cttccacttc aaccctcggt ttgaagatgg 240
agggtacgtg gtgtgcaaca cgaggcagaa cggaagctgg gggcccgagg agaggaagac 300
acacatgcct ttccagaagg ggatgccctt tgacctctgc ttcctggtgc agagctcaga 360
tttcaaggtg atggtgaacg ggatcctctt cgtgcagtac ttccaccgcg tgcccttcca 420
ccgtgtggac accatctccg tcaatggctc tgtgcanctg tcctacatca ncttccagac 480
ccagacagtc atccaca 497

<210> 280
<211> 544
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (451)
<223> n=A,T,C or G

0951189 9'6 0303ED

1154

<400> 280
gaattcggca ccagaatagg aacagctccg gtctacagct cccagcgtga gcgacgcaga 60
agacgggtga tttctgcatt tccatctgag gtaccgggtt catctcacta gggagtgcca 120
gacagtgggc gcaggccagt gtgtgtgcgc accgtgcgcg agccgaagca gggcgaggca 180
ttgcctcacc tgggaagcac aaggggtcag ggagttccct ttccgagtca aagaaagggg 240
tgacggacgc acctggaaaa tcgggtcact cccacccgaa tattgtgctt ttcagaccgg 300
cttaagaaac ggcgcaccac gagactatat cccacacctg gctcagaggg tcctacgccc 360
acggaatctc gctgattgct agcacagcag tcttagatca aactgcaagg ggggcaacga 420
ggctgggga ggggcgcccg ccattgccca ngcttgctta ggtaaacaaa gcagccggga 480
agcttgaact gggtggagcc caccacagct caaggaggcc tgcctgcctc tgtagctcca 540
cctc 544

<210> 281
<211> 527
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (456)
<223> n=A,T,C or G

<400> 281
gaattcggca cgaggcctcg ctcagctcca acatggcaaa aatctccagc cctacagaga 60
ctgagcggtg catcgagtcc ctgattgctg tcttccagaa gtatgctgga aaggatggtt 120
ataactacac tctctccaag acagagttcc taagcttcat gaatacagaa ctagctgcct 180
tcacaaagaa ccagaaggac cctggtgtcc ttgaccgcat gatgaagaaa ctggacacca 240
acagtgatgg tcagctagat ttctcagaat ttcttaatct gattggtggc ctagctatgg 300
cttgccatga ctccttcctc aaggctgtcc cttcccagaa gcggacctga ggacccctg 360
gccctggcct tcaaacccac ccccttttcct tccagcctt ctgtcatcat ctccacagcc 420
cacccatccc ctgagcacac taaccacctc atgcanggcc cccctgccaa tagtaataaa 480
gcaatgtcct tttttaaaac atgaaaaaaa aaaaaaaaaa actcgag 527

<210> 282
<211> 514
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> (494)
<223> n=A,T,C or G

<400> 282
ggaagactgg agcctttgcg gcggcgctgc ccctcccctg gtccccgcga gctcggaggg 60
cccggctggt gctgcggggg ccccgggagg ttgaaaacta agcatgggga agagctgcaa 120
ggtggtcgtg tgtggccagg cgtctgtggg caaaacttca atcctggagc agcttctgta 180
tgggaaccat gtagtgggtt cggagatgat cgagacgcag gaggacatct acgtgggctc 240
cattgagaca gaccgggggg tgcgagagca ggtgcgtttc tatgacaccc ggggctccg 300
agatggggcc gaactgcccc gacactgctt ctcttgcact gatggctacg tcctggtcta 360

09518809 - 030300

tagcacagat agcagagagt cttttcagcg tgtggagctg ctcaagaagg agattgacaa 420
atccaaggac aagaaggagg tcaccatcgt ggtccttggc aacaagtgtg acttacagga 480
gcagcggcgt gtanacccaa atgtggctca acac 514

<210> 283
<211> 484
<212> DNA
<213> Homo sapiens

<400> 283
gggcgggcgg tggacagtca tggcggcccg gcgcggggct ctcatagtgc tggagggcgt 60
ggaccgcgcc gggaagagca cgcagagccg caagctggtg gaagcgctgt gcgccgcggg 120
ccaccgcgcc gaactgctcc ggttcccgga aagatcaact gaaatcggca aacttctgag 180
ttcctacttg caaaagaaaa gtgacgtgga ggatcactcg gtgcacctgc ttttttctgc 240
aaatcgctgg gaacaagtgc cgttaattaa ggaaaagttg agccagggcg tgaccctcgt 300
cgtggacaga tacgcatttt ctggtgtggc cttcaccggt gccaaggaga atttttccct 360
agactggtgt aaacagccag acgtgggcct tcccaaaccc gacctggtcc tgttcctcca 420
gttacagctg gcggatgctg ccaagcgggg agcgtttggc catgagcgct atgagaacgg 480
ggct 484

<210> 284
<211> 514
<212> DNA
<213> Homo sapiens

<400> 284
gaattcggca cgaggcggag gccgcggagg ctcctcggtc cttcagcacc cctcggcccg 60
acgcacccac gccctcacc ccccgagagc cgaaaatgga cccaagtggg gtcaaagtgc 120
tggaaacagc agaggacatc caggagaggc ggcagcaggt cctagaccga taccaccgct 180
tcaaggaact ctcaacccct aggcgtcaga agctggaaga ttcctatcga ttccagttct 240
ttcaaagaga tgctgaagag ctggagaaat ggatacagga aaaacttcag attgcatctg 300
atgagaatta taaagaccca accaacttgc agggaaagct tcagaagcat caagcatttg 360
aagctgaagt gcaggccaac tcaggagcca ttgttaagct ggatgaaact ggaaacctga 420
tgatctcaga agggcatttt gcatctgaaa ccatacggac ccgtttgatg gagctgcacc 480
gccagtggga attacttttg gagaagatgc gaga 514

<210> 285
<211> 383
<212> DNA
<213> Homo sapiens

<400> 285
gaattcggca cgaggccggg ctccaccgcg catcctgctc cactctggcg accgcccccg 60
gggccccccgc cgcgggcgcg gcgcccgcca tgggcgagga ggactactat ctggagctgt 120
gcgagcggcc ggtgcagttc gagaaggcga accctgtcaa ctgcgtcttc ttcgatgagg 180
ccaacaagca ggtttttgct gttcgatctg gtggagctac tggcgtggta gttaaaggcc 240
cagatgatag gaatcccatc tcatttagaa tggatgacaa aggagaagtg aagtgcatta 300
agttttcctt agaaaataag atattggctg ttcagaggac ctcaaagact gtggattttt 360
gtaattttat ccctgataat tcc 383

<210> 286

09518809 030300

1156

<211> 943
<212> DNA
<213> Homo sapiens

<400> 286
gaattcggca ccagggccgt ggcggaggag gagcgctgca cggtggagcg tcgggccgac 60
ctcacctacg cggagttcgt gcagcagtac gtgcgccccc gatcgcggag gtcgcgtcct 120
gttcaccggc ccgtctgccc cgaccgccca aggccgcctt cccctgacct cgcgcgcacg 180
cgtggggctg gggcggcgag gctggcggtc cggcctggcc gcgactctgc ccttctttcc 240
agaggttccg ggccctgtgc tcccgcgaca ggttgctggc ttcgtttggg gacagagtgg 300
tccggctgag caccgccaac acctactcct accacaaagt ggacttgccc ttccaggagt 360
atgtggagca gctgctgcac ccccaggacc ccacctcccc gggcaatggt gaggcagccc 420
taggcggcgg taggggggtgg ggacgcttgg agtctccagg tgccaggatc cctgtccccg 480
ccgtctctgt tggcagacac cctgtacttc ttcggggaca acaacttcac cgagtgggcc 540
tctctctttc ggcactactc cccaccccca tttggcctgc tgggaaccgc tccagcttac 600
agctttggaa tcgcaggagc tggctcgggg gtgcccttcc actggcatgg acccgggtac 660
tcagaagtga tctacggtcg taagcgctgg ttcctttacc cacctgagaa gacgccagag 720
ttccacccca acaagaccac actggcctgg ctccgggaca catacccagc cctgccaccg 780
tctgcacggc ccctggagtg taccatccgg gctggtgagg tgctgtactt cccgaccgc 840
tggtggcatg ctacgcttcaa ccttgacacc agcgtcttca tctccacctt cctcggctag 900
ccaaaacagc tggcaggact gccggtcaca caccagcacg tcc 943

<210> 287
<211> 1143
<212> DNA
<213> Homo sapiens

<400> 287
gaattcggca cgagggaaga acagctgttg gaacaacaag aatatttaga aaaagaaatg 60
gaggaagcaa agaaaatgat atcaggacta caggccttac tgctcaatgg atccttacct 120
gaagatgaac aggagaggcc cttggccctc tgtgaaccag gtgtcaatcc cgaggaacaa 180
ctgattataa tccaaagtcg tctggatcag agtatggagg agaatcagga cttaaagaag 240
gaactgctga aatgtaaaca agaagccaga aacttacagg ggataaagga tgccttgcag 300
cagagattga ctcagcagga cacatctgtt cttcagctca aacaagagct actgagggca 360
aatatggaca aagatgagct gcacaaccag aatgtggatc tgcagaggaa gctagatgag 420
aggaaccggc tcttgggaga atataaaaaa gagctggggc agaaggatcg ccttcttcag 480
cagcaccagg ccaagttaga agaagcactc cggaaactct ctgatgtcag ttaccaccag 540
gtggatctag agcgagagct agaacacaaa gatgtcctct tggctcactg tatgaaaaga 600
gaggcagatg aggcgaccaa ctacaacagt cacaactctc aaagcaatgg ttttctcctt 660
ccaacggcag gaaaaggagc tacttcagtc agcaacagag ggaccagcga cctgcagctt 720
gttcgagatg ctctccgcag cctgcgcaac agcttcagtg gccacgatcc tcagcaccac 780
actattgaca gcttggagca gggcatttct agcctcatgg agcgcctgca tgttatggag 840
acgcagaaga aacaagaaag aaaggttcgg gtcaagtcac ccagaactca agtaggtagt 900
gaataccggg agtcctggcc ccctaactca aagttgcctc actcacagag ctctccaact 960
gtcagcagca cctgtactaa agtgctctat ttcactgacc ggtcacttac gcccttcatg 1020
gtcaatatac caaagaggtt ggaggaggtg acgttaaagg attttaaagc agctattgat 1080
cgggaaggaa atcaccggta tcacttcaaa gcactggatc ctgagtttgg cactgtcaaa 1140
gag 1143

<210> 288
<211> 881

0 5188809.030300

891
1/62
1157

09518880 030300

<212> DNA
<213> Homo sapiens

<400> 288
gtgagagcgg gccgaggaga ttggcgacgg tgtcgcccgt gttttcgttg gcgggtgcct 60
gggctggtgg gaacagccgc ccgaaggaag caccatgatt tcggccgcgc agttgttgga 120
tgagttaatg ggccgggacc gaaacctagc cccggacgag aagcgcagca acgtgcggtg 180
ggaccacgag agcgtttgta aatattatct ctgtggtttt tgtcctgcgg aattgttcac 240
aaatacacgt tctgatcttg gtccgtgtga aaaaattcat gatgaaaatc tacgaaaaca 300
gtatgagaag agctctcgtt tcatgaaagt tggctatgag agagattttt tgcgatactt 360
acagagctta cttgcagaag tagaacgtag gatcagacga ggccatgctc gtttggcatt 420
atctcaaaac cagcagtctt ctggggccgc tggcccaaca ggcaaaaatg aagaaaaaat 480
tcaggttcta acagacaaaa ttgatgtact tctgcaacag attgaagaat tagggtctga 540
aggaaaagta gaagaagccc aggggatgat gaaattagtt gagcaattaa aagaagagag 600
agaactgcta aggtccacaa cgtcgacaat tgaaagcttt gctgcacaag aaaaacaaat 660
ggaagtttgt gaagtatgtg gagccttttt aatagtagga gatgcccagt cccgggtaga 720
tgaccatttg atgggaaaac aacacatggg ctatgccaaa attaaagcta ctgtagaaga 780
attaaaagaa aagttaagga aaagaaccga agaacctgat cgtgatgagc gtctaaaaaa 840
ggagaagcaa gaaagagaaa aaaaaaaaaa aaaaactcga g 881

<210> 289
<211> 987
<212> DNA
<213> Homo sapiens

<400> 289
gaattcggca cgagggactg tggtttccag gaatggtggc gtctcacgct tcttgtgctt 60
tttcctttgg ggcctccgag cggctggggt tgggggactg ggcaggaggc tccctgtaaa 120
catttggact tgggctgggg cagggggctgg tgttgggcaa agctgggggt ccaggctgga 180
gaagcagggg cccctccaga cgcagccttg ggagactcag catgtgcccc cctccccctca 240
tcacagaaca agacaatggt taaaaaccag aacagatgcc cagaaggggg taccatggcc 300
attaccagca tctcagacaa gggcaggctt caaacaggga ggcctgtggc aacccctccc 360
ctacgtctgg agctgagggg acaggggggag ctgagaacaa agagaggaaa gaggagaaaa 420
gcggcggggg aacaggcggg gagcgtgatc ttcttgcccc catcttcctc aggggttggg 480
gggtacaaag tcggcggtgg cccatcccgc caggccccgc tgcccctcag aagaggccgc 540
agtccttcag gttgttcttg atgatgacat cggtgacggc gtcaaacacg aactgcacgt 600
tcttggtgtc ggtggcgcac gtgaagtgcg tgtagatctc cttggtgtct ttgcgcttat 660
tcaggtcctc aaacttactc tggatgtagc tggctgcctc atcatatttg ttggcccctg 720
tatactcagg gaagcagatg gtcaggggac tgtgtgtgat cttctcctca aacaggtcct 780
tcttgttgag gaagaggatg atggacgtgt ctgtgaacca cttgttgttg cagatgctat 840
cgaatagctt catgctctca tgcatgcggt tcatctcctc gtcctcagct agcaccaagt 900
cataggcgct caaggctacg cagaagatga tggctgtgac gccctcaaag cagtggatcc 960
acttcttccg ctcagaccgc tgaccac 987

<210> 290
<211> 300
<212> DNA
<213> Homo sapien

<220>

1158

09518809 030300

<221> misc_feature
<222> (1)...(300)
<223> n = A,T,C or G

<400> 290
gattcaagat gtaccccatt gactttgaga aggatgatga cagcaacttt catatggatt 60
tcatcgtggc tgcatccaac ctccgggcag aaaactatga cattccttct gcagaccggc 120
acaagagcaa gctgattgca gggaagatca tcccagccat tgccacgacc acagcagccg 180
tggttggcct tgtgtgtctg gagctgtaca aggttgtgca ggggcaccga cancttgact 240
cctacangaa tgggtgcctc aacttgagcc ctgcctttct ttggtttctc tgaaccccct 300

<210> 291
<211> 352
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(352)
<223> n = A,T,C or G

<400> 291
aaccaagctg ccaccggggg tggatcggat gcggcttgag aggcatctgt ctgccgagga 60
cttctcaagg gtatttgcca tgtcccctga agagtttggc aagctggctc tgtggaagcg 120
gaatgagctc aagaagaagg cctctctctt ctgatggccc ccacctgctc cgggacggcc 180
cccttacccc tgctgcttca gggtttttcc ccggcgggtt gggaggggca ggaggtgggg 240
tggaaatngg gtgggcncct ttcctcaggt agagngggggg gccaaaacct ctgcngtccc 300
cggagngagc tatggacttt cttccccctc acaaggntgg gggcctcctg ct 352

<210> 292
<211> 511
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(511)
<223> n = A,T,C or G

<400> 292
cgcggtggct gcgcactcng cctgagaaac tcggcaagcg cgcagtgtcg actccccggt 60
ctatgccagg cgcatctcag ctaatccaaa agtaaatgag aaacttagaa aaagattgcc 120
aattccaaat caacatattt agagaaaatt ggaaaaggag aagcttacta cagctttatt 180
tgaggacttt ttaaagaacg ctgggttcta tctgtgagct gcaaatcttg gagcaaaaac 240
cagagacatt gccagagcaa acaagaacag aaatacaaat ggagaactgg tcaaaagaca 300
taacccacag ttatcttgaa caagaaacta cggggataaa taaaagtacg canccagatg 360
agcaactgac tatgaattct gagaaaagta tgcatcggaa atccactgaa ttagntaatg 420
aaataacatg ngagaacaca gaatggccag gggcagagat caacgaattt tcanatcatc 480
agttcttatc cagatgatga gtctgtttac t 511

<210> 293

1154

09518 030200

<211> 526
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(526)
<223> n = A,T,C or G

<400> 293
gataaaaaga actttaatgg aaggcactgt tgtccaaaat cacataaagg gtaagagccc 60
acacggtacc accctgctct cctacttctc aaacccacat ccaccaccca gacaggaggg 120
tgcanacccc acaggaaatt acctcccgga gcactgactg atatttttcc ttaaaacaaa 180
aaaatggctg tctcagacta ataacagaac atcttaagag ctataccagc tattacagcc 240
tggtaatana agcagctttc taanaattcc caagtttata anaggcccaa naaatgcatt 300
tattctgttg tctattaagc ctccatgaca aggagaaagt tatgagtaaa tccttggttc 360
atcaggagtt aagagctgtg ngcctcatga ggagttaana gctgtgtgca taagcaggtt 420
caagaaacaa actcctgttt gtttgcctct ttgatggttc aaaaacattc agctgctttc 480
acctctanga caaaatgctt aaagaattta ctctcatcac cttggg 526

<210> 294
<211> 601
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(601)
<223> n = A,T,C or G

<400> 294
actttaaaag ccaaatatat ttttaaaaga tcatgcttat aataagtaaa ttacncatta 60
aggaaacatc aaaataaagt agatgaataa aaaggcacac tcgaaaaatt tgagcgcaga 120
aaggacagtt ctttttgttt tgtttctaat gtcggaagaa aaagaaagag atatattaaa 180
atcattgttt tcaagtgaag gtttctgtca gttgaagtag ttagcaatgg cttcttttct 240
cccgtgtcca aagcaggctc ttcctgcgct gacttctgag gaggngttca gtcctctgcc 300
atgtataggc gatacatcaa ggcgacggcc actgcagaga tggcagggat cacccagttg 360
gtccaccaac tggaactaga atcaatagta gtgataagag tttccggagg cttgtttaac 420
tttggtctgt catctggatg gagctcccca atgatgaatg ttttggacat ttccctggca 480
tctgtagant gcccgacatc ctcaaagttc tcagtagcng tcacctccac ttgttccctt 540
aaaacttctt ccccaccagg atgctcttcc agaaatttgg gncaaatcgn acaccttgtg 600
g 601

<210> 295
<211> 262
<212> DNA
<213> Homo sapien

<400> 295
cccttagccc caagggccct gggggcagcc accctcccgc ctgtcggccc gtagatttat 60
caagggtgtt atgggcccag ctttgggggg ccagtcccga tgcactttga ggggtgttgg 120

D30D'60881560

agaggggact cccccactcg cacttaactc aacggctctc gggccctggg gctgttttta 180
ccatgtttgt ttttgaagct caggtgtctc acgtctgggc tgcaccaggc gaagagagaa 240
attaaagatt tgaggttttt cc 262

<210> 296
<211> 598
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(598)
<223> n = A,T,C or G

<400> 296
gttagaacaa ctcagcaaaa taaaattcct gtttattgtt ggacaacatt gtttcacaca 60
tacatcaaac aggccaaaaa aaataaaacag caacttcata gacaaaaaag gaaaaaaaaa 120
gaaaccttct atcttggcc ttttaacca tctcatacaa accaactact tatagtacag 180
ctaagtacat acacaaaaaa gttactggaa tgctcggaat aagattgttt ttctgttgtc 240
atttttgctt tttttacaag gntttttttc tcctttgaga ttataatgaa catggncaca 300
ccacaagtaa agtcagaagt aggacagana acgctccgaa ggctggtttg gtcatccgan 360
atcattaaaa atggctgacc ctaacaatat gtacaaaaat ataaaatgta aataaaaaat 420
acaaacaaat ttccttttta aagtactttt aagaaaaaaa gcagggcctt ggaagttttg 480
gttctttttt cctcccctgt tgcaaattct catggtttgg gttgggtggn gganancccg 540
tgtcatctgc gggtggcact gccccggngg gcgggcgggc ctctctctcg aangngac 598

<210> 297
<211> 509
<212> DNA
<213> Homo sapien

<400> 297
agaacacagg tgtcgtgaaa actaccccta aaagccaaaa tgggaaagga aaagactcat 60
atcaacattg tcgtcattgg acacgtagat tcgggcaagt ccaccactac tggccatctg 120
atctataaat gcggtggcat cgacaaaaga accattgaaa aatttgagaa ggaggctgct 180
gagatgggaa agggctcctt caagtatgcc tgggtcttgg ataaactgaa agctgagcgt 240
gaacgtggta tcaccattga tatctccttg tggaaatttg agaccagcaa gtactatgtg 300
actatcattg atgccccagg acacagagac tttatcaaaa acatgattac agggacatct 360
caggctgact gtgctgtcct gattgttgct gctggtgttg gtgaatttga agctggtatc 420
tccaagaatg ggcaggaccc gagagcatgc ccttctggct tacacactgg gtgtgaaaca 480
actaattgtc ggtgttaaca aaatggatt 509

<210> 298
<211> 267
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(267)
<223> n = A,T,C or G

1161

09514 608 03030

<400> 298
gggacggggg aaaggagacg cttcttcctc ttgctgctct tctcgttccc gagatcagcg 60
gcggcggtga ccgcgagtgg gtcggcaccg tctccggctc cgggngcnaa cagtgctgac 120
tgatagcgga ggcggnggca cctccttnna ggaggacctg gactctgtgg ctccgcgatc 180
cgccccagct ggggcctcgg agccgcctcc gccgggaggg gtcggtctgg ggatccncac 240
cgngaggctn tttggggagg gcgggcc 267

<210> 299
<211> 121
<212> DNA
<213> Homo sapien

<400> 299
ggcacgaggg ccctcggagc tcgtttccag atcgaggtaa gagggacttt cttaaaggcc 60
tagtctatgg gatggggcgg cggagggaat tttttgagaa ataaaatgaa gctgcagtgt 120
a 121

<210> 300
<211> 533
<212> DNA
<213> Homo sapien

<400> 300
aaggtgcaca gtatttgatg caggctgctg gtcttggtcg tatgaagcca aacacacttg 60
tccttggatt taagaaagat tggttgcaag cagatatgag ggatgtggat atgtatataa 120
acttatttca tgatgctttt gacatacaat atggagtagt ggttattcgc ctaaaagaag 180
gtctggatat atctcatctt caaggacaag aagaattatt gtcatcacaa gagaaatctc 240
ctggcaccaa ggatgtggta gtaagtgtgg aatatagtaa aaagtccgat ttagatactt 300
ccaaaccact cagtgaaaaa ccaattacac acaaagttga ggaagaggat ggcaagactg 360
caactcaacc actgttgaaa aaagaatcca aaggccctat tgtgccttta aatgtagctg 420
accaaaagct tcttgaagct agtacacagt ttcagaaaaa acaaggaaag aatactattg 480
atgtctggtg gctttttgat gatggaggtt tgaccttatt gataccttac ctt 533

<210> 301
<211> 560
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(560)
<223> n = A,T,C or G

<400> 301
ataaatgatc ccttttattg taagtaatgc gcaacactgg cctggctttg cactgcaagc 60
cctcggtcaa gatatagtca aataactatg gctgcaggtt ccacagttcc acaataacca 120
tggctgcacg atccacaatt cagacacaga catagagctg gggtgggtgg aaggggcagg 180
agggtggcag agtgcggact gtccccagcc ctggcctctc catgcanagt tggcccaggc 240
agacacaccc catggaatga tgagaaagtg acggcacggc cccttcccac agcaagcctg 300
gggctgccag gaactgccct tcanaacctt tgggcccagg tcncccctgaa ncccccacaac 360

1162
1162

ttttatctg gaataagtat taaaaaacaa taaattaagc aaacaacntg gnccttgaag 420
gatgttgacc nacatggtcc acagtttttg gcncaaaaaa ataagggctg gtttgctttt 480
tttggaaggc agggtttgtg gnttggcttt caaatnattt tcaaaccatt ccccagggag 540
gganaacccc cgggggggaa 560

<210> 302
<211> 599
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(599)
<223> n = A,T,C or G

<400> 302
gcaaagttac aaatttattg gtctggaaat aaatacaaat atctcattaa naaactcctc 60
tggaaagact tgtgcacaat agtttcccat ccgtactcag cctctcttgc cccgatcccc 120
gacttttcta ctcaaggcca gggaaggcct ccaaggngat gggcggcagg taacgagtca 180
ttgcctctca cgccacctgg aaggctggac tacttcctcc tcccaactgc ggggtcccan 240
aaatcctcgg gtcccagngg ctgacttaca atattcaatt cactctgacc aaacttccta 300
tganaaaatc cacggngagc caaaatgaaa agtacaaggc agtagtacag gaacctggca 360
gccgcactgg ccgcccanaa acgtcagtgg ngctgcccca ttcggcgaaa ggttagggag 420
caggaaaaga ggaagcagga gagggaagga aagtcccatg gaatatgtat tccanaatcc 480
ttacattttc tcagccaccg ctccccacgt gagttcccac ccccaccccg acaagaagca 540
aagagttctg aggatccaag aacgtgaccg ggtcanacan gttcagctac tgagttcac 599

<210> 303
<211> 591
<212> DNA
<213> Homo sapien

<400> 303
cggagttgta acgctccact gactgataga gcgaccggcc gaccatggcg cccggagtgg 60
cccgcgggcc gacgccgtac tggaggttgc gcctcggtgg cgccgcgctg ctcctgctgc 120
tcatcccggt ggccgccgcg caggagcctc ccggagctgc ttgttctcag aacacaaaca 180
aaacctgtga agagtgcctg aagaacgtct cctgtctttg gtgcaacact aacaaggctt 240
gtctggacta cccagttaca agcgtcttgc caccggcttc cctttgtaaa ttgagctctg 300
cacgctgggg agtttgttgg gtgaactttg aggcgctgat catcaccatg tcggtagtcg 360
ggggaaccct cctcctgggc attgccatct gctgctgctg ctgctgcagg aggnagagga 420
gccggaagcc ggacaggagt gaggagaagg ccatgcgtga gcgggaggag aggcggatac 480
ggcaggagga acggagagca gagatgaaga caagacatga tgaaatcaga aaaaaatatg 540
gcctgtttaa agaagaaaac ccgtatgcta gatttgaaaa caactaaagc g 591

<210> 304
<211> 441
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature

09518809 030300

09/1888,09 030300

09
1168
1163

<222> (1)...(441)
<223> n = A,T,C or G

<400> 304

gctggacgga gacctgctgg aggaggagga gctggaggaa gcagaggagg aggaccggtc 60
gtcgctgctg ctgctgtcgc cgcccgcggc caccgcctct cagacccagc agatcccagg 120
cgggtccctg gggtctgtgc tgctgccagc cgccaggttc gatgcccggg aggcggcggc 180
ggcggcgggg gtgctgtacg gaggggacga tgcccagggc atgatggcgg cgatgctgtc 240
ccacgcctac ggccccggcg gttgtggggc ggcggcggcc gccctgaacg gggagcaggc 300
ggccctgctc cggagaaaga gcgtcaacac caccgagtgc gtcccggtgc ccagctccga 360
gcacgtcgcc gagatcgtcg gccgccaggg ttgtaaaatt aaagcactga nagccaagac 420
aaacacgtat atcaagactc c 441

<210> 305
<211> 491
<212> DNA
<213> Homo sapien

<400> 305

tcgccatgcc cccttcttag cactgcaccg ccaggtccat gctgctgcca ccccagacct 60
gggctttgcc tgccacctct gtgggcagag cttccgaggc tgggtggccc tggttctgca 120
tctgcgggcc cattcagctg caaagcggcc catcgcttgt cccaaatgcg agagacgctt 180
ctggcgacga aagcagcttc gagctcatct gcggcggtgc caccctcccg ccccggaggc 240
ccggcccttc atatgcggca actgtggccg gagctttgcc cagtgggacc agctagttgc 300
ccacaagcgg gtgcacgtag ctgaggccct ggaggaggcc gcagccaagg ctctggggcc 360
ccggcccagg ggccgccccg cggtgaccgc cccccggccc ggtggagatg ccgtcgaccg 420
ccccttccag tgtgcctgtt gtggcaagcg cttccggcac aagcccaact tgatcgctca 480
cccgcgcgtg c 491

<210> 306
<211> 547
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(547)
<223> n = A,T,C or G

<400> 306

tctctttctt ttaagacagg aatgtaagcc acaacattta caaatacaat gttttaactc 60
tctacatgta ggaagccaac ctgctccttt ttgatcttct tctttggcac aacctcagtg 120
gatttctctg attcagaacg agttctaatt gatcttctct gttgcttctt ttctactgag 180
cctgtagaac cagatgttgc ttcaggagat gatacactct gcgttggctt ttcatttctc 240
tggtttggtg tagaaattat aagcctgtct tgccccctga cacttatttc tgttttgtta 300
ccaattccct ttgttgaata aacaaattga tcgataaatt tcccatcccc tgtagcattc 360
tgaagagcaa acacttgttc aatttttcaca actggagaca tgttacactt ctgcaaatcc 420
aggctccctt tgtgcatccg taatggaagc tggtaaggat ttccttgctg ccgcagtttt 480
ccaggctatt ttaacaggcg gnggctcttc ctctttccgc acttgtgtgc cgcctctggc 540
tatgtct 547

1164

09518809 - 30300

<210> 307
<211> 571
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(571)
<223> n = A,T,C or G

<400> 307
cgctgcatgt gataatgtca tcatttattt ttaaatggtt ctaaattgca natttaagtt 60
gatttcaaat caaccctatt tttaaattac ttttaatagg aanaaatgaa gcaaggacat 120
acataatcta ctatatttga aggactcaaa caaatacatg tttggctgtg aattctgtac 180
tctcaccaaa acagagataa aaatccacct aaaatacact ttccttcatt tagtgcttgt 240
gggaaaaggt caagtattgc actttaaaat tactttcatc taacatttgc cccactttc 300
cccctgaatt cactatatgt tttcagcaaa catgatttta taaattttaa gtataaaagc 360
aactaggttt tctaattcaa ctttggaagg tttactttac tctacanagc tatttttgta 420
aaacggcata tttacttaca aaattganag ataggggcat ccagctgagg tacatttcct 480
ccttggcgt tgagtttctg gacttgggtc gggggcacag gcttgtgtga ctgccccgtg 540
gcccgataca tggcctggac cccaggatgc g 571

<210> 308
<211> 591
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(591)
<223> n = A,T,C or G

<400> 308
ctccttatgt gtctgcctac ttcattcttc ggcatttcct gcttatccaa gttcaccatt 60
tcaggtcacc actggatatc agttgcctgt atataattat caggcatttc ctgcttatcc 120
aagttcacca tttcaggtca ccactggata tcagttgcct gtatataatt atcaggcatt 180
tcctgcttat ccaagttcac catttcaggt caccactgga tatcagttgc ctgtatataa 240
ttatcaggca tttcctgctt atccaagttc accatttcag gtcaccactg gatatcagtt 300
gcctgtatat aattatcagg catttcctgc ttatccaagt tcaccatttc aggtcaccac 360
tggatatcag ttgcctgtat ataattatca ggcatttcct gcttatccaa gttcaccatt 420
tcaggtcacc actggatatc agttgcctgt atataattat caggcatttc ctgcttatcc 480
aaattcagca gttcaggtca ccactggata tcagttccat gtatacaatt accagatgcc 540
accgcagtgc cctgttgggg gagcaaagga gaaatntgtg gaccgaagca t 591

<210> 309
<211> 591
<212> DNA
<213> Homo sapien

<400> 309
aggggtgca cgtactccca actgtggtcg cgctctcacc ccttctgctg ctctcgtggc 60

0951880 030300

ccccctcgcga tggcgggcat cctgtttgag gatattttcg atgtgaagga tattgacccg 120
gagggcaaga agtttgaccg aggtaagtaa gtgtctcgac tgcattgtga gagtgaatct 180
ttcaagatgg atctaatctt agatgtaaac attcaaattt accctgtaga cttgggtgac 240
aagtttcggt tggtcatagc tagtaccttg tatgaagatg gtaccctgga tgatggtgaa 300
tacaacccca ctgatgatag gccttccagg gctgaccagt ttgagtatgt aatgtatgga 360
aaagtgtaca ggattgaggg agatgaaact tctactgaag cagcaacacg cctgctgaga 420
ttgagagctg ctgagtggca gtgctccaga atcacgggat ggggccttct gtttcagctc 480
tgcgtacgtg tcctatgggg gcctgctcat gaggctgcag ggggatgcca acaacctgca 540
tggattcgag gtggactcca gagtttatct cctgatgaag aagctagcct t 591

<210> 310
<211> 488
<212> DNA
<213> Homo sapien

<400> 310
tggtctcaag cctgaagagg ctccgcccac aagctggccc atgaagttag caatgcctgt 60
ggcttcagtc aattgtcttg agactgtgaa gaggctgaaa gacaccttcc cgggtggaag 120
aaggagttca ctgaaaactt atcttaaact gacccttccc tttgagtgag tcttcattcc 180
tctcccatgt gggaacccag cctccgatgc cccggggact aggggaaaca gttggaggtc 240
cgtgccgtcc ccagcctgcc acgggtgcga ggacagccaa gtcctgagtg actcaagatg 300
cttcacttac atggaagaaa cttctaaaac tctaccgagt ggtttttgta tatactaaag 360
ttctatttag agcttttctg ttttgggcaa gttcgctgct ccttctattt gggcactttg 420
gtttttgtac tgtcttttgt gacggcattg attgaacatt ttttactagt agtcttatga 480
cttttgta 488

<210> 311
<211> 511
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(511)
<223> n = A,T,C or G

<400> 311
cccgtttntg nagcaaaana gggggaagat ttataggtag aggcgacaaa cctaccgagc 60
ctggtgatag ctggttgtcc aagatagaat cttagttcaa ctttaaattt gcccacagaa 120
ccctctaaat ccccttgtaa atttaactgt tagtccaaag aggaacagct ctttggacac 180
taggaaaaaa ccttgtagag agagtaaaaa atttaacacc catagtaggc ctaaaagcag 240
ccaccaatta agaaagcgtt caagctcaac acccactacc taaaaaatcc caaacatata 300
actgaactcc tcacacccaa ttggaccaat ctatcaccct atagaagaac taatgttagt 360
ataagtaaca tgaaaacatt ctcctccgca taagcctgcg tcagattaaa acactgaact 420
gacaattaac agcccaatat ctacaatcaa ccaacaagtc attattaccc tcactgtcaa 480
cccaacacag gcatgctcat aaggaaaggt t 511

<210> 312
<211> 591
<212> DNA
<213> Homo sapien

1166

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<400> 312
gaacttgcgt tgaaggaagc agaaactgat gaaataaaaa ttttgctgga agaaagcaga 60
gcccagcaga aggagacctt gaaatctctt cttgaacaag agacagaaaa tttgagaaca 120
gaaattagta aactcaacca aaagattcag gataataatg aaaattatca ggtgggctta 180
gcagagctaa gaactttaat gacaattgaa aaagatcagt gtatttccga gttaattagt 240
agacatgaag aagaatctaa tatacttaaa gctgaattaa acaaagtaac atctttgcat 300
aaccaagcat ttgaaatага aaaaaaccta aaagaacaaa taattgaact gcagagtaaa 360
ttggattcag aattgagtgc tcttgaaaga caaaaagatg aaaaaattac ccaacaagaa 420
gagaaatacg aagctattat ccagaacctt gagaaagaca gacaaaaatt ggtcagcagc 480
caggagcaag acagagaaca gttaattcag aagcttaatt gtgaaaaaga tgaagctatt 540
cagactgccc taaaagaatt taaattggag agagaagttg ttgagaaaga g 591

<210> 313
<211> 373
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(373)
<223> n = A,T,C or G

<400> 313
ttgattttta ttctgnattt tattactgaa atangttgtc ctantnatcc caccccacaa 60
taaaaatntn acccangccc cccntttctt tncctnatnc cctnttccac cacaccatcc 120
cggaacaagt gctccaggat tccctgccca ctggccattt tggagtgtgn ccattgggta 180
gcaatgtgga aaccaccaag gcctttgtgg anaaaatgga gggggttgag ggagncccan 240
gaggggctna tttgagggcc tttgccactt gctcataggc gagctcnatc tcctcntnat 300
ctgnacangt ggaagcaaat tcttcccggg cgtnggnant gctnaagnac cgatgcactc 360
cccggaaggn ctn 373

<210> 314
<211> 591
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(591)
<223> n = A,T,C or G

<400> 314
cccgtgccgc cgccgcctcc tgggaagaga ggaagcggga gaggagccca cgtcgcctgt 60
cacccaatat ctccagccgc gcagtcccga agagtgtaag atgttcgcct gcgccaagct 120
cgcctgcacc ccctctctga tccgagctgg atccagagtt gcatacagac caatttctgc 180
atcagtgtta tctcgaccag aggctagtag gactggagag ggctctacgg tatttaatgg 240
ggcccagaat ggtgtgtctc agctaatcca aagggagttt cagaccagtg caatcagcag 300
agacattgat actgctgcca aatttattgg tgcaggtgct gcaacagtag gagtggctgg 360
ttctggtgct ggtattggaa cagtctttgg cagccttatc attggttatg ccagaaaccc 420
ttcgctgaag cagcagctgt tctcatatgc tatcctggga tttgccttgt ctgaagctat 480

961
1172
1167

09518809 .03 300

gggtctcttt tgtttgatgg ttgctttctt gattttgttt gccatgtaac aaattactgc 540
ttgacatgtt ggcattcata ttaattacng atgtaattct gtgtatctta c 591

<210> 315
<211> 591
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(591)
<223> n = A,T,C or G

<400> 315
aagcccttca ccaacaaaga tgcctatact tgtgcaaatt gcagtgcttt tgtccacaaa 60
ggctgccgag aaagtctagc ctcctgtgca aaggtcaaaa tgaagcagcc caaagggagc 120
cttcaggcac atgacacatc atcactgccc acggtcatta tgagaaacaa gccctcacag 180
cccaaggagc gtcctcggtc cgcagtcctc ctggtggatg aaaccgctac caccccaata 240
tttgccaata gacgatccca gcagagtgtc tcgctctcca aaagtgtctc catacagaac 300
attactggag ttggcaatga tgagaacatg tcaaacacct ggaaattcct gtctcattca 360
acagactcac taaataaaat cagcaaggtc aatgagtcaa cagaatcact tactgatgag 420
ggtacagaca tgaatgaagg acaactactg ggagactttg agattgagtc caaacagctg 480
gaagcagagt cttggagtcg gataatagac agcaagtttc taaaacagcc aaaagaaaga 540
tgtgggtcaa acngcgagaa gtaatatatg agttggatgc agacagagtt t 591

<210> 316
<211> 591
<212> DNA
<213> Homo sapien

<400> 316
gtttttataa gaataaaatt ccattcaagc cagatggtgt ttacattgaa gaagttctaa 60
gtaaatggaa aggagattat gaaaaactgg agcacaacca cacttacatt caatggcttt 120
tccccctgag agaacaaggc ttgaacttct atgccaaaga actaactaca tatgaaattg 180
aggaattcaa aaaaacaaaa gaagcaatta gaagattcct cctggcttat aaaatgatgc 240
tagaattttt tggaataaaa ctgactgata aaactggaaa tgttgctcgg gctgttaact 300
ggcaggaaag atttcagcat ctgaatgagt cccagcacaa ctatttaaga atcactcgta 360
ttcttaaaag ccttggtgag cttggatatg aaagttttaa atctcctctt gtaaaattta 420
ttcttcatga agctcttgtg gagaatacta ttcccaatat taagcagagt gctctagagt 480
attttgttta tacaattaga gacagaagag aaaggagaaa gctcctgcgg ttcgcccaga 540
aacactacac gccttcagag aactttatct ggggacccgc ctcgaaaaga a 591

<210> 317
<211> 323
<212> DNA
<213> Homo sapien

<400> 317
ccaagctacg gaagcaagtg gaagagattt ttaatttgaa atttgctcaa gctcttggac 60
tcaccgaggc agtaaaagta ccatatcctg tgtttgaatc aaacccggag ttcttctatg 120
tggaaggctt gccagagggg attcccttcc gaagccctac ctggtttgga attccacgac 180

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ttgaaaggat cgtccacggg agtaataaaa tcaagttcgt tgttaaaaaa cctgaactag 240
ttatttccta cttgcctcct gggatggcta gtaaaataaa cactaaagct ttgcagtccc 300
ccaaaagacc acgaagtcct ggg 323

<210> 318
<211> 591
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(591)
<223> n = A,T,C or G

<400> 318
gatggcgtac ttggcttgga gactggcgcg gcgttcgtgt ccgagttctc tgcaggtcac 60
tagtttcccg gtagttcagc tgcacatgaa tagaacagca atgagagcca gtcagaagga 120
ctttgaaaat tcaatgaatc aagtgaaact cttgaaaaag gatccaggaa acgaagtgaa 180
gctaaaactc tacgcgctat ataagcaggc cactgaagga ccttgtaaca tgcccaaacc 240
aggtgtattt gacttgatca acaaggccaa atgggacgca tggaatgccc ttggcagcct 300
gcccaaggaa gctgccaggc agaactatgt ggatttggtg tccagtttga gtccttcatt 360
ggaatcctct agtcaggtgg agcctggaac agacaggaaa tcaactgggt ttgaaactct 420
ggtggtgacc tccgaagatg gcatcacaaa gatcatgttc aaccggccca aaaagaaaaa 480
tgccataaac actgagatgt atcatgaaat tatgcgtgca cttaaagctg ccagcaanga 540
tgactcaatc atcacttgtt ttaacaggaa atggtgacta ttacagtagn g 591

<210> 319
<211> 591
<212> DNA
<213> Homo sapien

<400> 319
gaattcggca cgaggttgct gctaagcgaa cgccctttgg agcttacgga ggccttctga 60
aagacttcac tgctactgac ttgtctgaat ttgctgccaa ggctgccttg tctgctggca 120
aagtctcacc tgaaacagtt gacagtgtga ttatgggcaa tgtcctgcag agttcttcag 180
atgctatata tttggcaagg catgttggtt tgcgtgtggg aatcccaaag gagaccccag 240
ctctcacgat taataggctc tgtggttctg gttttcagtc cattgtgaat ggatgtcagg 300
aaatttgtgt taaagaagct gaagttgttt tatgtggagg aaccgaaagc atgagccaag 360
ctccctactg tgtcagaaat gtgcgttttg gaaccaagct tggatcagat atcaagctgg 420
aagattcttt atgggtatca ttaacagatc agcatgtcca gctccccatg gcaatgactg 480
cagagaatct tgctgtaaaa cacaaaataa gcagagaaga atgtgacaaa tatgccctgc 540
agtcacagca gagatggaaa gctgctaatg atgctggcta ctttaatgat g 591

<210> 320
<211> 591
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(591)

1169

<223> n = A,T,C or G

<400> 320

ggctccggcg tctgcagggg tcgccgagct aacccgtggc taggcgagtg gggcggggcg 60
gccggcacca tgtcgaggca ggcgaaccgt ggcaccgaga gcaagaaaat gagctctgag 120
ctcttcaccc tgacctatgg tgccctggtc acccagctat gtaaggacta tgaaaatgat 180
gaagatgtga ataaacagct ggacaaaatg ggctttaaca ttggagtccg gctgattgaa 240
gatttcttgg ctcggtcaaa tgttgggagg tgccatgact ttcgggaaac tgcggatgtc 300
attgccaagg tggcgttcaa gatgtacttg ggcatcactc caagcattac taattggagc 360
ccagctggtg atgaattctc cctcattttg gaaaataacc ccttggtgga ctttgtggaa 420
cttcctgata accactcatc ccttatttat tccaatctct tgtgtggggt gttgcgggga 480
gctttggaga tggtccagat ggctngngga ggcccaagtt tgtccaggac accctnaaag 540
gagacgggng tgacagaaat ccggatgaga ttcatcaggc ggattganga c 591

<210> 321
<211> 260
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(260)
<223> n = A,T,C or G

<400> 321

ctgcttggct ccacacgtgg gccgccgtag gtattccgac cggtaattcc tcctattggt 60
gtgcagcagc cacattgaag gatagagtgg cagcagaggc caaggatcgt gagttgatgg 120
agtttgctgc tgaaaatgaa gggaagtctg ggggaggtct ccacagcgta gctgaggggg 180
tgcggctaag tccagagcct ggcagggagg gagtaaggga cttagcaggg gcggaggagt 240
tctgcggngg anaggagggg 260

<210> 322
<211> 559
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(559)
<223> n = A,T,C or G

<400> 322

ttccacatga catggagtgt gaagctggat gagcacatca ttccactggg aagcatggca 60
nttaacagca tctcaaaact gactnanctc acccagtctt ccatgtattc acttcctaat 120
gcacccactc tggcanacct gnaggacnat acacatgaag ncantgatga tcagccagan 180
aancctcact ttgactctcg canngtgata tttgagctgg attcatgcaa tggnagtggg 240
aaagtttgcc ttgtctacaa aagtgggaaa ccagnattag cagaanacac tgagatctgg 300
ttcctgnaca nancgttata ctggcatttt ctcacanaca cctttactgc ctattaccgc 360
ctgctcatca cccacctggg cctgccccag tggcaatatg ccttcccagc tatggcatta 420
gcccacaggc caagcaatgg ttcagcatgt ataaacctat cacctacaac acaaacctgc 480
tcacagaaga naccgactcc tttgtgaata agctagatcc canctnagtg tttaagagca 540

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1170

agaacaagat cgttatccc 559

<210> 323
<211> 492
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(492)
<223> n = A,T,C or G

<400> 323
cctgtctccc agccgtacca gcgagggctc ggccggcagc gccgggctgg ggggcggcgg 60
cgccggcgcc ggagccgggg tgggtgcagg cggcggcggg ggcagcggcg cgagcagcgg 120
cggcggggcc gggggggctgc aacccagcag ccgcgctggc ggcggccggc cctccagccc 180
cagcccgtcg gtggtgagcg agaaggagaa ggaagagttg gagcggctgc agaaagagga 240
ggaggagagg aagaagaggc tgcagctgta tgtgttcgtg atgcgctgca tcgcctaccc 300
ctttaatgcc aagcagccca ccgacatggc tcgccggcag cagaagatca gcaaacagca 360
gctgcagaca gtcaaggacc ggtttcaggc tttcctcaat ggggaaaccc anatcatggc 420
tgacgaagcc ttcatgaacc gctgtngcag agttactatg aggtgttcct gaagaccacc 480
cgtgtggccg ca 492

<210> 324
<211> 474
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(474)
<223> n = A,T,C or G

<400> 324
aatttcagca acatacttct caatttcttc aggatttaaa atcttgaggg attgatctcg 60
cctcatgaca gcaagttcaa tgtttttgcc acctgactga accacttcca ggagtgcctt 120
gatcaccagc ttaatggtca natcatctgt ttcaatggct tcgtcagtat agttcttctc 180
cagnaactca cgcactgact tggcaccccg gcctatggca ttggccttcc aggcatggta 240
tgtgcccgag gggtcagtct gatagagcct aggagtgcca tcaaagtcga aacccacgat 300
gagggcagag atgccaaacg gcctgcgccc attgctctgc gtataacgct gcttcanact 360
ggcgatgtag cgggtgatgt actccacagt gaccgggtcc tccacagtca gccggtggct 420
ctggcactcc acccgggccc tgttgatgac tatccttgca tcggcggtga ggcc 474

<210> 325
<211> 532
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(532)

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<223> n = A,T,C or G

<400> 325

gaggagacag gacagagcgt ctggagaggc aggaggacac cgagttcccc gtgttggcct 60
ccaggtcctg tgcttgcgga gccgtccggc ggctgggatc gagccccgac aatgggcaac 120
gcgcaggagc ggccgtcaga gactatcgac cgcgagcgga aacgcctggt cgagacgctg 180
caggcggact cgggactgct gttggacgcg ctgctggcgc ggggcgtgct caccgggcca 240
gagtacgagg cattggatgc actgcctgat gccgagcgca gggtgcgccg cctactgctg 300
ctggtgcagg gcaagggcga ggccgcctgc caggagctgc tacgctgtgc ccagcgtacc 360
gcgggcgcgc cggaccccgc ttgggactgg cagcacgtgg gtccgggcta ccgggaccgc 420
agctatgacc ctccatgccc aggccactgg acgccggagg cacccggctc ggggaccaca 480
tgccccgggt tgcccagact tcagaccctg acgaggncgg gggccctgag gg 532

<210> 326
<211> 322
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(322)
<223> n = A,T,C or G

<400> 326

caaaattaac atttttatta aatcaagtta aaaaaaatgt tcagtgtana aaagtcaaca 60
agggttttaa caaaaccaaa atataccttt ttatacaata tatgtatata ttagcagcaa 120
actacttctg anattctctt tcttttatgt tcttctagtt attttaaaga aagcataaac 180
aatgtatatt agtatggaat gtcagcaaat ccactcttag tcctttattc tgtgatttgg 240
gccttctaca aaatactttg tgattctcac taatgaatat taagaacata cccaatttta 300
actaaaaagt agtgaaacag tg 322

<210> 327
<211> 387
<212> DNA
<213> Homo sapien

<400> 327

aaaaccgtgt actattagcc atggtcaacc ccaccgtgtt cttcgacatt gccgtcgacg 60
gcgagccctt gggccgcgtc tcctttgagc tgtttgcaga caaggtccca aagacagcag 120
aaaattttcg tgctctgagc actggagaga aaggatttgg ttataagggt tcctgctttc 180
acagaattat tccagggttt atgtgtcagg gtggtgactt cacacgccat aatggcactg 240
gtggcaagtc catctatggg gagaaatttg aagatgagaa cttcatccta aagcatacgg 300
gtcctggcat cttgtccatg gcaaatgctg gacccaacac aaatggttcc cagtttttca 360
tctgcactgc caagactgag tggttgg 387

<210> 328
<211> 502
<212> DNA
<213> Homo sapien

<220>

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1172

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<221> misc_feature
<222> (1)...(502)
<223> n = A,T,C or G

<400> 328
agcagcccgg cgcggccgcc gcgccggcgg gcggcaaggc tccgggccag catgggggct 60
tcgtggtgac tgtcaagcaa gagcgcggcg agggtccacg cgcgggcgag aaggggtccc 120
acgaggagga gccggtgaag aaacgcggct ggcccaaggg caagaagcgg aagaagattc 180
tgccgaatgg gcccaaggca ccggtcacgg gctacgtgcg cttcctgaac gagcggcgcg 240
agcagatccg cacgcgccac ccggatctgc cctttcccga gatcaccaag atgctgggcg 300
ccgagtggag caagctgcag ccaacggaaa agcagcggta cctggatgag gccnagagag 360
agaagcagca gtacatgaag gagctgcggg cgtaccagca gtctgaagcc tataagatgt 420
gcacggagaa gatccaggag aagaagatca agaaagaaga ctcgagctct gggctcatga 480
acactcttct gaatggacac aa 502

<210> 329
<211> 463
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(463)
<223> n = A,T,C or G

<400> 329
caagttgcac attttaattt acaatttttа ccaataaaaa ggattagttt acaaaaaggg 60
aagtccttta tacaaaataa ggacaatttg taaaganaat ccactgtcat gttttgcctt 120
gtcaagtcaa aactcaaata gcttgttttg gtaaaattat tccagaaaca taatccagac 180
aaaatcaata acgtcatcag cttcctaacc atgtttaana ggaataactt catgaacatt 240
ttgccctgaa ctgaanagtt ctaaatactt gtaaaccttt aggaaaaaat gactgctcgc 300
aggcagcttg actggtaaga gggtacacca nagactccgg gtcactcact gtcagaatat 360
tcttatacat acaatgagtc tccacgcctg tacaatgagt gtcgtgcaac ataattggag 420
taatggcctc taaaatttta caagtaaact ttattgnggc ccc 463

<210> 330
<211> 500
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(500)
<223> n = A,T,C or G

<400> 330
taattataga tctacaaaat atgaaatgta ttccaagaat gcagaaaaac catctagaag 60
caaaaggact ataaaacaaa aacagagaag aaaattcatg gctaaaccag ctgaagaaca 120
gcttgatgtg ggacagtcta aagatgaaaa catacataca tcacatatta cccaagacga 180
atttcaaaga aattcagaca gaaatatgga agagcatgaa gagatgggaa atgattgtgt 240
ttccaaaaaa acagatgcca cctgtgggaa gcaagaaaag tagcactaga aaagataagg 300

1193

aagaatctaa aaagaagcgc ttttccagtg agtccaagaa caaacttgtn cctgaagaag 360
tgacttcaac tgtcacgaaa agtcgaanaa tttccangcg tccatctgat tggtgggtgg 420
taaaancaga ggagagtcct gtttatagca attcttcagt aagaaatgaa ttaccaantg 480
catcacaatn ntgcccggaa 500

<210> 331
<211> 494
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(494)
<223> n = A,T,C or G

<400> 331
tctctctctc tctcaaaatt acagtgttca ttgtcattga cctcagcagc aaatttgact 60
tgaattcact taggatcgca ggaatcaggg gaaagtgatt ttaaaggtgg tttctccagc 120
acattttaag aaaagggacc aaaagttatt ttagcttcct caatagattg catgttgctt 180
attaggataa taaattaata ttaaatgcaa tatatgtctt gnctttatta tggcatctat 240
ttaggagttg ttcaaatcac tgcagtaggg ctctgcaaat aaaataatgn aacctattat 300
catggatcta atgnactgna actttatcag tgaaaggnaa aatctcaaat aacaagtaca 360
aacattggac aattacctat aaagatttgt aaaaggaaaa tttttccata gatttcattc 420
ttggcatttt gtaaagacga ccctgcagnc ccctgtttgn aacttttta ataaaataga 480
catctgttta cttg 494

<210> 332
<211> 538
<212> DNA
<213> Homo sapien

<400> 332
aaagaacaaa tggaacgcga tggttgttct gaacaagagt ctcaaccgtg tgcatttatt 60
gggataggaa atagtgacca agaaatgcag cagctaaact tggaaggaaa gaactattgc 120
acagccaaaa cattgtatat atctgactca gacaagcgaa agcacttcat gttgtctgta 180
aagatgttct atggcaacag tgatgacatt ggtgtgttcc tcagcaagcg gataaaagtc 240
atctccaaac cttccaaaaa gaagcagtca ttgaaaaatg ctgacttatg cattgcctca 300
ggaacaaagg tggctctgtt taatcgacta cgatcccaga cagttagtac cagatacttg 360
catgtagaag gaggtaattt tcatgccagt tcacagcagt ggggagcctt ttttattcat 420
ctcttggatg atgatgaatc agaaggagaa gaattcacag tccgagatgg ctacatccat 480
tatggacaaa cagtcaaact tgtgtgctca gttactggca tggcactccc aagattga 538

<210> 333
<211> 499
<212> DNA
<213> Homo sapien

<400> 333
ctcagcctgc gggactgctc ggctcggctt ctaggcggtt ttgatgaaca cctggcttta 60
ttcttgcaat gaagaaaggt tctcaacaaa aaatattctc caaagcaaag ataccatcat 120
catctcactc tcctatccca tcatctatgt ccaatatgag atctaggtca ctttcacctt 180

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tgattggatc agagactcta ccttttcatt ctggaggaca gtggtgtgag caagttgaga 240
ttgcagatga aaacaatatg cttttggact atcaagacca taaaggagct gattcacatg 300
caggagttag atatattaca gaggccctca ttaaaaaact tactaaacag gataatttgg 360
ctttgataaa atctctgaac ctttcacttt ctaaagacgg tggcaagaaa tttaagtata 420
ttgagaattt ggaaaaatgt gttaaacttg aagtactgaa tctcagctat aatctaatag 480
ggaagattga aaagtcgga 499

<210> 334
<211> 561
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(561)
<223> n = A,T,C or G

<400> 334
ttcccggtag ttcagctgca catgaatagn acagcaatga gagccagtca gaaggacttt 60
gaaaattcaa tgaatcaagt gaaactcttg aaaaaggatc caggaaacga agtgaagcta 120
aaactctacg cgctatataa gcaggccact gaaggacctt gtaacatgcc caaaccaggt 180
gtatttgact tgatcaacaa ggccaaatgg gacgcatgga atgcccttgg cagcctgccc 240
aaggaagctg ccaggcagaa ctatgtggat ttggtgtcca gtttgagtcc ttcattggaa 300
tcctctagtc aggtggagcc tggaacagac aggaaatcaa ctgggtttga aactctggtg 360
gtgacctccg aagatggcat cacaaagatc atgttcaacc cggcccaaaa agaaaaatgc 420
cataaacact gagatgtatc atgaaattat gcgtgcactt aaagctgcca gcaaggatga 480
ctcaatcatc actgttttaa cangaaatgg tgactattac agtagtggga atgatctgac 540
taacttcnct gatattcccc c 561

<210> 335
<211> 551
<212> DNA
<213> Homo sapien

<400> 335
aagctggtca tggctgggga gaccaccaac tcccgcggcc agcggctgcc ccagaaggga 60
gacgtggaga tgctgtgcgg cgggccgccc tgccagggct tcagcggcat gaaccgcttc 120
aattcgcgca cctactccaa gttcaaaaac tctctggtgg tttccttcct cagctactgc 180
gactactacc ggccccggtt cttcctcctg gagaatgtca ggaactttgt ctccttcaag 240
cgctccatgg tcctgaagct caccctccgc tgcctggtcc gcatgggcta tcagtgcacc 300
ttcggcgtgc tgcaggccgg tcagtacggc gtggcccaga ctaggaggcg ggccatcatc 360
ctggccgcgg cccctggaga gaagctcccc ctgttcccgg agccactgca cgtgtttgct 420
ccccgggcct gccagctgag cgtggtgggt ggatgacaag aagtttgtga gcaacataac 480
caggttgagc tcgggtcctt tccggaccat acggtgcgag aaacgatgtc cgacctgccg 540
gaagtgcgga a 551

<210> 336
<211> 540
<212> DNA
<213> Homo sapien

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<220>
<221> misc_feature
<222> (1)...(540)
<223> n = A,T,C or G

<400> 336
aggtctatgt ctactgaagg caataaacga ggaatgatcc agcttattgt tgcaaggaga 60
ataagcaagt gcaatgagct gaagtcacct gggagccccc ctggacctga gctgcccatt 120
gaaacagcgt tggatgatag agaacgaaga atttcccatt ccctctacag tgggattgag 180
gggcttgatg aatcgcccag cagaaatgct gccctcagta ggataatggg taaataccag 240
ctgtcccctа cagtgaatat gccccaagat gacactgtca ttatagaaga tgacaggttg 300
ccagtgcttc ctccacatct ctctgaccag tcctcttcca gctcccatga tgatgtgggg 360
tttgtgacgg cagatgctgg tacttgggcc aaggctgcaa tcagtgattc agccgactgc 420
tctttgagtc cagatgttga tccagttctt gcttttcaac gaaaaaggat ttggacgtca 480
gaagtatgtc agaaaaacgc accaaagcaa ttttcanatg ccagtcaatt ggatttcgtt 540

<210> 337
<211> 422
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(422)
<223> n = A,T,C or G

<400> 337
gcagcaggaa cagttacagc agcagcagca acagcagctg ttgcaacagc agcaggaaca 60
attgcagcag caacaactgc agcctcctcc cctggagccc gaggaggagg aagaggtgga 120
gctggagctc atgccggtgg acctggggtc agagcaggag ctggagcagc agcggcagga 180
gttggagcgg cagcaggagc tggaacggca gcaggagcag cggcagctgc agctcaaact 240
gcaggaggag ctgcagcagc tggagcaaca gctggagcag cagcagcagc agctggagca 300
gcaggaggtg cagctggagc tgaccccggt ggagctaggc gcccagcagc aggaggtgca 360
gctggagctg acccccgtgc agccggagct gcagctggaa ctggtgccan cccagggggc 420
gg 422

<210> 338
<211> 601
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(601)
<223> n = A,T,C or G

<400> 338
catcttacga acgctctatg atgtcttatg agcggtctat gatgtcccct atggctgaac 60
gctctatgat gtcagcctac gagcgctcta tgatgtcagc ctacgagcgc tctatgatgt 120
cccctatggc tgagcgctct atgatgtcag cttatgaacg ctccatgatg tcagcttatg 180
aacgctccat gatgtcccca atggctgatc gatctatgat gtccatgggt gctgaccggt 240

ctatgatgtc gtcatactct gctgctgacc ggtctatgat gtcatcgtac tctgcagctg 300
accgatctat gatgtcatct tatactgctg atcgttcaat gatgtctatg gctgctgatt 360
cttacaccga ttcttacact gacacatata cagaggcata tatggtgcca cctttgcctc 420
ctgaagagcc cccaacaatg ccaccgttgc cacctgagga gccaccaatg acaccaccat 480
tgcctnctga ggaaccaccc agagggtcca gcattgccca cttgagcagt cagcattaac 540
cagcttgaaa atacttggcc ctacanangg tgccatcatt accatctgaa gagctgtatc 600
g 601

<210> 339
<211> 440
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(440)
<223> n = A,T,C or G

<400> 339
agagggagga ggcccaactg gtgatgctgc tgctgctgct gctgccgccg ccgccgcctc 60
tattgctgat actctagtgg ggctggaagg gtggttccta ttcgcaccat cgccaaccag 120
agacagaggg aaaaaaaaaa ccggcagcca ctgctgatgt tgggttcgga ggctgcatcc 180
gactcggtca caaggaaaat ggattcagtt tgcatctctc cctcctttaa acagcttctc 240
cgggtctcag catggtatca aagcttgaaa gagagaagac tcaagaagcg aagaggattc 300
gtgagctgga gcagcgcaag cacacggtgc tggtgacaga actcaaagcc aagctccatg 360
aggagaagat gaaggagctg caggctgtga gggagaacct tatcaagcag cacgacagga 420
aatgtcaang acggtgaagg 440

<210> 340
<211> 450
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(450)
<223> n = A,T,C or G

<400> 340
gatttccagg ggcggatatt gagtgtcgac ccagaggaag aaagggagga gggcccgcct 60
aggattcctc aggccgacca gtggaagtct tcaaacaaga gcctggtgga ggctctgggg 120
ctggaagccg agggtgcagt tcctgagaca cagactttga ccggatggag taaggggttc 180
attggcatgc acagggaaat gcaagtcaac cccatttcaa agcggatggg gcccatgact 240
gtggtcagga tggacgcttc agtccagcca ggccctttcc ggaccctgct ccagtttctt 300
tatacgggac aactggatga aaaggaaaag gatttggtgg gcctggctca gatcgcagag 360
gtcctcgaga tgttcgattt gaggatgatg gtggaaaaca tcatgaacaa ggaagccttc 420
atgaaccagg agattacgaa nnccttccac 450

<210> 341
<211> 451
<212> DNA

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09518809 · 030300

<213> Homo sapien

<400> 341

aacagctatt aaaacagaaa atggatgaac ttcataagaa gttgcatcag gtggtggaga 60
catcccatga ggatctgccc gcttcccagg aaaggtccga ggttaatcca gcacgtatgg 120
ggccaagtgt aggctcccag caggaactga gagcgccatg tcttccagta acctatcagc 180
agacaccagt gaacatggaa aagaacccaa gagaggcacc tcctgttgtt cctcctttgg 240
caaatgctat ttctgcagct ttggtgtccc cagccaccag ccagagcatt gctcctcctg 300
ttcctttgaa agcccagaca gtaacagact ccatgtttgc agtggccagc aaagatgctg 360
gatgtgtgaa taagagtact catgaattca agccacagag tggagcagag atcaaagaag 420
ggtgtgaaac acataaggtt gccaacacaa g 451

<210> 342
<211> 498
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(498)
<223> n = A,T,C or G

<400> 342

ctcaagcagg ctattgaaga ggaaggaggc gatccagata atattgaatt aactgtttca 60
actgatactc caaacaagaa accaactaaa ggcaaaggta aaaaacatga agcagatgag 120
ttgagtggag atgcttctgt gggaagatga tgcttttatc aaggactgtg aattggagaa 180
tcaagaggca catgagcaag atggaaatga tgaactaaag gactctgaag aatttggtga 240
aaatgaagaa gaaaatgtgc attccaagga gttactctct gcagaagaaa acaagagagc 300
tcatgaatta atagaggcag aaggaataga agatatagaa aaagaggaca tcgaaagtca 360
ggaaattgaa gctcaagaag gtgaagatga taccttttcta acagcccaag atggtgagga 420
agaagaaaat gagaaagata tagcagggtt ctggtgatgg cncacaagaa gtatntaaac 480
ctcttccttc aaaaaggg 498

<210> 343
<211> 491
<212> DNA
<213> Homo sapien

<400> 343

ccgaccccta ctcggcggcg caactccaca accagtacgg ccccatgaat atgaacatgg 60
gtatgaacat ggcagcagcc gcggcccacc accaccacca ccaccaccac caccccggtg 120
ccttttccg ctatatgcgg cagcagtgca tcaagcagga gctaatctgc aagtggatcg 180
accccgagca actgagcaat cccaagaaga gctgcaacaa aactttcagc accatgcacg 240
agctggtgac acacgtctcg gtggagcacg tcggcggccc ggagcagagc aaccacgtct 300
gcttctggga ggagtgtccg cgcgagggca agcccttcaa ggccaaatac aaactggtca 360
accacatccg cgtgcacaca ggcgagaaac ccttccctgc ccttccgggt gtggcaaagt 420
cttcgcgcgc tccgagaacc tcaagatcca caaaaggacc acacagggga gaagccgtcc 480
agtggagttg a 491

<210> 344
<211> 412

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(412)
<223> n = A,T,C or G

<400> 344
gtgcgctgtc ttcccgcttg cgtcagggac ctgcccgact cagtggccgc catggcatca 60
gatgaaggca aacttttttgt tggagggctg agttttgaca ccaatgagca gtcgctggag 120
caggtcttct caaagtacgg acagatctct gaagtggtgg ttgtgaaaga cagggagacc 180
cagagatctc ggggatttgg gtttgtcacc tttgagaaca ttgacgacgc taaggatgcc 240
atgatggcca tgaatgggaa gtctgtagat ggacggcaga tccgagtaga ccaggcaggc 300
aagtcgtcan acaaccgatc ccgtgggtac cgtggtggct ctgccggggg ccggggcttc 360
ttccgtgggg gcccgangac ggggcccgtg ggttctctaa aagaagaggg ga 412

<210> 345
<211> 498
<212> DNA
<213> Homo sapien

<400> 345
aactagtctc gggccatcct ttctgcgcac ccggtgtcgc tgggctgcac cccgggcggg 60
gacgtccgcc gggcacggga gggggccaag atgccgatca ataaatcaga gaagccagaa 120
agctgcgata atgtgaaggt tgttgttagg tgccggcccc tcaatgagag agagaaatca 180
atgtgctaca aacaggctgt cagtgtggat gagatgaggg gaactatcac tgtacataag 240
actgattctt ccaatgaacc tccaaagaca tttacttttg atactgtttt tggaccagag 300
agtaaacaac ttgatgttta taacttaact gcaagaccta ttattgattc tgtacttgaa 360
ggctacaatg ggactatttt tgcatatgga caaaccggaa caggcaaaac ttttaccatg 420
gaaaggtgtc gagctattcc tgaacttaga ggaataattc cccaatttct ttgctcacaa 480
tatttgggcc atatttgc 498

<210> 346
<211> 427
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(427)
<223> n = A,T,C or G

<400> 346
agatggcggt cgccgtgaga actttgcagg aacagctgga aaaggccaaa gagagtctta 60
agaacgtgga tgagaacatt cgcaagctca ccgggcggga tccgaatgac gtgaggccca 120
tccaagccag attgctggcc ctttctggtc ctggtggagg tagaggacgt ggtagtttat 180
tactgaggcg tggattctca gatagtggag gaggaccccc agccaaacag agagaccttg 240
aaggggcagt cagtaggctg ggcggggagc gtcggaccag aagagaatca cgccaggaaa 300
gcgacccgga ggatgatgat gttaaaaagc cagcattgca gtcttcannt gtagctacct 360
cccaaagagc gccccacgta gagaccttat ccagggatca aaattttgga tgaaaaaggg 420

0951880 030300

1179

gaaagcc 427

<210> 347
<211> 280
<212> DNA
<213> Homo sapien

<400> 347
cacagaaagt tctccgctcc cagacatggg tccctcggct tcctgcctcg gaagcgcagc 60
agcaggcatc gtgggaaggt gaagagcttc cctaaggatg acccgtccaa gccggtccac 120
ctcacagcct tcctgggata caaggctggc atgactcaca tcgtgcggga agtcgacagg 180
ccgggatcca aggtgaacaa gaaggaggtg gtggaggctg tgaccattgt agagacacca 240
cccatggtgg ttgtgggcat tgtgggctac gtggaaaccc 280

<210> 348
<211> 411
<212> DNA
<213> Homo sapien

<400> 348
caactatgat gtgcctgaaa aatgggcacg attctatact gcagaagtag ttcttgcatt 60
ggatgcaatc cattccatgg gttttattca cagagatgtg aagcctgata acatgctgct 120
ggataaatct ggacatttga agttagcaga ttttggtact tgtatgaaga tgaataagga 180
aggcatggta cgatgtgata cagcggttgg aacacctgat tatatttccc ctgaagtatt 240
aaaatcccaa ggtggtgatg gttattatgg aagagaatgt gactggtggt cggttggggt 300
atttttatac gaaatgcttg taggtgatac acctttttat gcagattctt tggttggaac 360
ttacagtaaa attatgaacc attaaaaatt cacttacctt tcctgatgat a 411

<210> 349
<211> 408
<212> DNA
<213> Homo sapien

<400> 349
gatgggcatc tctcgggaca actggcacaa gcgccgcaaa accgggggca agagaaagcc 60
ctaccacaag aagcggaagt atgagttggg gcgcccagct gccaacacca agattggccc 120
ccgccgcatc cacacagtcc gtgtgcgggg aggtaacaag aaataccgtg ccctgaggtt 180
ggacgtgggg aatttctcct ggggctcaga gtgttgtact cgtaaaacaa ggatcatcga 240
tgttgtctac aatgcatcta ataacgagct ggttcgtacc aagacgctgg tgaagaattg 300
catcgtgctc atcgacagca caccgtaccg acagtggtac gagtcccact atgcgctgcc 360
cctgggccgc aagaagggag ccaaactgac ttctgaggaa gaagaaaa 408

<210> 350
<211> 409
<212> DNA
<213> Homo sapien

<400> 350
ggttccccca gctctgggta cccggctctg catcgcgtcg ccatgatggg ccatcgtcca 60
gtgctcgtgc tcagccagaa cacaaagcgt gaatccggaa gaaaagttca atctggaaac 120
atcaatgctg ccaagactat tgcagatatc atccgaacat gtttgggacc caagtccatg 180

09518809 030300

atgaagatgc ttttggaccc aatgggaggc attgtgatga ccaatgatgg caatgccatt 240
cttcgagaga ttcaagtcca gcatccagcg gccaagtcca tgatcgaaat tagccggacc 300
caggatgaag aggttggaga tgggaccaca tcagtaatta ttcttgcagg ggaaatgctg 360
tctgtagctg agcacttcct ggagcagcag atgcacccaa caggtgggg . 409

<210> 351
<211> 226
<212> DNA
<213> Homo sapien

<400> 351
aatcccaaac atataactga actcctcaca cccaattgga ccaatctatc accctataga 60
agaactaatg ttagtataag taacatgaaa acattctcct ccgcataagc ctgcgtcaga 120
ttaaaacact gaactgacaa ttaacagccc aatatctaca atcaaccaac aagtcattat 180
taccctcact gtcaacccaa cacaggcatg ctcataagga aaggtt 226

<210> 352
<211> 410
<212> DNA
<213> Homo sapien

<400> 352
gcggaggggc tggctgggca ggaggggttg gcggggcagc agggccgcgg ccatggggag 60
cttgaaggag gagctgctca aagccatctg gcacgccttc accgcactcg accaggacca 120
cagcggcaag gtctccaagt cccagctcaa ggtcctttcc cataacctgt gcacggtgct 180
gaaggttcct catgacccag ttgcccttga agagcacttc agggatgatg atgagggtcc 240
agtgtccaac cagggctaca tgccttattt aaacaggttc attttggaaa aggtccaaga 300
caactttgac aagattgaat tcaataggat gtgttggacc ctctgtgtca aaaaaaacct 360
cacaaagaat cccctgctca ttacagaaga agatgcattt aaaatatggg 410

<210> 353
<211> 380
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(380)
<223> n = A,T,C or G

<400> 353
gagtttattt agaaagtatc atagtgtaaa caaacaaatt gtaccacttt gattttcttg 60
gaatacaaga ctcgtgatgc aaagctgaag ttgtgtgtac aagactcttg acagttgtgc 120
ttctctagga ggntgggttt ttttaaaaaa agaattatct gngaaccata cgtgattaat 180
aaagatttcc tttaaggcan aggctggtcn agatgctgct gttatcttct gcctcagaca 240
gacagtataa gnggtcttgt ttctaagatt cctaccacca gttactttgg gccaagtatc 300
cacatcccct tgcgtatggg aggnggggtga anagtgttgg atgcaaagng gttattatgg 360
gaagnagctc natggtaaaa 380

<210> 354
<211> 379

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<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(379)
<223> n = A,T,C or G

<400> 354
caacacatct ttattaaaca cctgaagtta ctgggaggag gccatgatgc tggacacact 60
gtcaaagtca atcttctcca caatgttctt gggtttaatg ctctcttctt ggctacagan 120
gaanatctgc cccgactngt cggcactcca gccgtatttg ctcatccaca cctttagctg 180
gctgtccgac agancccega gcatntcggc cagcagccan cggncaatgt gctggtaagt 240
gatacccaca acatggcaga taaactttcg gacanagtct tcaaagccag ttataccttc 300
caagaggtcc atgttttcat ccagggcttg ccanaagcct ggaaatggca ggtctccaac 360
aggtccccca ggtacaaaa 379

<210> 355
<211> 499
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(499)
<223> n = A,T,C or G

<400> 355
gtccagagct gctggtgctc ccgttcccca gaccctaccc ctatccccag tggagccgga 60
gtgcgggcgc gccccaccac cgcccctcacc atggtgctgt tggcagcagc ggtctgcaca 120
aaagcaggaa aggctattgt ttctcgacag tttgtggaaa tgacccgaac tcggattgag 180
ggcttattag cagcttttcc aaagctcatg aacactggaa aacaacatac gtttgttgaa 240
acagagagtg taagatatgt ctaccagcct atggagaaac tgtatatggt actgatcact 300
accaaaaaca gcaacatttt agaagatttg gagaccctaa ggctcttctc aagagtgatc 360
cctgaatatt gcgagcctta gaagagaatg aaatatctga gcactgnttt gatttgattt 420
ttgcttttga tgaaaatgtc gcactgggat acccgggang aatgttaact tggcacagat 480
canaaccttt cacagaaaa 499

<210> 356
<211> 511
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(511)
<223> n = A,T,C or G

<400> 356
gggcttctgc tgagggggca ggcggagctt gaggaaaccg cagataagtt tttttctctt 60
tgaaagatag agattaatac aactacttaa aaaatatagt caataggtta ctaagatatt 120

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gcttagcgtt aagtttttaa cgtaatttta atagcttaag attttaagag aaaatatgaa 180
gacttagaag agtagcatga ggaaggaaaa gataaaaggt ttctaaaaca tgacggaggt 240
tgagatgaag cttcttcatg gagtaaaaaa tgtatttaaa agaaaattga gagaaaggac 300
tacagagccc cgaattaata ccaatagaag ggcaatgctt ttagattaaa atgaaggtga 360
cttaaacagc ttaaagttta ntttaaaagt tgtaggtgat taaaataatt tgaaggcgat 420
ctttttaaaaa gagattaaac ccgaaggtga ttaaaagacc ttgaaatcca tgacgccagg 480
gagaattgcc gtcatttaaa gcctagttaa c 511

<210> 357
<211> 511
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(511)
<223> n = A,T,C or G

<400> 357
gatacttcac atttccctag ggacgggagc ccgaggggtc cgttcggccc tcttcctctc 60
gctgggccga caccccgctg taggaccgta acccttagtc ccaatgcctc cgtaagcgga 120
gttgagtggg tgcctgtggt tggagctgtg gaggtgtccc cggtggcgag cgcggccaga 180
actgcggtca cttaagtttt ccgtgtgcgg gttgcaagga gcgtgcgtgc gtctggtata 240
atttggcttc ctgagattct gcttacaaga aaggagtggg aaataccctt ggaaagaaaa 300
ctaaaacagt aagaaaacca aaacttattt ttacatggnt gtcagcacat ttaccgatat 360
ggacactttt cccaataatt tcctcctggt ggagacagtg gattgacagg ttctcagtcg 420
gaattccaga aaaatgttaa ttgatgaaaa gggtacnatg tgagcatcat aaagntaatt 480
attaanacac tgaaggctga acacacaagg g 511

<210> 358
<211> 401
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

<400> 358
acggatgaag atgatgacct tcaagaaaat gaagacaata aacaacataa agaaagcttg 60
aaaagagtga cctttgcttt accagatgat gcggaaactg aagatacagg tgttttaaat 120
gtaaagaaaa attctgatga agttaaatcc tcctttgaaa aaagacagga aaagatgaat 180
gaaaaaattg catctttaga aaaagagttg ttagaaaaaa agcccgtggc agcttcaggg 240
ggaagtgaca gcacagaaga ggccagagaa cacctcctgg aggagaccct acctttgcca 300
tctgcccgat ggccctgtga ttacagagga acccccttca ctggagattt ctttaacnga 360
ngatagagat cngnttggga tatgtntcct taagaaaacc t 401

<210> 359
<211> 511
<212> DNA

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09SI 809'6030300

<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(511)
<223> n = A,T,C or G

<400> 359
gcgatgcccg cgcgcccagg acgcctcctc ccgctgctgg cccggccggc ggccctgact 60
gcgctgctgc tgctgctgct gggccatggc ggcggcgggc gctggggcgc ccgggcccag 120
gaggcggcgg cggcggcggc ggacgggccc cccgcggcag acggcgagga cggacaggac 180
ccgcacagca agcacctgta cacggccgac atgttcacgc acgggatcca gagcgcccgc 240
gcacttcgtc atgttcttcg cgccctggtg tggacacttg ccagcggctt gcagccgant 300
ttggaatgac cttgggangа acaaatacaa cagcatggaa agaatgccaa aagtctatgt 360
ggnttaaagt ggacttgcac nggccacttc gactngtgct ccccccaggg gnggggaagat 420
acccacctta aaactttтca accaagccaa aaactttgaa aaccaggtct cggattcaaa 480
atggaaaact gatgttcaac ctgaacaaga a 511

<210> 360
<211> 511
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(511)
<223> n = A,T,C or G

<400> 360
tactgggaga ctttgagatt gagtccaaac agctggaagc agagtcttgg agtcggataa 60
tagacagcaa gtttctaaaa cagcaaaaga aagatgtggt caaacggcaa gaagtaatat 120
atgagttgat gcagacagag tttcatcatg tcccgactct caagatcatg agtggtgtgt 180
cnagccnggg gatgatggcg gatctgnttt ttgagcanca gatggtagaa aaagctggtt 240
ccctgtttgg atgagcttga tcagtatccc atacccattc tttccagagg attcttggag 300
ccggaaagaa nggagtcttc ttggtgggat aaaaagtgaa aaagaacttt ctcttcaana 360
aggatagggg gatgtgcttt gtaaaatcan ttttтcaggg ngganaatgc cnnaaccgtt 420
ttaaagaaaa acatnttggg naagtttttg tgggccaaca ttacccggtc ttgtaaacct 480
accttcaaag aaccttttтg cccagggtta a 511

<210> 361
<211> 411
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(411)
<223> n = A,T,C or G

<400> 361
gctcagcggc ccgatcccac ggaagcgcgc tcggaggggt gggacccggc cggaccggag 60

948
1189
1184

09518809 "030300

atggcgccgc cagcgggcgg ggcggcggcg gcggcctcgg acttgggctc cgccgcagtg 120
ctcttggctg tgcacgccgc ggtgaggccg ctgggcgccg ggccagacgc cgaagcacaa 180
cttgcggagg ctgcagctta acgcggaccc tgagaagcct ggcgcttncn gctggaactt 240
cttggcgcgg gacctggggc ggtaatttga gtggccctga gtcatttcta caccatccag 300
gcccaccaca cgactaagct cacaagaagg ctgaactnnc tgattctnaa cctagaanta 360
cgtgcatcta tcagtgccng aagaaatgac aacataccac tggcaactct g 411

<210> 362
<211> 511
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(511)
<223> n = A,T,C or G

<400> 362
cgggggaccg ggctgccttg gcccctcagc gctcgcgtct tttccggcag ttggaacgct 60
tcctgttgtc ctcacccgta accgcctgtt gccccctgtc tcagagtccc tcacgcgtcc 120
cctcccgtct ttggctcgtt ggctgccgcc gccggggctt cgccagcctt caagtcgaga 180
ctactggccg aaggggcgtc tgcggctctc cgccgtcccc agccctgcct ctccctgggc 240
tctgccatgg caatgacagg ctcaacacct tgctcatcca tgagtaacca cacaaaggaa 300
agggtgacaa tgaccaaaag tgacactgga gaatttttat agcaacctta tcgctcacat 360
gaagaacgag aaatgagaca aaagaagtta gaaaaagggg atggaagaag aaggcctaaa 420
aaaatgaagg agaaaaccaa cttccgaaga tcaaccacat tgcttcggaa anggaaacaa 480
aantttcttt cgtttgaaan aaaaacaaan a 511

<210> 1
<211> 401
<212> DNA
<213> Homo sapien

<400> 1
caggatctgg ggagaaagag ccccatccct tctctctctg ccaccatttc ggacaccccg 60
cagggactcg ttttgggatt cgcactgact tcaaggaagg acgcgaaccc ttctctgacc 120
ccagctcggg cggccacctg tctttgccgc ggtgaccctt ctctcatgac cctgcggtgc 180
cttgagccct ccgggaatgg cggggaaggg acgcggagcc agtgggggac cgcggggtcg 240
gcggaggagc catccccgca ggcggcgcgt ctggcgaagg ccctgcggga gctcggtcag 300
acaggatggt actggggaag tatgactgtt aatgaagcca aagagaaatt aaaagaggca 360
ccagaaggaa ctttcttgat tagagatagc tcgcattcag a 401

<210> 2
<211> 401
<212> DNA
<213> Homo sapien

<400> 2
agtcaaaggt ttctttttccc tttttaccat ggtttctaca aaaataacct tcaggaaaaa 60
gaaaatcagg aaaaaaattt tttttcaata atcttattcc ctatattaaa ttagatttga 120

944 1/95 1185

agaggattaa cgttgtttta gtttgggtcc agatcagcct tatacaacat ttctaaactc 180
atttgtactt ttaaaaaatt taaacacaga cttctaaaat tacttgatgt aagtaattta 240
aatcacttat gaccaagtta ttaaccttat gaatcagaag tctgaccctt gtaggaaatt 300
atattcacat ataaagtaca tcagatcttt gccatatatt gatggttatt atgcataaac 360
acattgagtt gtgttggaag cagatttata aacctgcatg t 401

<210> 3
<211> 361
<212> DNA
<213> Homo sapien

<400> 3
atctggagtt gcacaaatag ttctttagaa cataaaacta aatggattta tacataacag 60
ttacattcag catttaagag aggcagtaca aaaatgtgtt ctgcttttat ctgatataaa 120
ttgcatgtaa taccatgatt taaacaatat cagttatatt aactaatgcc atgagatata 180
tcttactcag aacgtctgat gttttcccata atagacagaa aaaatgcagt tgtatgagca 240
actgagtttc ttttcatctt caaattcatt tgtgatggtg ggaagatcta aggacaatcc 300
ttccattgaa gaagtaggaa aaacagttca gcactgttct gaactcatca aaaatgaaat 360
t 361

<210> 4
<211> 401
<212> DNA
<213> Homo sapien

<400> 4
cgggagcagc agaggtctag cagccgggcg ccgcgggccg ggggcctgag gaggccacag 60
gacgggcgtc ttcccggcta gtggagcccg gcgcggggcc cgctgcggcc gcaccgtgag 120
gggaggaggc cgaggaggac gcagcgccgg ctgccggcgg gaggaagcgc tccaccaggg 180
cccccgacgg cactcgttta accacatccg cgcctctgct ggaaacgctt gctggcgcct 240
gtcaccggtt ccctccattt tgaaagggaa aaaggctctc cccacccatt cccctgcccc 300
taggagctgg agccggagga gccgcgctca tggcgttcag cccgtggcag atcctgtccc 360
ccgtgcagtg ggcgaaatgg acgtggtctg cggtacgcgg c 401

<210> 5
<211> 401
<212> DNA
<213> Homo sapien

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ccaatctttt acctctcctc ccccaagaga ttttttactg gatatcgcaa ggcagaaaaa 300
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<210> 6
<211> 401
<212> DNA

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<213> Homo sapien

<400> 6
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<220>

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09518 8T560
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<212> DNA
<213> Homo sapien

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<223> n = A,T,C or G

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<210> 11
<211> 401
<212> DNA
<213> Homo sapien

<400> 11
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<210> 13
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<212> DNA
<213> Homo sapien

<400> 13
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<213> Homo sapien

<220>
<221> misc_feature
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<210> 15
<211> 401
<212> DNA
<213> Homo sapien

<400> 15
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<210> 16

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<211> 401
<212> DNA
<213> Homo sapien

<400> 16
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<210> 17
<211> 401
<212> DNA
<213> Homo sapien

<400> 17
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<210> 18
<211> 401
<212> DNA
<213> Homo sapien

<400> 18
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tacagtattg gaaatggatc tgtctttggt aaagatcagc ctataattct tgtgctgttg 180
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<210> 19
<211> 401
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

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<400> 19
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<210> 20
<211> 491
<212> DNA
<213> Homo sapien

<400> 20
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<210> 21
<211> 491
<212> DNA
<213> Homo sapien

<400> 21
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<210> 22
<211> 491
<212> DNA
<213> Homo sapien

<400> 22
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cgggagcggg ggcgggaagt tccctgaagg agcgagacag ggagggacag ggcagaggag 180
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<210> 23
<211> 483
<212> DNA
<213> Homo sapien

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<212> DNA
<213> Homo sapien

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<210> 25
<211> 491
<212> DNA
<213> Homo sapien

<400> 25
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<210> 26
<211> 491
<212> DNA
<213> Homo sapien

<400> 26
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<210> 27
<211> 511
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(511)
<223> n = A,T,C or G

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ESTADOS UNIDOS DE AMERICA

A TODOS A QUIENES ESTOS PRESENTES LLEGAREN:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS

Junio 12 del 2000

POR EL PRESENTE CERTIFICO QUE ADJUNTA SE ENCUENTRA UNA COPIA FIEL DE LOS ARCHIVOS DE LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE AMÉRICA DE LOS DOCUMENTO DE LA SOLICITUD DE PATENTE IDENTIFICADOS ABAJO Y QUE CUMPLIERON CON LOS REQUISITOS PARA QUE SE LES OTORGARA UNA FECHA DE PRESENTACIÓN BAJO EL CÓDIGO DE COMERCIO DE LOS ESTADOS UNIDOS DE AMÉRICA TÍTULO 35 SECCIÓN 11.

NÚMERO DE SOLICITUD: *09/518,809*

FECHA DE PRESENTACIÓN: *3 de Marzo del 2000*

Por autoridad del

COMISARIO DE PATENTES Y MARCAS

(Firmado.)

T. LAWRENCE

Funcionario que Certifica

(SELLO DE OBLEA DE LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE AMÉRICA)

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Por favor escriba un signo mas (+) dentro de esta caja [+]

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PTO /SB/ /05/ (2/98) +

Aprobado para uso hasta 09/30/00. OMB 0651-0032

Funcionario de Patentes y Marcas Departamento de Comercio de los Estados Unidos. Bajo la Ley de Reducción de Papeleo de 1995, no se requiere que ninguna persona responda a una recolección de información a menos que ella reemplace un número válido de control OMB.

(Al margen, Códigos de Barras jc690 U.S. PTO; 09516809.030300)

TRANSMISIÓN DE SOLICITUD DE PATENTE DE UTILIDAD (*Solamente para solicitudes* nuevas no provisionales *bajo 37CFR 1 53 (b)*	No. de Expediente Oficial	210121.478C3
	Primer Inventor Nombrado o Identificación de Solicitud	
	Steven G. Reed	
	Título:	COMPUESTOS PARA TERAPIA Y DIAGNÓSTICO DE CÁNCER DE PULMON Y MÉTODOS PARA SU USO
	Guía de Correo Expreso No.	EL487465258US

ELEMENTOS DE SOLICITUD *Véase MPEP capítulo 600 referente al contenido de la solicitud para patentes de utilidad.*	Diríjase a:	Comisario Asistente de Patentes Casilla de Solicitud de Patentes Washington, D.C. 20231

1. [ ] Formulario de Transmisión de Pago *(Presentar original y copia para procesamiento de pago).*

   (Total de páginas [84] *)*

2. [x] Especificación *(arreglo preferido a continuación)*
   - Título Descriptivo de la Invención
   - Referencias Cruzadas con Aplicaciones Relacionadas

- Declaración Referente a R & D patrocinadas por Fed
- Referencia al Apéndice Microficha
- Antecedentes de la Invención
- Resumen Breve de la Invención
- Descripción Breve de los Dibujos *(si se entregaron)*
- Descripción Detallada
- Reivindicación(es)
- Resumen de la Divulgación

3. ☐ Dibujo(s) (*35 USC 113*) (Total de Páginas ☐)

4. Juramento o Declaración (Total de Páginas ☐)

a. ☐ Firmado por primera vez (original o copia)

b. ☐ Copia de una solicitud anterior (37 CFR 1.63 (d))
(para continuación/división con Casilla 17 llena)
(Nota Casilla 5 abajo)

I. ☐ ELIMINACIÓN DE INVENTOR(ES)

Adjunto declaración firmada eliminando el(los) inventor(es) nombrado(s) en la solicitud anterior, ver 37 CFR 1.63 (d) y 1.33(b).

5. ☐ Inclusión por Referencia *(se usa si se llena la casilla No.4b)*
La divulgación completa de la solicitud anterior de la cual se adjunta copia de juramento o declaración bajo la Casilla 4b, se considera como parte de la divulgación de la solicitud adjunta y por el presente se incluye por referencia en ella.

6. ☐ Programa de Computador Microficha (Apéndice)

7. Presentación de Secuencia de Aminoácidos y/o Nucleótidos
(*si es aplicable y/o necesario*)

a. [x] Copia en medio magnético (copia legible por computador)

b. [X] Copia en papel (idéntica a la copia de computador)

c. [X] Declaración que verifica la identidad de las copias mencionadas arriba

PARTES ADJUNTAS A LA SOLICITUD

8. [ ] Documentos de Cesión (carátula & documento(s))

9. [ ] 37 CFR 3.73(b) Declaración *(cuando existe cesionario)* [ ] Poder

10. [ ] Documento de Traducción del Inglés (*si se aplica*)

11. [ ] Declaración de Divulgación de Información (IDS) VPTO-1449 [ ] Copias de citaciones IDS

12. [ ] Modificación Preliminar

13. [X] Devolución de Recibo Postal (MPEP 503)

14. [ ] Declaración(es) de Entidades Pequeñas [ ] Declaración archivada en solicitudes anteriores
Condición actual propia y deseada

15. [ ] Copia Certificada de Documento(s) de Prioridad (*si se reivindica prioridad extranjera*)

16. [X] Otros Certificado de Correo Expreso

17. SI ES UNA CONTINUACIÓN DE SOLICITUD, *llene la casilla apropiada y suministre la información requerida, y la reforma preliminar.*

[ ] Continuación [ ] Divisional [X] Continuación parcial

de solicitud anterior No. 09/476,235 presentada en Diciembre 30, 1999

DIRECCIÓN DE CORRESPONDENCIA

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Respetuosamente presentado,

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FIRMA: (Firmado)

No. DE REGISTRO: 31,392

FECHA: 3/3/00

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CORREO EXPRESO NO. EL487465258US

PATENTE

EN LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE AMÉRICA

Solicitantes: Steven G. Reed, Michael J. Lodes, Raodoh Mohamath y Heather Secrist

Presentado: Marzo 3, 2000

Para: COMPUESTOS PARA TERAPIA Y DIAGNÓSTICO DE CÁNCER DE PULMÓN Y MÉTODOS PARA SU USO

Expediente No. 210121475C3

Fecha: Marzo 3, 2000

Casilla de Solicitudes de Patentes

Comisario Asistente de Patentes

Washington D.C. 20231

DECLARACIÓN

Señor:

Y , Lawrence Teague, de conformidad con el Título 37 del C.F.R. Sección 1.821(f) por el presente declaro que, en mi leal saber y entender, el contenido del artículo titulado "Listado de Secuencias" *("Sequence Listing")* y la copia legible por computador contenida en un disquete son idénticas.

Además declaro que todas las afirmaciones hechas en la presente de mi propio conocimiento son verdaderas y que todas las declaraciones hechas sobre la información y creencia se toman por verdaderas y además que dichas afirmaciones fueron hechas bajo el conocimiento que hacer declaraciones falsas y similares intencionalmente se castiga con multa o prisión o ambos, bajo la Sección 1001 del Título 18 del Código de los Estados Unidos, y dichas declaraciones falsas intencionales pueden atentar contra la validez de la solicitud o de cualquier otorgamiento de patente que resulte de éste.

Fechado hoy día 3 de marzo del 2000.

(Firmado)

Lawrence Teague

Asistente Legal

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Comisario Asistente de Patentes

Washington D.C. 20231

CERTIFICADO DE CORREO EXPRESO

Comisario Asistente para Patentes:

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Por el presente certifico que los anexos listados abajo están siendo depositados en el Servicio Postal de los Estados Unidos como "CORREO EXPRESO Oficina Postal del Destinatario" servicio bajo 37 C.F.R. § 1.10, Etiqueta de Certificado de Envío No. EL487465258US en Marzo 3, 2000, dirigido al la Casilla de Solicitud de Patentes, Comisario Asistente para Patentes, Washington D.C. 20231.

Respetuosamente presentado,

Seed Intellectual Property Law Group PLLC

(Firmado)

Judith A. Breaks / Jeanette West / Susan Johnson

DJM:jabl

Anexos:

Postal

Formulario PTO/SB/05

Especificación, Reivindicaciones, Resumen (84 Páginas)

Copia Impresa de los Listados de Secuencias

Declaración re Listados de Secuencias

Disquete que contiene los Listados de Secuencias

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REIVINDICACIONES:

1. Un polipéptido aislado, CARACTERIZADO PORQUE comprende por lo menos una porción inmunogénica de una proteína tumoral de pulmón, o una variante de la misma, donde dicha proteína tumoral comprende una secuencia de aminoácidos codificada por una secuencia de polinucleótidos seleccionada del grupo formado por:

(a) las secuencias representadas en las SEQ ID Nº: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168, 170-182, 184, 189, 191-193, 196, 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303, 310-313, 315, 317, 320, 322, 324, 332-335, 345, 347, 356, 358, 361, 362, 366, 369, 371-378, 380-404, 406, 409-417, 419-423, 425, 427-429, 433-436, 438-441, 443, 446-451, 454, 455, 457-461, 476, 477, 479, 483, 488, 491, 492, 497, 498, 500, 510, 519, 527, 528, 543, 545, 547, 553, 556, 559, 561, 564, 565, 568, 569, 574-577, 579, 580, 584, 585, 587, 592, 595, 598, 603, 608, 610, 613, 621-623, 626, 642, 648 y 668;

(b) las secuencias que se hibridizan con una secuencia representada en cualquiera de las SEQ ID Nº: 2, 8, 15, 16, 22, 24, 30, 32-34, 36, 38, 40, 41, 46-49, 52, 54, 59, 60, 65-69, 79, 89, 90, 93, 99-101, 109-111, 116-119, 123-132, 138-142, 143, 148, 149, 156, 168, 170-182, 184, 189, 191-193, 196, 205, 207, 210-212, 214, 215, 218, 224-226, 228, 233, 234, 236, 238, 241, 242, 245, 246, 248, 250, 253, 254, 256, 259, 260, 262, 263, 266, 267, 270-273, 279, 282, 291, 293, 294, 298, 300, 302, 303, 310-313, 315, 317, 320, 322, 324, 332-335, 345, 347, 356, 358, 361, 362, 366, 369, 371-378, 380-404, 406, 409-417, 419-423, 425, 427-429, 433-436, 438-441, 443, 446-451, 454, 455, 457-461, 476, 477, 479, 483, 488, 491, 492, 497, 498, 500, 510, 519, 527, 528, 543, 545, 547, 553, 556, 559, 561, 564, 565, 568, 569, 574-577, 579, 580, 584, 585, 587, 592, 595, 598, 603, 608, 610, 613, 621-623, 626, 642, 648 y 668 bajo

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condiciones moderadamente astringentes; y

(c) complementos de las secuencias de (a) o (b).

2. El polipéptido aislado acorde con la cláusula 1, CARACTERIZADO PORQUE el polipéptido comprende una secuencia de aminoácidos codificada por una secuencia de polinucleótidos representada en cualquiera de las SEQ ID Nº: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379 y 386, o un complemento de cualquiera de las secuencias de polinucleótidos anteriores.

3. Un polinucleótido aislado, CARACTERIZADO PORQUE codifica por lo menos 15 residuos de aminoácidos de una proteína tumoral de pulmón, o una variante de la misma que difiera en una o varias substituciones, supresiones, adiciones y/o inserciones de manera tal que la capacidad de la variante para reaccionar con antisueros específicos de antígenos no disminuya substancialmente, donde la proteína tumoral comprenda una secuencia de aminoácidos codificada por un polinucleótido que comprende una de las secuencias representadas en cualquiera de las SEQ ID Nº: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379 y 386, o un complemento de cualquiera de las secuencias anteriores.

4. Un polinucleótido aislado, CARACTERIZADO PORQUE codifica una proteína tumoral de pulmón, o una variante de la misma, donde dicha proteína tumoral comprende una secuencia de aminoácidos codificada por un polinucleótido que comprende una secuencia representada en cualquiera de las SEQ ID Nº: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379 y 386, o un complemento de cualquiera de las secuencias anteriores.

5. Un polinucleótido aislado, CARACTERIZADO PORQUE comprende una secuencia representada en cualquiera de las SEQ ID Nº: 218-222, 224-226, 249, 250,

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253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379 y 386.

6. Un polinucleótido aislado, CARACTERIZADO PORQUE comprende una secuencia que se hibridiza con una secuencia representada en cualquiera de las SEQ ID Nº: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379 y 386 bajo condiciones moderadamente astringentes.

7. Un polinucleótido aislado, CARACTERIZADO PORQUE es complementario de un polinucleótido acorde con cualquiera de las cláusulas 3-6.

8. Un vector de expresión, CARACTERIZADO PORQUE comprende un polinucleótido acorde con cualquiera de las cláusulas 3-8.

9. Una célula huésped, CARACTERIZADA PORQUE fue transformada o transfectada con el vector de expresión acorde con la cláusula 8.

10. Un anticuerpo aislado, o un fragmento capaz de unirse a un antígeno del mismo, CARACTERIZADO PORQUE se une específicamente a una proteína tumoral de pulmón que comprende una secuencia de aminoácidos codificada por una secuencia de polinucleótidos representada en cualquiera de las SEQ ID Nº: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379 y 386, o un complemento de cualquiera de las secuencias de polinucleótidos anteriores.

11. Una proteína de fusión, CARACTERIZADA PORQUE comprende por lo menos un polipéptido acorde con la cláusula 1.

12. La proteína de fusión acorde con la cláusula 11, CARACTERIZADA PORQUE dicha proteína de fusión comprende un potenciador de la expresión que incrementa la expresión de la proteína de fusión en una célula huésped transfectada con un polinucleótido que codifica dicha proteína de fusión.

13. La proteína de fusión acorde con la cláusula 11, CARACTERIZADA PORQUE la

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proteína de fusión comprende un epitope de una célula ayudante T que no está presente en el polipéptido de la cláusula 1.

14. La proteína de fusión acorde con la cláusula 11, CARACTERIZADA PORQUE dicha proteína de fusión comprende una marca de afinidad.

15. Un polinucleótido aislado, CARACTERIZADO PORQUE codifica la proteína de fusión acorde con la cláusula 11.

16. Una composición farmacéutica, CARACTERIZADA PORQUE comprende un vehículo fisiológicamente aceptable y por lo menos un componente seleccionado del grupo formado por:

(a) un polipéptido acorde con la cláusula 1;

(b) un polinucleótido acorde con la cláusula 3;

(c) un anticuerpo acorde con la cláusula 10;

(d) una proteína de fusión acorde con la cláusula 11; y

(e) un polinucleótido acorde con la cláusula 15.

17. Una vacuna, CARACTERIZADA PORQUE comprende una sustancia inmunoestimulante y por lo menos un componente seleccionado del grupo formado por:

(a) un polipéptido acorde con la cláusula 1;

(b) un polinucleótido acorde con la cláusula 3;

(c) un anticuerpo acorde con la cláusula 10;

(d) una proteína de fusión acorde con la cláusula 11; y

(e) un polinucleótido acorde con la cláusula 15.

18. La vacuna acorde con la cláusula 17, CARACTERIZADA PORQUE la sustancia inmunoestimulante es un adyuvante.

19. Una vacuna acorde con cualquiera de las cláusulas 17-18, CARACTERIZADA PORQUE la sustancia inmunoestimulante induce una respuesta predominantemente de Tipo I.

20. Un método para inhibir el desarrollo de un tipo de cáncer en un paciente,

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CARACTERIZADO PORQUE comprende la administración a un paciente de una cantidad efectiva de una composición farmacéutica acorde con la cláusula 16.

21. Un método para inhibir el desarrollo de un tipo de cáncer en un paciente, CARACTERIZADO PORQUE comprende la administración a un paciente de una cantidad efectiva de la vacuna acorde con la cláusula 17.

22. Una composición farmacéutica, CARACTERIZADA PORQUE comprende una célula que presenta antígenos que exprese un polipéptido acorde con la cláusula 1, en combinación con un vehículo o excipiente aceptable para uso farmacéutico.

23. Una composición farmacéutica acorde con la cláusula 22, CARACTERIZADA PORQUE la célula que presenta antígenos es una célula dendrítica o un macrófago.

24. Una vacuna, CARACTERIZADA PORQUE comprende una célula que presenta antígenos que exprese un polipéptido que comprende por lo menos una porción inmunogénica de una proteína tumoral de pulmón, o una variante de la misma, donde dicha proteína tumoral comprende una secuencia de aminoácidos codificada por una secuencia de polinucleótidos seleccionada del grupo formado por:

(a) las secuencias representadas en las SEQ ID Nº: 217-389;

(b) secuencias que se hibridizan con una secuencia representada en cualquiera de las SEQ ID Nº: 217-389 bajo condiciones moderadamente astringentes; y

(c) los complementos de secuencias de (i) o (ii);

en combinación con una sustancia inmunoestimulante.

25. La vacuna acorde con la cláusula 24, CARACTERIZADA PORQUE la sustancia inmunoestimulante es un adyuvante.

26. La vacuna acorde con la cláusula 24, CARACTERIZADA PORQUE la sustancia inmunoestimulante induce una respuesta predominantemente de Tipo I.

27. La vacuna acorde con la cláusula 24, CARACTERIZADA PORQUE la célula que presenta antígenos es una célula dendrítica.

28. Un método para inhibir el desarrollo de un tipo de cáncer en un paciente,

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CARACTERIZADO PORQUE comprende la administración a dicho paciente de una cantidad efectiva de una célula que presenta antígenos que exprese un polipéptido que comprende por lo menos una porción inmunogénica de una proteína tumoral de pulmón, o una variante de la misma, donde dicha proteína tumoral comprende una secuencia de aminoácidos codificada por una secuencia de polinucleótidos seleccionada del grupo formado por:

(a) las secuencias representadas en las SEQ ID Nº: 217-389;

(b) secuencias que se hibridizan con una secuencia representada en cualquiera de las SEQ ID Nº: 217-389 bajo condiciones moderadamente astringentes; y

(c) los complementos de secuencias de (i) o (ii)codificados por un polinucleótido representado en cualquiera de las SEQ ID Nº: 217-389;

y de esa manera inhibir el desarrollo de un tipo de cáncer en el paciente.

29. El método acorde con la cláusula 28, CARACTERIZADO PORQUE la célula que presenta antígenos es una célula dendrítica.

30. El método acorde con cualquiera de las cláusulas 20, 21 y 28, CARACTERIZADO PORQUE el cáncer es cáncer de pulmón.

31. Un método para separar células tumorales de una muestra biológica, CARACTERIZADO PORQUE comprende poner una muestra biológica en contacto con células T que reaccionen específicamente con una proteína tumoral de pulmón, donde dicha proteína tumoral comprende una secuencia de aminoácidos codificada por una secuencia de polinucleótidos seleccionada del grupo formado por:

(i) los polinucleótidos representadas en cualquiera de las SEQ ID Nº: 217-389; y

(ii) los complementos de los polinucleótidos anteriores;

donde el paso del contacto se lleva a cabo bajo condiciones y por el tiempo necesarios como para permitir la separación de células que expresan el antígeno de la muestra.

32. El método acorde con la cláusula 31, CARACTERIZADO PORQUE la muestra biológica es sangre o una fracción de la misma.

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33. Un método para inhibir el desarrollo de un tipo de cáncer en un paciente, CARACTERIZADO PORQUE comprende la administración a un paciente de una muestra biológica tratada de acuerdo con el método de la cláusula 31.

34. Un método para estimular y/o expandir células T específicas para una proteína tumoral de pulmón, CARACTERIZADO PORQUE comprende poner células T en contacto con por lo menos un componente seleccionado del grupo formado por:

(a) polipéptidos que comprenden por lo menos una porción inmunogénica de una proteína tumoral de pulmón, o una variante de la misma, donde dicha proteína tumoral comprende una secuencia de aminoácidos codificada por una secuencia de polinucleótidos seleccionada del grupo formado por:

(i) las secuencias representadas en las SEQ ID Nº: 217-389;

(ii) secuencias que se hibridizan con una secuencia representada en cualquiera de las SEQ ID Nº: 217-389 bajo condiciones moderadamente astringentes; y

(iii) los complementos de las secuencias de (i) o (ii);

(b) polinucleótidos que codifica un polipéptido de (a); y

(c) células que presentan antígenos que expresen un polipéptido de (a);

bajo las condiciones y por el tiempo necesarios como para permitir la estimulación y/o expansión de las células T.

35. Una población aislada de células T, CARACTERIZADA PORQUE comprende células T preparadas de acuerdo con el método de la cláusula 34.

36. Un método para inhibir el desarrollo de un tipo de cáncer en un paciente, CARACTERIZADO PORQUE comprende la administración a un paciente de una cantidad efectiva de una población de células T acorde con la cláusula 35.

37. Un método para inhibir el desarrollo de un tipo de cáncer en un paciente, CARACTERIZADO PORQUE comprende los pasos de:

(a) incubar células T $CD4^+$ y/o CD8+ aisladas de un paciente con por lo menos un componente seleccionado del grupo formado por:

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(i) polipéptidos que comprenden por lo menos una porción inmunogénica de una proteína tumoral de pulmón, o una variante de la misma, donde dicha proteína tumoral comprende una secuencia de aminoácidos codificada por una secuencia de polinucleótidos seleccionada del grupo formado por:

(1) las secuencias representadas en las SEQ ID Nº: 217-389;

(2) secuencias que se hibridizan con una secuencia representada en cualquiera de las SEQ ID Nº: 217-389 bajo condiciones moderadamente astringentes; y

(3) los complementos de las secuencias de (1) o (2);

(ii) polinucleótidos que codifica un polipéptido de (i); y

(iii) células que presentan antígenos que expresen un polipéptido de (i);

de manera tal que proliferen las células T; y

(b) administrar al paciente una cantidad efectiva de las células T proliferadas,

y de esa manera inhibir el desarrollo de un tipo de cáncer en el paciente.

38. Un método para inhibir el desarrollo de un tipo de cáncer en un paciente, CARACTERIZADO PORQUE comprende los pasos de:

(a) incubar células T $CD4^+$ y/o CD8+ aisladas de un paciente con por lo menos un componente seleccionado del grupo formado por:

(i) polipéptidos que comprenden por lo menos una porción inmunogénica de una proteína tumoral de pulmón, o una variante de la misma, donde dicha proteína tumoral comprende una secuencia de aminoácidos codificada por una secuencia de polinucleótidos seleccionada del grupo formado por:

(1) las secuencias representadas en las SEQ ID Nº: 217-389;

(2) secuencias que se hibridizan con una secuencia representada en cualquiera de las SEQ ID Nº: 217-389 bajo condiciones moderadamente astringentes; y

(3) los complementos de las secuencias de (1) o (2);

(ii) polinucleótidos que codifica un polipéptido de (i); y

(iii) células que presentan antígenos que expresan un polipéptido de (i);

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de manera tal que proliferen las células T;

(b) clonar por lo menos una célula proliferada con el fin de obtener células T clonadas; y

(c) administrar al paciente una cantidad efectiva de las células T clonadas

y de esa manera inhibir el desarrollo de un tipo de cáncer en el paciente.

39. Un método para determinar la presencia o ausencia de un tipo de cáncer en un paciente, CARACTERIZADO PORQUE comprende los pasos de:

(a) poner una muestra biológica, obtenida de un paciente, en contacto con un agente de unión que se una a una proteína tumoral de pulmón, donde dicha proteína tumoral comprende una secuencia de aminoácidos codificada por una secuencia de polinucleótidos representada en cualquiera de las SEQ ID Nº: 217-389 o un complemento de cualquiera de las secuencias de polinucleótidos anteriores;

(b) detectar en la muestra la cantidad de polipéptido que se une al agente de unión; y

(c) comparar la cantidad de polipéptido con un valor de corte predeterminado, y a partir de allí determinar la presencia o ausencia de un tipo de cáncer en el paciente.

40. El método acorde con la cláusula 39, CARACTERIZADO PORQUE el agente de unión es un anticuerpo.

41. El método acorde con la cláusula 42, CARACTERIZADO PORQUE el anticuerpo es un anticuerpo monoclonal.

42. El método acorde con la cláusula 39, CARACTERIZADO PORQUE el cáncer es cáncer de pulmón.

43. Un método para monitorear el avance de un tipo de cáncer en un paciente, CARACTERIZADO PORQUE comprende los pasos de:

(a) poner una muestra biológica, obtenida de un paciente en un primer tiempo, en contacto con un agente de unión que se una a una proteína tumoral de pulmón, donde dicha proteína tumoral comprende una secuencia de aminoácidos codificada por

una secuencia de polinucleótidos representada en cualquiera de las SEQ ID Nº: 217-389 o un complemento de cualquiera de las secuencias de polinucleótidos anteriores;

(b) detectar en la muestra la cantidad de polipéptido que se une al agente de unión;

(c) repetir los pasos (a) y (b) usando una muestra biológica obtenida del paciente en un tiempo posterior; y

(d) comparar la cantidad de polipéptido detectada en el paso (c) con la cantidad detectada en el paso (b) y a partir de allí monitorear el avance del cáncer en el paciente.

44. El método acorde con la cláusula 43, CARACTERIZADO PORQUE el agente de unión es un anticuerpo.

45. El método acorde con la cláusula 44, CARACTERIZADO PORQUE anticuerpo es un anticuerpo monocional.

46. El método acorde con la cláusula 43, CARACTERIZADO PORQUE el cáncer es un cáncer de pulmón.

47. Un método para determinar la presencia o ausencia de un tipo de cáncer en un paciente, CARACTERIZADO PORQUE comprende los pasos de:

(a) poner una muestra biológica, obtenida de un paciente, en contacto con un oligonucleótido que se hibridice con un polinucleótido que codifica una proteína tumoral de pulmón, donde dicha proteína tumoral comprende una secuencia de aminoácidos codificada por una secuencia de polinucleótidos representada en cualquiera de las SEQ ID Nº: 217-389 o un complemento de cualquiera de las secuencias de polinucleótidos anteriores;

(b) detectar en la muestra la cantidad de polinucleótido que se hibridiza con el oligonucleótido; y

(c) comparar la cantidad de polinucleótido que se hibridiza con el oligonucleótido con un valor de corte predeterminado, y a partir de allí determinar la presencia o

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ausencia de un tipo de cáncer en el paciente.

48. El método acorde con la cláusula 47, CARACTERIZADO PORQUE la cantidad de polinucleótido que se hibridiza con el oligonucleótido se determina usando la reacción en cadena de la polimerasa.

49. El método acorde con la cláusula 47, CARACTERIZADO PORQUE la cantidad de polinucleótido que se hibridiza con el oligonucleótido se determina usando un ensayo de hibridización.

50. Un método para monitorear el avance de un tipo de cáncer en un paciente, CARACTERIZADO PORQUE comprende los pasos de:

(a) poner una muestra biológica, obtenida de un paciente, en contacto con un oligonucleótido que se hibridice con un polinucleótido que codifica una proteína tumoral de pulmón, donde dicha proteína tumoral comprende una secuencia de aminoácidos codificada por una secuencia de polinucleótidos representada en cualquiera de las SEQ ID Nº: 217-389 o un complemento de cualquiera de las secuencias de polinucleótidos anteriores;

(b) detectar en la muestra la cantidad de polinucleótido que se hibridiza con el oligonucleótido;

(c) repetir los pasos (a) y (b) usando una muestra biológica obtenida del paciente en un tiempo posterior; y

(d) comparar la cantidad de polinucleótido detectada en el paso (c) con la cantidad detectada en el paso (b) y a partir de allí monitorear el avance del cáncer en el paciente.

51. El método acorde con la cláusula 50, CARACTERIZADO PORQUE la cantidad de polinucleótido que se hibridiza con el oligonucleótido se determina usando la reacción en cadena de la polimerasa.

52. El método acorde con la cláusula 50, CARACTERIZADO PORQUE la cantidad de polinucleótido que se hibridiza con el oligonucleótido se determina usando un

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ensayo de hibridización.

53. Un kit de diagnóstico, CARACTERIZADO PORQUE comprende:

(a) uno o varios anticuerpos acordes con la cláusula 10; y

(b) un reactivo de detección que comprende un grupo informante.

54. El kit acorde con la cláusula 53, CARACTERIZADO PORQUE los anticuerpos son inmovilizados sobre un soporte sólido.

55. El kit acorde con la cláusula 53, CARACTERIZADO PORQUE el reactivo de detección comprende una antiinmunoglobulina, proteína G, proteína A o lectina.

56. El kit acorde con la cláusula 53, CARACTERIZADO PORQUE el grupo informante se selecciona del grupo formado por radioisótopos, grupos fluorescentes, grupos luminiscentes, enzimas, biotina y partículas colorantes.

57. Un oligonucleótido, CARACTERIZADO PORQUE comprende 10 a 40 nucleótidos contiguos que se hibridizan bajo condiciones moderadamente astringentes con un polinucleótido que codifica una proteína tumoral de pulmón, donde dicha proteína tumoral comprende una secuencia de aminoácidos codificada por una secuencia de polinucleótidos representada en cualquiera de las SEQ ID Nº: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379 y 386, o un complemento de cualquiera de los polinucleótidos anteriores.

58. El oligonucleótido acorde con la cláusula 57, CARACTERIZADO PORQUE el oligonucleótido comprende 10-40 nucleótidos contiguos representados en cualquiera de las SEQ ID Nº: 218-222, 224-226, 249, 250, 253, 256, 266, 276, 277, 282, 285, 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359, 361, 364, 369, 372, 373, 377, 379 y 386.

59. Un kit de diagnóstico, CARACTERIZADO PORQUE comprende:

(a) un oligonucleótido acorde con la cláusula 58; y

(b) un reactivo de diagnóstico para su uso en una reacción en cadena de la

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polimerasa o un ensayo de hibridización.

C MPUESTOS PARA LA TERAPIA Y EL DIAGNÓSTICO DE CÁNCER DE PULMÓN Y MÉTODOS DE USO DE LOS MISMOS

RESUMEN

Se describen composiciones y métodos para la terapia y el diagnóstico de cáncer, tal como cáncer de pulmón. Las composiciones pueden comprender una o varias proteínas tumorales de pulmón, porciones inmunogénicas de las mismas o polinucleótidos que codifican dichas porciones. Como alternativa, la composición terapéutica puede comprender una célula que presenta antígenos que exprese una proteína tumoral de pulmón o una célula T específica de las células que expresan dicha proteína. Dichas composiciones se pueden usar, por ejemplo, para la prevención y el tratamiento de enfermedades, tal como cáncer de pulmón. También e proveen métodos de diagnóstico basados en la detección de una proteína tumoral de pulmón, o del ARNm que codifica dicha proteína, en una muestra.