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(54) Title: COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF OVARIAN AND ENDOMETRIAL CANCER

(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, such as ovarian or endometrial cancer, are disclosed. Compositions may comprise one or more ovarian carcinoma proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses such an antigen, or a T cell that is specific for cells expressing such an antigen. Such compositions may be used, for example, for the prevention and treatment of diseases such as ovarian and endometrial cancer. Diagnostic methods based on detecting an ovarian carcinoma protein, or mRNA encoding such an antigen, in a sample are also provided.



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COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF OVARIAN AND ENDOMETRIAL CANCER

TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to therapy and diagnosis of
5 cancer, such as ovarian or endometrial cancer. The invention is more specifically
related to polypeptides comprising at least a portion of an ovarian carcinoma protein,
and to polynucleotides encoding such polypeptides. Such polypeptides and
polynucleotides may be used in vaccines and pharmaceutical compositions for
prevention and treatment of cancers such as ovarian and endometrial cancer, and for the
10 diagnosis and monitoring of such cancers.

BACKGROUND OF THE INVENTION

Ovarian cancer is a significant health problem for women in the United
States and throughout the world. Although advances have been made in detection and
therapy of this cancer, no vaccine or other universally successful method for prevention
15 or treatment is currently available. Management of the disease currently relies on a
combination of early diagnosis and aggressive treatment, which may include one or
more of a variety of treatments such as surgery, radiotherapy, chemotherapy and
hormone therapy. The course of treatment for a particular cancer is often selected
based on a variety of prognostic parameters, including an analysis of specific tumor
20 markers. However, the use of established markers often leads to a result that is difficult
to interpret, and high mortality continues to be observed in many cancer patients.

Immunotherapies have the potential to substantially improve cancer
treatment and survival. Such therapies may involve the generation or enhancement of
an immune response to an ovarian carcinoma protein. However, to date, relatively few
25 ovarian carcinoma proteins are known and the generation of an immune response
against such antigens has not been shown to be therapeutically beneficial.

Accordingly, there is a need in the art for improved methods for
detecting and treating cancers such as ovarian cancer. The present invention fulfills
these needs and further provides other related advantages.

SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compositions and methods for the diagnosis and therapy of cancer, such as ovarian and endometrial cancer. In one aspect, the present invention provides polypeptides comprising at least a portion of an ovarian carcinoma 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 NO:1-222; (b) variants of a sequence recited in SEQ ID NO:1-222 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 amino acid residues of an ovarian carcinoma 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 for prophylactic or therapeutic use 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 an ovarian carcinoma 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) 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
5 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.

10 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 patient may be afflicted with ovarian or endometrial cancer, in which case the methods provide treatment for the disease, or patient considered at risk for such a disease may be treated
15 prophylactically.

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 an ovarian carcinoma protein, wherein the step of contacting is performed under conditions and for a time sufficient to permit
20 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
25 and/or expanding T cells specific for an ovarian carcinoma 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
30 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 an ovarian carcinoma protein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expresses 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 ovarian or endometrial 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 an ovarian carcinoma 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 an ovarian carcinoma 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. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

BRIEF DESCRIPTION OF THE SEQUENCE IDENTIFIERS

SEQ ID NOs: 1-41 are identified in Example 1.

SEQ ID NO:42 is the determined cDNA sequence for clone R0198:A03
SEQ ID NO:43 is the determined cDNA sequence for clone R0198:A07
SEQ ID NO:44 is the determined cDNA sequence for clone R0198:A08
SEQ ID NO:45 is the determined cDNA sequence for clone R0198:A09
5 SEQ ID NO:46 is the determined cDNA sequence for clone R0198:B01
SEQ ID NO:47 is the determined cDNA sequence for clone R0198:B02
SEQ ID NO:48 is the determined cDNA sequence for clone R0198:B04
SEQ ID NO:49 is the determined cDNA sequence for clone R0198:B08
SEQ ID NO:50 is the determined cDNA sequence for clone R0198:B11
10 SEQ ID NO:51 is the determined cDNA sequence for clone R0198:C01
SEQ ID NO:52 is the determined cDNA sequence for clone R0198:C02
SEQ ID NO:53 is the determined cDNA sequence for clone R0198:C03
SEQ ID NO:54 is the determined cDNA sequence for clone R0198:C04
SEQ ID NO:55 is the determined cDNA sequence for clone R0198:C05
15 SEQ ID NO:56 is the determined cDNA sequence for clone R0198:C06
SEQ ID NO:57 is the determined cDNA sequence for clone R0198:C08
SEQ ID NO:58 is the determined cDNA sequence for clone R0198:C09
SEQ ID NO:59 is the determined cDNA sequence for clone R0198:C10
SEQ ID NO:60 is the determined cDNA sequence for clone R0198:C12
20 SEQ ID NO:61 is the determined cDNA sequence for clone R0198:D01
SEQ ID NO:62 is the determined cDNA sequence for clone R0198:D02
SEQ ID NO:63 is the determined cDNA sequence for clone R0198:D03
SEQ ID NO:64 is the determined cDNA sequence for clone R0198:D04
SEQ ID NO:65 is the determined cDNA sequence for clone R0198:D05
25 SEQ ID NO:66 is the determined cDNA sequence for clone R0198:D06
SEQ ID NO:67 is the determined cDNA sequence for clone R0198:D07
SEQ ID NO:68 is the determined cDNA sequence for clone R0198:D08
SEQ ID NO:69 is the determined cDNA sequence for clone R0198:D09
SEQ ID NO:70 is the determined cDNA sequence for clone R0198:D11
30 SEQ ID NO:71 is the determined cDNA sequence for clone R0198:E01
SEQ ID NO:72 is the determined cDNA sequence for clone R0198:E03
SEQ ID NO:73 is the determined cDNA sequence for clone R0198:E05

SEQ ID NO:74 is the determined cDNA sequence for clone R0198:E06
SEQ ID NO:75 is the determined cDNA sequence for clone R0198:E09
SEQ ID NO:76 is the determined cDNA sequence for clone R0198:E10
SEQ ID NO:77 is the determined cDNA sequence for clone R0198:E11
5 SEQ ID NO:78 is the determined cDNA sequence for clone R0198:E12
SEQ ID NO:79 is the determined cDNA sequence for clone R0198:F01
SEQ ID NO:80 is the determined cDNA sequence for clone R0198:F02
SEQ ID NO:81 is the determined cDNA sequence for clone R0198:F03
SEQ ID NO:82 is the determined cDNA sequence for clone R0198:F04
10 SEQ ID NO:83 is the determined cDNA sequence for clone R0198:F06
SEQ ID NO:84 is the determined cDNA sequence for clone R0198:F07
SEQ ID NO:85 is the determined cDNA sequence for clone R0198:F09
SEQ ID NO:86 is the determined cDNA sequence for clone R0198:F10
SEQ ID NO:87 is the determined cDNA sequence for clone R0198:F11
15 SEQ ID NO:88 is the determined cDNA sequence for clone R0198:F12
SEQ ID NO:89 is the determined cDNA sequence for clone R0198:G01
SEQ ID NO:90 is the determined cDNA sequence for clone R0198:G02
SEQ ID NO:91 is the determined cDNA sequence for clone R0198:G03
SEQ ID NO:92 is the determined cDNA sequence for clone R0198:G04
20 SEQ ID NO:93 is the determined cDNA sequence for clone R0198:G05
SEQ ID NO:94 is the determined cDNA sequence for clone R0198:G06
SEQ ID NO:95 is the determined cDNA sequence for clone R0198:G09
SEQ ID NO:96 is the determined cDNA sequence for clone R0198:G11
SEQ ID NO:97 is the determined cDNA sequence for clone R0198:G12
25 SEQ ID NO:98 is the determined cDNA sequence for clone R0198:H01
SEQ ID NO:99 is the determined cDNA sequence for clone R0198:H03
SEQ ID NO:100 is the determined cDNA sequence for clone R0198:H04
SEQ ID NO:101 is the determined cDNA sequence for clone R0198:H06
SEQ ID NO:102 is the determined cDNA sequence for clone R0198:H09
30 SEQ ID NO:103 is the determined cDNA sequence for clone R0198:H10
SEQ ID NO:104 is the determined cDNA sequence for clone R0199:A03
SEQ ID NO:105 is the determined cDNA sequence for clone R0199:A05

SEQ ID NO:106 is the determined cDNA sequence for clone R0199:A06
SEQ ID NO:107 is the determined cDNA sequence for clone R0199:A07
SEQ ID NO:108 is the determined cDNA sequence for clone R0199:A08
SEQ ID NO:109 is the determined cDNA sequence for clone R0199:A11
5 SEQ ID NO:110 is the determined cDNA sequence for clone R0199:B01
SEQ ID NO:111 is the determined cDNA sequence for clone R0199:B03
SEQ ID NO:112 is the determined cDNA sequence for clone R0199:B06
SEQ ID NO:113 is the determined cDNA sequence for clone R0199:B07
SEQ ID NO:114 is the determined cDNA sequence for clone R0199:B08
10 SEQ ID NO:115 is the determined cDNA sequence for clone R0199:B09
SEQ ID NO:116 is the determined cDNA sequence for clone R0199:B11
SEQ ID NO:117 is the determined cDNA sequence for clone R0199:C01
SEQ ID NO:118 is the determined cDNA sequence for clone R0199:C02
SEQ ID NO:119 is the determined cDNA sequence for clone R0199:C06
15 SEQ ID NO:120 is the determined cDNA sequence for clone R0199:C07
SEQ ID NO:121 is the determined cDNA sequence for clone R0199:C08
SEQ ID NO:122 is the determined cDNA sequence for clone R0199:C09
SEQ ID NO:123 is the determined cDNA sequence for clone R0199:C10
SEQ ID NO:124 is the determined cDNA sequence for clone R0199:C11
20 SEQ ID NO:125 is the determined cDNA sequence for clone R0199:C12
SEQ ID NO:126 is the determined cDNA sequence for clone R0199:D01
SEQ ID NO:127 is the determined cDNA sequence for clone R0199:D02
SEQ ID NO:128 is the determined cDNA sequence for clone R0199:D04
SEQ ID NO:129 is the determined cDNA sequence for clone R0199:D06
25 SEQ ID NO:130 is the determined cDNA sequence for clone R0199:D07
SEQ ID NO:131 is the determined cDNA sequence for clone R0199:D08
SEQ ID NO:132 is the determined cDNA sequence for clone R0199:D11
SEQ ID NO:133 is the determined cDNA sequence for clone R0199:E02
SEQ ID NO:134 is the determined cDNA sequence for clone R0199:E03
30 SEQ ID NO:135 is the determined cDNA sequence for clone R0199:E05
SEQ ID NO:136 is the determined cDNA sequence for clone R0199:E06
SEQ ID NO:137 is the determined cDNA sequence for clone R0199:E-8

SEQ ID NO:138 is the determined cDNA sequence for clone R0199:E09
SEQ ID NO:139 is the determined cDNA sequence for clone R0199:E10
SEQ ID NO:140 is the determined cDNA sequence for clone R0199:E12
SEQ ID NO:141 is the determined cDNA sequence for clone R0199:F01
5 SEQ ID NO:142 is the determined cDNA sequence for clone R0199:F03
SEQ ID NO:143 is the determined cDNA sequence for clone R0199:F04
SEQ ID NO:144 is the determined cDNA sequence for clone R0199:F06
SEQ ID NO:145 is the determined cDNA sequence for clone R0199:F09
SEQ ID NO:146 is the determined cDNA sequence for clone R0199:F10
10 SEQ ID NO:147 is the determined cDNA sequence for clone R0199:G01
SEQ ID NO:148 is the determined cDNA sequence for clone R0199:G05
SEQ ID NO:149 is the determined cDNA sequence for clone R0199:G06
SEQ ID NO:150 is the determined cDNA sequence for clone R0199:G08
SEQ ID NO:151 is the determined cDNA sequence for clone R0199:G11
15 SEQ ID NO:152 is the determined cDNA sequence for clone R0199:G12
SEQ ID NO:153 is the determined cDNA sequence for clone R0199:H02
SEQ ID NO:154 is the determined cDNA sequence for clone R0199:H03
SEQ ID NO:155 is the determined cDNA sequence for clone R0200:A05
SEQ ID NO:156 is the determined cDNA sequence for clone R0200:A06
20 SEQ ID NO:157 is the determined cDNA sequence for clone R0200:A10
SEQ ID NO:158 is the determined cDNA sequence for clone R0200:A12
SEQ ID NO:159 is the determined cDNA sequence for clone R0200:B03
SEQ ID NO:160 is the determined cDNA sequence for clone R0200:B04
SEQ ID NO:161 is the determined cDNA sequence for clone R0200:B07
25 SEQ ID NO:162 is the determined cDNA sequence for clone R0200:B08
SEQ ID NO:163 is the determined cDNA sequence for clone R0200:B12
SEQ ID NO:164 is the determined cDNA sequence for clone R0200:C02
SEQ ID NO:165 is the determined cDNA sequence for clone R0200:C07
SEQ ID NO:166 is the determined cDNA sequence for clone R0200:C09
30 SEQ ID NO:167 is the determined cDNA sequence for clone R0200:C10
SEQ ID NO:168 is the determined cDNA sequence for clone R0200:D01
SEQ ID NO:169 is the determined cDNA sequence for clone R0200:D03

SEQ ID NO:170 is the determined cDNA sequence for clone R0200:D05
SEQ ID NO:171 is the determined cDNA sequence for clone R0200:D06
SEQ ID NO:172 is the determined cDNA sequence for clone R0200:D07
SEQ ID NO:173 is the determined cDNA sequence for clone R0200:D08
5 SEQ ID NO:174 is the determined cDNA sequence for clone R0200:D09
SEQ ID NO:175 is the determined cDNA sequence for clone R0200:D11
SEQ ID NO:176 is the determined cDNA sequence for clone R0200:D12
SEQ ID NO:177 is the determined cDNA sequence for clone R0200:E03
SEQ ID NO:178 is the determined cDNA sequence for clone R0200:E04
10 SEQ ID NO:179 is the determined cDNA sequence for clone R0200:E06
SEQ ID NO:180 is the determined cDNA sequence for clone R0200:E07
SEQ ID NO:181 is the determined cDNA sequence for clone R0200:E08
SEQ ID NO:182 is the determined cDNA sequence for clone R0200:E09
SEQ ID NO:183 is the determined cDNA sequence for clone R0200:E12
15 SEQ ID NO:184 is the determined cDNA sequence for clone R0200:F01
SEQ ID NO:185 is the determined cDNA sequence for clone R0200:F04
SEQ ID NO:186 is the determined cDNA sequence for clone R0200:F05
SEQ ID NO:187 is the determined cDNA sequence for clone R0200:F07
SEQ ID NO:188 is the determined cDNA sequence for clone R0200:F08
20 SEQ ID NO:189 is the determined cDNA sequence for clone R0200:F09
SEQ ID NO:190 is the determined cDNA sequence for clone R0200:F10
SEQ ID NO:191 is the determined cDNA sequence for clone R0200:F11
SEQ ID NO:192 is the determined cDNA sequence for clone R0200:F12
SEQ ID NO:193 is the determined cDNA sequence for clone R0200:G02
25 SEQ ID NO:194 is the determined cDNA sequence for clone R0200:G07
SEQ ID NO:195 is the determined cDNA sequence for clone R0200:G08
SEQ ID NO:196 is the determined cDNA sequence for clone R0200:G09
SEQ ID NO:197 is the determined cDNA sequence for clone R0200:G10
SEQ ID NO:198 is the determined cDNA sequence for clone R0200:G12
30 SEQ ID NO:199 is the determined cDNA sequence for clone R0200:H03
SEQ ID NO:200 is the determined cDNA sequence for clone R0200:H05
SEQ ID NO:201 is the determined cDNA sequence for clone R0200:H07

- SEQ ID NO:202 is the determined cDNA sequence for clone R0200:H09
SEQ ID NO:203 is the determined cDNA sequence for clone R0200:H11
SEQ ID NO:204 is the determined cDNA sequence for clone 57877.2
SEQ ID NO:205 is the determined cDNA sequence for clone 57879.3
5 SEQ ID NO:206 is the determined cDNA sequence for clone 57881.2
SEQ ID NO:207 is the determined cDNA sequence for clone 57882.1
SEQ ID NO:208 is the determined cDNA sequence for clone 57884.2
SEQ ID NO:209 is the determined cDNA sequence for clone 57888.2
SEQ ID NO:210 is an extended cDNA sequence for clone RO198 C12
10 (SEQ ID NO: 60), also referred to as O593S
SEQ ID NO:211 is an extended cDNA sequence for clone RO198 F2
(SEQ ID NO: 80), also referred to as O594S
SEQ ID NO:212 is an extended cDNA sequence for clone RO199 A7
(SEQ ID NO: 107), also referred to as O595S
15 SEQ ID NO:213 is an extended cDNA sequence for clone RO199 C12
(SEQ ID NO: 125), also referred to as O596S
SEQ ID NO:214 is a full length cDNA sequence for HSPCO67, a
sequence having homology with O596S
SEQ ID NO:215 is an extended cDNA sequence for clone RO200 A10
20 (SEQ ID NO: 157), also referred to as O597S
SEQ ID NO:216 is an extended cDNA sequence for clone RO200 A12
(SEQ ID NO: 158), also referred to as O598S
SEQ ID NO:217 is a full length cDNA sequence for monocarboxylate
transporter (MCT3), a sequence having homology with O598S
25 SEQ ID NO:218 is an extended cDNA sequence for clone RO200 E10
(57881.2; SEQ ID NO: 206), also referred to as O599S
SEQ ID NO:219 is an extended cDNA sequence for clone RO200 G2
(SEQ ID NO: 193), also referred to as O600S
SEQ ID NO:220 is an extended cDNA sequence for clone RO200 B4
30 (57882.1; SEQ ID NO: 207), also referred to as O601S
SEQ ID NO:221 is a full length cDNA sequence for lysophospholipase I
(LYPLA1), a sequence having homology with O601S

SEQ ID NO:222 is an extended cDNA sequence for clone RO201 D1 (57884.2; SEQ ID NO: 208), also referred to as O602S

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for using the compositions, for example in the therapy and diagnosis of cancer, such as ovarian and endometrial cancer. Certain illustrative compositions described herein include ovarian tumor polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (*e.g.*, T cells). An "ovarian tumor protein," as the term is used herein, refers generally to a protein that is expressed in ovarian 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 ovarian 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 ovarian cancer.

Therefore, in accordance with the above, and as described further below, the present invention provides illustrative polynucleotide compositions having sequences set forth in SEQ ID NO:1-222, antibody compositions capable of binding polypeptides encoded by the polynucleotides, and numerous additional embodiments employing such compositions, for example in the detection, diagnosis and/or therapy of human ovarian cancer.

POLYNUCLEOTIDE COMPOSITIONS

As used herein, the terms "DNA segment" and "polynucleotide" refer to a DNA molecule that has been isolated free of total genomic DNA of a particular species. Therefore, a DNA segment encoding a polypeptide refers to a DNA segment that contains one or more coding sequences yet is substantially isolated away from, or purified free from, total genomic DNA of the species from which the DNA segment is obtained. Included within the terms "DNA segment" and "polynucleotide" are DNA segments and smaller fragments of such segments, and also recombinant vectors, including, for example, plasmids, cosmids, phagemids, phage, viruses, and the like.

As will be understood by those skilled in the art, the DNA segments of this invention can include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may be naturally
5 isolated, or modified synthetically by the hand of man.

"Isolated," as used herein, means that a polynucleotide is substantially away from other coding sequences, and that the DNA segment does not contain large portions of unrelated coding DNA, such as large chromosomal fragments or other functional genes or polypeptide coding regions. Of course, this refers to the DNA
10 segment as originally isolated, and does not exclude genes or coding regions later added to the segment by the hand of man.

As will be recognized by the skilled artisan, 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,
15 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.

20 Polynucleotides may comprise a native sequence (*i.e.*, an endogenous sequence that encodes an ovarian tumor protein or a portion thereof) or may comprise a variant, or a biological or antigenic functional equivalent of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions, as further described below, preferably such that the immunogenicity
25 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. The term "variants" also encompasses homologous genes of xenogenic origin.

When comparing polynucleotide or polypeptide sequences, two
30 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
5 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
10 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 Phylogenies pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989)
15 *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.

20 Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these
25 algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0
30 algorithms, which are described in Altschul *et al.* (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul *et al.* (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent

sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. In one illustrative example, cumulative scores can be calculated using, for nucleotide sequences, the parameters M (reward score for a pair of
5 matching residues; always >0) and N (penalty score for mismatching residues; always <0). For amino acid sequences, a scoring matrix can be used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or
10 more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments,
15 (B) of 50, expectation (E) of 10, M=5, N=-4 and a comparison of both strands.

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
20 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
25 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.

Therefore, the present invention encompasses polynucleotide and polypeptide sequences having substantial identity to the sequences disclosed herein, for example those comprising at least 50% sequence identity, preferably at least 55%, 60%,
30 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher, sequence identity compared to a polynucleotide or polypeptide sequence of this invention using the methods described herein, (*e.g.*, BLAST analysis using standard parameters, as

described below). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like.

5 In additional embodiments, the present invention provides isolated polynucleotides and polypeptides comprising various lengths of contiguous stretches of sequence identical to or complementary to one or more of the sequences disclosed herein. For example, polynucleotides are provided by this invention that comprise at least about 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more
10 contiguous nucleotides of one or more of the sequences disclosed herein as well as all intermediate lengths there between. It will be readily understood that "intermediate lengths", in this context, means any length between the quoted values, such as 16, 17, 18, 19, *etc.*; 21, 22, 23, *etc.*; 30, 31, 32, *etc.*; 50, 51, 52, 53, *etc.*; 100, 101, 102, 103, *etc.*; 150, 151, 152, 153, *etc.*; including all integers through 200-500; 500-1,000, and the
15 like.

The polynucleotides of the present invention, or fragments thereof, regardless of the length of the coding sequence itself, may be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their
20 overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant DNA protocol. For example, illustrative DNA segments with total lengths of about 10,000, about 5000, about 3000, about 2,000, about 1,000, about 500, about 200, about 100, about 50 base
25 pairs in length, and the like, (including all intermediate lengths) are contemplated to be useful in many implementations of this invention.

In other embodiments, the present invention is directed to polynucleotides that are capable of hybridizing under moderately stringent conditions to a polynucleotide sequence provided herein, or a fragment thereof, or a complementary
30 sequence thereof. Hybridization techniques are well known in the art of molecular biology. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide of this invention with other

polynucleotides 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.

5 Moreover, 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
10 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
15 identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

PROBES AND PRIMERS

In other embodiments of the present invention, the polynucleotide sequences provided herein can be advantageously used as probes or primers for nucleic
20 acid hybridization. As such, it is contemplated that nucleic acid segments that comprise a sequence region of at least about 15 nucleotide long contiguous sequence that has the same sequence as, or is complementary to, a 15 nucleotide long contiguous sequence disclosed herein will find particular utility. Longer contiguous identical or complementary sequences, *e.g.*, those of about 20, 30, 40, 50, 100, 200, 500, 1000
25 (including all intermediate lengths) and even up to full length sequences will also be of use in certain embodiments.

The ability of such nucleic acid probes to specifically hybridize to a sequence of interest will enable them to be of use in detecting the presence of complementary sequences in a given sample. However, other uses are also envisioned,
30 such as the use of the sequence information for the preparation of mutant species primers, or primers for use in preparing other genetic constructions.

Polynucleotide molecules having sequence regions consisting of contiguous nucleotide stretches of 10-14, 15-20, 30, 50, or even of 100-200 nucleotides or so (including intermediate lengths as well), identical or complementary to a polynucleotide sequence disclosed herein, are particularly contemplated as hybridization probes for use in, *e.g.*, Southern and Northern blotting. This would allow a gene product, or fragment thereof, to be analyzed, both in diverse cell types and also in various bacterial cells. The total size of fragment, as well as the size of the complementary stretch(es), will ultimately depend on the intended use or application of the particular nucleic acid segment. Smaller fragments will generally find use in hybridization embodiments, wherein the length of the contiguous complementary region may be varied, such as between about 15 and about 100 nucleotides, but larger contiguous complementarity stretches may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 15-25 nucleotides in length allows the formation of a duplex molecule that is both stable and selective. Molecules having contiguous complementary sequences over stretches greater than 15 bases in length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained. One will generally prefer to design nucleic acid molecules having gene-complementary stretches of 15 to 25 contiguous nucleotides, or even longer where desired.

Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequence set forth in SEQ ID NO:1-222, or to any continuous portion of the sequence, from about 15-25 nucleotides in length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various factors. For example, one may wish to employ primers from towards the termini of the total sequence.

Small polynucleotide segments or fragments may be readily prepared by, for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCRTM

technology of U. S. Patent 4,683,202 (incorporated herein by reference), by introducing selected sequences into recombinant vectors for recombinant production, and by other recombinant DNA techniques generally known to those of skill in the art of molecular biology.

5 The nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of the entire gene or gene fragments of interest. Depending on the application envisioned, one will typically desire to employ varying conditions of hybridization to achieve varying degrees of selectivity of probe towards target sequence. For applications requiring high
10 selectivity, one will typically desire to employ relatively stringent conditions to form the hybrids, *e.g.*, one will select relatively low salt and/or high temperature conditions, such as provided by a salt concentration of from about 0.02 M to about 0.15 M salt at temperatures of from about 50°C to about 70°C. Such selective conditions tolerate little, if any, mismatch between the probe and the template or target strand, and would
15 be particularly suitable for isolating related sequences.

Of course, for some applications, for example, where one desires to prepare mutants employing a mutant primer strand hybridized to an underlying template, less stringent (reduced stringency) hybridization conditions will typically be needed in order to allow formation of the heteroduplex. In these circumstances, one
20 may desire to employ salt conditions such as those of from about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hybridizations. In any case, it is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide, which serves to
25 destabilize the hybrid duplex in the same manner as increased temperature. Thus, hybridization conditions can be readily manipulated, and thus will generally be a method of choice depending on the desired results.

POLYNUCLEOTIDE IDENTIFICATION AND CHARACTERIZATION

Polynucleotides may be identified, prepared and/or manipulated using
30 any of a variety of well established 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 two fold greater in a tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed, for example, 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, polynucleotides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as ovarian 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 of a polynucleotide of the present invention may be used to isolate a full length gene from a suitable library (*e.g.*, an ovarian 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 ³²P) using well known techniques. A bacterial or bacteriophage library is then generally 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 can then be 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. Full length DNA sequences may also be obtained by analysis of genomic fragments.

POLYNUCLEOTIDE EXPRESSION IN HOST CELLS

In other embodiments of the invention, polynucleotide sequences or fragments thereof which encode polypeptides of the invention, or fusion proteins or functional equivalents thereof, may be used in recombinant DNA molecules to direct
5 expression of a polypeptide in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and these sequences may be used to clone and express a given polypeptide.

As will be understood by those of skill in the art, it may be advantageous
10 in some instances to produce polypeptide-encoding nucleotide sequences possessing non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce a recombinant RNA transcript having desirable properties, such as a half-life which is longer than that of a transcript generated from the naturally occurring
15 sequence.

Moreover, the polynucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter polypeptide encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the gene product. For
20 example, DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. In addition, site-directed mutagenesis may be used to insert new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, or introduce mutations, and so forth.

25 In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence to encode a fusion protein. For example, to screen peptide libraries for inhibitors of polypeptide activity, it may be useful to encode a chimeric protein that can be recognized by a commercially available antibody. A fusion protein may also be
30 engineered to contain a cleavage site located between the polypeptide-encoding sequence and the heterologous protein sequence, so that the polypeptide may be cleaved and purified away from the heterologous moiety.

Sequences encoding a desired polypeptide may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M. H. *et al.* (1980) *Nucl. Acids Res. Symp. Ser.* 215-223, Horn, T. *et al.* (1980) *Nucl. Acids Res. Symp. Ser.* 225-232). Alternatively, the protein itself may be produced using chemical
5 methods to synthesize the amino acid sequence of a polypeptide, or a portion thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J. Y. *et al.* (1995) *Science* 269:202-204) and automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer, Palo Alto, CA).

10 A newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (*e.g.*, Creighton, T. (1983) *Proteins, Structures and Molecular Principles*, WH Freeman and Co., New York, N.Y.) or other comparable techniques available in the art. The composition of the synthetic peptides may be confirmed by amino acid analysis or sequencing (*e.g.*, the Edman
15 degradation procedure). Additionally, the amino acid sequence of a polypeptide, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

In order to express a desired polypeptide, the nucleotide sequences
20 encoding the polypeptide, or functional equivalents, may be inserted into appropriate expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding a polypeptide of interest and appropriate transcriptional and
25 translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. Such techniques are described in Sambrook, J. *et al.* (1989) *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Press, Plainview, N.Y., and Ausubel, F. M. *et al.* (1989) *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, N.Y.

30 A variety of expression vector/host systems may be utilized to contain and express polynucleotide sequences. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid,

or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (*e.g.*, baculovirus); plant cell systems transformed with virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (*e.g.*, Ti or pBR322 plasmids); or animal cell systems.

The "control elements" or "regulatory sequences" present in an expression vector are those non-translated regions of the vector--enhancers, promoters, 5' and 3' untranslated regions--which interact with host cellular proteins to carry out transcription and translation. Such elements may vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, may be used. For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the PBLUESCRIPT phagemid (Stratagene, La Jolla, Calif.) or PSFORT1 plasmid (Gibco BRL, Gaithersburg, MD) and the like may be used. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are generally preferred. If it is necessary to generate a cell line that contains multiple copies of the sequence encoding a polypeptide, vectors based on SV40 or EBV may be advantageously used with an appropriate selectable marker.

In bacterial systems, a number of expression vectors may be selected depending upon the use intended for the expressed polypeptide. For example, when large quantities are needed, for example for the induction of antibodies, vectors which direct high level expression of fusion proteins that are readily purified may be used. Such vectors include, but are not limited to, the multifunctional *E. coli* cloning and expression vectors such as BLUESCRIPT (Stratagene), in which the sequence encoding the polypeptide of interest may be ligated into the vector in frame with sequences for the amino-terminal Met and the subsequent 7 residues of β -galactosidase so that a hybrid protein is produced; pIN vectors (Van Heeke, G. and S. M. Schuster (1989) *J. Biol. Chem.* 264:5503-5509); and the like. pGEX Vectors (Promega, Madison, Wis.) may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. Proteins made in such systems may be designed to

include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

In the yeast, *Saccharomyces cerevisiae*, a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH may be used. For reviews, see Ausubel *et al.* (supra) and Grant *et al.* (1987) *Methods Enzymol.* 153:516-544.

In cases where plant expression vectors are used, the expression of sequences encoding polypeptides may be driven by any of a number of promoters. For example, viral promoters such as the 35S and 19S promoters of CaMV may be used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J.* 6:307-311. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used (Coruzzi, G. *et al.* (1984) *EMBO J.* 3:1671-1680; Broglie, R. *et al.* (1984) *Science* 224:838-843; and Winter, J. *et al.* (1991) *Results Probl. Cell Differ.* 17:85-105). These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. Such techniques are described in a number of generally available reviews (see, for example, Hobbs, S. or Murry, L. E. in McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York, N.Y.; pp. 191-196).

An insect system may also be used to express a polypeptide of interest. For example, in one such system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in *Spodoptera frugiperda* cells or in *Trichoplusia* larvae. The sequences encoding the polypeptide may be cloned into a non-essential region of the virus, such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of the polypeptide-encoding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein. The recombinant viruses may then be used to infect, for example, *S. frugiperda* cells or *Trichoplusia* larvae in which the polypeptide of interest may be expressed (Engelhard, E. K. *et al.* (1994) *Proc. Natl. Acad. Sci.* 91 :3224-3227).

In mammalian host cells, a number of viral-based expression systems are generally available. For example, in cases where an adenovirus is used as an expression vector, sequences encoding a polypeptide of interest may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader

sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain a viable virus which is capable of expressing the polypeptide in infected host cells (Logan, J. and Shenk, T. (1984) *Proc. Natl. Acad. Sci.* 81:3655-3659). In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used
5 to increase expression in mammalian host cells.

Specific initiation signals may also be used to achieve more efficient translation of sequences encoding a polypeptide of interest. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding the polypeptide, its initiation codon, and upstream sequences are inserted into the
10 appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous translational control signals including the ATG initiation codon should be provided. Furthermore, the initiation codon should be in the correct reading frame to ensure translation of the entire insert. Exogenous translational
15 elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used, such as those described in the literature (Scharf, D. *et al.* (1994) *Results Probl. Cell Differ.* 20:125-162).

In addition, a host cell strain may be chosen for its ability to modulate
20 the expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to facilitate correct insertion, folding and/or function. Different host cells such as
25 CHO, HeLa, MDCK, HEK293, and WI38, which have specific cellular machinery and characteristic mechanisms for such post-translational activities, may be chosen to ensure the correct modification and processing of the foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is generally preferred. For example, cell lines which stably express a
30 polynucleotide of interest may be transformed using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction

of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed
5 cells may be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler, M. *et al.* (1977) *Cell* 11:223-32) and adenine phosphoribosyltransferase (Lowy, I. *et al.* (1990) *Cell* 22:817-23) genes which can be employed in tk.sup.- or
10 apt.sup.- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler, M. *et al.* (1980) *Proc. Natl. Acad. Sci.* 77:3567-70); npt, which confers resistance to the aminoglycosides, neomycin and G-418 (Colbere-Garapin, F. *et al.* (1981) *J. Mol. Biol.* 150:1-14); and als or pat, which confer resistance to
15 chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, *supra*). Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine (Hartman, S. C. and R. C. Mulligan (1988) *Proc. Natl. Acad. Sci.* 85:8047-51). Recently, the use of visible markers has gained popularity with such
20 markers as anthocyanins, beta-glucuronidase and its substrate GUS, and luciferase and its substrate luciferin, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system (Rhodes, C. A. *et al.* (1995) *Methods Mol. Biol.* 55:121-131).

Although the presence/absence of marker gene expression suggests that
25 the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the sequence encoding a polypeptide is inserted within a marker gene sequence, recombinant cells containing sequences can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a polypeptide-encoding sequence under the control of a single promoter.
30 Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

Alternatively, host cells which contain and express a desired polynucleotide sequence may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations and protein bioassay or immunoassay techniques which include
5 membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein.

A variety of protocols for detecting and measuring the expression of polynucleotide-encoded products, using either polyclonal or monoclonal antibodies specific for the product are known in the art. Examples include enzyme-linked
10 immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on a given polypeptide may be preferred for some applications, but a competitive binding assay may also be employed. These and other assays are described, among other places, in Hampton, R. *et al.* (1990;
15 Serological Methods, a Laboratory Manual, APS Press, St Paul, Minn.) and Maddox, D. E. *et al.* (1983; *J. Exp. Med.* 158:1211-1216).

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to
20 polynucleotides include oligolabeling, nick translation, end-labeling or PCR amplification using a labeled nucleotide. Alternatively, the sequences, or any portions thereof may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6
25 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits. Suitable reporter molecules or labels, which may be used include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with a polynucleotide sequence of interest may be
30 cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a recombinant cell may be secreted or contained intracellularly depending on the sequence and/or the vector used. As will be understood

by those of skill in the art, expression vectors containing polynucleotides of the invention may be designed to contain signal sequences which direct secretion of the encoded polypeptide through a prokaryotic or eukaryotic cell membrane. Other recombinant constructions may be used to join sequences encoding a polypeptide of interest to nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). The inclusion of cleavable linker sequences such as those specific for Factor XA or enterokinase (Invitrogen, San Diego, Calif.) between the purification domain and the encoded polypeptide may be used to facilitate purification. One such expression vector provides for expression of a fusion protein containing a polypeptide of interest and a nucleic acid encoding 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues facilitate purification on IMIAC (immobilized metal ion affinity chromatography) as described in Porath, J. *et al.* (1992, *Prot. Exp. Purif.* 3:263-281) while the enterokinase cleavage site provides a means for purifying the desired polypeptide from the fusion protein. A discussion of vectors which contain fusion proteins is provided in Kroll, D. J. *et al.* (1993; *DNA Cell Biol.* 12:441-453).

In addition to recombinant production methods, polypeptides of the invention, and fragments thereof, may be produced by direct peptide synthesis using solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc.* 85:2149-2154). Protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Alternatively, various fragments may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.

SITE-SPECIFIC MUTAGENESIS

Site-specific mutagenesis is a technique useful in the preparation of individual peptides, or biologically functional equivalent polypeptides, through specific

mutagenesis of the underlying polynucleotides that encode them. The technique, well-known to those of skill in the art, further provides a ready ability to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more nucleotide sequence changes into the DNA.

- 5 Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Mutations may be employed in a selected
- 10 polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

In certain embodiments of the present invention, the inventors contemplate the mutagenesis of the disclosed polynucleotide sequences to alter one or

15 more properties of the encoded polypeptide, such as the antigenicity of a polypeptide vaccine. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA molecule. In such embodiments, a primer comprising typically about 14 to about 25 nucleotides or so

20 in length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis

25 include vectors such as the M13 phage. These phage are readily commercially-available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

In general, site-directed mutagenesis in accordance herewith is

30 performed by first obtaining a single-stranded vector or melting apart of two strands of a double-stranded vector that includes within its sequence a DNA sequence that encodes the desired peptide. An oligonucleotide primer bearing the desired mutated

sequence is prepared, generally synthetically. This primer is then annealed with the single-stranded vector, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original
5 non-mutated sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected which include recombinant vectors bearing the mutated sequence arrangement.

The preparation of sequence variants of the selected peptide-encoding
10 DNA segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence
15 variants. Specific details regarding these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kuby, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.

As used herein, the term "oligonucleotide directed mutagenesis procedure" refers to template-dependent processes and vector-mediated propagation
20 which result in an increase in the concentration of a specific nucleic acid molecule relative to its initial concentration, or in an increase in the concentration of a detectable signal, such as amplification. As used herein, the term "oligonucleotide directed mutagenesis procedure" is intended to refer to a process that involves the template-dependent extension of a primer molecule. The term template dependent
25 process refers to nucleic acid synthesis of an RNA or a DNA molecule wherein the sequence of the newly synthesized strand of nucleic acid is dictated by the well-known rules of complementary base pairing (see, for example, Watson, 1987). Typically, vector mediated methodologies involve the introduction of the nucleic acid fragment into a DNA or RNA vector, the clonal amplification of the vector, and the recovery of
30 the amplified nucleic acid fragment. Examples of such methodologies are provided by U. S. Patent No. 4,237,224, specifically incorporated herein by reference in its entirety.

POLYNUCLEOTIDE AMPLIFICATION TECHNIQUES

A number of template dependent processes are available to amplify the target sequences of interest present in a sample. One of the best known amplification methods is the polymerase chain reaction (PCRTM) which is described in detail in U.S. Patent Nos. 4,683,195, 4,683,202 and 4,800,159, each of which is incorporated herein by reference in its entirety. Briefly, in PCRTM, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target sequence. An excess of deoxynucleoside triphosphates is added to a reaction mixture along with a DNA polymerase (*e.g.*, *Taq* polymerase). If the target sequence is present in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction product and the process is repeated. Preferably reverse transcription and PCRTM amplification procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well known in the art.

Another method for amplification is the ligase chain reaction (referred to as LCR), disclosed in Eur. Pat. Appl. Publ. No. 320,308 (specifically incorporated herein by reference in its entirety). In LCR, two complementary probe pairs are prepared, and in the presence of the target sequence, each pair will bind to opposite complementary strands of the target such that they abut. In the presence of a ligase, the two probe pairs will link to form a single unit. By temperature cycling, as in PCRTM, bound ligated units dissociate from the target and then serve as "target sequences" for ligation of excess probe pairs. U.S. Patent No. 4,883,750, incorporated herein by reference in its entirety, describes an alternative method of amplification similar to LCR for binding probe pairs to a target sequence.

Qbeta Replicase, described in PCT Intl. Pat. Appl. Publ. No. PCT/US87/00880, incorporated herein by reference in its entirety, may also be used as still another amplification method in the present invention. In this method, a replicative sequence of RNA that has a region complementary to that of a target is added to a

sample in the presence of an RNA polymerase. The polymerase will copy the replicative sequence that can then be detected.

An isothermal amplification method, in which restriction endonucleases and ligases are used to achieve the amplification of target molecules that contain
5 nucleotide 5'-[α -thio]triphosphates in one strand of a restriction site (Walker *et al.*, 1992, incorporated herein by reference in its entirety), may also be useful in the amplification of nucleic acids in the present invention.

Strand Displacement Amplification (SDA) is another method of carrying out isothermal amplification of nucleic acids which involves multiple rounds of strand
10 displacement and synthesis, *i.e.* nick translation. A similar method, called Repair Chain Reaction (RCR) is another method of amplification which may be useful in the present invention and is involves annealing several probes throughout a region targeted for amplification, followed by a repair reaction in which only two of the four bases are present. The other two bases can be added as biotinylated derivatives for easy
15 detection. A similar approach is used in SDA.

Sequences can also be detected using a cyclic probe reaction (CPR). In CPR, a probe having a 3' and 5' sequences of non-target DNA and an internal or "middle" sequence of the target protein specific RNA is hybridized to DNA which is present in a sample. Upon hybridization, the reaction is treated with RNaseH, and the
20 products of the probe are identified as distinctive products by generating a signal that is released after digestion. The original template is annealed to another cycling probe and the reaction is repeated. Thus, CPR involves amplifying a signal generated by hybridization of a probe to a target gene specific expressed nucleic acid.

Still other amplification methods described in Great Britain Pat. Appl.
25 No. 2 202 328, and in PCT Intl. Pat. Appl. Publ. No. PCT/US89/01025, each of which is incorporated herein by reference in its entirety, may be used in accordance with the present invention. In the former application, "modified" primers are used in a PCR-like, template and enzyme dependent synthesis. The primers may be modified by labeling with a capture moiety (*e.g.*, biotin) and/or a detector moiety (*e.g.*, enzyme). In
30 the latter application, an excess of labeled probes is added to a sample. In the presence of the target sequence, the probe binds and is cleaved catalytically. After cleavage, the

target sequence is released intact to be bound by excess probe. Cleavage of the labeled probe signals the presence of the target sequence.

Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (Kwoh *et al.*, 1989; PCT Intl. Pat. Appl. Publ. No. WO 88/10315, incorporated herein by reference in its entirety), including nucleic acid
5 sequence based amplification (NASBA) and 3SR. In NASBA, the nucleic acids can be prepared for amplification by standard phenol/chloroform extraction, heat denaturation of a sample, treatment with lysis buffer and minispin columns for isolation of DNA and RNA or guanidinium chloride extraction of RNA. These amplification techniques
10 involve annealing a primer that has sequences specific to the target sequence. Following polymerization, DNA/RNA hybrids are digested with RNase H while double stranded DNA molecules are heat-denatured again. In either case the single stranded DNA is made fully double stranded by addition of second target-specific primer, followed by polymerization. The double stranded DNA molecules are then multiply
15 transcribed by a polymerase such as T7 or SP6. In an isothermal cyclic reaction, the RNAs are reverse transcribed into DNA, and transcribed once again with a polymerase such as T7 or SP6. The resulting products, whether truncated or complete, indicate target-specific sequences.

Eur. Pat. Appl. Publ. No. 329,822, incorporated herein by reference in its
20 entirety, disclose a nucleic acid amplification process involving cyclically synthesizing single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA), which may be used in accordance with the present invention. The ssRNA is a first template for a first primer oligonucleotide, which is elongated by reverse transcriptase (RNA-dependent DNA polymerase). The RNA is then removed from resulting
25 DNA:RNA duplex by the action of ribonuclease H (RNase H, an RNase specific for RNA in a duplex with either DNA or RNA). The resultant ssDNA is a second template for a second primer, which also includes the sequences of an RNA polymerase promoter (exemplified by T7 RNA polymerase) 5' to its homology to its template. This primer is then extended by DNA polymerase (exemplified by the large "Klenow"
30 fragment of *E. coli* DNA polymerase I), resulting as a double-stranded DNA ("dsDNA") molecule, having a sequence identical to that of the original RNA between the primers and having additionally, at one end, a promoter sequence. This promoter

sequence can be used by the appropriate RNA polymerase to make many RNA copies of the DNA. These copies can then re-enter the cycle leading to very swift amplification. With proper choice of enzymes, this amplification can be done isothermally without addition of enzymes at each cycle. Because of the cyclical nature
5 of this process, the starting sequence can be chosen to be in the form of either DNA or RNA.

PCT Intl. Pat. Appl. Publ. No. WO 89/06700, incorporated herein by reference in its entirety, disclose a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA
10 ("ssDNA") followed by transcription of many RNA copies of the sequence. This scheme is not cyclic; *i.e.* new templates are not produced from the resultant RNA transcripts. Other amplification methods include "RACE" (Frohman, 1990), and "one-sided PCR" (Ohara, 1989) which are well-known to those of skill in the art.

Methods based on ligation of two (or more) oligonucleotides in the
15 presence of nucleic acid having the sequence of the resulting "di-oligonucleotide", thereby amplifying the di-oligonucleotide (Wu and Dean, 1996, incorporated herein by reference in its entirety), may also be used in the amplification of DNA sequences of the present invention.

BIOLOGICAL FUNCTIONAL EQUIVALENTS

20 Modification and changes may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a polypeptide with desirable characteristics. As mentioned above, it is often desirable to introduce one or more mutations into a specific polynucleotide sequence. In certain circumstances, the resulting encoded polypeptide
25 sequence is altered by this mutation, or in other cases, the sequence of the polypeptide is unchanged by one or more mutations in the encoding polynucleotide.

When it is desirable to alter the amino acid sequence of a polypeptide to create an equivalent, or even an improved, second-generation molecule, the amino acid changes may be achieved by changing one or more of the codons of the encoding DNA
30 sequence, according to Table 1.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated by the inventors that various changes may be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences which encode said peptides without appreciable loss of their biological utility or activity.

Table 1

Amino Acids			Codons						
Alanine	Ala	A	GCA	GCC	GCG	GCU			
Cysteine	Cys	C	UGC	UGU					
Aspartic acid	Asp	D	GAC	GAU					
Glutamic acid	Glu	E	GAA	GAG					
Phenylalanine	Phe	F	UUC	UUU					
Glycine	Gly	G	GGA	GGC	GGG	GGU			
Histidine	His	H	CAC	CAU					
Isoleucine	Ile	I	AUA	AUC	AUU				
Lysine	Lys	K	AAA	AAG					
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU	
Methionine	Met	M	AUG						
Asparagine	Asn	N	AAC	AAU					
Proline	Pro	P	CCA	CCC	CCG	CCU			
Glutamine	Gln	Q	CAA	CAG					
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU	
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU	
Threonine	Thr	T	ACA	ACC	ACG	ACU			
Valine	Val	V	GUA	GUC	GUG	GUU			
Tryptophan	Trp	W	UGG						
Tyrosine	Tyr	Y	UAC	UAU					

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (−0.4); threonine (−0.7); serine (−0.8); tryptophan (−0.9); tyrosine (−1.3); proline (−1.6); histidine (−3.2); glutamate (−3.5); glutamine (−3.5); aspartate (−3.5); asparagine (−3.5); lysine (−3.9); and arginine (−4.5).

It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are within ± 2 is preferred, those within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U. S. Patent 4,554,101 (specifically incorporated herein by reference in its entirety), states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein.

As detailed in U. S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 $\pm$ 1); glutamate (+3.0 $\pm$ 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (−0.4); proline (−0.5 $\pm$ 1); alanine (−0.5); histidine (−0.5); cysteine (−1.0); methionine (−1.3); valine (−1.5); leucine (−1.8); isoleucine (−1.8); tyrosine (−2.3); phenylalanine (−2.5); tryptophan (−3.4). It is understood that an amino

acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within ± 2 is preferred, those within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred.

As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that take various of the foregoing characteristics into consideration are well known to those of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

In addition, 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.

IN VIVO POLYNUCLEOTIDE DELIVERY TECHNIQUES

In additional embodiments, genetic constructs comprising one or more of the polynucleotides of the invention are introduced into cells *in vivo*. This may be achieved using any of a variety of well known approaches, several of which are outlined below for the purpose of illustration.

1. ADENOVIRUS

One of the preferred methods for *in vivo* delivery of one or more nucleic acid sequences involves the use of an adenovirus expression vector. "Adenovirus expression vector" is meant to include those constructs containing adenovirus sequences sufficient to (a) support packaging of the construct and (b) to express a polynucleotide that has been cloned therein in a sense or antisense orientation. Of

course, in the context of an antisense construct, expression does not require that the gene product be synthesized.

The expression vector comprises a genetically engineered form of an adenovirus. Knowledge of the genetic organization of adenovirus, a 36 kb, linear, double-stranded DNA virus, allows substitution of large pieces of adenoviral DNA with foreign sequences up to 7 kb (Grunhaus and Horwitz, 1992). In contrast to retrovirus, the adenoviral infection of host cells does not result in chromosomal integration because adenoviral DNA can replicate in an episomal manner without potential genotoxicity. Also, adenoviruses are structurally stable, and no genome rearrangement has been detected after extensive amplification. Adenovirus can infect virtually all epithelial cells regardless of their cell cycle stage. So far, adenoviral infection appears to be linked only to mild disease such as acute respiratory disease in humans.

Adenovirus is particularly suitable for use as a gene transfer vector because of its mid-sized genome, ease of manipulation, high titer, wide target-cell range and high infectivity. Both ends of the viral genome contain 100-200 base pair inverted repeats (ITRs), which are *cis* elements necessary for viral DNA replication and packaging. The early (E) and late (L) regions of the genome contain different transcription units that are divided by the onset of viral DNA replication. The E1 region (E1A and E1B) encodes proteins responsible for the regulation of transcription of the viral genome and a few cellular genes. The expression of the E2 region (E2A and E2B) results in the synthesis of the proteins for viral DNA replication. These proteins are involved in DNA replication, late gene expression and host cell shut-off (Renan, 1990). The products of the late genes, including the majority of the viral capsid proteins, are expressed only after significant processing of a single primary transcript issued by the major late promoter (MLP). The MLP, (located at 16.8 m.u.) is particularly efficient during the late phase of infection, and all the mRNA's issued from this promoter possess a 5'-tripartite leader (TPL) sequence which makes them preferred mRNA's for translation.

In a current system, recombinant adenovirus is generated from homologous recombination between shuttle vector and provirus vector. Due to the possible recombination between two proviral vectors, wild-type adenovirus may be

generated from this process. Therefore, it is critical to isolate a single clone of virus from an individual plaque and examine its genomic structure.

Generation and propagation of the current adenovirus vectors, which are replication deficient, depend on a unique helper cell line, designated 293, which was transformed from human embryonic kidney cells by Ad5 DNA fragments and constitutively expresses E1 proteins (Graham *et al.*, 1977). Since the E3 region is dispensable from the adenovirus genome (Jones and Shenk, 1978), the current adenovirus vectors, with the help of 293 cells, carry foreign DNA in either the E1, the D3 or both regions (Graham and Prevec, 1991). In nature, adenovirus can package approximately 105% of the wild-type genome (Ghosh-Choudhury *et al.*, 1987), providing capacity for about 2 extra kB of DNA. Combined with the approximately 5.5 kB of DNA that is replaceable in the E1 and E3 regions, the maximum capacity of the current adenovirus vector is under 7.5 kB, or about 15% of the total length of the vector. More than 80% of the adenovirus viral genome remains in the vector backbone and is the source of vector-borne cytotoxicity. Also, the replication deficiency of the E1-deleted virus is incomplete. For example, leakage of viral gene expression has been observed with the currently available vectors at high multiplicities of infection (MOI) (Mulligan, 1993).

Helper cell lines may be derived from human cells such as human embryonic kidney cells, muscle cells, hematopoietic cells or other human embryonic mesenchymal or epithelial cells. Alternatively, the helper cells may be derived from the cells of other mammalian species that are permissive for human adenovirus. Such cells include, *e.g.*, Vero cells or other monkey embryonic mesenchymal or epithelial cells. As stated above, the currently preferred helper cell line is 293.

Recently, Racher *et al.* (1995) disclosed improved methods for culturing 293 cells and propagating adenovirus. In one format, natural cell aggregates are grown by inoculating individual cells into 1 liter siliconized spinner flasks (Technique, Cambridge, UK) containing 100-200 ml of medium. Following stirring at 40 rpm, the cell viability is estimated with trypan blue. In another format, Fibra-Cel microcarriers (Bibby Sterlin, Stone, UK) (5 g/l) is employed as follows. A cell inoculum, resuspended in 5 ml of medium, is added to the carrier (50 ml) in a 250 ml Erlenmeyer flask and left stationary, with occasional agitation, for 1 to 4 h. The medium is then

replaced with 50 ml of fresh medium and shaking initiated. For virus production, cells are allowed to grow to about 80% confluence, after which time the medium is replaced (to 25% of the final volume) and adenovirus added at an MOI of 0.05. Cultures are left stationary overnight, following which the volume is increased to 100% and shaking
5 commenced for another 72 h.

Other than the requirement that the adenovirus vector be replication defective, or at least conditionally defective, the nature of the adenovirus vector is not believed to be crucial to the successful practice of the invention. The adenovirus may be of any of the 42 different known serotypes or subgroups A-F. Adenovirus type 5 of
10 subgroup C is the preferred starting material in order to obtain a conditional replication-defective adenovirus vector for use in the present invention, since Adenovirus type 5 is a human adenovirus about which a great deal of biochemical and genetic information is known, and it has historically been used for most constructions employing adenovirus as a vector.

15 As stated above, the typical vector according to the present invention is replication defective and will not have an adenovirus E1 region. Thus, it will be most convenient to introduce the polynucleotide encoding the gene of interest at the position from which the E1-coding sequences have been removed. However, the position of insertion of the construct within the adenovirus sequences is not critical to the
20 invention. The polynucleotide encoding the gene of interest may also be inserted in lieu of the deleted E3 region in E3 replacement vectors as described by Karlsson *et al.* (1986) or in the E4 region where a helper cell line or helper virus complements the E4 defect.

Adenovirus is easy to grow and manipulate and exhibits broad host
25 range *in vitro* and *in vivo*. This group of viruses can be obtained in high titers, *e.g.*, 10^9 - 10^{11} plaque-forming units per ml, and they are highly infective. The life cycle of adenovirus does not require integration into the host cell genome. The foreign genes delivered by adenovirus vectors are episomal and, therefore, have low genotoxicity to host cells. No side effects have been reported in studies of vaccination with wild-type
30 adenovirus (Couch *et al.*, 1963; Top *et al.*, 1971), demonstrating their safety and therapeutic potential as *in vivo* gene transfer vectors.

Adenovirus vectors have been used in eukaryotic gene expression (Levrero *et al.*, 1991; Gomez-Foix *et al.*, 1992) and vaccine development (Grunhaus and Horwitz, 1992; Graham and Prevec, 1992). Recently, animal studies suggested that recombinant adenovirus could be used for gene therapy (Stratford-Perricaudet and Perricaudet, 1991; Stratford-Perricaudet *et al.*, 1990; Rich *et al.*, 1993). Studies in administering recombinant adenovirus to different tissues include trachea instillation (Rosenfeld *et al.*, 1991; Rosenfeld *et al.*, 1992), muscle injection (Ragot *et al.*, 1993), peripheral intravenous injections (Herz and Gerard, 1993) and stereotactic inoculation into the brain (Le Gal La Salle *et al.*, 1993).

10 2. RETROVIRUSES

The retroviruses are a group of single-stranded RNA viruses characterized by an ability to convert their RNA to double-stranded DNA in infected cells by a process of reverse-transcription (Coffin, 1990). The resulting DNA then stably integrates into cellular chromosomes as a provirus and directs synthesis of viral proteins. The integration results in the retention of the viral gene sequences in the recipient cell and its descendants. The retroviral genome contains three genes, gag, pol, and env that code for capsid proteins, polymerase enzyme, and envelope components, respectively. A sequence found upstream from the gag gene contains a signal for packaging of the genome into virions. Two long terminal repeat (LTR) sequences are present at the 5' and 3' ends of the viral genome. These contain strong promoter and enhancer sequences and are also required for integration in the host cell genome (Coffin, 1990).

In order to construct a retroviral vector, a nucleic acid encoding one or more oligonucleotide or polynucleotide sequences of interest is inserted into the viral genome in the place of certain viral sequences to produce a virus that is replication-defective. In order to produce virions, a packaging cell line containing the gag, pol, and env genes but without the LTR and packaging components is constructed (Mann *et al.*, 1983). When a recombinant plasmid containing a cDNA, together with the retroviral LTR and packaging sequences is introduced into this cell line (by calcium phosphate precipitation for example), the packaging sequence allows the RNA transcript of the recombinant plasmid to be packaged into viral particles, which are then secreted into

the culture media (Nicolas and Rubenstein, 1988; Temin, 1986; Mann *et al.*, 1983). The media containing the recombinant retroviruses is then collected, optionally concentrated, and used for gene transfer. Retroviral vectors are able to infect a broad variety of cell types. However, integration and stable expression require the division of
5 host cells (Paskind *et al.*, 1975).

A novel approach designed to allow specific targeting of retrovirus vectors was recently developed based on the chemical modification of a retrovirus by the chemical addition of lactose residues to the viral envelope. This modification could permit the specific infection of hepatocytes *via* sialoglycoprotein receptors.

10 A different approach to targeting of recombinant retroviruses was designed in which biotinylated antibodies against a retroviral envelope protein and against a specific cell receptor were used. The antibodies were coupled *via* the biotin components by using streptavidin (Roux *et al.*, 1989). Using antibodies against major histocompatibility complex class I and class II antigens, they demonstrated the infection
15 of a variety of human cells that bore those surface antigens with an ecotropic virus *in vitro* (Roux *et al.*, 1989).

3. ADENO-ASSOCIATED VIRUSES

AAV (Ridgeway, 1988; Hermonat and Muzyczka, 1984) is a parovirus, discovered as a contamination of adenoviral stocks. It is a ubiquitous virus (antibodies
20 are present in 85% of the US human population) that has not been linked to any disease. It is also classified as a dependovirus, because its replications is dependent on the presence of a helper virus, such as adenovirus. Five serotypes have been isolated, of which AAV-2 is the best characterized. AAV has a single-stranded linear DNA that is encapsidated into capsid proteins VP1, VP2 and VP3 to form an icosahedral virion of
25 20 to 24 nm in diameter (Muzyczka and McLaughlin, 1988).

The AAV DNA is approximately 4.7 kilobases long. It contains two open reading frames and is flanked by two ITRs (FIG. 2). There are two major genes in the AAV genome: *rep* and *cap*. The *rep* gene codes for proteins responsible for viral replications, whereas *cap* codes for capsid protein VP1-3. Each ITR forms a T-shaped
30 hairpin structure. These terminal repeats are the only essential *cis* components of the AAV for chromosomal integration. Therefore, the AAV can be used as a vector with

all viral coding sequences removed and replaced by the cassette of genes for delivery. Three viral promoters have been identified and named p5, p19, and p40, according to their map position. Transcription from p5 and p19 results in production of rep proteins, and transcription from p40 produces the capsid proteins (Hermonat and Muzyczka,
5 1984).

There are several factors that prompted researchers to study the possibility of using rAAV as an expression vector. One is that the requirements for delivering a gene to integrate into the host chromosome are surprisingly few. It is necessary to have the 145-bp ITRs, which are only 6% of the AAV genome. This
10 leaves room in the vector to assemble a 4.5-kb DNA insertion. While this carrying capacity may prevent the AAV from delivering large genes, it is amply suited for delivering the antisense constructs of the present invention.

AAV is also a good choice of delivery vehicles due to its safety. There is a relatively complicated rescue mechanism: not only wild type adenovirus but also
15 AAV genes are required to mobilize rAAV. Likewise, AAV is not pathogenic and not associated with any disease. The removal of viral coding sequences minimizes immune reactions to viral gene expression, and therefore, rAAV does not evoke an inflammatory response.

4. OTHER VIRAL VECTORS AS EXPRESSION CONSTRUCTS

20 Other viral vectors may be employed as expression constructs in the present invention for the delivery of oligonucleotide or polynucleotide sequences to a host cell. Vectors derived from viruses such as vaccinia virus (Ridgeway, 1988; Coupar *et al.*, 1988), lentiviruses, polio viruses and herpes viruses may be employed. They offer several attractive features for various mammalian cells (Friedmann, 1989;
25 Ridgeway, 1988; Coupar *et al.*, 1988; Horwich *et al.*, 1990).

With the recent recognition of defective hepatitis B viruses, new insight was gained into the structure-function relationship of different viral sequences. *In vitro* studies showed that the virus could retain the ability for helper-dependent packaging and reverse transcription despite the deletion of up to 80% of its genome (Horwich *et al.*, 1990). This suggested that large portions of the genome could be replaced with
30 foreign genetic material. The hepatotropism and persistence (integration) were

particularly attractive properties for liver-directed gene transfer. Chang *et al.* (1991) introduced the chloramphenicol acetyltransferase (CAT) gene into duck hepatitis B virus genome in the place of the polymerase, surface, and pre-surface coding sequences. It was cotransfected with wild-type virus into an avian hepatoma cell line. Culture media containing high titers of the recombinant virus were used to infect primary duckling hepatocytes. Stable CAT gene expression was detected for at least 24 days after transfection (Chang *et al.*, 1991).

5. NON-VIRAL VECTORS

In order to effect expression of the oligonucleotide or polynucleotide sequences of the present invention, the expression construct must be delivered into a cell. This delivery may be accomplished *in vitro*, as in laboratory procedures for transforming cells lines, or *in vivo* or *ex vivo*, as in the treatment of certain disease states. As described above, one preferred mechanism for delivery is *via* viral infection where the expression construct is encapsulated in an infectious viral particle.

Once the expression construct has been delivered into the cell the nucleic acid encoding the desired oligonucleotide or polynucleotide sequences may be positioned and expressed at different sites. In certain embodiments, the nucleic acid encoding the construct may be stably integrated into the genome of the cell. This integration may be in the specific location and orientation *via* homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the nucleic acid may be stably maintained in the cell as a separate, episomal segment of DNA. Such nucleic acid segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the host cell cycle. How the expression construct is delivered to a cell and where in the cell the nucleic acid remains is dependent on the type of expression construct employed.

In certain embodiments of the invention, the expression construct comprising one or more oligonucleotide or polynucleotide sequences may simply consist of naked recombinant DNA or plasmids. Transfer of the construct may be performed by any of the methods mentioned above which physically or chemically permeabilize the cell membrane. This is particularly applicable for transfer *in vitro* but

it may be applied to *in vivo* use as well. Dubensky *et al.* (1984) successfully injected polyomavirus DNA in the form of calcium phosphate precipitates into liver and spleen of adult and newborn mice demonstrating active viral replication and acute infection. Benvenisty and Reshef (1986) also demonstrated that direct intraperitoneal injection of calcium phosphate-precipitated plasmids results in expression of the transfected genes. It is envisioned that DNA encoding a gene of interest may also be transferred in a similar manner *in vivo* and express the gene product.

Another embodiment of the invention for transferring a naked DNA expression construct into cells may involve particle bombardment. This method depends on the ability to accelerate DNA-coated microprojectiles to a high velocity allowing them to pierce cell membranes and enter cells without killing them (Klein *et al.*, 1987). Several devices for accelerating small particles have been developed. One such device relies on a high voltage discharge to generate an electrical current, which in turn provides the motive force (Yang *et al.*, 1990). The microprojectiles used have consisted of biologically inert substances such as tungsten or gold beads.

Selected organs including the liver, skin, and muscle tissue of rats and mice have been bombarded *in vivo* (Yang *et al.*, 1990; Zelenin *et al.*, 1991). This may require surgical exposure of the tissue or cells, to eliminate any intervening tissue between the gun and the target organ, *i.e. ex vivo* treatment. Again, DNA encoding a particular gene may be delivered *via* this method and still be incorporated by the present invention.

ANTISENSE OLIGONUCLEOTIDES

The end result of the flow of genetic information is the synthesis of protein. DNA is transcribed by polymerases into messenger RNA and translated on the ribosome to yield a folded, functional protein. Thus there are several steps along the route where protein synthesis can be inhibited. The native DNA segment coding for a polypeptide described herein, as all such mammalian DNA strands, has two strands: a sense strand and an antisense strand held together by hydrogen bonding. The messenger RNA coding for polypeptide has the same nucleotide sequence as the sense DNA strand except that the DNA thymidine is replaced by uridine. Thus, synthetic

antisense nucleotide sequences will bind to a mRNA and inhibit expression of the protein encoded by that mRNA.

The targeting of antisense oligonucleotides to mRNA is thus one mechanism to shut down protein synthesis, and, consequently, represents a powerful and targeted therapeutic approach. For example, the synthesis of polygalacturonase and the muscarine type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to their respective mRNA sequences (U. S. Patent 5,739,119 and U. S. Patent 5,759,829, each specifically incorporated herein by reference in its entirety). Further, examples of antisense inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal GABA_A receptor and human EGF (Jaskulski *et al.*, 1988; Vasanthakumar and Ahmed, 1989; Peris *et al.*, 1998; U. S. Patent 5,801,154; U. S. Patent 5,789,573; U. S. Patent 5,718,709 and U. S. Patent 5,610,288, each specifically incorporated herein by reference in its entirety). Antisense constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, *e.g.* cancer (U. S. Patent 5,747,470; U. S. Patent 5,591,317 and U. S. Patent 5,783,683, each specifically incorporated herein by reference in its entirety).

Therefore, in exemplary embodiments, the invention provides oligonucleotide sequences that comprise all, or a portion of, any sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the antisense oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment, the oligonucleotides are modified DNAs comprising a phosphorothioated modified backbone. In a fourth embodiment, the oligonucleotide sequences comprise peptide nucleic acids or derivatives thereof. In each case, preferred compositions comprise a sequence region that is complementary, and more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein.

Selection of antisense compositions specific for a given gene sequence is based upon analysis of the chosen target sequence (*i.e.* in these illustrative examples the rat and human sequences) and determination of secondary structure, T_m , binding energy, relative stability, and antisense compositions were selected based upon their

relative inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell.

Highly preferred target regions of the mRNA, are those which are at or near the AUG translation initiation codon, and those sequences which were substantially complementary to 5' regions of the mRNA. These secondary structure analyses and target site selection considerations were performed using v.4 of the OLIGO primer analysis software (Rychlik, 1997) and the BLASTN 2.0.5 algorithm software (Altschul *et al.*, 1997).

The use of an antisense delivery method employing a short peptide vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic domain derived from the fusion sequence of HIV gp41 and a hydrophilic domain from the nuclear localization sequence of SV40 T-antigen (Morris *et al.*, 1997). It has been demonstrated that several molecules of the MPG peptide coat the antisense oligonucleotides and can be delivered into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further, the interaction with MPG strongly increases both the stability of the oligonucleotide to nuclease and the ability to cross the plasma membrane (Morris *et al.*, 1997).

RIBOZYMES

Although proteins traditionally have been used for catalysis of nucleic acids, another class of macromolecules has emerged as useful in this endeavor. Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cech, 1987; Gerlach *et al.*, 1987; Forster and Symons, 1987). For example, a large number of ribozymes accelerate phosphoester transfer reactions with a high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cech *et al.*, 1981; Michel and Westhof, 1990; Reinhold-Hurek and Shub, 1992). This specificity has been attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

Ribozyme catalysis has primarily been observed as part of sequence-specific cleavage/ligation reactions involving nucleic acids (Joyce, 1989; Cech *et al.*,

1981). For example, U. S. Patent No. 5,354,855 (specifically incorporated herein by reference) reports that certain ribozymes can act as endonucleases with a sequence specificity greater than that of known ribonucleases and approaching that of the DNA restriction enzymes. Thus, sequence-specific ribozyme-mediated inhibition of gene
5 expression may be particularly suited to therapeutic applications (Scanlon *et al.*, 1991; Sarver *et al.*, 1990). Recently, it was reported that ribozymes elicited genetic changes in some cells lines to which they were applied; the altered genes included the oncogenes H-*ras*, c-*fos* and genes of HIV. Most of this work involved the modification of a target mRNA, based on a specific mutant codon that is cleaved by a specific ribozyme.

10 Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds *in trans* (and thus can cleave other RNA molecules) under physiological conditions. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close
15 proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and
20 cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nature of a ribozyme is advantageous over many technologies, such as antisense technology (where a nucleic acid molecule simply binds to a nucleic acid target to block its translation) since the concentration of ribozyme
25 necessary to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target
30 RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action

(Woolf *et al.*, 1992). Thus, the specificity of action of a ribozyme is greater than that of an antisense oligonucleotide binding the same RNA site.

The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis δ virus, group I intron or RNaseP RNA (in association with an RNA
5 guide sequence) or Neurospora VS RNA motif. Examples of hammerhead motifs are described by Rossi *et al.* (1992). Examples of hairpin motifs are described by Hampel
et al. (Eur. Pat. Appl. Publ. No. EP 0360257), Hampel and Tritz (1989), Hampel *et al.* (1990) and U. S. Patent 5,631,359 (specifically incorporated herein by reference). An
example of the hepatitis δ virus motif is described by Perrotta and Been (1992); an
10 example of the RNaseP motif is described by Guerrier-Takada *et al.* (1983); Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, 1990; Saville and Collins, 1991; Collins and Olive, 1993); and an example of the Group I intron is described in (U. S. Patent 4,987,071, specifically incorporated herein by reference). All that is important in an enzymatic nucleic acid molecule of this invention
15 is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

20 In certain embodiments, it may be important to produce enzymatic cleaving agents which exhibit a high degree of specificity for the RNA of a desired target, such as one of the sequences disclosed herein. The enzymatic nucleic acid molecule is preferably targeted to a highly conserved sequence region of a target mRNA. Such enzymatic nucleic acid molecules can be delivered exogenously to
25 specific cells as required. Alternatively, the ribozymes can be expressed from DNA or RNA vectors that are delivered to specific cells.

Small enzymatic nucleic acid motifs (*e.g.*, of the hammerhead or the hairpin structure) may also be used for exogenous delivery. The simple structure of these molecules increases the ability of the enzymatic nucleic acid to invade targeted
30 regions of the mRNA structure. Alternatively, catalytic RNA molecules can be expressed within cells from eukaryotic promoters (*e.g.*, Scanlon *et al.*, 1991; Kashani-Sabet *et al.*, 1992; Dropulic *et al.*, 1992; Weerasinghe *et al.*, 1991; Ojwang *et al.*, 1992;

Chen *et al.*, 1992; Sarver *et al.*, 1990). Those skilled in the art realize that any ribozyme can be expressed in eukaryotic cells from the appropriate DNA vector. The activity of such ribozymes can be augmented by their release from the primary transcript by a second ribozyme (Int. Pat. Appl. Publ. No. WO 93/23569, and Int. Pat. Appl. Publ. No. WO 94/02595, both hereby incorporated by reference; Ohkawa *et al.*,
5 1992; Taira *et al.*, 1991; and Ventura *et al.*, 1993).

Ribozymes may be added directly, or can be complexed with cationic lipids, lipid complexes, packaged within liposomes, or otherwise delivered to target cells. The RNA or RNA complexes can be locally administered to relevant tissues *ex vivo*, or *in vivo* through injection, aerosol inhalation, infusion pump or stent, with or
10 without their incorporation in biopolymers.

Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each specifically incorporated herein by reference) and synthesized to be tested *in vitro* and *in vivo*, as
15 described. Such ribozymes can also be optimized for delivery. While specific examples are provided, those in the art will recognize that equivalent RNA targets in other species can be utilized when necessary.

Hammerhead or hairpin ribozymes may be individually analyzed by computer folding (Jaeger *et al.*, 1989) to assess whether the ribozyme sequences fold
20 into the appropriate secondary structure. Those ribozymes with unfavorable intramolecular interactions between the binding arms and the catalytic core are eliminated from consideration. Varying binding arm lengths can be chosen to optimize activity. Generally, at least 5 or so bases on each arm are able to bind to, or otherwise interact with, the target RNA.

Ribozymes of the hammerhead or hairpin motif may be designed to anneal to various sites in the mRNA message, and can be chemically synthesized. The method of synthesis used follows the procedure for normal RNA synthesis as described in Usman *et al.* (1987) and in Scaringe *et al.* (1990) and makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and
25 30 phosphoramidites at the 3'-end. Average stepwise coupling yields are typically >98%. Hairpin ribozymes may be synthesized in two parts and annealed to reconstruct an active ribozyme (Chowrira and Burke, 1992). Ribozymes may be modified extensively

to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-fluoro, 2'-O-methyl, 2'-H (for a review see *e.g.*, Usman and Cedergren, 1992). Ribozymes may be purified by gel electrophoresis using general methods or by high pressure liquid chromatography and resuspended in water.

5 Ribozyme activity can be optimized by altering the length of the ribozyme binding arms, or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see *e.g.*, Int. Pat. Appl. Publ. No. WO 92/07065; Perrault *et al.*, 1990; Pieken *et al.*, 1991; Usman and Cedergren, 1992; Int. Pat. Appl. Publ. No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur.
10 Pat. Appl. Publ. No. 92110298.4; U. S. Patent 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

15 Sullivan *et al.* (Int. Pat. Appl. Publ. No. WO 94/02595) describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable
20 nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination may be locally delivered by direct inhalation, by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular,
25 subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of ribozyme delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO 93/23569, each specifically incorporated herein by reference.

30 Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for

eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, *etc.*) present nearby.

5 Prokaryotic RNA polymerase promoters may also be used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990; Gao and Huang, 1993; Lieber *et al.*, 1993; Zhou *et al.*, 1990). Ribozymes expressed from such promoters can function in mammalian cells (*e.g.* Kashani-Saber *et al.*, 1992; Ojwang *et al.*, 1992; Chen *et al.*, 1992; Yu *et al.*, 1993;

10 L'Huillier *et al.*, 1992; Lisiewicz *et al.*, 1993). Such transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as retroviral, semliki forest virus, sindbis virus vectors).

15 Ribozymes may be used as diagnostic tools to examine genetic drift and mutations within diseased cells. They can also be used to assess levels of the target RNA molecule. The close relationship between ribozyme activity and the structure of the target RNA allows the detection of mutations in any region of the molecule which alters the base-pairing and three-dimensional structure of the target RNA. By using

20 multiple ribozymes, one may map nucleotide changes which are important to RNA structure and function *in vitro*, as well as in cells and tissues. Cleavage of target RNAs with ribozymes may be used to inhibit gene expression and define the role (essentially) of specified gene products in the progression of disease. In this manner, other genetic targets may be defined as important mediators of the disease. These studies will lead to

25 better treatment of the disease progression by affording the possibility of combinational therapies (*e.g.*, multiple ribozymes targeted to different genes, ribozymes coupled with known small molecule inhibitors, or intermittent treatment with combinations of ribozymes and/or other chemical or biological molecules). Other *in vitro* uses of ribozymes are well known in the art, and include detection of the presence of mRNA

30 associated with an IL-5 related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with a ribozyme using standard methodology.

PEPTIDE NUCLEIC ACIDS

In certain embodiments, the inventors contemplate the use of peptide nucleic acids (PNAs) in the practice of the methods of the invention. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and
5 Nielsen, 1997). PNA is able to be utilized in a number of methods that traditionally have used RNA or DNA. Often PNA sequences perform better in techniques than the corresponding RNA or DNA sequences and have utilities that are not inherent to RNA or DNA. A review of PNA including methods of making, characteristics of, and methods of using, is provided by Corey (1997) and is incorporated herein by reference.
10 As such, in certain embodiments, one may prepare PNA sequences that are complementary to one or more portions of the ACE mRNA sequence, and such PNA compositions may be used to regulate, alter, decrease, or reduce the translation of ACE-specific mRNA, and thereby alter the level of ACE activity in a host cell to which such PNA compositions have been administered.

15 PNAs have 2-aminoethyl-glycine linkages replacing the normal phosphodiester backbone of DNA (Nielsen *et al.*, 1991; Hanvey *et al.*, 1992; Hyrup and Nielsen, 1996; Nielsen, 1996). This chemistry has three important consequences: firstly, in contrast to DNA or phosphorothioate oligonucleotides, PNAs are neutral molecules; secondly, PNAs are achiral, which avoids the need to develop a
20 stereoselective synthesis; and thirdly, PNA synthesis uses standard Boc (Dueholm *et al.*, 1994) or Fmoc (Thomson *et al.*, 1995) protocols for solid-phase peptide synthesis, although other methods, including a modified Merrifield method, have been used (Christensen *et al.*, 1995).

PNA monomers or ready-made oligomers are commercially available
25 from PerSeptive Biosystems (Framingham, MA). PNA syntheses by either Boc or Fmoc protocols are straightforward using manual or automated protocols (Norton *et al.*, 1995). The manual protocol lends itself to the production of chemically modified PNAs or the simultaneous synthesis of families of closely related PNAs.

As with peptide synthesis, the success of a particular PNA synthesis will
30 depend on the properties of the chosen sequence. For example, while in theory PNAs can incorporate any combination of nucleotide bases, the presence of adjacent purines can lead to deletions of one or more residues in the product. In expectation of this

difficulty, it is suggested that, in producing PNAs with adjacent purines, one should repeat the coupling of residues likely to be added inefficiently. This should be followed by the purification of PNAs by reverse-phase high-pressure liquid chromatography (Norton *et al.*, 1995) providing yields and purity of product similar to those observed during the synthesis of peptides.

Modifications of PNAs for a given application may be accomplished by coupling amino acids during solid-phase synthesis or by attaching compounds that contain a carboxylic acid group to the exposed N-terminal amine. Alternatively, PNAs can be modified after synthesis by coupling to an introduced lysine or cysteine. The ease with which PNAs can be modified facilitates optimization for better solubility or for specific functional requirements. Once synthesized, the identity of PNAs and their derivatives can be confirmed by mass spectrometry. Several studies have made and utilized modifications of PNAs (Norton *et al.*, 1995; Haaime *et al.*, 1996; Stetsenko *et al.*, 1996; Petersen *et al.*, 1995; Ulmann *et al.*, 1996; Koch *et al.*, 1995; Orum *et al.*, 1995; Footer *et al.*, 1996; Griffith *et al.*, 1995; Kremsky *et al.*, 1996; Pardridge *et al.*, 1995; Boffa *et al.*, 1995; Landsdorp *et al.*, 1996; Gambacorti-Passerini *et al.*, 1996; Armitage *et al.*, 1997; Seeger *et al.*, 1997; Ruskowski *et al.*, 1997). U.S. Patent No. 5,700,922 discusses PNA-DNA-PNA chimeric molecules and their uses in diagnostics, modulating protein in organisms, and treatment of conditions susceptible to therapeutics.

In contrast to DNA and RNA, which contain negatively charged linkages, the PNA backbone is neutral. In spite of this dramatic alteration, PNAs recognize complementary DNA and RNA by Watson-Crick pairing (Egholm *et al.*, 1993), validating the initial modeling by Nielsen *et al.* (1991). PNAs lack 3' to 5' polarity and can bind in either parallel or antiparallel fashion, with the antiparallel mode being preferred (Egholm *et al.*, 1993).

Hybridization of DNA oligonucleotides to DNA and RNA is destabilized by electrostatic repulsion between the negatively charged phosphate backbones of the complementary strands. By contrast, the absence of charge repulsion in PNA-DNA or PNA-RNA duplexes increases the melting temperature (T_m) and reduces the dependence of T_m on the concentration of mono- or divalent cations (Nielsen *et al.*, 1991). The enhanced rate and affinity of hybridization are significant

because they are responsible for the surprising ability of PNAs to perform strand invasion of complementary sequences within relaxed double-stranded DNA. In addition, the efficient hybridization at inverted repeats suggests that PNAs can recognize secondary structure effectively within double-stranded DNA. Enhanced
5 recognition also occurs with PNAs immobilized on surfaces, and Wang *et al.* have shown that support-bound PNAs can be used to detect hybridization events (Wang *et al.*, 1996).

One might expect that tight binding of PNAs to complementary sequences would also increase binding to similar (but not identical) sequences, reducing
10 the sequence specificity of PNA recognition. As with DNA hybridization, however, selective recognition can be achieved by balancing oligomer length and incubation temperature. Moreover, selective hybridization of PNAs is encouraged by PNA-DNA hybridization being less tolerant of base mismatches than DNA-DNA hybridization. For example, a single mismatch within a 16 bp PNA-DNA duplex can reduce the T_m by
15 up to 15°C (Egholm *et al.*, 1993). This high level of discrimination has allowed the development of several PNA-based strategies for the analysis of point mutations (Wang *et al.*, 1996; Carlsson *et al.*, 1996; Thiede *et al.*, 1996; Webb and Hurskainen, 1996; Perry-O'Keefe *et al.*, 1996).

High-affinity binding provides clear advantages for molecular
20 recognition and the development of new applications for PNAs. For example, 11-13 nucleotide PNAs inhibit the activity of telomerase, a ribonucleo-protein that extends telomere ends using an essential RNA template, while the analogous DNA oligomers do not (Norton *et al.*, 1996).

Neutral PNAs are more hydrophobic than analogous DNA oligomers,
25 and this can lead to difficulty solubilizing them at neutral pH, especially if the PNAs have a high purine content or if they have the potential to form secondary structures. Their solubility can be enhanced by attaching one or more positive charges to the PNA termini (Nielsen *et al.*, 1991).

Findings by Allfrey and colleagues suggest that strand invasion will
30 occur spontaneously at sequences within chromosomal DNA (Boffa *et al.*, 1995; Boffa *et al.*, 1996). These studies targeted PNAs to triplet repeats of the nucleotides CAG and used this recognition to purify transcriptionally active DNA (Boffa *et al.*, 1995) and to

inhibit transcription (Boffa *et al.*, 1996). This result suggests that if PNAs can be delivered within cells then they will have the potential to be general sequence-specific regulators of gene expression. Studies and reviews concerning the use of PNAs as antisense and anti-gene agents include Nielsen *et al.* (1993b), Hanvey *et al.* (1992), and
5 Good and Nielsen (1997). Koppelhus *et al.* (1997) have used PNAs to inhibit HIV-1 inverse transcription, showing that PNAs may be used for antiviral therapies.

Methods of characterizing the antisense binding properties of PNAs are discussed in Rose (1993) and Jensen *et al.* (1997). Rose uses capillary gel electrophoresis to determine binding of PNAs to their complementary oligonucleotide,
10 measuring the relative binding kinetics and stoichiometry. Similar types of measurements were made by Jensen *et al.* using BIAcore™ technology.

Other applications of PNAs include use in DNA strand invasion (Nielsen *et al.*, 1991), antisense inhibition (Hanvey *et al.*, 1992), mutational analysis (Orum *et al.*, 1993), enhancers of transcription (Mollegaard *et al.*, 1994), nucleic acid purification
15 (Orum *et al.*, 1995), isolation of transcriptionally active genes (Boffa *et al.*, 1995), blocking of transcription factor binding (Vickers *et al.*, 1995), genome cleavage (Veselkov *et al.*, 1996), biosensors (Wang *et al.*, 1996), *in situ* hybridization (Thisted *et al.*, 1996), and in a alternative to Southern blotting (Perry-O'Keefe, 1996).

POLYPEPTIDE COMPOSITIONS

20 The present invention, in other aspects, provides polypeptide compositions. Generally, a polypeptide of the invention will be an isolated polypeptide (or an epitope, variant, or active fragment thereof) derived from a mammalian species. Preferably, the polypeptide is encoded by a polynucleotide sequence disclosed herein or a sequence which hybridizes under moderately stringent conditions to a polynucleotide
25 sequence disclosed herein. Alternatively, the polypeptide may be defined as a polypeptide which comprises a contiguous amino acid sequence from an amino acid sequence disclosed herein, or which polypeptide comprises an entire amino acid sequence disclosed herein.

In the present invention, a polypeptide composition is also understood to
30 comprise one or more polypeptides that are immunologically reactive with antibodies generated against a polypeptide of the invention, particularly a polypeptide having the

amino acid sequence encoded by SEQ ID NOs:1-222, or to active fragments, or to variants or biological functional equivalents thereof.

Likewise, a polypeptide composition of the present invention is understood to comprise one or more polypeptides that are capable of eliciting antibodies
5 that are immunologically reactive with one or more polypeptides encoded by one or more contiguous nucleic acid sequences contained in SEQ ID NOs:1-222, or to active fragments, or to variants thereof, or to one or more nucleic acid sequences which hybridize to one or more of these sequences under conditions of moderate to high stringency.

10 As used herein, an active fragment of a polypeptide includes a whole or a portion of a polypeptide which is modified by conventional techniques, *e.g.*, mutagenesis, or by addition, deletion, or substitution, but which active fragment exhibits substantially the same structure function, antigenicity, etc., as a polypeptide as described herein.

15 In certain illustrative embodiments, the polypeptides of the invention will comprise at least an immunogenic portion of an ovarian tumor protein or a variant thereof, as described herein. As noted above, an "ovarian tumor protein" is a protein that is expressed by ovarian tumor cells. Proteins that are ovarian tumor proteins also react detectably within an immunoassay (such as an ELISA) with antisera from a
20 patient with ovarian 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
25 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 an ovarian tumor protein or a variant thereof. Certain preferred immunogenic portions include peptides in which an N-terminal leader sequence and/or
30 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 ovarian 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, ¹²⁵I-labeled Protein A.

As noted above, a composition may comprise a variant of a native ovarian tumor protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native ovarian 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 encompassed by the present invention include those exhibiting at least about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%,
5 97%, 98%, or 99% or more identity (determined as described above) to the polypeptides disclosed herein.

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
10 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
15 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;
20 (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
25 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
30 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, such as mammalian cells and plant 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 less than about 100 amino acids, and generally less 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 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.

5 Fusion proteins are also provided. Such proteins comprise a polypeptide as described herein 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).

10 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
15 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
20 (hemagglutinin). 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
25 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
30 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 an ovarian tumor protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to an ovarian tumor protein if it reacts at a detectable level (within, for example, an ELISA) with an ovarian 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 ovarian cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to an ovarian 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, sputum, 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
5 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.
10 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
15 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,
20 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
25 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
30 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 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, diphtheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a
5 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
10 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
15 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
20 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
25 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
30 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 that 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 an ovarian 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 an ovarian tumor polypeptide, polynucleotide encoding an ovarian 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, an ovarian 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 an ovarian tumor polypeptide if the T cells specifically proliferate, secrete cytokines or 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 an ovarian 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 an ovarian tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4⁺ and/or CD8⁺. Ovarian tumor protein-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient, a related donor or an unrelated donor, and are administered
5 to the patient following stimulation and expansion.

For therapeutic purposes, CD4⁺ or CD8⁺ T cells that proliferate in response to an ovarian 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 an
10 ovarian 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 an ovarian tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of an ovarian tumor protein can be expanded in number by cloning. Methods for cloning cells are well
15 known in the art, and include limiting dilution.

PHARMACEUTICAL COMPOSITIONS

In additional embodiments, the present invention concerns formulation of one or more of the polynucleotide, polypeptide, T-cell and/or antibody compositions disclosed herein in pharmaceutically-acceptable solutions for administration to a cell or
20 an animal, either alone, or in combination with one or more other modalities of therapy.

It will also be understood that, if desired, the nucleic acid segment, RNA, DNA or PNA compositions that express a polypeptide as disclosed herein may be administered in combination with other agents as well, such as, *e.g.*, other proteins or polypeptides or various pharmaceutically-active agents. In fact, there is virtually no
25 limit to other components that may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or host tissues. The compositions may thus be delivered along with various other agents as required in the particular instance. Such compositions may be purified from host cells or other biological sources, or alternatively may be chemically synthesized as described herein.
30 Likewise, such compositions may further comprise substituted or derivatized RNA or DNA compositions.

Formulation of pharmaceutically-acceptable excipients and carrier solutions is well-known to those of skill in the art, as is the development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including *e.g.*, oral, parenteral, intravenous, intranasal, and intramuscular administration and formulation.

1. ORAL DELIVERY

In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet.

The active compounds may even be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like (Mathiowitz *et al.*, 1997; Hwang *et al.*, 1998; U. S. Patent 5,641,515; U. S. Patent 5,580,579 and U. S. Patent 5,792,451, each specifically incorporated herein by reference in its entirety). The tablets, troches, pills, capsules and the like may also contain the following: a binder, as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar, or both. A syrup or elixir may contain the active compound sucrose as a sweetening agent methyl and propylparabens as preservatives, a dye and flavoring, such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparation and formulations.

Typically, these formulations may contain at least about 0.1% of the active compound or more, although the percentage of the active ingredient(s) may, of course, be varied and may conveniently be between about 1 or 2% and about 60% or 70% or more of the weight or volume of the total formulation. Naturally, the amount of active compound(s) in each therapeutically useful composition may be prepared in such a way that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

For oral administration the compositions of the present invention may alternatively be incorporated with one or more excipients in the form of a mouthwash, dentifrice, buccal tablet, oral spray, or sublingual orally-administered formulation. For example, a mouthwash may be prepared incorporating the active ingredient in the required amount in an appropriate solvent, such as a sodium borate solution (Dobell's Solution). Alternatively, the active ingredient may be incorporated into an oral solution such as one containing sodium borate, glycerin and potassium bicarbonate, or dispersed in a dentifrice, or added in a therapeutically-effective amount to a composition that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants. Alternatively the compositions may be fashioned into a tablet or solution form that may be placed under the tongue or otherwise dissolved in the mouth.

2. INJECTABLE DELIVERY

In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein parenterally, intravenously, intramuscularly, or even intraperitoneally as described in U. S. Patent 5,543,158; U. S. Patent 5,641,515 and U. S. Patent 5,399,363 (each specifically incorporated herein by reference in its entirety). Solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of

storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (U. S. Patent 5,466,468, specifically incorporated herein by reference in its entirety). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be facilitated by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a sterile aqueous medium that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject. Moreover, for human

administration, preparations should meet sterility, pyrogenicity, and the general safety and purity standards as required by FDA Office of Biologics standards.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

The compositions disclosed herein may be formulated in a neutral or salt form. Pharmaceutically-acceptable salts, include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective. The formulations are easily administered in a variety of dosage forms such as injectable solutions, drug-release capsules, and the like.

As used herein, "carrier" includes any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

The phrase "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when

administered to a human. The preparation of an aqueous composition that contains a protein as an active ingredient is well understood in the art. Typically, such compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection can also be prepared. The preparation can also be emulsified.

3. NASAL DELIVERY

In certain embodiments, the pharmaceutical compositions may be delivered by intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering genes, nucleic acids, and peptide compositions directly to the lungs *via* nasal aerosol sprays has been described *e.g.*, in U. S. Patent 5,756,353 and U. S. Patent 5,804,212 (each specifically incorporated herein by reference in its entirety). Likewise, the delivery of drugs using intranasal microparticle resins (Takenaga *et al.*, 1998) and lysophosphatidyl-glycerol compounds (U. S. Patent 5,725,871, specifically incorporated herein by reference in its entirety) are also well-known in the pharmaceutical arts. Likewise, transmucosal drug delivery in the form of a polytetrafluoroethylene support matrix is described in U. S. Patent 5,780,045 (specifically incorporated herein by reference in its entirety).

4. LIPOSOME-, NANOCAPSULE-, AND MICROPARTICLE-MEDIATED DELIVERY

In certain embodiments, the inventors contemplate the use of liposomes, nanocapsules, microparticles, microspheres, lipid particles, vesicles, and the like, for the introduction of the compositions of the present invention into suitable host cells. In particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like.

Such formulations may be preferred for the introduction of pharmaceutically-acceptable formulations of the nucleic acids or constructs disclosed herein. The formation and use of liposomes is generally known to those of skill in the art (see for example, Couvreur *et al.*, 1977; Couvreur, 1988; Lasic, 1998; which describes the use of liposomes and nanocapsules in the targeted antibiotic therapy for intracellular bacterial infections and diseases). Recently, liposomes were developed

with improved serum stability and circulation half-times (Gabizon and Papahadjopoulos, 1988; Allen and Choun, 1987; U. S. Patent 5,741,516, specifically incorporated herein by reference in its entirety). Further, various methods of liposome and liposome like preparations as potential drug carriers have been reviewed (Takakura, 5 1998; Chandran *et al.*, 1997; Margalit, 1995; U. S. Patent 5,567,434; U. S. Patent 5,552,157; U. S. Patent 5,565,213; U. S. Patent 5,738,868 and U. S. Patent 5,795,587, each specifically incorporated herein by reference in its entirety).

Liposomes have been used successfully with a number of cell types that are normally resistant to transfection by other procedures including T cell suspensions, 10 primary hepatocyte cultures and PC 12 cells (Renneisen *et al.*, 1990; Muller *et al.*, 1990). In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery systems. Liposomes have been used effectively to introduce genes, drugs (Heath and Martin, 1986; Heath *et al.*, 1986; Balazsovits *et al.*, 1989; Fresta and Puglisi, 1996), radiotherapeutic agents (Pikul *et al.*, 1987), enzymes (Imaizumi *et al.*, 15 1990a; Imaizumi *et al.*, 1990b), viruses (Faller and Baltimore, 1984), transcription factors and allosteric effectors (Nicolau and Gersonde, 1979) into a variety of cultured cell lines and animals. In addition, several successful clinical trails examining the effectiveness of liposome-mediated drug delivery have been completed (Lopez-Berestein *et al.*, 1985a; 1985b; Coune, 1988; Sculier *et al.*, 1988). Furthermore, several 20 studies suggest that the use of liposomes is not associated with autoimmune responses, toxicity or gonadal localization after systemic delivery (Mori and Fukatsu, 1992).

Liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs). MLVs generally have diameters of from 25 25 nm to 4 μ m. Sonication of MLVs results in the formation of small unilamellar vesicles (SUVs) with diameters in the range of 200 to 500 Å, containing an aqueous solution in the core.

Liposomes bear resemblance to cellular membranes and are contemplated for use in connection with the present invention as carriers for the peptide 30 compositions. They are widely suitable as both water- and lipid-soluble substances can be entrapped, *i.e.* in the aqueous spaces and within the bilayer itself, respectively. It is

possible that the drug-bearing liposomes may even be employed for site-specific delivery of active agents by selectively modifying the liposomal formulation.

In addition to the teachings of Couvreur *et al.* (1977; 1988), the following information may be utilized in generating liposomal formulations.

5 Phospholipids can form a variety of structures other than liposomes when dispersed in water, depending on the molar ratio of lipid to water. At low ratios the liposome is the preferred structure. The physical characteristics of liposomes depend on pH, ionic strength and the presence of divalent cations. Liposomes can show low permeability to ionic and polar substances, but at elevated temperatures undergo a phase transition
10 which markedly alters their permeability. The phase transition involves a change from a closely packed, ordered structure, known as the gel state, to a loosely packed, less-ordered structure, known as the fluid state. This occurs at a characteristic phase-transition temperature and results in an increase in permeability to ions, sugars and drugs.

15 In addition to temperature, exposure to proteins can alter the permeability of liposomes. Certain soluble proteins, such as cytochrome c, bind, deform and penetrate the bilayer, thereby causing changes in permeability. Cholesterol inhibits this penetration of proteins, apparently by packing the phospholipids more tightly. It is contemplated that the most useful liposome formations for antibiotic and
20 inhibitor delivery will contain cholesterol.

The ability to trap solutes varies between different types of liposomes. For example, MLVs are moderately efficient at trapping solutes, but SUVs are extremely inefficient. SUVs offer the advantage of homogeneity and reproducibility in size distribution, however, and a compromise between size and trapping efficiency is
25 offered by large unilamellar vesicles (LUVs). These are prepared by ether evaporation and are three to four times more efficient at solute entrapment than MLVs.

In addition to liposome characteristics, an important determinant in entrapping compounds is the physicochemical properties of the compound itself. Polar compounds are trapped in the aqueous spaces and nonpolar compounds bind to the lipid
30 bilayer of the vesicle. Polar compounds are released through permeation or when the bilayer is broken, but nonpolar compounds remain affiliated with the bilayer unless it is

disrupted by temperature or exposure to lipoproteins. Both types show maximum efflux rates at the phase transition temperature.

Liposomes interact with cells *via* four different mechanisms: endocytosis by phagocytic cells of the reticuloendothelial system such as macrophages and neutrophils; adsorption to the cell surface, either by nonspecific weak hydrophobic or electrostatic forces, or by specific interactions with cell-surface components; fusion with the plasma cell membrane by insertion of the lipid bilayer of the liposome into the plasma membrane, with simultaneous release of liposomal contents into the cytoplasm; and by transfer of liposomal lipids to cellular or subcellular membranes, or vice versa, without any association of the liposome contents. It often is difficult to determine which mechanism is operative and more than one may operate at the same time.

The fate and disposition of intravenously injected liposomes depend on their physical properties, such as size, fluidity, and surface charge. They may persist in tissues for h or days, depending on their composition, and half lives in the blood range from min to several h. Larger liposomes, such as MLVs and LUVs, are taken up rapidly by phagocytic cells of the reticuloendothelial system, but physiology of the circulatory system restrains the exit of such large species at most sites. They can exit only in places where large openings or pores exist in the capillary endothelium, such as the sinusoids of the liver or spleen. Thus, these organs are the predominate site of uptake. On the other hand, SUVs show a broader tissue distribution but still are sequestered highly in the liver and spleen. In general, this *in vivo* behavior limits the potential targeting of liposomes to only those organs and tissues accessible to their large size. These include the blood, liver, spleen, bone marrow, and lymphoid organs.

Targeting is generally not a limitation in terms of the present invention. However, should specific targeting be desired, methods are available for this to be accomplished. Antibodies may be used to bind to the liposome surface and to direct the antibody and its drug contents to specific antigenic receptors located on a particular cell-type surface. Carbohydrate determinants (glycoprotein or glycolipid cell-surface components that play a role in cell-cell recognition, interaction and adhesion) may also be used as recognition sites as they have potential in directing liposomes to particular cell types. Mostly, it is contemplated that intravenous injection of liposomal preparations would be used, but other routes of administration are also conceivable.

Alternatively, the invention provides for pharmaceutically-acceptable nanocapsule formulations of the compositions of the present invention. Nanocapsules can generally entrap compounds in a stable and reproducible way (Henry-Michelland *et al.*, 1987; Quintanar-Guerrero *et al.*, 1998; Douglas *et al.*, 1987). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1 μm) should be designed using polymers able to be degraded *in vivo*. Biodegradable polyalkyl-cyanoacrylate nanoparticles that meet these requirements are contemplated for use in the present invention. Such particles may be easily made, as described (Couvreux *et al.*, 1980; 1988; zur Muhlen *et al.*, 1998; Zambaux *et al.*, 1998; Pinto-Alphandry *et al.*, 1995 and U. S. Patent 5,145,684, specifically incorporated herein by reference in its entirety).

VACCINES

In certain preferred embodiments of the present invention, vaccines are provided. The vaccines will generally comprise one or more pharmaceutical compositions, such as those discussed above, in combination with an immunostimulant. An immunostimulant may be any substance that enhances or potentiates an immune response (antibody and/or cell-mediated) 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.

Illustrative vaccines 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. It will be apparent that a vaccine may comprise both a polynucleotide and a polypeptide component. Such vaccines may provide for an enhanced immune response.

It will be apparent that a vaccine may contain pharmaceutically acceptable salts of the polynucleotides and polypeptides provided herein. Such salts may be prepared from pharmaceutically acceptable non-toxic bases, including organic bases (e.g., salts of primary, secondary and tertiary amines and basic amino acids) and inorganic bases (e.g., sodium, potassium, lithium, ammonium, calcium and magnesium salts).

While any suitable carrier known to those of ordinary skill in the art may be employed in the vaccine 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
5 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
10 pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763; 5,814,344 and 5,942,252. One may also employ a carrier comprising the particulate-protein complexes described in U.S. Patent No. 5,928,647, which are capable of inducing a class I-restricted cytotoxic T lymphocyte
15 responses in a host.

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, bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum
20 hydroxide), solutes that render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents 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.

25 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, *Bordetella pertussis* or *Mycobacterium tuberculosis* derived proteins. Suitable
30 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); AS-2 (SmithKline Beecham, Philadelphia, PA);

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
5 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 , TNF α , IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast,
10 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
15 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-
20 de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Corixa Corporation (Seattle, WA; *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,
25 for example, in WO 96/02555, WO 99/33488 and U.S. Patent Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by Sato *et al.*, *Science* 273:352, 1996. Another preferred adjuvant is a saponin, preferably QS21 (Aquila Biopharmaceuticals Inc., Framingham, MA), which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the
30 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 comprise 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.

Other preferred adjuvants include Montanide ISA 720 (Seppic, France),
5 SAF (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series of adjuvants (*e.g.*, SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium), Detox (Corixa, Hamilton, MT), RC-529 (Corixa, Hamilton, MT) and other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. Patent Application Serial Nos. 08/853,826 and 09/074,720, the disclosures
10 of which are incorporated herein by reference in their entireties.

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
15 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 (*see, e.g.*, Coombes *et al.*, *Vaccine* 14:1429-1438, 1996) and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a
20 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. Such carriers include microparticles of poly(lactide-co-glycolide), polyacrylate, latex, starch, cellulose, dextran and the like. Other delayed-release carriers include supramolecular biovectors, which comprise a non-liquid hydrophilic core (*e.g.*, a cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer comprising an amphiphilic compound, such as a phospholipid (*see e.g.*, U.S. Patent No. 5,151,254 and PCT applications WO 94/20078,
30 WO/94/23701 and WO 96/06638). 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
5 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
10 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
15 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
20 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,
25 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
30 cytokines such as GM-CSF, IL-4, IL-13 and/or TNF α 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, TNF α , CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, 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 Fc γ receptor and mannose receptor. 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).

APCs may generally be transfected with a polynucleotide encoding an ovarian tumor protein (or portion or other variant thereof) such that the ovarian 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 ovarian 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.

Vaccines and pharmaceutical compositions may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are preferably hermetically sealed to preserve sterility of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily or aqueous vehicles. Alternatively, a vaccine or pharmaceutical composition may be stored in a freeze-dried condition requiring only the addition of a sterile liquid carrier immediately prior to use.

CANCER THERAPY

In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as ovarian 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. Administration may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical and oral routes.

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 as provided 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
5 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
10 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
15 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,
20 monocyte, fibroblast and/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
25 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
30 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 described 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 an ovarian 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.

CANCER DETECTION AND DIAGNOSIS

In general, a cancer may be detected in a patient based on the presence of one or more ovarian tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum 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 ovarian 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, an ovarian 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 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 ovarian

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
5 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
10 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).
15 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
20 polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 μ g, and preferably about 100 ng to about 1 μ g, 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
25 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
30 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 20TM (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 ovarian 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 20TM. 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).

- 5 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 ovarian cancer, the signal detected from the reporter group that remains bound to the solid
10 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
15 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%-
20 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
25 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
30 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 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 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 ovarian tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such ovarian 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 an ovarian 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 an ovarian 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 ovarian 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.

10 As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding an ovarian 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 an ovarian 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 ovarian 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 an ovarian 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 an ovarian tumor protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described 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.

30 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:1-222. 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
5 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
10 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.

15 In another embodiment, the compositions described herein 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(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter
20 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.
25 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 ovarian tumor protein
30 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

5 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 an ovarian
10 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.

15 Alternatively, a kit may be designed to detect the level of mRNA encoding an ovarian 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 an ovarian tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that
20 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 an ovarian tumor protein.

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

EXAMPLE 1

IDENTIFICATION OF CDNAS ENCODING OVARIAN AND ENDOMETRIAL TUMOR PROTEINS

An ovarian/endometrial tumor cell line subtracted library was constructed. A library was prepared from endometrial and ovarian tumor cell lines: EndoTL 391-73 (100% undifferentiated endometrial carcinoma), OTL 298-95 (100% moderately differentiated papillary serous ovarian adenocarcinoma) and OTL 522-24 (30% mesothelial cells/70% poorly differentiated metastatic ovarian adenocarcinoma). This library was subtracted with liver, pancreas, skin, bone marrow, resting PBMC, stomach, and brain cDNA and spiked with eukaryotic elongation factor 1 α . Resulting cDNA was cloned into the pcDNA3.1(+) (Invitrogen) vector to generate the ovarian tumor cell line subtraction 4 library (OTCLS4). The OTCLS4 library contained 117,200 clones (background 58,400), with a 1333 bp average insert size (inserts ranged from 200 to 5650 bp).

Thirty clones were sequenced. Of these 12 were full length. The clones may be grouped as follows (SEQ ID NOs are provided in Table 2):

- 7 Novel
- 4 Homo sapiens aldehyde dehydrogenase 6 (ALDH6) mRNA
- 3 Human ferritin heavy chain mRNA, complete cds
- 2 Human lysyl oxidase gene, partial cds
- 2 Human mitochondrion, complete genome
- 1 Homo sapiens aldehyde reductase 1 (low Km aldose reductase) ALDR1) mRNA
- 1 Homo sapiens chromosome 11q12.2 PAC clone pDJ519o13
- 1 Homo sapiens chromosome-associated polypeptide C (CAP-C) mRNA
- 1 Homo sapiens clone 24452 mRNA sequence
- 1 Homo sapiens dipeptidylpeptidase IV (CD26, adenosine deaminase complexing protein 2) (DPP4 mRNA)
- 1 Homo sapiens guanine nucleotide binding protein (G protein), beta polypeptide 2-like 1 (GNB2L1), mRNA
- 1 Homo sapiens heat shock 27kD protein 1 (HSPB1) mRNA
- 1 Homo sapiens homeo box B2 (HOXB2) mRNA

- 1 Homo sapiens mRNA for KIAA0865 protein, partial cds
- 1 Homo sapiens mRNA; cDNA DKFZp564A2416 (from clone DKFZp564A2416)
- 1 Homo sapiens NADH-ubiquinone oxidoreductase 39kDA subunit mRNA,
5 nuclear gene encoding mitochondrial protein, complete cds
- 1 Homo sapiens Sk/Dkk-1 protein precursor, mRNA, complete cds
- 1 Homo sapiens sodium channel, nonvoltage-gated 1 alpha (SCNN1A) mRNA
- 1 Homo sapiens SRP1 mRNA, partial sequence
- 1 Homo sapiens zinc finger protein SLUG (SLUG) gene, complete cds
- 10 1 Human 28S ribosomal RNA gene
- 1 Human cofilin mRNA, partial cds
- 1 Human DNA sequence from clone 967N21 on chromosome 20p12.3-13
- 1 Human fibroblast collagenase inhibitor mRNA, complete cds
- 1 Human fibroblast mRNA for aldolase A
- 15 1 Human HepG2 3' region MboI cDNA, clone hmd6a06m3
- 1 Human MAP kinase kinase MEK5c mRNA, complete cds
- 1 Human mRNA for coupling protein G(s) alpha-subunit (alpha-S1)
- 1 Human mRNA for KIAA0026 gene, completecds|gi|4808630|gb|AF100620.1|
AF100620 Homo sapiens transcription factor-like protein MRGX (MRGX)
20 mRNA, complete cds
- 1 Human mRNA for KIAA0064 gene, complete cds
- 1 Human mRNA for KIAA0204 gene, complete cds
- 1 Human plasminogen activator inhibitor-1 (PAI-1) mRNA, complete cds
- 1 Human protocadherin 43 mRNA, 3' end of cds for alternative splicing PC43-
25 12
- 1 Human putative RNA binding protein Koc1 mRNA, complete cds
- 1 Human TCB gene encoding cytosolic thyroid hormone-binding protein,
complete cds
- 1 Human ubiquitin-homology domain protein PIC1 mRNA, complete cds
- 30

Table 2

Ovarian/Endometrial Carcinoma Associated cDNA Sequences

Sequence	SEQ ID NO	Comments
32609	36	<i>Homo sapiens</i> aldehyde dehydrogenase 6 (ALDH6) mRNA
32515	4	<i>Homo sapiens</i> aldehyde reductase 1 (low Km aldose reductase) (ALDR1) mRNA
32562	29	<i>Homo sapiens</i> Chromosome 11q12.2 PAC clone pDJ519o13
32523	9	<i>Homo sapiens</i> chromosome-associated polypeptide C (CAP-C) mRNA
32551	24	<i>Homo sapiens</i> clone 24452 mRNA sequence
32518	6	<i>Homo sapiens</i> dipeptidylpeptidase IV (CD26, adenosine deaminase complexing protein 2) (DPP4) mRNA
32534	13	<i>Homo sapiens</i> guanine nucleotide binding protein (G protein), beta polypeptide 2-like 1 (GNB2L1), mRNA
32507	2	<i>Homo sapiens</i> heat shock 27kD protein 1 (HSPB1) mRNA
32533	12	<i>Homo sapiens</i> homeo box B2 (HOXB2) mRNA
32565	20	<i>Homo sapiens</i> mRNA for KIAA0865 protein, partial cds
32553	19	<i>Homo sapiens</i> mRNA; cDNA DKFZp564A2416 (from clone DKFZp564A2416)
32561	28	<i>Homo sapiens</i> NADH-ubiquinone oxidoreductase 39kDa subunit mRNA, nuclear gene encoding mitochondrial protein, complete cds
32510	3	<i>Homo sapiens</i> Sk/Dkk-1 protein precursor, mRNA, complete cds
32546	16	<i>Homo sapiens</i> sodium channel, nonvoltage-gated 1 alpha (SCNN1A) mRNA
32559	27	<i>Homo sapiens</i> SRP1 mRNA, partial sequence
32506	1	<i>Homo sapiens</i> zinc finger protein SLUG gene, complete cds
32519	7	Human 28S ribosomal RNA gene
32602	22	Human cofilin mRNA, partial cds
32569	31	Human DNA sequence from clone 967N21 on chromosome 20p12.3-13
32525	10	Human ferritin heavy chain mRNA, complete cds
32557	26	Human fibroblast collagenase inhibitor mRNA, complete cds
32517	5	Human fibroblast mRNA for aldolase A
32568	30	Human HepG2 3' region MboI cDNA, clone hmd6a06m3
32548	17	Human lysyl oxidase gene, partial cds
32520	8	Human mitochondrion, complete genome
32617	23	Human mRNA for coupling protein G(s) alpha-subunit (alpha-S1)

32572	32	Human mRNA for KIAA0026 gene, complete cds gi 4808630 gb AF100620.1 AF100620 <i>Homo sapiens</i> transcription factor-like protein MRGX (MRGX) mRNA, complete cds
32600	21	Human mRNA for KIAA0064 gene, complete cds
32537	14	Human mRNA for KIAA0204 gene, complete cds
32552	25	Human plasminogen activator inhibitor-1 (PAI-1) mRNA, complete cds
32615	39	Human protocadherin 43 mRNA, 3' end of cds for alternative splicing PC43-12
32613	38	Human putative RNA binding protein Koc1 mRNA, complete cds
32610	37	Human TCB gene encoding cytosolic thyroid hormone-binding protein, complete cds
32539	15	Human ubiquitin-homology domain protein PIC1 mRNA, complete cds
32619	40	Novel
32576	33	Novel
32608	35	Novel
32607	34	Novel
32620	41	Novel
32550	18	Novel
32529	11	Novel

Using the methods outlined above, an additional 162 clones were isolated and sequenced. The cDNA sequences are shown in SEQ ID NO:42-203.

SEQ ID NO:204-209 represent additional clones from the OTCL S4 library. SEQ ID NO:206 (clone 57881), 208 (clone 57884), 107 (clone R0199:A07) and 80 (clone R0198:F02) represent novel sequences. The remaining sequences are shown in Table 3, which includes additional results from homology searches.

Table 3

Sequence	SEQ ID NO	Comments
57877	204	H. Sapiens novel gene from PAC 117P20, chromosome 1
57879	205	Urokinase plasminogen activator surface receptor (uPAR)
57882	207	Lysophospholipase 1 (LYPA1)
57888	209	IGF-II mRNA binding protein 3 (IMP-3) mRNA
R0198:H03	99	<i>Homo sapiens</i> laminin
R0199:B03	111	Human cyclin protein gene, complete cds
R0200:A12	158	<i>Homo sapiens</i> monocarboxylate transporter (MCT3) mRNA
R0199:C12	125	Unigene: Hs93379
R0200:A10	157	Human mRNA for KIAA0101 gene, complete cds
R0198:D01	61	Unigene: Hs42116
R0200:C02	164	Human proliferating cell nuclear antigen (PCNA) gene
R0200:G02	193	<i>Homo sapiens</i> Xq28 BAC RP5-1014016

EXAMPLE 2

5 ANALYSIS OF cDNA EXPRESSION USING MICROARRAY TECHNOLOGY

In additional studies, sequences disclosed herein were found to be overexpressed in specific tumor tissues as determined by microarray analysis. Using this approach, cDNA sequences are PCR amplified and their mRNA expression profiles in tumor and normal tissues are examined using cDNA microarray technology essentially as described (Shena *et al.*, 1995). In brief, the clones are arrayed onto glass slides as multiple replicas, with each location corresponding to a unique cDNA clone (as many as 5500 clones can be arrayed on a single slide, or chip). Each chip is hybridized with a pair of cDNA probes that are fluorescence-labeled with Cy3 and Cy5, respectively. Typically, 1 μ g of polyA⁺ RNA is used to generate each cDNA probe.

15 After hybridization, the chips are scanned and the fluorescence intensity recorded for both Cy3 and Cy5 channels. There are multiple built-in quality control steps. First, the probe quality is monitored using a panel of ubiquitously expressed genes. Secondly, the control plate also can include yeast DNA fragments of which complementary RNA may be spiked into the probe synthesis for measuring the quality of the probe and the

20 sensitivity of the analysis. Currently, the technology offers a sensitivity of 1 in 100,000

copies of mRNA. Finally, the reproducibility of this technology can be ensured by including duplicated control cDNA elements at different locations.

A total of 428 clones from the OCTLS4 library were analyzed on Ovarian Chip-3. The following table, Table 4, provides a list of probes used to
 5 interrogate these clones. A total of 16 clones were identified which showed at least 2-fold overexpression in ovarian tumors when compared to non-ovarian essential normal tissues and had a mean non-ovarian essential normal tissue expression of less than 0.2. These clones are represented by SEQ ID NO:204-209 and by SEQ ID NO:61, 99, 111, 125, 157, 158, 164 and 193.

10

Table 4

Tissue	Clone ID	Microarray ID	Tumor information
Ovarian tumor Adrenal gland normal	261A SPACT37	391cy3 391cy5	Stage IIIC
Ovary tumor Skin normal	264A 396A	392cy3 392cy5	Stage IIIC
Ovary tumor Thymus normal	265A SPACT56	393cy3 393cy5	Stage IIIC
Ovary tumor Bronchus normal	288A 600C	394cy3 394cy5	Stage IIIC
Ovary tumor	854A 785B	395cy3 395cy5	
Ovary tumor Bone normal	855A 407B	396cy3 396cy5	Grade III, Stage IA
Ovary tumor Peritoneum epithelium normal	856A 484A	397cy3 397cy5	Serous papillary
Ovary tumor Pituitary gland	603A SPACT52	398cy3 398cy5	Metastatic adenocarcinoma, Grade III, Stage III
Ovary tumor Skeletal muscle normal	857A SPACT40	399cy3 399cy5	Papillary serous cystadenocarcinoma Grade III, Stage IB
Ovary tumor Stomach normal	385A SPACT55	400cy3 400cy5	Papillary serous adenocarcinoma
Ovary tumor Spleen normal	392A SPACT54	401cy3 401cy5	Papillary serous neoplasm, Stage IC
Ovary tumor Pancreas normal	858A 862A	402cy3 402cy5	Papillary serous cystadenocarcinoma Grade II-III, Stage IA

Ovary tumor Ovary normal	859A S27	403cy3 403cy5	Papillary serous adenocarcinoma Grade II-III, Stage IIB
Ovary tumor Spinal cord normal	605A SPACT45	404cy3 404cy5	Serous borderline tumor, stage IIIC
Ovary tumor Heart normal	495A SPAAm1	405cy3 405cy5	Papillary serous carcinoma, Grade II, Stage III
Ovary tumor Ovary normal	381C S7	414cy3 414cy5	Mucinous adenocarcinoma, Grade I, Sage IB
Ovary tumor Ovary normal	382A S449A	416cy3 416cy5	Mucinous adenocarcinoma
Ovary tumor metastases Small intestine normal	428B SPACT53	417cy3 417cy5	Mucinous adenocarcinoma
Ovary tumor Esophagus normal	491A 502B	418cy3 418cy5	Endometriod adenocarcinoma
Ovary tumor Colon normal	335A 199A	419cy3 419cy5	Endometriod adenocarcinoma Grade II, Stage II
Ovary tumor Thyroid gland normal	494A SPACT46	421cy3 421cy5	Adenocarcinoma Grade III, Stage II- III
Ovary tumor PBMC (resting)	860A 783A	42cy3 422cy5	Endometriod adenocarcinoma Grade II-III, Stage IIIC
Ovary tumor Aorta normal	604A 415A	423cy3 423cy5	Clear cell carcinoma
Ovary tumor Trachea normal	607A 776A	424cy3 424cy5	Clear cell, Stage IA
Ovary tumor Trachea normal	S25 CT25	425cy3 425cy5	Granulosa cell tumor, Stage IA
Ovary tumor Pancreas normal pool	S22 PAN2000	426cy3 426cy5	Granulosa cell tumor, Stage IA
Ovary tumor Breast (HMEC) normal	386A S92	427cy3 427cy5	Germ cell tumor, Stage I
Ovary tumor Bladder normal	602A 328B/C	429cy3 429cy5	Papillary serous carcinoma, Grade III, Stage IIIB
Ovary tumor Bone marrow normal	S23 SPACT49	430cy3 430cy5	Papillary serous adenocarcinoma Grade III, Stage IIIC

Ovary tumor Lung normal	606A SPAAm2	428cy3 428cy5	Papillary serous cystadenocarcinoma Grade II, Stage IIIB
Ovary tumor metastases Kidney normal	383A 302B	431cy3 431cy5	Metastatic papillary adenocarcinoma, Grade III, Stage IIIA
Ovary tumor metastases PBMC (activated)	384A S40.782A	423cy3 423cy5	Papillary serous adenocarcinoma Grade II, Stage IIIB
Ovary tumor metastases Ovary tumor match with CY3	426A 603A	433cy3 433cy5	Papillary serous adenocarcinoma Grade III, Stage IIIB
Ovary tumor metastases Liver normal	429A 270B	434cy3 434cy5	Papillary adenocarcinoma Grade III, Stage III
Ovary tumor Brain normal	427A SPACT50	435cy3 435cy5	Papillary serous adenocarcinoma Grade III, Stage IIIC
Ovary tumor Bone normal	855A 407B	436cy3 436cy5	Grade III, Stage IA
Ovary tumor Spinal cord normal	605A SPACT45	437cy3 437cy5	Serous borderline tumor, Stage IIIC
Ovary tumor Heart normal	495A SPAAm1	438cy3 438cy5	Papillary serous carcinoma, Grade II, Stage III
Ovary tumor Ovary normal	381C S7	439cy3 439cy5	Mucinous adenocarcinoma, Grade I, Stage IB

EXAMPLE 3

SYNTHESIS OF POLYPEPTIDES

- 5 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.*
- 10 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
- 15 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.

- From the foregoing it will be appreciated that, although specific
- 20 embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

What is claimed:

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

- (a) sequences provided in SEQ ID NO: 1-222;
- (b) complements of the sequences provided in SEQ ID NO: 1-222;
- (c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NO: 1-222;
- (d) sequences that hybridize to a sequence provided in SEQ ID NO: 1-222, under moderately stringent conditions;
- (e) sequences having at least 75% identity to a sequence of SEQ ID NO: 1-222;
- (f) sequences having at least 90% identity to a sequence of SEQ ID NO: 1-222; and
- (g) degenerate variants of a sequence provided in SEQ ID NO: 1-222.

2. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

- (a) sequences encoded by a polynucleotide of claim 1; and
- (b) sequences having at least 70% identity to a sequence encoded by a polynucleotide of claim 1; and
- (c) sequences having at least 90% identity to a sequence encoded by a polynucleotide of claim 1.

3. An expression vector comprising a polynucleotide of claim 1 operably linked to an expression control sequence.

4. A host cell transformed or transfected with an expression vector according to claim 3.

5. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a polypeptide of claim 2.

6. A method for detecting the presence of a cancer in a patient, comprising the steps of:

- (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with a binding agent that binds to a polypeptide of claim 2;
- (c) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (d) comparing the amount of polypeptide to a predetermined cut-off value and therefrom determining the presence of a cancer in the patient.

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

8. An oligonucleotide that hybridizes to a sequence recited in SEQ ID NO: 1-222 under moderately stringent conditions.

9. A method for stimulating and/or expanding T cells specific for a tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:

- (a) polypeptides according to claim 2;
- (b) polynucleotides according to claim 1; and
- (c) antigen-presenting cells that express a polypeptide according to claim 2,

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

10. An isolated T cell population, comprising T cells prepared according to the method of claim 9.

11. A composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component selected from the group consisting of:

- (a) polypeptides according to claim 2;
- (b) polynucleotides according to claim 1;
- (c) antibodies according to claim 5;
- (d) fusion proteins according to claim 7;
- (e) T cell populations according to claim 10; and
- (f) antigen presenting cells that express a polypeptide according to claim 2.

12. A method for stimulating an immune response in a patient, comprising administering to the patient a composition of claim 11.

13. A method for the treatment of a cancer in a patient, comprising administering to the patient a composition of claim 11.

14. A method for determining the presence of a cancer in a patient, comprising the steps of:

- (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with an oligonucleotide according to claim 8;
- (c) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and
- (d) compare the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence of the cancer in the patient.

15. A diagnostic kit comprising at least one oligonucleotide according to claim 8.

16. A diagnostic kit comprising at least one antibody according to claim 5 and a detection reagent, wherein the detection reagent comprises a reporter group.

17. 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 according to claim 2; (ii) polynucleotides according to claim 1; and (iii) antigen presenting cells that express a polypeptide of claim 2, such that T cell proliferate;

(b) administering to the patient an effective amount of the proliferated T cells,

and thereby inhibiting the development of a cancer in the patient.

SEQUENCE LISTING

<110> Corixa Corporation
 Xu, Jiangchun
 Pyle, Ruth
 Secrist, Heather

<120> COMPOSITIONS AND METHODS FOR THE THERAPY
 AND DIAGNOSIS OF OVARIAN AND ENDOMETRIAL CANCER

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<220>
<221> misc_feature
<222> (1)...(375)
<223> n = A,T,C or G

```

```

<400> 12
tttttttttt tttttttttt ttttttggnn ttataaanac atttatttaa tctatgaaaa 60
taatgnacaa taaatacttt ccccttttcc tattattaaa naattttaat aaataatnta 120
cagtctaaaa cataaaaaag aggaaaaatag gncctcttag ttatttttaa naaagncccc 180
ctanagttaa attattcctg anatttcatt ggaaggagtc taccaaacgg aatttttctg 240
ngngaatttt aaaanataac cgagtgccca atattttaga agaagaagaa aggaagngga 300
ttaaacgcta attcagtaat acctgaattt tagcaaaaca cataagtcta tgcgactgag 360
ggngggagan gntcg 375

```

```

<210> 13
<211> 658
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(658)
<223> n = A,T,C or G

```

```

<400> 13
ctctctcttt cactgcaagg cggcggcagg agaggttgtg gtgctagttt ctctaagcca 60
tccagtgcca tcctcgtcgc tgcagcgaca cacgctctcg ccgccgccat gactgagcag 120
atgacccttc gtggcaccct caagggccac aacggctggg taaccagat cgctactacc 180
ccgcagttcc cggacatgat cctctccgcc tctcgagata agaccatcat catgtggaag 240
ctgaccaggg atgagaccaa ctatggaatt ccacagcgtg ctctgcgggg tcaactccac 300
tttgtagtg atgtggttat ctctcagat ggccagtttg ccctctcang ctctggggat 360
ggaaccctgc gcctctggga tctcacaacg ggcaccacca cgaggcgatt tgtgggccat 420
accaaggatg tgcttgagtg tggccttctc tttgacaacc cggcagattg ncttttggat 480
ctcnanaata aaaccatcaa nctattgaat accctggngg tgggtgcaaat ccntgtcca 540
ngaaganaac cncttcanaa nggggtctt tgtgnncnt ttttnnccca acncaacaac 600
cctnttattn nntnccctngg gttggaaaan ctggcnnggn tnganccggn tnactggg 658

```

```

<210> 14
<211> 686
<212> DNA
<213> Homo sapien

```

```

<220>

```

<221> misc_feature
 <222> (1)...(686)
 <223> n = A,T,C or G

<400> 14
 cctttttttt tttttttttt tttttttttt aacattatac tgn cattttt atcataacaa 60
 tataaacaat ttttatcatc atcctgaata ttactttata aanatatata ttttaaaagg 120
 ntttcaaaac atttttcaac ccagcatttg agaataaagc attaagagtt ttgnatacag 180
 taacacattc atgngataag ngnatgaatt tacaaccata cataatatgg atatatggat 240
 atatatattat ataaaaaaca aacttggcca naagttaagg ntacctacna agttgtccaa 300
 gtaaatattg ctgggcaaaa caattataaa attcaaatca cacatgcatt tttaaatcat 360
 ctaaatcact gcaaaccaang gtcaagcatt ccaaangttt taaaatnang ggggangang 420
 ggaancnggc cctccaannt taaagggcc gtttaaaacc cccttgacct cccccccaca 480
 ggngnttttt aactnccncc catttntggt gtttgnncnt ttcnccgggg ccttcttttg 540
 cccttggang gggccncccc cccttgggcc ttccnaaata aaaggaggga aaanngnntt 600
 cccacgnccc ccccgcnatg natnctctcc tntaaaaaaa ngggngggnc gngannctaa 660
 nnggagnggt ttggcnaanc acttct 686

<210> 15
 <211> 725
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(725)
 <223> n = A,T,C or G

<400> 15
 cctttttttt tttttttgat ttttacaat attgnttatt ttaatgaagc tggtagagac 60
 aatgtccatt taaaacccat atcccaggcc aaaaagtaca aataaaatca aaaagagcag 120
 tgtttctgntg tattcatttc tgnatgtata gctttattaa ttngctaag aaaattanaa 180
 cttttctggg atcttctgac aagattttta aaaaatotta aaatgccttt tcttcagtga 240
 aggcactttt ggagttncca ataaagggn cccccctnc catcttnact tnaacctgat 300
 attnntnttg tgnngggggg ggngggngaa attttaaaaa tatnttaatt taaggaaagg 360
 ncattttttc acagtctaag ttctntgnaa aacttncatt ttcccacnga aagnganagt 420
 tnangaannc ccccnngggc ncnccccacc ntngggggca anttgnaaan tnattatnga 480
 acncttggtt ttgnttgaat tnttntgnt aacgnnnaat tgcgtgnaag aangctatcg 540
 ttntctgtaa aaaaagggga aacttttntc atantntccn ntannttctt tttanaaacc 600
 ccnccccccc ctaaatgtga ncnccgatn ttttncgggg gntggatntt nntcngccct 660
 tcnncncccg cctttttttt anacgcenat ttatatnttn taantttatn taantttctca 720
 tntct 725

<210> 16
 <211> 196
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(196)
 <223> n = A,T,C or G

<400> 16
 cngaaggtn gctnccacct ggcacacct cctccttccn acttntgccc ccaccccatg 60
 tctctgtcct tgtcccagcc aggccctgct ccctctccag ccttgacagc ccctccccct 120
 gcctatgcc cctggggccc ccgcccattc ccagggggct ctgcaggggc cagttcctcc 180
 gcctgtcttc tggggg 196

<210> 17
<211> 667
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(667)
<223> n = A,T,C or G

<400> 17
cagccgtgaa actggaaagt cattttgatg actgatgtga tacatccaga ggtaaaatgc 60
atttaaaccat attaaagtat ttgccaaaga tacaattttc ttgctgacat aaaaatcaca 120
caaacaagtc ccccccaaac cacaactgtc tctcaaatag cttaaaaaaa ttgaaaaaca 180
ttttaggatt tttcaagttt tctagatttt aaaaagatgt tcagctatta gaggaatggt 240
aaaaatttta tattatctag aacacaggaa catcatcctg ggttattcag gaatcagtca 300
cacatgtgtg tgtgtctgag atatagtcta aattagcaaa gcacatagta ttacatactt 360
gaggggttgg tgaacaaagg aaaaatatac tttctgcaaa accaangact gtgctgcgta 420
atgagacagc tgtgatttca tttgaaactg tgaaaccatg tgccataata gaattttgag 480
aattttgctt ttacctaaat tcaagaaat gaaattacac ttttnagtta gngngngctt 540
aacataattt tttctatntt aaccctgatt naaatctcaa gtaagaattt nccgtggccc 600
gaaacttggt angggggaat tttaaaaggg cctcgcattc cgggttacat ggcntanaan 660
tggaagg 667

<210> 18
<211> 1493
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(1493)
<223> n = A,T,C or G

<400> 18
ccccatttct ccattttgtg gaccaagcca tcctgagggc atggacattg tctctgagga 60
aattggggcc acccttaaga tacciaagaaa agctcctgcc catggtccca ctggaaatgg 120
actctgctga gcaaaagccac cagttgaaga gaacagaatc cacacctgca ttgaatacct 180
gtttctccat gtgtatcgtc tctgagatta ccttcttgcc ctttccaaca ccttagtgat 240
tcctcaattt ctccccattt gggaaggcca tagggcatta actgaaggaa ctgacctctc 300
tccttttctt gtacctttaa cctttagtct gtcaaggaaa acccttagga cctctgaatc 360
aagaggactg agtttgtggg tgaaccttga aggtgctctt tctgctacaa gggccctggg 420
agatagcatg ggacgtgcat tgagaagcca gcctcagacc ttagcttgaa gcancttgag 480
gccagacctc ctgtacctca gcactctgct aggaggcatg gaagtgatct atcctgccag 540
gaggcctcag agtgatctgt cctgccagga ggggtgagag tgatctgtcc tgtgaggcat 600
ttaggggctt taggaattan taaaaggggg agtatgcctt tccagaatct tccatcttcc 660
tttgganacc tggccttctc ccatttctc ccttttgccc ccaggtanga aggatggagg 720
gaggnttggt actnttnccc ttctgggggc ccttctggg ggcctaacc tgncaathtt 780
anttcnccc tcctttacct nggatgnng ggnccctttn ccgggattta anccttgggg 840
ctgggcccta anttttttcc ctttttttcc ccnaaaaaaa aaaaaagggg ggggcccccc 900
ctgnnnnnng ntttttnnaa aatncccccc nngncntnng gncccnccn nccccnntt 960
tnnttnancc nccctgggg ggtccnttt ngggggnnt tnnnttttna nccnnnnnn 1020
ggggnntttt ttttnnnnaa aaantttttt ttnnnnnnc nnnnnnnnn nncnnttttn 1080
nnnnnggggg gnggntnnnn nnttttnann nccccnttt tnnngnnnaa annccnnnn 1140
nnnnnggggg gggnnnnnnn nnnnnnnnnn nnnncnccc cnnnnnnnnn nnnnnnnnn 1200
nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnn 1260
nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnn 1320

nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 1380
nnnnncngnnn cnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 1440
nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnc 1493

<210> 19
<211> 1602
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(1602)
<223> n = A,T,C or G

<400> 19
ggaaaatcaa gatgtggctg aagatcagag gctcagttag caacctgtgt tgtagcagtg 60
atgtcagtc attgattgtc tttagagagt taatgttaca aaaaagaatt cttataaatc 120
agacaaacat gatctgctga ggacacatgc gctttttagt aatttaacat ctggtgtttt 180
tctgaaaaaa tatatatata tatattgctt tatttgaaac aaattaaaat atgctgcatt 240
tgaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 300
aaaanaaaaa aaaaaaaaaa angggggggg cccccccng gnnngnnttt ttgnaaantc 360
cccccccn n gapntnggg ncccnacnnc ggccccannt ttantttaan cccncccc 420
cttggggccc ccctnnnggg ggggntttna tttccaaan ccccaanng ngggggtnt 480
tnntttcncc aaaaancnnt ttttttnna accncccc ggaaccccn ccccccttt 540
ttcntttaag ggggggnggg gntttnttc ccccttttg gaaaancccc ctttttttt 600
tggggggccc aaaaaaacc cccctttng naccnnnnan gggggggggg ggggnaancc 660
tttgggaaaa ccccccnng gggagngaaa anccccctt tccccccc cctttttgt 720
tttcctnngc cccaaaaacc ccntccccc ntgggggann tnggcngng anncnannan 780
cccnnaaaan gnccccccc cccnnnggn gaaaaanncc cccnaangg ggnntntntc 840
ccnggggana aaanccng ggggggngcn ttttccccg tttngncccc naaanggggg 900
gggccccct tgggcnnnna aaaccccc ttnntnccn ccccgnggg ggggnnttt 960
cccccnaaa ntccccccc ctngcccna anggaaaac cccnnngng gggcccttn 1020
gggncccc cnntttttc cccccnggg gggggggng nngggggga nccccgng 1080
gggcctttc nnnngtttt cncncncc cctntnnng gggtgaaan accccccn 1140
ngnnttnntn anccccca nannngncc ccnnttttg tccccccn cngaanncn 1200
acccccccc ccanntttt ttgnnngg gncccccn gngnntntt nccccccc 1260
cccccccc cgggggngn ggnnttttt gnnnnnnnn nccccnggg gggngcccc 1320
ncccccncc ggnntttgg ngnncccc ctnntttnt tnnnccncc cccccccc 1380
cgcnnttnn gngngngng nnnnngcn cccctnnn gntcnntnt ccccccn 1440
nnnnnnnnn nnnnnnnnn nnnnnnnnn nnnnnnnnn cnnnnnnnn nnnnnntnc 1500
ncnngcn ncnnnnnnn nnnnnnnnn nnnnnnnnn nngnnngng nnnnnncn 1560
nnnncnnn nnnngcn nnnngcnc cgcncnnn cc 1602

<210> 20
<211> 1633
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(1633)
<223> n = A,T,C or G

<400> 20
agcacgccag ccatcagccc ctgaatcac ctcacccact cgccagacct ttttgtcgaa 60
gttcatgtcc ttccttagcc ttccaatgaa gcctctacct gcctgagatg tccaaggtaa 120
tccatcagct gaggtctca gagaatgaaa gtgtggccct gcaggaaact ttggactgga 180
ggagaaagct ctgtgaggaa ggacaagact ggcagcagat cctgcaccac gctgagccca 240

```

gggtgcctcc cccaccacct tgcaagaagc ccagccttct gaagaagccg gaaggggcct 300
cctgcaacag gctgccgtct gagctctggg acaccaccat ttgatgtggc ctgaactgca 360
gacttacaaa atagaactgc ctactgattc cgggctgcaa caacagaagg ctgccttctg 420
acatgcgctg gggcttctct ccacgcattt agacaaaaaa agcacaggac acagacacta 480
aatatatgag atcccggtgt tgtgtgtgtg tgtttgtgtg tgtgtgtgtg ggttctttct 540
tatccatctc gngnggatac actctgattt tcaagctcct catttacggg tcttgtgcta 600
cccctaggta ncaagaaaaa aggctgggaa aaagtgtggn cgtggncnan agcgananaa 660
gtancggngg gaaaggagcn antccatgca cacttctgta ccngtngttt tttntacngg 720
ntcaaacagg nntgnntnat tggncnttnc caangggggg tttntttant aannaccnng 780
nnntnncngg ggannaanan nannnnnnna nnnnnnttt nggnnnccn cccttggggg 840
ggnnnnantt ggggcnct cctcccccc cctcncnccc cctccccct tcacnncgnc 900
ncnccntnnn ccncggcgcn nctcncntc nncnccnnn ntcgncccn nngngggggg 960
gcggggngn nccccnctc nctcncnnn cccccccnn cncnncnnc ncnncnccc 1020
cnccnccnc nnnncnccc cnncnccc ncccccnnn nnnngnnnnn nnnnnnnnn 1080
ncnnncccc cccccnccc cccccnncn cennnnnnn nnnnnnnnn nnnnnnnnn 1140
nnnnnnnnn nnnnnnnnn nnnnnnnnn nngggggccn ngnnnnnnn nnnnnnnnn 1200
nnnnnnnnc ncccccccc cnnnnnnnn nnnnnnnnn ncccccnnn nnnngnnccn 1260
nnnnnnngnn ngnggggggn gnnnnnnnn nnnnnnnnn nnnngnnng nnnnnnnnn 1320
nnnnnnnnng gnnnnnnnn nnnnnnnnn nnnnnnnng nnnnnngnn nnnnnnnnn 1380
ngnnnnnnnn nnnnnnnnn nnnnnnnnn nngnnnnnn nnnnnnnnn nnnnnngnn 1440
nnnnnnnnnn nccgncccc cgnnnnnnn nnnngnnnn nnnnnnnnn nnnnnnnnn 1500
nnnnnnnnnn nnnnnnnng gggnnngcgg ngngnggggn nnnnggnnn nnnnnnnnn 1560
cncccccn nnnnnnnnn nnnnnnnnn nnnngnnnn nngnnnnng nnnnnnccn 1620
nncccccnng nnn 1633

```

<210> 21

<211> 1462

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(1462)

<223> n = A,T,C or G

<400> 21

```

gggctcccaa aatggcgaag tgaggctgcy gggactcgct gagcagcgga gggggagcgt 60
gcagagccgc tgcggccctc acagtcggga gccgggccgt gccgtgccgt agggaaacatg 120
cacttttcca ttcccgaaac cgagtcgccg agcggggaca gcggcggtc cgcctacgtg 180
gctataaca ttacagtga tggagtctg cactgtcggg tgcgtacag ccagctcctg 240
gggctgcacg agcagcttcg gaaggagtat ggggccaatg tgcctcctgc attccccca 300
aagaagcttt tctctctgac tcctgctgag gtagaacaga ggagagagca gttagagaag 360
tacctgcaag ctgttcggca agaccattg cttgggagca gcgagacttt caacagtttc 420
ctgcgtcggg cacaacagga gacacagcag gtccccacag aggaagtgtc cttggaagtg 480
ctgctcagca acgggcagaa agttctggtc aacgtgctaa cttcagatca gactgaggat 540
gtcctggagg ctgtagctgc aaagctggat cttccagatg acttgattgg atactttagt 600
ctattcttag ttcgagaaaa agaggatgga gccttttctt ttgtacngaa gttgcaanaa 660
tttganctgc cttatgtgtc tgtcaccagc cttcagatca anantataa atgtgctaag 720
gaaganttat tgggactctc ctatgatnac nattnatgga naaccgggtt ggccttnaac 780
cttctttttg ctcnacggt nttaaaatat ttagnngng gnggggatct ttggtcaccc 840
aaggaaaaan naccggnaa ntttaaaatt ttttgnnaa aaaaaaannn ttccnaaaa 900
gggaatttct ttnaaanttg gccccaaana ccttngngnn ctttngnnn ntttgnnctt 960
ttanncccn nngggggng nntnccna aaaaaattt nttttnngg gnnnnccnn 1020
nncaannnna annnnnnnn nnnnnccnc cngngnnnn nnttnnaaag nttttnng 1080
gncccnnaa aatngggggn ncnnttttt ntttncnn nnnnnnnnn nnnnnnggg 1140
ggggggggnc cnnnnnttt ttnnnnnann nnnnnnnnn nnnncnnnc cennntnaa 1200
annnnnnnn nnnnnnnnn aannnnnnn nnnnnnnnn nngggggggn nnnnnnnnn 1260
nnnnnnnnnc cnnnnnnnn ncnnnnnnn nnnnnnnnn nnnnnnnnn nnnnnnnnn 1320

```

```

nnnnnnnnnt ntntngnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn gnnnnnnnnn 1380
tnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn 1440
nnnnnnnnnn nnnnnnaaaa an 1462

```

```

<210> 22
<211> 1601
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(1601)
<223> n = A,T,C or G

```

```

<400> 22
cccgaagcac gacgcagagc ctccggtgtg gctgtctctg atggtgtcat caaggtgttc 60
aacgacatga aggtgcgtaa gtcttcaacg ccagaggagg tgaagaagcg caagaaggcg 120
gtgctcttct gcctgagtga ggacaagaag aacatcatcc tggaggaggg caaggagatc 180
ctgggtggcg atgtgggcca gactgtcgac gacccctacg ccacctttgt caagatgctg 240
ccagataagg actgccgcta tgccctctat gatgcaacct atgagaccaa ggagagcaag 300
aaggaggatc tgggtgttat cttctgggcc ccgagtgctg cgcctcttaa gagcaaatg 360
atztatgcca gctccaagga cgccatcaag aagaagctga cagggatcaa gcatgaattg 420
caagcaaact gctacgaaga ggtcaaggac cgetgcaccc tgcagaaaan ctgggggggca 480
gtgcccgtea tctccttgaa ggcaaagcct tttgtgaacc ccttctggc cccctgcctg 540
gaagcatctt ggcaagcccc ccncctgcc ccttgggggg ttgcnaggct tgccccctt 600
ccttccana accggaagg gcttgggggg gatcccccnn caggggggga aggggcnant 660
ccctttqccc cccannttgg cnaaacccng nccccccc ncccccttg nantttttcc 720
ntntttnccc tccccatncc cntttngcng gggtnnttng gnccctttcc ccnaaanntg 780
gggntttttt gnaancnttt ttnnaaannn ncccntnttt gggggnctnn nnaaannccn 840
naancccnna nngtntnccc ccccccccn ngggnccccc ccccccnnt ntntnnnnng 900
gggggggggn aaanccccc nnnnnnnnnn nnnnnnnnnn nnaaaaaana aannantnccn 960
ccccccnntt tttccccccc ncccccnngg gggnnccnnn tcccccccn tttttcccc 1020
nannnnnnnt gggnnncnna anntttttt tnnancccn cnnntnnnnn nnnnnnctcn 1080
nngnnnnntt ttnncntnt nttnnnnnnn nnnnnnnnnn nnnnnnantn nnaannnnnn 1140
nnnngnnaaa acnatnccc ctncctttn cccnngggn ncnnnnncct ttnnccccnn 1200
nnnnnnnnnn ttttncngn nnnncnnnaa nggnccttn nntnaannn nccccctccc 1260
nngnnnngnn nccccaaang nganaantgg ggnncccccc cccnngcn nnnnaanttt 1320
nnnttngggg gnnnnnnccc ccgcgcgc ctccnctcc ccttcgcgcc gcccgcgcc 1380
gccgtccgcc ccgccccccc nctccnctc ccgcgcgtcn ctnccttnc tctcncgcc 1440
gccccgcgcg cgcgcgcgct cgnctcncg ncncncnnn cennnnnnnn nnncgnnnnn 1500
ananaagnnc nccnaccnat cccccccgcc nccccccnt nccgnnnnng nnnnnnnnn 1560
nncgcccnc ncccccncc cccnttcgt nccccccnt n 1601

```

```

<210> 23
<211> 1566
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(1566)
<223> n = A,T,C or G

```

```

<400> 23
tttttttttt tttttgattt tttttaatgc tgcacaacac aatatttatt tcatttgttt 60
cttttatctt attttatttg tttgtgctg ctgttttatt tatttttact gaaagtgaga 120
gggaactttt gtggcctttt ttcttttttc tgtaggccgc cttaagcttt ctaaatttgg 180
aacatctaag caagctgaag ggaaaagggg gtttcgcaa atcactcggg ggaaggga 240

```

```

ggttgctttg ttaatcatgc cctatggtgg gtgattaact gcttgtacaa ttaccgtttc 300
acttttaatt aattgtgctt aaggctttaa ttaaatttgg gggttccctt cttagagcag 360
ctcgtactga cgaagggtgca tgcgctgaat gatgtcacgg cagtcgttga acacacggcg 420
gatgtttctca gtgtcccagc gcanagtaaa tgagggtagc agtagtgaag cccatctcca 480
ctggcagtgct tgatcctcag aaactcatct cgaatgaagt acttgcccn ggtagcgcgt 540
gggtncctctt cnggctcngg agtancatnc tcangagtag ggtagcgagc aaattctgga 600
aagaagcctc aatcttcnat ttcccncaa ggactttctc ancganccan atcttgcttg 660
tttganggaa ccaggaatcc cngnnnaatg gngcncaacc ccttcttggt ggttncccaa 720
aangcccntt gaaaaaaggg ttcaaaaanc cctccctgcc anggccgggg ttngggncct 780
gggnttgnc cccccccgg naaaaaancn ctnttttnnn naaancctgn nttggnttgg 840
ggnccccc cccnnaaaaa aaaanaaaag gggnnnnnnn cnccccnn nttnnaaa 900
aanacccng gggnaannccc ccccttttgg gggggggggn tnnnttttnn nnnncnnngg 960
ggccccccc cccnnnnnaa aaanaattnt ggggaaannn nnnanntttt ttnccccc 1020
ccnnngnaa aantnngnnn tnncnnaaaa tnnccnaaa nnnnnngccc cnnnnnnnn 1080
aaaaannnnn nntnnnnnnn nnnnnaanaa nnnnncccn tntannncn nnnnntnncn 1140
naaaanngng gcncnnnann nnnnnnnncn tngnnnnnnn nnnnnnnnnn cnttttttn 1200
ccnaanntn nnnntnnnn nngngggggn aannngncn cncncncna annnccnc 1260
nnngggggn nccccnngg gccnnnnnn nnnncnngn nnnnnnnnnn nnnnnnnnn 1320
nnnnnnnnn nccccngnn nnnnnnnnnn nnnncnnnn cnnnnnnnnn nnnnnnnnn 1380
nnnnccnnn nnnnnnnnn nnnnnnnnn nnnnnnnnn nnnnnnnnn nnnngnnncn 1440
nngncncnc nnnnnnnann nnnnnnnnn nnnnnnnnn nnnnnnnnn nnnnnnnnn 1500
nnnnnnnnn nnnnnnnnn nnnnnnnnn nnnnnnnnn nnnnnnnnc nnnnnnnncn 1560
nncccc 1566

```

```

<210> 24
<211> 651
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(651)
<223> n = A,T,C or G

```

```

<400> 24
cgtcggttgg cgactccgg acgtaggtag tttgttgggc cgggttctga ggccttgctt 60
ctctttactt ttccactcta ggccacgatg ccgcagtacc agacctggga ggagttcagc 120
cgcgctgccg agaagcttta cctcgtgac cctatgaagg cacgtgtggt tctcaaata 180
aggcattctg atgggaactt gtgtgttaaa gtaacagatg atttagtttg tttggtgtat 240
aaaacagacc aagctcaaga tgtaagaag attgagaaat tccacagtca actaatgcga 300
cttatggtag ccaaggaagc ccgcaatggt accatggaaa ctgagtgaat ggtttgaaat 360
gaagactttg tcgtgtactt aggaagtaaa tatcttttat tagagaaagt gttgggacag 420
aaagtacttt atgtactaa gtgggctggt cagaacttan aggcattttt tgtaatttct 480
ttttaattac ttananaagc tagggatgca aatgttttca gttagaaagc ctttatttac 540
ttttggaaat tgaacaanaa atgctttgtc ttanaactgg agaataattg atggtaggga 600
aacatgtaat ggttctctgg caaattggn tcannatttg aatgaaann n 651

```

```

<210> 25
<211> 676
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(676)
<223> n = A,T,C or G

```

```

<400> 25

```

```

gggggacaga gactcagatg aggacagagt ggtttccaat gtgttcaata gatttaggag      60
cagaaatgca aggggctgca tgacctacca ggacagaact ttccccaatt acagggtgac      120
tcacagccgc attggtgact cacttcaatg tgtcatttcc ggctgctgtg tgtgagcagt      180
tggacacgtg aggggggggt ggggtgagaga gacaggcagc ttgnanntnn ttgcttngan      240
ntttcncnta naaccgcna gcgcttnggt agggtnngcn anggatgncn nncntttttc      300
nnaagncncc ngttcngngt canttgcttg nctentctaa ctcnnnnnnc ccccnntttn      360
gtctcctnng ngntcnaccc nntctgnttc ttngntcnng nttgncctcg nntttnnttc      420
nnngctcngc ncgtntgggt nnntgngnat nannctnanc gngtttntnn attntnnctn      480
ncgtngancn catntgancc ttntnnngnt nttcngctnn ntcgancgtn ttcngggncn      540
cncncgntt ctntctnncc tcnccctttt ntctcttgn ttgtggcntn acctnntctn      600
ttctntgtnt ncnngccttn nngtgnnncn gatagtcnnc cctntttggn aatatctntn      660
tnntcncccc cctccc

```

```

<210> 26
<211> 657
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(657)
<223> n = A,T,C or G

```

```

<400> 26
tttttttttt tttttgctgg gtggttaactc tttatttcat tgtccggaag aaagatggga      60
gtgggaacag ggtggacact gtgcaggctt cagcttccac tccgggcagg attcaggcta      120
tctgggaccg cagggactgc caggtgcaca gccctggctc ccgaggcagg caggcaaggt      180
gacgggactg gaagcccttt tcanagcctt ggaggagctg gtccgtccac aagcaatgag      240
tgccaactctg cagtttgcag gggatggata aacagggaaa cactgtgcat tcctcacagc      300
caacagtgtg ggtcttgggtg aagccccggc gctgagctaa gctcaggctg ttccaggagg      360
ccacaaaact gcaggtagtg atgtgcaaga ntccatcctg cagttttcca gcaatganaa      420
actcctcctg cgttgtgtggg acctggggaa gtatccgcan acctctcctg gcgggggtgt      480
agacnaaccg gatgtcaccg gcattccccta aagnttggaa ccctttatac atcttgggca      540
tcttgancctc ataacgctgg tataagngng ntnggtngac ttttggnggt cccccaant      600
gcccttgana ccaaggccgn aattncnaaa gggccctgng gggggggggg acccagn      657

```

```

<210> 27
<211> 646
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(646)
<223> n = A,T,C or G

```

```

<400> 27
ggaangctga agaattaaca ntttgactnc taaatgtgat actggntngt anattccctt      60
agagcagaaa ggagaggggc acatattaat ttgtatcgct tttgcttctc tttggtcttt      120
tgtgtcttag aatttggag tggttcattt ctgttgcctg tatgaggatt tcgaataact      180
agtaatcgaa aaccatatcc tgaattttaa taaaaaaaac taaggaagaa aaaaccctcc      240
aattttccca aatgcaatca gtgtaactag gggctgtgtt tctgcattaa aataaatggt      300
tcangctttg tggtcctgat caaggctctc attaaaaaat tggagtccac cctagngctt      360
ttcccctctg tgaactgggt cntccccac cncctcttag tatcgagtt attatggnt      420
ncaaatnaag naatangntt nncaaatttn accaaaanaa gcattttttt cactgcnttn      480
tnattggggg gttggcccaa ccnntcaat gnttcttanc atggntggnt acccgcnacc      540
tttncntnaa cttggngnaa ncnnnggcnn tacnnttcct gggggnaaat ngntccnnc      600
cantccccnc ncntncnanc cgaancnaa agggnaancn ngggggg      646

```

<210> 28
 <211> 407
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(407)
 <223> n = A,T,C or G

<400> 28
 caagagtctt tgaaataagc ccatttgagc cctggataac aagggataaa gtggagcgga 60
 tgcacatcac agacatgaaa ttgcctcacc tgcttggtt agaagacctt ggtattcagg 120
 caacaccact ggaactcaag gccattgagg tgctgcggcg tcatcgact taccgctggc 180
 tgtctgctga aattgaggat gtgaagccgg ccaagaccgt caacatttag tgctcctga 240
 gcagctcttg gttttggcgt cttttgggtc ggcccatgtg gtttgagcac ccagccaggc 300
 ggtctcttta gaggatcctg tacacagttc cactattaaa acatttcagg ttgaaaaana 360
 nnnannnnnn nnnnnnnnnn nanannnnnn nnnnnnnnnn nnnnnng 407

<210> 29
 <211> 625
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(625)
 <223> n = A,T,C or G

<400> 29
 tttttttttt tttttttttt tttttttttg gggaccaaatt ttctttnttt gaaggaatgg 60
 nacaaatcaa acgaacttaa gnggatgttt tggnacaaact tattgaaaag gnaaaggaaa 120
 cccaacatg catgcaactgn cttggggacc anggaagtca cccacgggt ntggggaaat 180
 tancccnagg nttancttct attatcactg nntcccangg ngngcttgna aaanaaanat 240
 tcnccccagc cacattnnng cncctccatn ttgcncaggt tggncacgtg gncacccaat 300
 tctttgaagg ctttcaccng ctnattnaag naanggggtct caatgaaanc acaccantgg 360
 ggggnatttt tgntnnnngc ccattgggca attcccaana tggctgaatc aaattttttt 420
 nccaaagnca ngcccctcca atggattnaa anccccntnc caatanaaca nnnngntttt 480
 ttatcctcca agaaaaattn ggcccntntn gggntggaag gtttnantat tacaagcncc 540
 ttccttttaa tggggaaaaa nttttgnnaa annttaaaac cncntcgcca agnttttnaa 600
 aggnaggna ngcngngggt tacnn 625

<210> 30
 <211> 643
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(643)
 <223> n = A,T,C or G

<400> 30
 cttaagaatt ggccagcct cagatcctgt ctttagcaac cagctaatat ttacccagag 60
 gtactgcaat agagtatttc aaaatggaat caggatctgg tgggcctcag aaattgtctc 120
 tttctgagt ttcaatttgg ttctcctgga tgttttgctc tgttttggtta cctgtaatat 180
 agggaacac aactttttttt gggaaagccc tttgacccca gcttgctagt tgcataataa 240

15

```

taaattttct gttcctaaaa aaaaaaaaaa aaaaaaaaaa aaaaanaaaaa aaaaaaaaaa 300
aaaaaaaaaa aaggngnnaa naaaaaaaaa ananggggcc gntaaaacnn ggggggggcc 360
cntcaanttt aaagggccct ttaancccc tnnnaancc nccntgggcc nttnntttc 420
ccaccttttg gnggnggnc ccccccccg nctttttttg ncctgggggg ncccccccc 480
tggctcntnc ttanaaaaaa nangaantt cctcccttnt cngaaaangg ntcttttttt 540
ttnggggggg gggggggggg ggaannnggg ggggggtggg ggaaaaattn nggggntttg 600
ggaaccnggg gcccttgccc ttngaaaaa aaccntggg ttt 643

```

```

<210> 31
<211> 645
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(645)
<223> n = A,T,C or G

```

```

<400> 31
gtgaaagctg taaacacact tttatggaag aaaagaaata aaatgtagtt gtcaagtcta 60
aaaaatagta gcaacgggaa tcataatgaa tacatgcaat gaatttaaaa tgtaaaaatg 120
aatttaaaaa gtaaaaaggg ctctgtggtg taatttttct taactacaag agtctaaata 180
cactgctttt cttaagagt tcattttaat tagtaacgtc aaacaaaatt attctagata 240
atgagcccta caaattacta ctactagcaa ctgtcatttt ttactcgggc atoctctagg 300
tgtcttacat tctcatttta ttcttacaac gaactcatcc tccagaagga ctctcatctc 360
cagaaggact catctccag aangactcat cctccaaagg acttctccag aagggggaaa 420
tggaagaccc gggtaacttg ctcagggctt atcacagaac tatgtttgag cctgacttcg 480
tttgaactct aaagcccaca tgctctttct actgccccat gcttctcaag gnaccagact 540
cttattnct gcacttttga gaatctnaag atcctgantc attttaata aatttagttt 600
tttggggagn agccnnaaaa aaaaaaaaaa ggcgccctcc ncnnt 645

```

```

<210> 32
<211> 668
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(668)
<223> n = A,T,C or G

```

```

<400> 32
tccggttctg ttttaaacag aaaataaaag gagtgtaaag tccttttctc atttcaaagt 60
tgctaccagt gtatgcagta attagaacaa agaanaaaaca ttcagtagaa cattttattg 120
cctagtgtgac aacattgctt gaatgctggt gggtccctatc cctttgacac tacacaattt 180
tctaataatgn gttaatgcta tgtgacaaaa cgccctgatt cctagtgcc aaggttnaac 240
ttaatgtata tacctgaaaa cccatgcatt tgtgctcttt ttttttttta tggngcttga 300
agtaaaacag cccatnctnt gcaagtccat gtatgcngcn cttaagcntt ctatctttgc 360
tcaaantngnt gaangatggg gaccttgget catggcttgc gnatttgatc ntaangnncn 420
tttctancta tgnatgagg cacnngccct attggaggnc gcccngggt tccggaaaag 480
ngcnntnntg tngngaattg cnnectcgan ttcaanaata tncggcnntt gntttgnang 540
ccnngnnnan caatcaggng ngccctcna antcatgnaa gcccgnntn aanncnctnc 600
nctnttctcg nnntgggnnt tccattgccn gcctcgacgn ggttngcctc tcnccggcnn 660
cncgncg 668

```

```

<210> 33
<211> 682
<212> DNA

```

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(682)

<223> n = A,T,C or G

<400> 33

ggcttgctccg agttgatatg cgtatgcttt gcctaaaaag ccttaggaaa ttagacttga	60
gtcacaacca tataaaaaag cttccagcta caattggaga cctcatacac cttcaagaac	120
ttaacctgaa tgacaatcac ttggagtcac ttagtgtagc cttgtgtcat tctacactcc	180
agaagtcact tcggagtttg gacctcagca agaacaaaat caaggcactc cctgtgcagt	240
tttgccagct ccaggaaactt aagaatttaa aacttgacga taatgaattg attcaatttc	300
cttgcaagat aggacaacta ataaaccttc gctttttgtc agcagctcga aataagcttc	360
catTTTTgccc tagtgaattt agaaatttat cccttgaata cttggatctt tttggaaata	420
cttttgaaca accaaaagtc cttccagtaa taaagctgca agcaccatta actttatttg	480
aatcttctgc acgaaccata ttacataata aggattccat atggctcttc atattcattt	540
ccattccatc tctgcccagn atttggggat acccgcanaa aatttggggg tttgggggaa	600
aaatntggnc tggaactttt tttanttnaa gggaaataat naggggngga aggggggggt	660
ttntggnatgc ccccccccg gn	682

<210> 34

<211> 1549

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(1549)

<223> n = A,T,C or G

<400> 34

ttgagagata cctccctcct tctgctcagc tgccttgacg taattaaaact ctttctctgc	60
tgcaacaccc ctactgttct ccgtgtattg gctttttctgg gcagcaggaa ggaaaagctg	120
atgcatgctc ctacgtgccc cgtcgccaaa tactgtagtg ctaagtgtca gaaaaagctg	180
tggccagacc acaagcggga atgcaaatgc cttaaaagct gcaaaccagc atatcctcca	240
gactccgttc gacttcttgg cagagttgtc ttcaaaacta tggatggagc accttcagaa	300
tcagagaagc tttactcatt ttatgatctg gagtcaaata ttaacaaact gactgaagat	360
aagaaagagg gcctcaggca actcgtaatg acatttcaac atttcatgag agaagaaata	420
caggatgcct ctacgtgccc acctgccttt gacctttttg aagcctttgc aaaagtgatc	480
tgcaactcct tcaccatctg taatgcggag atgcaggaag ttggtgttgg cctatatccc	540
agtatctctt tgctcaatca cagctgtgac cccaactggt cgattgtgtt caatgggccc	600
cacctcttac tgcgagcagt ccgagacatc gagtgaggag aggagctccc atctgtcctt	660
ggatatgctg atgaccagtg agggagcgcc cggaagcagc tgagggacca gtactgcttt	720
tgaatgtgac tgggtttccc ttgccaaaac ccaggacaan ggatgctgga tatggcttaa	780
cctgggggga tgaaccaang tttttgggaa ngggaaagnt tnaaanaaaa tcccctggna	840
aaaaaaantt tnaaanaaaa accttggaan ggggcccccc ttgggaaaaa ngggggggan	900
nnnggggtnt tnggnccnnt ttnnccccn nnnnannnct ttaannnnng nnantttttt	960
nnaanggggg nntnnccccn ntttnnaann ntntntcccc nnnnnanggg ggggtnnncn	1020
nnnccccngg ggggnncnnn ntnaacnccn nctntnggn ggaaancntt ttttntcttc	1080
nnccnnggnc ccnnaanntt tttcccagaa nccccccng gggngnnng gaaangnnnn	1140
nnnccctcnn ggggggttnc ccnnnaaaaa aaannnggnt ttttttttna nganccgggg	1200
acnccccnnn naaanntttt ttnaaagcgc cccccnnnt nnggnnnnnn nggnannnnn	1260
nnnttngnnn ntngcccnc cnttnnnngn nccnctcnnn nnnnnnnnnn nnnnnnnnnn	1320
nnnnnnnnnn nnnnnnnnnn cntntanntn ntgnaaaaaa nggnnnnnng nnnnnnnnnn	1380
nnnnnnnnng cccccnngg nnnnnnnnnn nnnnnnnnnn ggggggngn ggnngcnnn	1440
nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn ncgnnnnnnn nnnnnnnnnn	1500
nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnncngnng nnggnnanc	1549

<210> 35
<211> 1440
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(1440)
<223> n = A,T,C or G

<400> 35
ctaatactaag cctcaaaactc gttattgggg ctataaaagaa aacgtttact taccagctg 60
aaacaggtta agaataattct taatctcatt atagataatt gcccccatgg gacttgaaat 120
acaacacctt gtgctgaaaa cttcaggttg gcaatatattg aagggttctgt tgtagaagag 180
tttaacatta actcctatatt tgacttacaa atcttggttc tcatcactaa aatgcttttg 240
aattaataat ccaaccacaca tgagctgaga gtttttcttt tgttagaaaa gaaacagaca 300
tctttctgta tgaaagtata aattgtatgg ttttagatac ataagaattg acaaaagcga 360
gcgaaatcct tgtacttctg agttcttgct gtatgtatgt tttgttttaa atctgattag 420
ggacacccag cagctggccg ggattcttgg attgctcctt gggagttaag attgtcaata 480
ctcctgtgaa gcaagggatt tcagccatag aacaaaagatt tattgttgcc acctgaaaag 540
tttacaagta tttatttgtt atttgataca ttgcttgaaa aagatgaaat ctgttaaaga 600
ttcttttccg atgtccaggt taagaagaaa cctccttgta ttgagtgaat ttatatgtta 660
aatggtatta gagaatgtag gtggnataga aattggattt ttcttgngng tngaacaacc 720
tcaagttcgg caaagttaa aatttgattt aaacaagaaa aannggttca ngggtgnaaa 780
angggacttg nttagggang ggacaanggc ctttaanna cncgcgtccc ttctcnggc 840
nggcnnngc ggccnnccc caanctntc cangccttcg nccncnaccn nccncccttt 900
cctnntnca cnaanntctt tnnccntttt tacngggggn ggggnnnccn ncncggcnn 960
cngnntnccg cncccanaaa nncnncntt ttccnncnnc ccttttncnn nnnctttnc 1020
cnnnnccccc cccgnnnnnn nnnnnnnnnn nnnnnnnnnn nggnnnnnnn cccnnnnnnn 1080
nnnnnnnnnn nnnnnnnnnn nnnnnnggnc nngggnnnnn ttntnnnnnn ggggncnnn 1140
nnnnnnngcg nnnnnnnnnn ngnnnnnnnn nnnnncgnc nnnnnnnnnn nnnnnnnnnn 1200
nnnnnnnnnn ncccnngna ncnannncn nnnnnnnnnn nnnnnnnnnn nnnnnnnncn 1260
cnnnnnnnnn nnnngnnngn nngnnncnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnngn 1320
nnnnnncggn nnnnnnnnnn nnnnnnnnnn nnnnnnnngg nnnnnnnnnn nnnnnnnnnn 1380
nnnnnnncnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn gnnncgaaga nggcnaccg 1440

<210> 36
<211> 1496
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(1496)
<223> n = A,T,C or G

<400> 36
tgcataccgt ggaagggcgc cagggctctt gtggattgca tgttgacatt gaccgtgaga 60
ttcggcttca aaccaatact gcctttggaa tatgacagaa tcaatagccc agagagctta 120
gtcaaagacg atatcacggt ctaccttaac caaggcactt tcttaagcag aaaatattgt 180
tgaggttacc tttgctgcta aagatccaat cttctaacgc cacaacagca tagcaaatcc 240
taggataatt cacctcctca ttgacaaaat cagagctgta attcacttta acaaattacg 300
catttctatc acgttcacta acagcttatg ataagtctgt gtagtcttcc ttttctccag 360
ttctgttacc caatttagat taagtaaagc gtacacaact ggaaagactg ctgtaataac 420
acagccttgt tattttttaag tcctatatttg atattaattt ctgattaagt tagtaataaa 480
cacctggatt ctatggagga cctcggctct catccaagtg gcctgagtat ttcactggca 540
ggttgngaatt ttttcttttc ctctttgggg atccaaatga tgatgtgcaa ttcattgtta 600

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acttggggaa acttgaaagg ggttcccata tancttcaaa acaaaaacca aatggtgtta      660
tcnngacgga tctttttatg ggtncctaact agtactttnc taattgggga aaagnaannng      720
cttttagttt tgcnaatta agtttggggg aagggcnata attaaaaatt gagggccccg      780
tnacnaaaac caactggggg ngntaaacga aaaaccctgt tttnaaaagg gggccttttn      840
ccccctnnnn ngnaatntna nttccccnt ttgccttttc cntttttnnn naaacttttt      900
nnnttttctc cccnancnnn naaangngna nngggtntcc ccccnangtt nnnnttnttc      960
nnnnnannna nccccctt ngnggnccn nngggcntt ttctcntnng naanngttnt      1020
nnnannccct tttgncnnnn gggntttng ntteggngn ccnnggggn nnnnccnnnn      1080
gnnngnnnnn gannangann nngngngnc gtntnnnng ccgcggnnn nngngnnncg      1140
ngnnnnnngn nnnnnngnnn cnnngnnnnn nngnnnnnnn nnnnnangnn nnnnnnnnnn      1200
nnngngnnng ngnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn nnnnnnnnnn      1260
nnnnnnnnnn nnnnnnnnn nnnnnnnnnn nggnnnnnng nnnnnngnng nnnnnngnnn      1320
nnnnnnnnnn nnggnnnnnn nncnnnnng nggnnnngcg nnnnnngnnn nnnngnnnnn      1380
nnnnnnngng gnnnnnnngn gnnnnnnnn nnnccgenn nngngnnn nnnnnnnnn      1440
gncnnnnnn cnnngnnnn nncnnnnnn nngnnntnng nnnnnccgnn gnnntc      1496

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```

<210> 37
<211> 1604
<212> DNA
<213> Homo sapien

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```

<220>
<221> misc_feature
<222> (1)...(1604)
<223> n = A,T,C or G

```

```

<400> 37
atgcagtcct ggtggagcc gactgcatca tgctgtctgg agaaacagcc aaaggggact      60
atcctctgga ggctgtgccc atgcagcacc tgattgcccg tgaggcagag gctgccatct      120
accacttgca attatttgag gaactccgcc gcctggcgcc cattaccagc gaccccacag      180
aagccaccgc cgtgggtgcc gtggaggcct ccttcaagtg ctgcagtggg gccataatcg      240
tcctcaccaa gtctggcagg tctgctcacc aggtggccag ataccgcca cgtgccccca      300
tcattgctgt gaccgggaat cccagacagc ctgcagcagg ccacctgtac cgtggcatct      360
tcctgtgtgt gtgcaaggac ccagtcagg aggcctgggc tgaggacgtg gacctccggg      420
tgaactttgc catgaatggt ggcaaggccc gaggttctt caagaaggga gatgtgtgca      480
ttgtgctgac ccggatggcg ccctgctccg gnttcaccaa caccatgctg gttgttcctg      540
tgccgngatg gacccanag cccctccttc agcncctgtg ccacccctt tccanccaa      600
tccattaagn cannaangct tgtanaactt cactctggnc tgtaaactng gncacntgtt      660
nggtngggac acctgggaa ggaaaaatca acnctcant tgnaaaattg gggtaangnt      720
tgccantcnt gtttttaaan gggacnagnc gcgaggagg gctnanttnn ttanantnnn      780
agggggcccc cnnccccnat nnanangggg caaanaacgg nanggnaaat ngntttnnnn      840
cttngnnngc nccccnnng gannnccnn nncngngnn nnnnagnggg gntcancnn      900
ntncccttnt nctnnntng gttnnccnn nnnccnnnn cacgttnaaa annnaaatnn      960
ngnccnnnn gnnngcctca cncnttngn ggnnngaccn anccaccng cnnatngng      1020
ntggnggggn ctctnccnca aancantng gncctcgtna ngngtgnnn nnnnnnnna      1080
ncnngntnnn nncnccnngc nannngtnn cngnntccn cccactgtg tnnccannng      1140
ngtnnnngnn tngannntcn nngnttgnat cccgnaana cnannnccg ncncnggcnn      1200
nccnnccnn gnnccntccc nnnccnatn nngngggnn nctgchanct nnnnngancn      1260
cnnnnnnnn gncncanncg antngngng nnnntnccnn nnnnnnnnn nnnnnnnnn      1320
nntnnnnnn nccgnttntg ctngcagtag tntcngnnt ntcnnnnnn ngnnnnnnn      1380
ncnnnnnnn nctngnacnt tngnagcnn nagtcagant nctnggacnt nntnnncant      1440
cnngecngt nnnngntngn ngcnnacnn nnnacnnng cgnnnnnnn ncatnccnn      1500
nctnanannn ggtngngng nnnccctccn nnnnagnnnn natannngcn nnannccnn      1560
nnnnnnnnn ngnnnnncnn nntcnnccga nanntgncac nacg      1604

```

```

<210> 38
<211> 280
<212> DNA

```

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(280)

<223> n = A,T,C or G

<400> 38

tttttttttt	tttttaattt	atcagngctt	aaaaatcttc	aaaatagctt	agtgaggctc	60
atgacagtgc	tggcccatg	gaaatgtagc	cttttggtgc	gtttaaacac	tgtcacacca	120
tctatgactg	tcccatggg	ctgaagtgtg	gtggcaaac	aagcatccta	taagacaagc	180
taaagcttgc	tttttgccag	tcagttgaaa	gtcttgcatc	tcttctactga	tgcactttct	240
ttaggtattg	atagtcagaa	gcacaaagca	tttattatgc			280

<210> 39

<211> 378

<212> DNA

<213> Homo sapien

<400> 39

cgagtttata	atcctataat	gaagaatact	ggcacaggca	atgctcactc	gaaaacttca	60
agtaatttct	agttggtttt	ggaatgcttg	ataaagttcc	tttacagctt	tattttcctg	120
atttgttttg	gttttagatca	aagttcaaat	taattttaac	ttagctaata	aactcatcac	180
caggacagtt	ggagggggta	ggccgaggtt	aaatggtcca	cgtttcaaaa	atgttaatgg	240
ctaattccata	attaaagaag	gttttaactgt	tactgaagtt	tacaagtttt	attgtcatga	300
acatgaaata	caaacacgat	ggcttcgaaa	tgtctttcaa	taaatgtttc	tgcattttata	360
tggaaaaaaa	aaaaaaaa					378

<210> 40

<211> 2039

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(2039)

<223> n = A,T,C or G

<400> 40

caacttttgt	agaagtattt	ttttctctgt	aatattttta	ttggctcata	aagatgtttt	60
catatctgaa	ctcctaaata	agtgaatta	cagtagatta	tattaacaaa	atacttttta	120
ggtagccatg	cttgagactt	tttaaaaata	taactttttc	cttaaagttt	tcagctatag	180
caaaaaggtag	ttatgtatgc	cagacctaat	atgagctgcc	accaacaccc	ctagaacttt	240
cagccatggt	gtcttcagaa	ttgtagcgca	tttctgaatc	tagcaaatcc	tccttttacc	300
cgttgaatgt	tttgaatgcc	ctgactctac	cagcgcccat	aatgatctc	tagaaggact	360
gttagtacca	acctgttttt	caactttgaa	gctaaaaacc	ctgatatggt	aatattatgg	420
tgcatagcag	aggctctogga	aaaaaaatat	ttctgttcac	tttactttca	ggttaaaaat	480
gtttctaaca	cgcttgcaac	ttcccttatg	gcattaatct	tgttgagggg	gagagacaga	540
atcctggact	ctccaaagta	tttaactgaa	agtagggcct	gctctgacag	ggcccatgtc	600
ccacaaggct	ggcttnggcc	tcaggggggg	gctttggctg	gtgcttggga	tgaaaattgn	660
tgganncnng	tnnttggggg	taaaaggacc	aaanggacca	gccaaaagcn	aaaaaatngg	720
gnnttttaaa	ngccttgggg	ggnttacctt	tttcntttta	angnnggttt	naaagnatta	780
gggctaaang	ccanttttnc	aaaaaangct	ccnanaanaa	aatggtggaa	aagggnccct	840
tttggnncgac	aggncccttg	nggaaaattg	ccccancng	ggcccttttt	tgnccccccc	900
nncccaaaaa	aaagntgggn	ngaagnnttn	ttaaaacct	nnngngccc	ntttttttng	960
nnaaanccnc	cnccnngggg	gncgccccnc	ttntttnttt	ntnttccng	ggngnccnnt	1020
ttttttncgg	cngaccnnc	gggntcaan	nnctgnanaa	gnngntatct	ggcnggggnn	1080
gcgcnnngaaa	gnnnnngggn	ncngngggg	nnnncgcncg	nnannnttnt	gnggggnaaa	1140

```

aaaaaaganc cctctnttnc tctcttntnt naanntnnnn ngnnnnnnan ncnngcnnnn 1200
gngngngngn nnnnnnngnc nnnncnnann ggggggnggg cncncncnc nnnnantnng 1260
gggcgncctn tnnnnnccc cncctcgggn nccnnnnncn ggngngngcn nntntngng 1320
tcngnntgt gtntgnnng ncnncncnc cncgnnnnnc tnnntntng nntnngnng 1380
gggnggncn nccccncncg tgnnnntnt nnnnnnnnn nnganggna nnnccnnncn 1440
nnnnnnnnn gggnggcnn ncnncnnncn tnnnnnnngg gnggnggggn gnnnnnnnn 1500
nnngggnng nnnnnnnnn nnnncncncn nnnnnntng cgnnnnnncn nncnnngnn 1560
nnnnntnnnn nnnnnnnnn nnnncnnnnn nnnnnnnnn nnnnnnnng nnnnnnnnn 1620
nnnnccnnnn nnnnnnngng gnnnnancgn tngcngngng tnnnnnnnn nnnnnnnnn 1680
nnnnnnnnn nnnnnnnngn nnnnnnnnn nnangnnnn nnnngnnnn nncnnnnnn 1740
gnnnnnnnn cntgcgagc nnnngncnn nncnnntggn nnnnnnnngn tcgncncnn 1800
nnnnncgngg ggcgntnnnn nccncccgcn gntgncnnnn nngncnnnn ncnnnnnnn 1860
ngnnntnnn cnnnnnnncg nnnnnnnnc nnnagngnn ngngnncnc nncnnnatn 1920
gannnnnnn nccnncnnnn nnnnncggn nngcnnngn ngnnnnnnn nnnntcncn 1980
nncnnngnn nngnnnnnn nnnncncng gngnnngnn cccgtccgc cngcgcgcg 2039

```

```

<210> 41
<211> 319
<212> DNA
<213> Homo sapien

```

```

<400> 41
ttttttttt aaaaaaaag agtttattta gaaagtatca tagtgtaaac aaacaaattg 60
taccactttg attttcttgg aatacaagac tcgtgatgca aagctgaagt tgtgtgtaca 120
agactottga cagttgtgct tctctaggag gttgggtttt tttaaaaaa gaattatctg 180
tgaaccatac gtgattaata aagatttcct ttaaggcaga ggctggtcga gatgctgctg 240
ttatcttctg cctcagacag acagtataag tgggtctgtt tctaagattc ctaccaccag 300
ttactttggg ccaagtatc 319

```

```

<210> 42
<211> 524
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(524)
<223> n = A,T,C or G

```

```

<400> 42
cctttttttt tttttttttt ttttctgatt tcaagtcag atttattgct ttacaaacaa 60
acattatact tgggtctaat agaaaaatga caccagatac atccaaaata catttcacat 120
tgggatagct gccagttcag cacaaaacat acattactag gagcagggag gcatgaaaat 180
aaactatata ttactttttg gtacgtcagg aacacttttg cctgaagtaa gccctttagt 240
actatttttt attttattta tttttttaat ccacccatct gcacactggn ccttttagtac 300
tctttaagta taaaacttta cttgtcctgg gctttgaccc ttgtgtttga tctaaatgac 360
atttcaaaca taaatgtctt ttgactagt cgcttactgn tatgtacana atttaaaatg 420
tgatcgttng aatntaaaat ctggtttgat acatgatata aaagttgtat atttaaaatn 480
caagaaatgt ttttggggaa tattctact aaagaatttt aaat 524

```

```

<210> 43
<211> 103
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(103)

```

<223> n = A,T,C or G

<400> 43

```
cctttttttt ttttttttgc nngaaataag gaatctataa atctgaaata aagaaatccc    60
attttaaatt aaattgttaa agagacacat aagaaaaaac act                          103
```

<210> 44

<211> 425

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(425)

<223> n = A,T,C or G

<400> 44

```
gtcgacaaga taatgtactg acatctctag caatcttttt tgccagtggc tttaaattgc    60
caataagtta aagaatattg ttcctatggg ttaaattttt attcttattt tcacatttaa    120
atttattttt cttaattttt gtggatacat aatatgtgta tatatgtatg ccatatatgg    180
tatattttga tgcaggcata ctctatataa taatcacatt agaggaaatg agatatccat    240
tacctctagc atttattctt tttattacaa gncaattcaa ttgtacactt tttagttatt    300
tttaaattta caatgttatt gattacaggg tcatttttat ggtcataata aaaaatttta    360
tacaaaacgt gtaaaatcta tacatttctg agttctgaat aaatattttt taaaaatttt    420
aaaaa                                              425
```

<210> 45

<211> 492

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(492)

<223> n = A,T,C or G

<400> 45

```
gtcgactgcc cccaccgctg ggcggcgctg cggggcaccc aggetctgca gtcagcgccg    60
cgccgggaat cctgtaccog ggcgggaata agtaccagac cattgacaac taccagccgt    120
accogtgctg agaggacgag gagtgcggca ctgatgagta ctgcgctagt cccaccgctg    180
gaggggacgc aggcgtgcaa atctgtctog cctgcaggaa gcgccgaaaa cgctgcatgc    240
gtcacgctat gtgctgcccc gggaattact gcaaaaatgg aatatgtgtg tcttctgatc    300
aaaatcattt ccgaggagaa attgaggaaa ccatcactga aagctttggg aatgatcata    360
gcaccttgga tgggtattcc agaagaacca ccttgtcttc aaaaatgtat cacaccaaaag    420
gacaagaagg ttctgtttgt ctccggtcat cagactgtgc ctcanattg tgttgtgcta    480
gacatttctg gt                                              492
```

<210> 46

<211> 499

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(499)

<223> n = A,T,C or G

<400> 46

```

cctttttttt ttttttttat aacattttata taatgtgcta acaatgaatc catccatgat      60
ttattgtttg taatgaactt aaaataaacc tttacaaatt aaaatcattt tttcaaact      120
gacttcatat tgaaatggtt ctgttaaaaa agtaaaagt gaattttcca gccaatntag      180
catctaggac ctgaatcttg ccaatatcct acccactatc ttcattccta cctcctaccc      240
cttcaaata gctcctccag actttcctat ttctgtcacc ccagttcaaa atggttttca      300
ccatgcattt gatgtaaaat gtgcaagtgc gatatgacit cacaaagtat caattgtgtg      360
gacaatgata actactgtga cactgctagc acccctggct aaaagtaaga agcaacaaaa      420
ttacacaggg ttcctttctg atgaatgcag nanggattca agaaatccca gantgggaaa      480
aagattttca atagatctg

```

```

<210> 47
<211> 537
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(537)
<223> n = A,T,C or G

```

```

<400> 47
gtcgacattt ttctgaggaa tagtttgtga ttccaatgca ggtgtcttca ttaccattac      60
ctctacactg cagaagaagc aaaactcctt tattagaatt actgcacatg tgtatgggga      120
aaatagttct gaaaggctag aatgatacaa gtgagcaaaa gttggtcagc ttggctatgg      180
agtgggtggc ataactctcta aacattccaa aagaccatga gctgaacctt aactcccttg      240
gaatctgaac aaagggaatat aaaattgcca ttgaaaact gaccagctaa tctggacctc      300
agagatagat cagccagtgg cccaaagcca tttcaagtac agaaattata gagactacag      360
ctaaataaat ttgaacatta aatataatit taccactttt tgtctttata agcatatttg      420
taaactcaga actgagcaga agtgacttta ctttctcaag tttgatactg agttgactgn      480
ttcccttatc cctcaccctt tccccttccc tttcctaagg caatagtgca caactta      537

```

```

<210> 48
<211> 556
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(556)
<223> n = A,T,C or G

```

```

<400> 48
gtcgactttt tttttttttt ttagnnntat aaaatatit atttacagta gagctttaca      60
aaaatagtct taaattaata caaatccctt ttgcaatata acttatatga ctatcttctc      120
aaaaacgtga cattcgatta taacacataa actacattta tagttgttaa gtcaccttgt      180
agtataaata tgttttcatc ttttttttgt aataaggtag ataccaataa caatgaacaa      240
tggaacaaca atcttatttt gttattcttc caatgtaaaa ttcattctctg gccaaaacaa      300
aattaacca agaaaagtaa aacaattgtc cctctgttca acaatacagt cttttttaat      360
tatttgagag tttatctgac agagacacag cattaaactg aaagcaccat ggcataaagt      420
ctagtaacat tatcctcaaa agctttttoc aatgncttct ctncaactgn ttattcagta      480
tttgccagat acaaaataaa gattgggtct caactctctc tttcattagt ctcaagngtt      540
cctattatgc actgag

```

```

<210> 49
<211> 355
<212> DNA
<213> Homo sapien

```

```

<400> 49
gtcgaccgag cctctccac cctcagtcgc atagacttat gtgttttgct aaaattcagg      60
tattactgaa ttagcgttta atccacttcc tttcttcttc ttctaaaata ttgggcactc     120
ggttatcttt taaaattcac acagaaaaat tocgttttgt agactccttc caatgaaatc     180
tcaggaataa ttaaaactcta gggggacttt cttaaaaata actagaggga cctattttcc     240
tcttttttat gtttttagact gtagattatt tattaataat ctttaataat aggaaaaggg     300
gaaagtattt attgtacatt attttcatag attaaataaa tgtctttata atacc          355

```

```

<210> 50
<211> 507
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(507)
<223> n = A,T,C or G

```

```

<400> 50
cctttttttt ttttttttaa aaaaaaaaaa ttctgtttat tgtaataatt aaataagagt      60
aaacatttta aaacatataa aaataacttt aaaatatagt aacactttac aaaatatgta     120
tctaattaaa aatacattaa catagcatcc ctcaaactat acaaatatag aatatatatt     180
catgaaattc tttanaaata taacatctat tctttgaata aagcttaaaa tttgtttata     240
attttcaaac taanaaaaga agtagngaat aatagctcca tocaatttat aattgtctta     300
aagagaatga ttatgtatca tttcttgctt gtcttttcta ataccagtc aatcacctgt     360
acagcattgt tgtttgctgt tttcttcatt tcttcaaata gacccttga aagtttttaa     420
gatccttttag atagaactta gagatttcaa agagacgctg gctgcatgca gtgaaacatt     480
catgagtctc ggtaataactg ngtttct

```

```

<210> 51
<211> 538
<212> DNA
<213> Homo sapien

```

```

<400> 51
gtcgacgcaa aagtttgact aaactttacc tttttatagt ttcacttttt aagttatatt      60
tagaatatat tgatagatta taaattgatt gtgaaacttt tttctgaatt ttttcaacat     120
gttttactca gttacatgag ttaaaggata ttttcagtc tgttatcttc aattgcagtc     180
tttaaaaaaa cccaccctat tgtttacttt gttatatgtc tattcataca gtaaattcat     240
ttcaagggtt atgccagtgg gtattattgg tgctttttga agttgaggtg aaccatccag     300
gaaggtcttg ttaatgttat gttcatctat aatggcatag gggaaatata tatattttta     360
atattgtaaa catttgtact gaataacctt tttttccccc cctccgcaag caaaactggt     420
tgaacagcgg atgaagatat ggaattcaaa gctctaattg acctttttga agagaagttg     480
tggcttatgt ggagtttaca tgggcctctg atggaagaaa gctaactctg ttagtatt       538

```

```

<210> 52
<211> 504
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(504)
<223> n = A,T,C or G

```

```

<400> 52
cctttttttt ttttttttta aagtacaaat tcagtttatt catctgttta tgacacagta      60
cacaggaggc aaagtgtttc acatcataga cttcacttcc aactccttgg aatgttcatt     120

```

```

tctttggctt acaggagaga ctagacagga aggccaggca atgcttaggc aactaaaatg      180
aggttggggg taatgctaac gtcaccctca cagggatggc cacggggact gttattcgca      240
agctggtttt ctagacctgt tagctggaag catggtgagc accatttctg gacgctcagg      300
ccgtntcggg cttcagtcac ntccaccaca caggtacagc agcgctttct ggtagtcgcc      360
cttagtgtct tgctggatat aatagtacag ggacttgccg tactttctct tgaattcaga      420
cctaattttc aacatgtcca cttcactgng ggagaccatg attctgatca ggacccttat      480
ctcgcgtccc cttgcccttc atgg                                           504

```

```

<210> 53
<211> 489
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(489)
<223> n = A,T,C or G

```

```

<400> 53
gtcgacttta gatgtacagg ctgacanana agattcccga gagtaaatca tctttccaat      60
ccagaggaac aagcatgtct ctctgccaaag atccatctaa actggagtga tgtagcaga      120
cccagcttag agttcttctt tctttcttaa gccctttgct ctggaggaag ttctccagct      180
tcagctcaac tcacagcttc tccaagcatc accctgggag tttcctgagg gttttctcat      240
aaatgagggc tgcacattgc ctgttctgct tcgaagtatt caataccgct cagtatttta      300
aatgaagtga ttctannatt tggtttgga tcaatnggaa agcatatgca gccaaccaag      360
atgcaaagt tttgaaatga tatgaccaa attttaagta ggaaagtcac ccaaacttt      420
ctgctttcac ttaagtgtct ggcccgnaat actgtaggaa caagcatgat cttgntactg      480
tgatatttt                                           489

```

```

<210> 54
<211> 577
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(577)
<223> n = A,T,C or G

```

```

<400> 54
cctttttttt tttttttttt aagaactcaa tacatggctt ttaattattg tctataattt      60
aaggaaataa tcacctacaa ataggatggt tctcaagttg gcttacaaat ttgttacttg      120
gcagactgaa aacatttccc acagaacaaa tattatacac aatggttggg ttcctttggt      180
taatgcataa tgtttactcc ataatttatt taccacacaa catgaattga acatttcttt      240
gtgccanaaa ctattctaac actagaaata caatagtaat gaacaaatag aaaaaaatcc      300
tattgtcatt ggtattacat ccatagtttt ttctccaaga gaataaaagt aagtaaaata      360
tatagaatta tagataatga tatatgctat ggtgaaaaac aaagctgggt aaagggatag      420
agaatggggg aaggataatt ttaactgatt attagtagaa tgtactagta tctctgttct      480
aaaaggattt aagataggta ttacttaccg aacctaaagta ttacaaataa aatagcaatg      540
cttacactag gaaagacttt caactgagaa gcattat                                           577

```

```

<210> 55
<211> 483
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature

```

<222> (1)...(483)

<223> n = A,T,C or G

<400> 55

```

cctttttttt tttttttcac caataattat tttattcagg gagtaaagt tattaattgc      60
caaaatacga attttaaaatt tgagaagtac agatttgtaa gtatatattt gtttgaatag      120
tatcanattg gccttttatt ggcttatttg tatttagngc cagcacttac aatgtgaact      180
cagcaacaga agataattct tatgaaatca acattcaact tacatgaaat aacttaaaaa      240
cttaccaaca atagtctaatt gattatatac ctttaccaaa caatgtctaa tgaaagtcca      300
aatgtaaaaa tttaaaaaatt aaaattatag aatataattt ttacacatca attgttttgt      360
agcaccatct cgcaaaagaa atatcatgtt tattctgtag ctaaaatttc tcccacaag      420
cagaaattgt ttggaatata caaaaagaca acccattaac aagtaacttt aagtaatgta      480
ggt

```

<210> 56

<211> 521

<212> DNA

<213> Homo sapien

<400> 56

```

gtcgaccaga cttaagcatc gagtttttac catcttccac ttttaagctaa gttatgatac      60
ctattccatt cacaattggg gttcttttta aggtttgcaa atttcagcca attttgtagc      120
taagattgtt ctgatcagct caaaaagatt tggcttagtg ttttcattgc aaattataat      180
tgctgtagag ccacacacaa cttttgaact ttttaattata agtgttatgg ctaaagttat      240
ttactgaaaa tttcagtaaa atgtgtgaat gtttctttat gtattaacct catagcagta      300
aatgacttgc tgttgtttaa tttttctaag gcatcttaat agacttctgt tgaaaacttc      360
agtgtaaca tttttatagt ttgtactaaa ttttaaccgtg atataaaaaat gaattttatg      420
catagatcag gaatttttaa ttaaagggtt tttcttttaa aaaaaaaaaa aaaaagggcg      480
gccgctcgag tctagagggc ccgtttaaac ccgctgatca g

```

<210> 57

<211> 542

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(542)

<223> n = A,T,C or G

<400> 57

```

cctttttttt tttttttaca acttcacatt ctttaatgtt cattcagaat attaaatgcc      60
attaattgac catcattatt ataaaaatta ctatttagat aagtgagtt tagtacagt      120
ctattttaaag tatggaactg ttactggtgt gtgatcagta cagaaattga gactaagcat      180
ttagaaacct agagcaattt gacgtagcaa tcttctgtct gttgaatcta ataacaaaaa      240
aaattttttc aattttgcatt atctttttta aatttaattt gtcaagggaat tcatttttag      300
catattttac aaaaacatca ttctcctatg gagactattt ggaaatacaa ataagaaaac      360
tggttcttac cacagatagt ttttagaaac ctgttttagn gtaaagccat catttagtat      420
aaagnocatct attattactg ttactctgaa gtggttactg agcattacaa cagtnggtng      480
gattataagt ttgtttacta aanatgctag gattttattaa ctcatgtata tattttattga      540
ga

```

<210> 58

<211> 261

<212> DNA

<213> Homo sapien

<400> 58

```

gtcgacagag aaggtctatg tcaacagagt tgttatctca tagagccagt tttcaaagct    60
ccttctgcat tgtcactcac tgatcaggtg atgaattctt cctagatagt cgccactcc    120
acctcctact taacctgaga ctcatatttt agctatttct gcttttgtaa aaataattca    180
gatatataac tccaatttta atctatcatc caagggtaga tgtagttgct tagtagcatt    240
ttggaaaaaa aaaaaaaaaa g                                     261

```

```

<210> 59
<211> 480
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(480)
<223> n = A,T,C or G

```

```

<400> 59
cctttttttt tttttttaaa atatagaagt tctgagttag acctgttttag ctcanaatag    60
tggtgctaaac taccataaaa ttctctgtat atcttaaatg gtaatgggtc aaaaactcca    120
gaaaatcatc agttgataac acacctacag ataagtgcac gggtagggag ggatagccaa    180
gtgcccataa taatttgacc tcagtaaatt aaactgggca atacacatat ttgctattct    240
gatactgcat tagacttata aaattccatc taataagcat tcataaaaact ggacctctct    300
gtatatatct agcttagaca gggataggga aaagaataac tgaagaaact agcttacaat    360
agctagggtt cgtcagggtt attctatcca gccagaaacc accaccagag agaagctgag    420
ccattcagct gnctgtctcc tctccctctg tttgaatagt catgcctagg ccttgctgca    480

```

```

<210> 60
<211> 493
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(493)
<223> n = A,T,C or G

```

```

<400> 60
cctttttttt tttttttggt ccttctgttt atttcatttt ggatactcag tgaatgttaa    60
ttaaccagga aacttaaaag ttatttcaat tatgaacctc ttcaatcctt catcaattat    120
tttgagtatt ctggtcttaa aaacatctct ttcttctaca aacttctgaa agagatgaac    180
acctocacct acacaaaat aatgtgcttt gctggccaaa agtacacgtc catttttact    240
taacagtcta aggaaagtct ggtgcaaatt actataataa tctgggttgt aaatggtttc    300
tgaggtgaga atgagatcat attttcaaaa aagtttttca ctacttagta caagcttaca    360
aaactcagac cactcaccag aaaaaaatcg gcatttataat agttgngtta cttttggttt    420
cctgcatctt ttcacatctg gctcatttac atcattttct tcactttcca aagtggagtt    480
agctactaca tta                                     493

```

```

<210> 61
<211> 532
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(532)
<223> n = A,T,C or G

```

```

<400> 61

```

27

```

tttttttttt tttttttgaa aaatataaaa ttttaataaa ggctacatct ctttaattaca 60
ataattattg taccaagtaa ttttccttaa atgaactctt tataatgcat aattttacagt 120
ataagtagaa caaaatgtca tgacaaaagt cattgagtag aagacttgta ataaaaagc 180
ataaaatata tttatacata aacccttttc aaaaaacaag ggaaagcttg agccctcaat 240
atagggcgac acacggagcg ggtgaccgtg caggtagagg tactgtactg atttaaagtc 300
aagcactaga gatagnggat taatactctt ttgccgtaca ctatatacag atgtatagta 360
caagtaacaa tggcaaacag aatgtacaga ttaacttaac acaaaaaccc gaacatcaaa 420
atgaagggtg gtggaggaaa ggtgctgctg ggtctcccta caactgttca tttctttgng 480
gggcaggggg tagttcctga atggctgngg tccaatgact aatgtaaaac aa 532

```

<210> 62

<211> 567

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(567)

<223> n = A,T,C or G

<400> 62

```

gtcgactttt tttttttttt taagtatttt aggcataattt aataaataac ttcagtaaat 60
agcactgtaa aaagtgaact gttaaaaacta aaggcactta aaacaagaat gtgactagt 120
tgaaacaaga tgggcaactc aaatggtgag aagtaaact acagtggctt gttatggcac 180
taactcaaag taagactcgc gtaggtgaga gctgttgcat agccacagta taacttcaca 240
tgttcattaa aaaggcaaat tgaccgctaa aacttcaaag aaaaagtact cataaaaaaa 300
gtcttaccoc aaaattgcaa acaaatatcat taaaagatta gaagagggtga tagaaagcac 360
cagacattaa acaaaaataaa aataataaaa taaattcaac tcaaaaggtc occattcagc 420
aaatactttg taaaagtatg gcctgtatgt aaatagttgc taaatcaagg acttttttagc 480
agaaaattgc tcggttcttt tatctaaggc ttgaatttgt aaagngaagg cataaaagtt 540
nccaaacatt aagtaactct taaaatg 567

```

<210> 63

<211> 247

<212> DNA

<213> Homo sapien

<400> 63

```

gtcgacaaac aaacttggtc tgataatcat ttgggcagct tgggtaagta cgcaacttac 60
ttttccacca agaactgtc agcagctgcc tgcttttctg tgatgtatgt atcctgttga 120
cttttccaga aattttttta gagtttgagt tactattgaa tttaatcaga ctttctgatt 180
aaagggtttt ctttcttttt taataaaaaca catctgtctg gtgtggtatg aaaaaaaaaa 240
aaaaaag 247

```

<210> 64

<211> 330

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(330)

<223> n = A,T,C or G

<400> 64

```

cctttttttt tttttttttt tttttgacat ggagtcttac tctgtcacc aggctggagt 60
gcagtagtgc aagctcggct cactgcaacc tcaggcagga ctatttttaa ttatttttaa 120
tacctgcaaa agggaatctg cacatgcaca tccgtgtttc tacanaaatc tgcgatcgat 180

```

28

```

ggcagatctg tttgcctttg nggtgtccaca tgaaccattt ggcaaaggca tccaatgcta      240
acggggccca ccaactacaa cggaggcaac aactctgnng atttntttc acagaaagag      300
taaaattttca ttcaaccgtt ccatgtcgac                                     330

```

<210> 65
 <211> 486
 <212> DNA
 <213> Homo sapien

```

<400> 65
cctttttttt tttttttact aggcaaagaa ctttattaat ctttgtttca aacttgattc      60
ccaggcttct tcggcttaat tagctgcaaa gaatgaattg tgtataagca aaaactgaaa      120
agagctgcag tgtccaaggg gcttgggctt aaaaatatta gagatctaga ttttatcaga      180
tccataaaca aaaatttctt aaaaagcagt cataatataa aatagcagct cccagtaact      240
tcttcagggt ttatcttcag aagttgactc aattcagttt gcctcattct tggaagcctc      300
atcaaaattc tccacaagat ctggaacttc atcatcatca tcctctccag tagcaagtgg      360
tgcttttcca tccacagatt gtttgggcag agcttcggcc agtctcetta aactagtcag      420
actatccgca ccaagctggt ttaagatgct gggtagcatt tctgtcagct gctttgtctc      480
agcatg                                     486

```

<210> 66
 <211> 503
 <212> DNA
 <213> Homo sapien

```

<400> 66
gtcgaccgtc agacagcaac tcagagaata accagagaac aaccagattg aaacaatgga      60
ggatctttgt gtggcaaaaca cactctttgc cctcaattta ttcaagcatc tggcaaaagc      120
aagcccccac cagaacctct tcctctcccc atggagcatc tcgtccacca tggccatggt      180
ctacatgggc tccaggggca gcaccgaaga ccagatggcc aagggtgctc agtttaatga      240
agtgggagcc aatgcagtta cccccatgac tccagagaac tttaccagct gtgggttcat      300
gcagcagatc cagaagggtg gttatcctga tgcgattttg caggcacaag ctgcagataa      360
aatccattca tccttcgctc ctctcagctc tgcaatcaat gcatccacag ggaattattt      420
actgaaaagt gtcaataaagc tgtttggtga gaagtctgcg agcttccggg aagaatatat      480
tcgactctgt cagaaatatt act                                     503

```

<210> 67
 <211> 519
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(519)
 <223> n = A,T,C or G

```

<400> 67
cctttttttt tttttttgaa taaatttttt ttttattttt acaccataat ccaattctag      60
ttatcttaat tgaatttgaa aacttttttca attgcattaa atttacaaaa aagttctccc      120
acattacact aaagcattcc tcatgtttca cttccagtac tcagatactg aatgagtaaa      180
atcattttat tggctctctt ttaattaact ctttcaaatg cacattgttt aaaaactgac      240
taggtcaaaa atagttaonc ctgcaggttg acctatcag actttgcaa actcctccaa      300
gttcaatata aattgacgtt ttcagagtac aaagtcaatt ttacggaaac gctgttctc      360
cttttccatg gagccaatct gggtaathtt ttcattaaaa ttcttcttct gcctgtttgc      420
tgcggaactc tttgagctgc tgtagccgct cgatagtttc anaaatggtg cgttccccgt      480
ggaccttatt gtcctcttgt gcggatatna acagtgcga                                     519

```

<210> 68

<211> 495
<212> DNA
<213> Homo sapien

<400> 68
gtcgactaaa gctgaagaga taaaagaggt tgtggggcta tgtcttaaga caaaagaaca 60
tttagaaaac ctcaggaaat gatcagagtg ggatagatgt tactagaaga aacaaagaaa 120
ttgaattcaa ttaggagtta gaatcattta caaagcaatg gggaaagtaa gccctaaaa 180
actattgtag catatagtaa ccagagccaa actctcataa tatattcccc aaggcaaaag 240
aaaaatattt acaagattgg cgttggtttta tatgtttgca aacttattta ataagtctgg 300
ctttgtagat ttcatactct agtctgcatt caatcaaaat gtcttggcta aacttcatga 360
aaaaacccca gcctcataaa ttagtagttg gaaaaaggag gcatatttag agctttttca 420
gataattgta tttctttgat acattagact ggacacacag tagtttgttt aaggtttaatt 480
gcaatattgc aatga 495

<210> 69
<211> 525
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(525)
<223> n = A,T,C or G

<400> 69
gtcgacgcca ccatgttcga ggcgcgccctg gtccagggtt ccatcctcaa gaaggtgttg 60
gaggcactca aggacctcat caacgaggcc tgctgggata ttagctccag cgggtgtaaac 120
ctgcagagca tggactcgtc ccacgtctct ttgggtgcagc tcaccctgcg gtctgagggc 180
ttcgacacct accgctgcga ccgcaacctg gccatgggag tgaacctcac cagtatgtcc 240
aaaatactaa aatgcgcggc caatgaagat atcattacac taagggccga agataacgcg 300
gataccttgg cgctagtatt tgaagcacca aaccaggaga aagtttcaga ctatgaaatg 360
aagttgatgg atttagatgt tgaacaactt ggaattccag aacaggagta cagctgtgta 420
gtaaagatgc cttctggtga atttgcacgt atatgccgag atctcagcca tattggagat 480
gctgntgtaa tttcctgtgc aaaagacgga gtgaaatttt ctgca 525

<210> 70
<211> 511
<212> DNA
<213> Homo sapien

<400> 70
gtcgacattt tatatataat actactaatg gcatagatta acaaaatatt ttacatgtag 60
gaaaggacat aagattactt ttaaagaata gtatgaaata cacaatatc aaatgtgttt 120
gcaatgccta ccaaatttca aatgtgcctg gatcatgtat aaattaagga aagaaaaaag 180
gatcatgtat aaattaagga aagaaaaaat gtaagtatac aacctacacg gtaaaaaaca 240
aaaccaaaca cctgggttaa aatatctatt taagctcgag tgtataacct taaacaattt 300
gtgtatcact agaaaaatgg atttattagt aaaatttagg gcagagattt tattttggac 360
accactgcct ttgtagaaaa atccaaagtg gcataaaaag aaaaataaaa tattaataaga 420
aaaaatatat attatcattc ccatgttccc atcctgttac tagcattgct gttctggtgc 480
atcaatcctg agtactctaa cttttgattt a 511

<210> 71
<211> 464
<212> DNA
<213> Homo sapien

<400> 71

30

```

cctttttttt ttttttttga agagcttctt gcactgttat aagaaagaac atgtgggaga      60
ttgcaaacaa agcaacataa agagtataca gcctgttaga gtctgactaa agtaaaaaaa      120
actcatgtct ttgttttagtg agtatctgta tactaagtta atgcaatgcc aatttagattc      180
aaattaaatc aagtacaagc aaatgtactg aaagtattag gaatgcatca tctactttgc      240
taaataattt gcactccgca ttctgcaatt acatgagcat gccattggta taatattgggt      300
tatataacat ttaacatggt agttttttaa agaattgtaga tacattcata gagatcagta      360
tttttacaga tgtttttact ataaaaggaa ccatgtataa cattgatttt taccttcagt      420
tttgataata ggctgaagac tgccttcaat cactttaatt ttg                          464

```

```

<210> 72
<211> 234
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(234)
<223> n = A,T,C or G

```

```

<400> 72
aataaaannt gaacaaaagg aaaagggtga tataaagtgg aacctgtggg aaagaggcaa      60
gggtgcagg acagaagaga ctgggaactg caggggccct gggactcagg aggagatgct      120
gattcagctc ataggtgacc cagtcctggc cccggctgtt cccaagagaa ggctgtaagt      180
accaggggag gtggttaagca ggatggagga aaaatcagag gactgggggt cgac          234

```

```

<210> 73
<211> 143
<212> DNA
<213> Homo sapien

```

```

<400> 73
gtcgactaaa taagtcaatt cctggaattt gaaagagcaa ataaagacct gagaaccttc      60
cagaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa      120
aaaaaaaaaa aaaaaaaaaa ggg                                     143

```

```

<210> 74
<211> 533
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(533)
<223> n = A,T,C or G

```

```

<400> 74
gtcgacataa tctagggcatg aagagcaaaa atatcccttc cggagtcttt gaagctgaaa      60
atataaaaca aataaaaaaat aaaaaaataa aaaccacaca aaatgttgaa ccaaacttcc      120
ctgctaattc ccatgcccac gttctttccc accctgttcc cagtcttctg acaaactgtg      180
tacatagcgg actcctcctt tctcctccga ggtggtttta aaggcttttt ggtgtataga      240
agtttgtcca ttgttaaaac tccggattgc gttcctcccc gccttccgcc ctttcccttc      300
cctaaagtga tgggctttct cttttctctt tttagtttac ccggtttctt ttttaagtaat      360
gtggaagaaa atggtttatt ttgtattgng gtattgaata ttgngttcct ttttatgagg      420
caaacctgat tgtaaaactt atgtaactat agactggaaa aaaaatgagcc gngccaaaag      480
tctncccttc tgtttcttca gcacattgac ccatnncaca cacatacaca cca          533

```

```

<210> 75
<211> 485

```

<212> DNA

<213> Homo sapien

<400> 75

gtcgaccttc	cctaggtgt	ttctgctggg	cgctccgcga	agatgcagct	caagccgatg	60
gagatcaacc	ccgagatgct	gaacaaagt	ctgtcccggc	tgggggtcgc	cggccagtgg	120
cgcttcgtgg	acgtgctggg	gctggaagag	gagtctctgg	gctcggtgcc	agcgcctgcc	180
tgcgcgtcgc	tgctgctgtt	ccccctcacg	gcccagcatg	agaacttcag	gaaaaagcag	240
attgaagagc	tgaagggaca	agaagttagt	cctaaagtgt	acttcatgaa	gcagaccatt	300
gggaattcct	gtggcacaat	cggacttatt	cacgcagtgg	ccaataatca	agacaaactg	360
ggatttgagg	atggatcagt	tctgaaacag	tttctttctg	aaacagagaa	aatgtcccct	420
gaagacagag	caaaatgctt	tgaaaagaat	gaggccatac	aggcagccca	tgatgccgtg	480
gcaca						485

<210> 76

<211> 417

<212> DNA

<213> Homo sapien

<400> 76

cacgctgggt	ttgcatcttc	aggagacgct	cgtagccctc	gcgcttctcc	tcggccaatt	60
cgcggaagaa	gtggctcacg	ccttcagag	ccacatcatc	gcggtcgaaa	tagaagccca	120
gagagaggta	ggtgtaggag	gcctgcaggt	acaaattgac	caggctgttg	acggctgcct	180
ccacgtcggg	ggaataattc	tgacgaatct	gggagctcat	ggttggttgg	caagaaggag	240
ctaaccacaa	aaacggtgct	ggcaggtccc	agaagcagga	gatggccgag	aagatgggtcc	300
cggaggttgc	aagcggagag	gaaatcggag	ggcggtcgga	ggctggaaga	gagtcccggg	360
atctgttccg	tccaaacact	gttgaagcaa	gagacagacc	cgcgggaccg	cgtcgac	417

<210> 77

<211> 547

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(547)

<223> n = A,T,C or G

<400> 77

gtcgaccttt	tattaagaat	atattttattc	aggcattttg	ataacaaact	gttactctaa	60
gtataggtga	tttaccaggt	gtatttttaaa	aagtaaatga	atcccactgt	agtttttctt	120
gaaggaaaaa	tcattttctcc	agttgctgag	gggtactaaa	agcttcatac	acattagcag	180
caaagtcttt	cacttgctcc	attgtcaaca	gatcctgaac	aaaatgacta	ggtgtttcac	240
tgcaaaactga	atggatctgt	ccgtttacta	ttggaattat	cttagctaaa	ggcaggctga	300
cactggaaaag	actattcata	gagttacat	gttgcaggtc	ctgttcagta	ggtcgaaaga	360
actcagccat	attgtctaga	agtctactaa	aacctcgggt	taaacaggta	ttcaaaactg	420
tactaaaatc	tgggctttcc	aacatgtctc	tagtttcatt	gagaagttta	atagtggtaa	480
tgtctcgagg	agaangtcca	caggcctgca	ctgctaattg	agtttcttca	tctggcatca	540
tataatg						547

<210> 78

<211> 499

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(499)

<223> n = A,T,C or G

<400> 78

```

cctttttttt tttttttttt ttttnaaaaa aaatcttttt ttattttcaa gattgcttct      60
tataattgaag ctcatattaa agcaacagta caatgttcat aaaatataag tgtgatgccg      120
taacattttt ttacatgtca gaatactgat atttatatgt ataataaaat aagaacttta      180
aaattgtaca aatagataca ttaaaaaatga catagaaata gggcgtctnt cactgaaaca      240
agacagttat atctggcacg tattagttta agatgaaagt agaagcaaaa agatttacaa      300
gaatcagcag taacaagatt gatgctcaag agacataatt gtacattgna ttgtacatac      360
attgtatggg ttttaagctgg ctgaatntta tatatttcaa gtttaaaaaat gcactacata      420
tagagtgtcc agagtttaag gcgaaattac agctcanaac tgntgncctt tctaattttg      480
gggaagcttn tttgacaac

```

<210> 79

<211> 370

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(370)

<223> n = A,T,C or G

<400> 79

```

cctttttttt tttttttttt ttttaaggag caatgacatt tcctagaagt tactttaaga      60
atttccctag agggtcgggt atcatctcan ccagatcttt ctcaccttc aaggccctgt      120
ttggtacagc ttgctaggaa gctgttccag actgcagcag ccctctctgg ggtctctcta      180
ccacttccca ggcactcana acttgtgcct cannanaactg ttttgtggca ctgnccatt      240
ctctgattct ccatgtgagc tgggtttatc ccatccagca tggctgtgaa atcctaaagg      300
ttcaaaccoc agccactctt cacctatatt tcccccaat ggctagcacg ggaaagggcc      360
caaaggtagg

```

<210> 80

<211> 428

<212> DNA

<213> Homo sapien

<400> 80

```

gtcgacaaaa agggaaggaa ggagagacag ataactctca gtcatttaaa aaactacaat      60
aaaatattat gaattatcaa ttagatcaaa gttcctcaca gctatattta tataggtaaa      120
aaaaaattaa ataggctaaa tgcccaaaaa ttttaagactg gcaaaatata cttggctaaa      180
tactgtgctg ctctattaaa taccatgttt cagaagaatt attaatgaca tgagaatatg      240
ctcaaaatac atattgatat gtgcaaatat atattgcaaa gtaagattat agaattatcc      300
tagttcaaaa atgtcacata tatatgtatt taaaaaaaaa ggcagttaag atttacaaca      360
aaatgttagt ggtgggacct tctggtagga atacagattt ttttttattc agaagttttt      420
tgatgtcg

```

<210> 81

<211> 533

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(533)

<223> n = A,T,C or G

<400> 81

```

cctttttttt tttttttatt tttaaaattt tttttttttg aaataattat aaattatcag      60
aaagttgcaa acaaagccca gtcaggtccc atgtaccagt ttcactgcca ccatctttaa      120
aggaggatta gacgaatctg actgctaaaa gtggcccagg gattctggag aaaatccaac      180
aggtttgcta tcaggaaagc aatttcactt acaattcagg tttgactgca agtgaaagtg      240
gttgaaacaa gtgagaagnt gattgcttcc tcatataata gtctaaatgt aggtgtccaa      300
gcctggaata gaggtcctgg tctctctaagt tctcaggaac acaggcttct tttagccact      360
ccacatctct aggggtgttg cctcatggtc caaaatggng actggaattc cagccatcac      420
atntgctttc caggcagcaa aatggaagaa ggggcacana agaacagaga tgacaatagg      480
tataaacaag ctctcttttt aaaggagatt cccaggagct gctacatgac act          533

```

```

<210> 82
<211> 493
<212> DNA
<213> Homo sapien

```

```

<400> 82
gtcgaccgcg gaagatgcag ctcaagccga tggagatcaa ccccgagatg ctgaacaaag      60
tgctgtcccg gctgggggtc gccggccagt ggogcttcgt ggacgtgctg gggctggaag      120
aggagtctct gggctcgggt ccagcgcctg cctgcgcgct gctgctgctg tttccctca      180
cggcccagca tgagaacttc aggaaaaagc agattgaaga gctgaaggga caagaagtta      240
gtcctaaagt gtacttcatg aagcagacca ttgggaattc ctgtggcaca atcggactta      300
ttcacgcagt ggccaataat caagacaaac tgggatttga ggatggatca gttctgaaac      360
agtttctttc tgaaacagag aaaatgtccc ctgaagacag agcaaaatgc tttgaaaaga      420
atgaggccat acaggcagcc catgatgccg tggcacagga aggccaatgt cggggtagat      480
gacaaggtga att          493

```

```

<210> 83
<211> 501
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G

```

```

<400> 83
cctttttttt tttttttgta ataaagacac tgctttttatt tagtttgata tgtttcttta      60
cagaatgcag aaaacacatc ttaaaatcat atagaaggaa ataaaaacac atcagtggtt      120
ggtgaacact tgaatgtgag attggctctc catctcacag agtccaacgg ccatcaccag      180
cccagcgctc aggggagcag gctgcctgca aaggcattgt tgctgttggt attctgttca      240
ctgccccatc gcctccagtt gctatggcaa caggccattc tgggccagcc acgtctctgc      300
atggcagtg ccaatggtgg agttgctagg ggcgacggag ctgttttgaa ggcccttcaa      360
agccctcacc tggaacattg ggaattgttt attttttgat gaggncatca gaaataatct      420
tcaccaggtc agatcccact tgtgctcctg tctctggggc accaggggaa actctgactt      480
ggaggcatga gccagtcac c          501

```

```

<210> 84
<211> 454
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(454)
<223> n = A,T,C or G

```

```

<400> 84

```

```

cctttttttt tttttttttt ttttatgcta ataaaacatc ataattttaag gactacactg      60
catttttttaa ttccataaat tataatcctt taacatatat gaaagtttca tattctttaa      120
gngcttttaa atatatttta tttttttaac aagtggaaaa gaatgtttct taaaagacat      180
ttaatttttt agtggaattt aatattacca aaaacattct gtgcataaca atttgaataa      240
caattttttt atcttcaaga aatgggattt ttatataaaa tacacatgta gcactgaatg      300
ccaaagtgat gggatcccat ggtcanaatt caaaattaga ttcgctatta aacctgtctg      360
gtttgtgtcc tgagtgaana atgatctcga gctggggagg gaggtgcatt gggtaatcag      420
tgcttttgaa ggtgaatttc cttgctgnga aata                                     454

```

```

<210> 85
<211> 509
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(509)
<223> n = A,T,C or G

```

```

<400> 85
gtcgaccgct ctcagctctc ggcgcacggc ccagcttcct tcaaaatgtc tactgttcac      60
gaaatcctgt gcaagctcag cttggagggt gatcactcta caccaccaag tgcataatgg      120
tctgtcaaag cctatactaa ctttgatgct gagcgggatg ctttgaacat tgaaacagcc      180
atcaagacca aagggtgtga tgaggtcacc attgtcaaca ttttgacca cgcagcaat      240
gcacagagac aggatattgc cttcgcttac cagagaagga ccaaaaagga acttgcatca      300
gcactgaagt cagccttatc tggccacctg gagacggtga ttttgggcct attgaagaca      360
cctgctcagt atgacgcttc tgagctaaaa gcttccatga aggggctggg aaccgacgag      420
gactctctca ttgagatcat ctgctccaga accaaccagg agctgcagga aattaacaga      480
gtctacaang aaatgtacaa gactgatct                                     509

```

```

<210> 86
<211> 520
<212> DNA
<213> Homo sapien

```

```

<400> 86
gtcgacgggc gccagggtct ttgtggattg catgttgaca ttgaccgtga gattcggctt      60
caaaccaata ctgccttttg aatatgacag aatcaatagc ccagagagct tagtcaaaga      120
cgatatcacg gtctacctta accaaggcac tttcttaagc agaaaatatt gttgaggtta      180
cctttgctgc taaagatoca atcttctaac gccacaacag catagcaaat cctaggataa      240
ttcacctcct catttgacaa atcagagctg taattcactt taacaaaatta cgcatttcta      300
tcacgttcac taacagctta tgataagtct gtgtagtctt ccttttctcc agttctgtta      360
cccaatttag attagtaaag cgtacacaac tggaaagact gctgtaataa cacagccttg      420
ttatttttaa gtcctatttt gatattaatt tctgattagt tagtaaataa cacctggatt      480
ctatggagga cctcgggtct catccaagtg gcctgagtat                                     520

```

```

<210> 87
<211> 171
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(171)
<223> n = A,T,C or G

```

```

<400> 87
gtcgacgagt acagtatcag ctgagctgac cttactctga ggactaaact ttttgctgga      60

```

35

agcggttttct gatttacagc tcttggtttc tcccagacat gttggtggga gagattttgg 120
 tttttaaggg gttgtagat ggagtaaann ttctttaagn nttaattttt t 171

<210> 88

<211> 508

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(508)

<223> n = A,T,C or G

<400> 88

cctttttttt tttttttttt tttttgnagt aaaaaatctt tatttccaaa atgatttggt 60
 agccaaaaga actataaacc acctaacaag actttggtta gaaagagact tgatgcttct 120
 tataaattcc ccattgcaaa caaaaaataa caatccaaca agagtcattgt taccattctt 180
 tagccattaa cctggtttta agtctccaaa atcaggattt taaaatgtac ccaactggga 240
 ccaaatacaa acatgagaca ctaggngggc ttgtccttga ttaggaatca ccagcttaag 300
 gaaactttatc atgggctgag agtttagatag atagcttana acaacattgc aaaagnnggt 360
 gcttctacat gaggaactttt ttccccccaa gtagaaaaat aattaaatct tgngtttctt 420
 tataattgngc tttttttggg agaaagcaat tcatttaagg atttaaaaaca tgttggatac 480
 aaaggtagtt canagatgta ataatggt 508

<210> 89

<211> 508

<212> DNA

<213> Homo sapien

<400> 89

gtcgacggga taaatagaaa gcagaatgaa ttaatggaaa agaactcggc tgtaggcca 60
 ttctctaaat tctagttag ccaaaagttt atgtgtgggt tggggcttca tttatttatt 120
 tcatgagtaa aatggaataa tacctaacag gcaggctctg gaagttggaa atcacatata 180
 cacacacaca cacacagaca cacacacaca cgatcaatca ttagtagtcat attagatggt 240
 caataaaataa cagctactac agatgcctat cagttgagta agtagttcat taaattgagc 300
 tcccaaaggt ctcttctctt cacatccata tccgtttctg cagcaatcaa atagatacat 360
 gattgttttt ctgtaagaaa ttactgcaaa gagaatcttt ttctcctact aactgttctt 420
 tctacctggg ataggagata aatgtacgtt tcttaattag ctgacttttt agtatgtcat 480
 ttctgaagga aaaataaatt aaccttaa 508

<210> 90

<211> 531

<212> DNA

<213> Homo sapien

<400> 90

gtcgacacga gtcccgogtt ctctccttga atccactcgc cagcccgcgc ccctctgcgc 60
 ccgcaccctg cacaccgcgc cctctcctgt gccaggaaact tgctactacc agcaccatgc 120
 cctaccaata tccagcactg accccggagc agaagaagga gctgtctgac atcgtccacc 180
 gcatcgtggc acctggcaag ggcatcctgg ctgcagatga gtccactggg agcattgcca 240
 agcggctgca gtccattggc accgagaaca ccgaggagaa ccggcgcttc taccgccagc 300
 tgctgtctgac agctgacgac cgcgtgaacc cctgcattgg ggggtgcata ctcttccatg 360
 agacactcta ccagaaggcg gatgatgggc gtcccttccc ccaagttatc aaatccaagg 420
 gcggtgttgt gggcatcaag gtagacaagg gcgtggtccc cctggcaggg acaaatggcg 480
 agactaccac ccaagggttg gatgggctgt ctgagcgctg tgcccagtac a 531

<210> 91

<211> 426

36

<212> DNA

<213> Homo sapien

<400> 91

gtcgacaatt gaggcctaca agagagggga gcctaggagc ttggattgac cttctagtca	60
accacctgac ttcagcacac cattacaatc gggagactaa accaacaacc agaggatcta	120
aaatgtcaca ttcagatttt caggaagaaa atcttcatta cagtggagca caaatgttcc	180
atacaagaca tcattgagga gccatgctgt ccccttctaa cctgaaacac attctttccc	240
atcctgggtg ggcttctgta cctccttatt aatttatgaa cctgaagttg cttgaagtgt	300
tttgggctta ataaatgggg tgaaagtata ggtagcagta acacctacat gaaacaatac	360
accttggatc ttttaatac aattactttt cttttttaag tctactttta aaataaatac	420
ttctgt	426

<210> 92

<211> 223

<212> DNA

<213> Homo sapien

<400> 92

gtcgactttt aaagcaattg actaggagaa actattttgta gottatataa caaggactat	60
atataaataa aaaactatct ctatgaaaat cttaaaatta cacacagtcc gatgaaata	120
atcatatatt aaaaaggcaa accagaaaaa taaatacaga tgacaaaat ccatgtgaca	180
tatttggcct aattagtaat tagaaaaaaa aaaaaaaaaa aaa	223

<210> 93

<211> 486

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(486)

<223> n = A,T,C or G

<400> 93

cctttttttt tttttttttt tttttttttt tctcaaatat ccaattttat tttatcattc	60
tcgcattggg ggatgcgatc tgcagctagg atcggaattc ccaggcctat anatttttaa	120
accacaccac aggggtaaac cttaaaagaa gngaaaccta acactatata tatttccatt	180
tctaaataca gtataattaca naagttaaata tatnccacct ntgngtactt acaactntaa	240
aaagatncaa tancctctacc aattataaat aatgtancat ttcataattaa agacattatc	300
gtncaatgga anaataggaa ccctntaagc tatcactatc aagggttagng tctatatcta	360
cttganataa aatactgaaa attcagncta tgaagccaaa tcctgattta acaagttatt	420
ggtagtataa gtgataagtg ttanctgatg aagggaaggc aaatgtggta atttataatc	480
ctgaca	486

<210> 94

<211> 214

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(214)

<223> n = A,T,C or G

<400> 94

cctttttttt tttttttttt tttttttttt ttttngcaa cacaagtcaa tctttattga	60
aaactgcagt attaatacat aacaattcct gttacaataa acgtgctttt ganattttta	120

```

aatctgagct catctcatca gattgcataa aaaattaaaa tagtntcaat tgacacctaa    180
ctgaactggc tcaggatgga aattccattc cttg                                214

```

```

<210> 95
<211> 463
<212> DNA
<213> Homo sapien

```

```

<400> 95
gtcgaccaga attcagagcg aatggtcaca gttggtcgct gggcaaaggg aatgagtgca    60
gactatgaag aaatttttga tgtacctaaa ccgcaaaaac ccaaaacaaa aatacctaaa    120
gttggttaatt tttgataaca gctagcacta tcatgagtta ctacctcatt gttactttct    180
aaaccaggcc cgcttcacga gttagagttg agctcccctg tagccaggac tatgctgtag    240
atatcagtat gatctgggtg tggccaaaaa caatttttctt tattctgtct atcaaatagt    300
actttctacca ctgtttggag aaaattgaag aaaagaataa gatgattaaa tgaattctct    360
aaaagaacat attttaagag acagaactta gacataacca agtagttgta tacctgattg    420
taacaatcat cttttataaa agcaaaatta tgcataaatg taa                    463

```

```

<210> 96
<211> 606
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(606)
<223> n = A,T,C or G

```

```

<400> 96
gtcgacttta aaagtgcctc ggcacacctgt attacatgtc atagaattgt aaagtcaaca    60
tcaattacta gtaatcattc tgcactcact ggggtgcatag catgggttaga ggggctagag    120
atggacagtc atcaactggc ggatatagcg gtacatatga tcttagcca ccagggcaca    180
agcttaccag tagacaatac agacagagct tttggtgagc tgtaactgag ctatggaata    240
gcttctttga tgtacctctt tgccttaaat tgccttttag ttctaagatt gtagaatgat    300
cctttcaaat tgtaatcttt tctaacagag atattttta atacttgctt tcttaaaaaa    360
caaaaaaact actgtcagta ttaatactga gccagactgg catctacaga tttcagatct    420
atcattttat tgattcttaa gcttgtatta aaaactagcg aatatcatca tggatacata    480
ggagaagaca catttacaat cattcattgg gcctttttatc tgtctatcca tccatcatca    540
tttgaggcct aatatatgcc aagtactcac atggtatgca ttngnacata aaaaagactg    600
tctata                                606

```

```

<210> 97
<211> 530
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(530)
<223> n = A,T,C or G

```

```

<400> 97
cctttttttt tttttttgta gattttttgc tatgttactc aggctggtct tggactcctg    60
ggctcaagcg atcctcccac cttggcttcc caaagtgcc aagattatagg catgagccac    120
catgctcggc ctgctccttt tcttgaaaca cctcctctgt ggttttagatt ccaggagact    180
ggaatgggtct gccctgggtgg gctgctgagt cagggacctg aggtgtttgt tcaactggga    240
ggcggggttca gatcaggaat gtaaggatga tggaaagaag ggagtcactc tggtttggtg    300
ggactgggga gcaatcttga tcacggccac ttacagcttc tgccattgtc cttcaccact    360

```

```

atctcagcat ctcggtccct cacgatgtcc ctccagtcaa ttgtgtccat gtgacaaaagc 420
ttatcgttct tctcaatata aacacccccc gacagaatct cggtgagctg agtcaagcgg 480
agctggcgca naggctggct ggagttggtg ttatagttca acatgacgaa 530

```

```

<210> 98
<211> 479
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(479)
<223> n = A,T,C or G

```

```

<400> 98
gtcgacgggt agtttctgcg acttgtgttg ggactgctga taggaagatg tcttcaggaa 60
atgctaaaaat tgggcaccct gcccacaact tcaaagccac agctgttatg ccagatggtc 120
agtttaaaga tatcagcctg tctgactaca aaggaaaata tgttggtgtc ttcttttacc 180
ctcttgactt cacctttgtg tgccccacgg agatcattgc tttcagtgat agggcagaag 240
aatttaagaa actcaactgc caagtgattg gtgcttctgt ggattctcac ttctgtcatc 300
tagcatgggt caatacacct aagaaacaag gaggactggg acccatgaac attccttttg 360
tatcagaccc gaagcgacc attgctcang attatgggggt cttaaaggct gatgaaggca 420
tctcgttcag ggggcctttt tatcattgat gataagggtg ttcttcggca gatcactgt 479

```

```

<210> 99
<211> 502
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(502)
<223> n = A,T,C or G

```

```

<400> 99
cctttttttt tttttttgta agtttaaatt tattttttta aaatgcttgt cttcctcaact 60
agacaatcaa ctctatgagg gcagagacta tgtcaccact gtcccaccag cccctggcac 120
acagtaggta ctcaataaat atatgttga aggatggatg gaggtaatgg atggaaagat 180
ggatggaagg atgaatggag ggatggatgt gaccacgtg aagtgtgagt aggaacattc 240
tcttattatg ggtggaggaa agagagagga gattgagaaa ataagataaa atacattgat 300
gagcatcatt tttggtgttc gaaaagtagg attgaattag gactaataaa tctagagaat 360
tttacctctt tcaatgcccc agccacactt ttctatcact ttgaaaccga aaaagtaaat 420
actttcccaa catttgcttt gctggttaga aatgctttta taaaaatgca atctctangt 480
tgccatggca tcattaaaag aa 502

```

```

<210> 100
<211> 537
<212> DNA
<213> Homo sapien

```

```

<400> 100
gtcgaccctt tccataaatc cttgatgatt gacaacaccc atttttcctt ttgccgaccc 60
caagagtttt gggagtgtga gttaatcatc aagagaatth ggggcttcca agttgttcgg 120
gccaaggacc tgagacctga aggggtgact ttaccatttt ggggtggagt gttgagcatc 180
tgtccccctt tagatctctg aagccacaaa taggatgctt gggaagactc ctagctgtcc 240
tttttcctct ccacacagtg ctcaaggcca gcttatagtc atatatatca cccagacata 300
aaggaaaaga cacatttttt aggaaatggt tttaataaaa gaaaattaca aaaaaaatt 360
ttaagacccc ctaacccttt gtgtgctctc cattctgctc cttcccatc gttgccccca 420

```

39

```

tttctgagggt gcaactgggag gctccccttc tatttggggc ttgatgactt ttctttttgt 480
agctgggggct ttgatgttcc ttccagtggt catttctcat ccacataccc tgacctg 537

```

```

<210> 101
<211> 611
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(611)
<223> n = A,T,C or G

```

```

<400> 101
gtcgacctaa aatgaagtgt ttgaaatcag aaatctatct ctaatgtctc atagcttttaa 60
aactattttt gtccttatac tcatacttgt tattttatct tattcatcct atatagccat 120
ttgactgaaa tgtagaaaat aatttattaa attgagaaaa tatgcaggca ttgaacaatc 180
tttcaagtat tttgaataaa aattcaaatt attatagatt gcctggaatt gttaagactg 240
tcagaaggto agctcattga tagctaagta gtatacactc tgaaaaacag aatgtagaaa 300
tgggttttat aaaagctgac ctctagagta aaggaggacc cagcatgtgt aattcttctc 360
cttaatactt taagaccact aatttgagga cttatggttt ctccaccactg cactcttgca 420
gctttcaaga aagtacttaa gttttaaatg cccagggtgat ttctaagact cttgaataga 480
attggttggg ttcttctgat attgcatttt catgagaaaa aatttcagtg gtacattaat 540
ttttattttt ctttttgctt atagacttcg catatcattt aaagtgatgg ttcgagcttn 600
ctctggatac t 611

```

```

<210> 102
<211> 498
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(498)
<223> n = A,T,C or G

```

```

<400> 102
cctttttttt ttttttttta acgcataattt gtttttattt ataggtaact accacatgaa 60
ttataaagac aacaaaggat gtcagaatga acatggatag gtgtatgcat actacggcta 120
aggagaaaca atgttcctac atattatggg tagtgagaac attatctgta taacagggaa 180
ctgtgattat ttaaaaatat gcagaactta ttcatctgtt gctttanaaa taactgtata 240
cagtgttata agttgaaaag aactcaaaat aactaatacc aaatatacac ctatgtatta 300
naattcaaaa aagctgcttt ctgtgaagtc aatcagctat attaaaaaat gacacaaatc 360
caaaacaaga tgcattgttat atataaaggg acattgtaag ttctccttgc gcattaaacc 420
catggtttta tccatgaaat ttccttttaa ttatcattta gacagaagca tgcaaatagt 480
ctcaggatct acttaaga 498

```

```

<210> 103
<211> 446
<212> DNA
<213> Homo sapien

```

```

<400> 103
gtcgactctt ggtgtttttg tatttccacc tcacccccag cacatagccc agtctcttgc 60
acaaattaag tacttaatgt gtgttgagct aaattgaata aaggattatt agcattagca 120
tattttgtgc cttggttgta taagctgggt gtttggtttg ttacctttgc aaatatttat 180
gattatcacc ccccacata ctaaatgtgt tttaaaagtt ttgcctttcc ttcagatact 240
accccaggca atttgctgta gataatgtga ttgcttccaa tgacataatt atcccaaact 300

```

40

```

ctctgccccg gatatacttt gccaaacgaa atttgaattc tctgaataaa ttgggtcatgt    360
cctaaaaaaa aaaaaaaaaa aaaaaaaggg gcggccgctc gagtctagag ggccccgttt    420
taaaccgccg tgatcagcct cgactg                                         446

```

```

<210> 104
<211> 286
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(286)
<223> n = A,T,C or G

```

```

<400> 104
gtcgaccttc gttatccgcg atgcgtntcc tggcagctac attcctgctc ctggcgctca    60
gcaccgctgc ccaggccgaa ccggtgcagt tcaaggactg cggttctgtg gatggagtta    120
taaagggaagt gaatgtgagc ccatgccccca cccaaccctg ccagctgagc aaaggacagt    180
cttacagcgt caatgtcacc ttcaccagca atattcagtc taaaagcagc aaggccgtgg    240
tgcattggcat cctgatgggc gtcccanttc cttttcccat tctga                    286

```

```

<210> 105
<211> 406
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(406)
<223> n = A,T,C or G

```

```

<400> 105
gtcgacgcgt agcagagtgg tcgttgtctt tctaggtctc agccggtcgt cgcgacgttc    60
gcccgctcgc tctgaggctc ctgaagccga aaccagctag actttcctcc ttcccgcctg    120
cctgtagcgg cggtgttgcc actccgccac catgttcgag gcgcgcctgg tccagggctc    180
catcctcaag aagggtgttg aggcactcaa ggacctcacc aacgaggcct gctgggatat    240
tagctccagc ggtgtaaaacc tgcagagcat ggactcgtcc cacgtctctt tgggtgcagct    300
caccctgcgg tctgagggct tgcacaccta ccgctgcgac cgcaacctgg ccattggcgt    360
gaacctcacc agtatgttca aaatactaaa atgcgccggc aatgaa                    406

```

```

<210> 106
<211> 258
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(258)
<223> n = A,T,C or G

```

```

<400> 106
gtcgacgatt ttttttgtac attttgctg cagtattggg ggtagaatat actataatat    60
ggatcatctc tacttctgta tttatttatt tattactaga cctcaaccac agtcttcttt    120
ttccccttcc acctctcttt gcctgtagga tgtactgtat gtagtcatgc actttgtatt    180
aatatattan aaatctacag atctgttttg nactttttat actgttggat acttataatc    240
aaaactttta ctagggta                                         258

```

```

<210> 107

```

<211> 369
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(369)
 <223> n = A,T,C or G

<400> 107
 gtcgacgtaa aatagaaaca gaaggggact ttatcaacct gattaacttt ctcaacatgt 60
 taaccctaca gttaacatta taatcaatgg tgaatcattg agtactttcc ttctaagatc 120
 agaaacagtt caaagtccac tctcaccatt tctattcaac attgtactgg aatcccagcc 180
 agtgcagtaa taccaataat aaaaaattaa agtcataaag attgaaaagg atgaagtaaa 240
 gctatttcaa ttntattttag aagtattttag aaaccccaaa gaatctacaa aaaactaata 300
 gaaataagtg aatatatgaa ggtcttacta tacaagatca acatatcaaa agcagtggta 360
 tttaagaaa 369

<210> 108
 <211> 289
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(289)
 <223> n = A,T,C or G

<400> 108
 gtcgacattg catccttgaa atcctgggct caggtgatcc tcccgcctga gcctcctgag 60
 tatctggggac tacagatgcg tgccaccaag cctggctaata tttgtctcat gtcttctaaa 120
 aattattttg tgaagcccct tcacaaaaaa cottaaggga aatctgatgg tgctcaggaa 180
 tctaactctc cctaaaccat cctctttaac tgcttctaaa atatctctgt tggcctttct 240
 tanccttttt ctgtttccat tcagtgtctc aagcgctttt tgtttctaa 289

<210> 109
 <211> 444
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(444)
 <223> n = A,T,C or G

<400> 109
 gtcgacctgg cgttggcacc gctgaggaat gggcctgggc ggggagggac atctctacac 60
 cgttcccacg cggaacagg gcaacatcta caagcccaac aacaaggcca tggcagacga 120
 gctgagcgag aagcaagtgt acgacgcgca caccaaggag atcgacctgg tcaaccgcga 180
 ccctaaacac ctcaacgatg acgtggtaaa gattgacttt gaagatgtga ttgcagaacc 240
 agaagggaca cacagttttg acggcatttg gaaggccagc ttcaccacct tcaactgtgac 300
 naaatactgg ttttacggct tgctgtctgc cctcttttggc atcccgatgg cactcatctg 360
 gggcatttaa cttcgccatt ctctctttcc tgcacatntg ggcagttgta accatgcatt 420
 aagagcttcc tgattgagat tcag 444

<210> 110
 <211> 196
 <212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(196)

<223> n = A,T,C or G

<400> 110

cctttttttt	ttttttcatt	aaataancca	tcatcacatt	agtacaatac	aattttatat	60
tttttaaata	tactatatat	gttaaggata	aggggtgaag	ttttcttcct	ttgtaatacc	120
tggtcaagag	tttaatggat	taggagatta	gngttaacct	tgaggataaa	agtncaaatt	180
tgtctcatta	ggacac					196

<210> 111

<211> 544

<212> DNA

<213> Homo sapien

<400> 111

gtcgacctca	gccggtcgtc	gcgacgttcg	cccgtcgcct	ctgaggctcc	tgaagccgaa	60
accagctaga	ctttcctcct	tcccgctgc	ctgtagcggc	gttggttgcca	ctccgccacc	120
atgttcgagg	cgcgctcgtt	ccagggtccc	atcctcaaga	aggtgttgga	ggcactcaag	180
gacctcatca	acgaggcctg	ctgggatatt	agctccagcg	gtgtaaacct	gcagagcatg	240
gactcgtccc	acgtctcttt	ggtgcagctc	accctgcggt	ctgagggtct	cgacacctac	300
cgctgcgacc	gcaacctggc	catgggcgtg	aacctcacca	gtatgtccaa	aataactaaaa	360
tgcgccggca	atgaagatat	cattacacta	agggccgaag	ataacgcgga	taccttggtg	420
ctagtatttg	aagcaccaaa	ccaggagaaa	gtttcagact	atgaaatgaa	gttgatggat	480
ttagatgttg	aacaacttgg	aattccagaa	caggagtact	gctgtgtagt	aaagatgcct	540
tctg						544

<210> 112

<211> 378

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(378)

<223> n = A,T,C or G

<400> 112

gtcgacacgg	cttccgcacg	gtcatccgcc	ccttctacct	gaccaactcc	tcagggtgtg	60
actagacggc	gtggcccaag	ggtggtgaga	accggagaac	cccaggacgc	cctcactgca	120
ggctcccctc	ctcggttcc	ttcctctctg	caatgacctt	caacaaccgg	ccaccagatg	180
tcgccctact	cacctgagcg	ctcagcttca	agaaattact	ggaaggcttc	cactagggtc	240
caccaggagt	tctcccacca	cctcaccagt	ttccagggtg	taagcaccag	gacgcctcgc	300
aggttgctct	gggatcccc	cacagcccct	ggnacgtctg	cccttgncac	tggtctgaag	360
gtcattaaaa	ttacattg					378

<210> 113

<211> 530

<212> DNA

<213> Homo sapien

<400> 113

gtcgacgtcg	ttgtctttct	aggtctcagc	cggtcgtcgc	gacgttcgcc	cgctcgtctt	60
gaggctcctg	aagccgaaac	cagctagact	ttcctccttc	ccgcctgcct	gtagcggcgt	120
tggtgccact	ccgccaccat	gttcgaggcg	cgcttggtcc	agggctccat	cctcaagaag	180

gtgttggagg	cactcaagga	cctcatcaac	gaggcctgct	gggatattag	ctccagcgg	240
gtaaacctgc	agagcatgga	ctcgtccac	gtctcttttg	tgcagctcac	cctgcggct	300
gagggttcg	acacctaacc	ctgcgaccgc	aacctggcca	tgggcgtgaa	cctcaccagt	360
atgtccaaaa	tactaaaatg	cgccggcaat	gaagatatca	ttacactaag	ggccgaagat	420
aacgcggata	ccttggcgct	agtatttgaa	gcaccaaacc	aggagaaagt	ttcagactat	480
gaaatgaagt	tgatggattt	agatgttgaa	caacttggaa	ttccagaaca		530

<210> 114

<211> 178

<212> DNA

<213> Homo sapien

<400> 114

gtcgacattt	cttcctaata	ttctataatc	tccaactcct	gaaaaccct	ctctcaacta	60
atactttgct	gttgaaatgt	tgtgaaatgt	taagtgtctg	gaaatttttt	ttttctaaga	120
aaaactatta	aagtacttcc	tagtagggca	aaaaaaaaa	aaaaaaaaa	aaaaaaaaa	178

<210> 115

<211> 211

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(211)

<223> n = A,T,C or G

<400> 115

ccittttttt	ttttttttng	gntcaatcct	ttatttggaa	caaaggaaaa	aaggactgac	60
accagtttag	cctttgagtg	tgcaaagctc	tgccctccct	cccaccctn	agccccaaat	120
ccaanatttc	atagccctaa	caccacacca	agcagnttcc	ctcacacatg	ccctttgnnt	180
tcttcctctc	ttctatggtt	ccttaggnaa	a			211

<210> 116

<211> 439

<212> DNA

<213> Homo sapien

<400> 116

gtcgacctgt	cactcactac	atgaataagc	aaatattgtc	ttcaaaagaa	tgcacaagaa	60
ccacaattaa	gatgtcatat	tattttgaaa	gtacaaaata	tactaaaaga	gtgtgtgtgt	120
attcacgcag	ttactogctt	ccatttttat	gacctttcaa	ctataggtaa	taactcttag	180
agaaattaat	ttaatatatt	aatctctatt	atgaatcatg	tgaagcatg	acattcggtc	240
acaatagcac	tattttaaat	aaattataag	ctttaaggta	cgaagtattt	aatagatcta	300
atcaaatatg	ttgattcatg	gctataataa	agcaggagca	attataaaat	cttcaatcaa	360
ttgaactttt	acaaaaacca	cttgagaatt	tcatgagcac	tttaaaatct	gaactttcaa	420
agcttgctat	taaatcatt					439

<210> 117

<211> 357

<212> DNA

<213> Homo sapien

<400> 117

gtcgactcca	aattgaactt	gcagcagggt	ggcagggtca	ggagagtctg	gtcctgccta	60
gctcagattt	catggcacct	gcacttgaag	caagtcactt	ctttatcaca	ggtgtcttga	120
aacattagct	tctttttacca	acctgagaaa	attaggatga	cctggcaaat	aagatcttga	180
ataggccaaa	agcaagtatc	ttgctgtgtg	tagtctcttg	gttaaagtga	agaaacagta	240

```

ctgttcacac ctttcttcac tgagattcca gtgtacatga gaacatatat ttattgcatg 300
attttctaga tacacagtct atgcattatt catatacatt tatttttagcc taaagtg 357

```

```

<210> 118
<211> 431
<212> DNA
<213> Homo sapien

```

```

<400> 118
cctccctgag gaaattagga acctgttggc agatgttgaa acattttagtag cagatatatact 60
gaaaggagaa aatttatcca agaaagcaaa ggaaaagaga gaatccctta ttaagaagat 120
aaaagatgta agtctatct atcttcagga atttcaagac aaaggtgatg cagaagatgg 180
ggaagaatat gatgaccctt ttgctgggcc tcagacact atttcattag cctcagaacg 240
atatgataaa gacgatgaag cccctctga tggagcccag ttccctccaa ttgcagcaca 300
agaccttctt tttgttctaa aggctggcta ccttgaaaaa cgcagaaaag atcacagctt 360
tctgggattt gaatggcaga aaacggtggg gtgctctcag taaaacggta ttctattatt 420
atggaagtga t 431

```

```

<210> 119
<211> 131
<212> DNA
<213> Homo sapien

```

```

<400> 119
cccctcgccc gtcacgcacc gcacgttcgt ggggaacctg gcgctaaacc attcgtagac 60
gacctgcttc tgggtcgggg tttcgtacgt agcagagcag ctccctcgct gcgatctatt 120
gaaaggtcga c 131

```

```

<210> 120
<211> 409
<212> DNA
<213> Homo sapien

```

```

<400> 120
gtcgacgtaa aagccacaca gaaatcaaaa gataagaata tagtttcagc taccaaaaag 60
cagcctcaga ataaaagtgc atttcagaag acaggaccca gtccttgaa gtctcctggc 120
cgtacccac tgtccatcgt gagcctaccc cagtcttcta ccaaaacaca aactgcaccg 180
aagtcagcac agactgtcgc taagagccag cattcaacta aagggcctcc cagaagtggc 240
aaaaccccag cttcaatcag gaaaccaccc tcatctgtta aggatgcaga tagtggagat 300
aaaaaaccta ctgcaaagaa aaaggaagat gatgaccatt attttgtcat gactggaagt 360
aagaaacctt gaaaataaat acatactcat tataaaaaaa aaaaaaaag 409

```

```

<210> 121
<211> 131
<212> DNA
<213> Homo sapien

```

```

<400> 121
cccctcgccc gtcacgcacc gcacgttcgt ggggaacctg gcgctaaacc attcgtagac 60
gacctgcttc tgggtcgggg tttcgtacgt agcagagcag ctccctcgct gcgatctatt 120
gaaaggtcga c 131

```

```

<210> 122
<211> 130
<212> DNA
<213> Homo sapien

```

```

<400> 122

```

```

gtcgaccttt caatagatcg cagcgagggg gctgctctgc tacgtacgaa accccgaccc 60
agaagcaggt cgtctacgaa tggtttagcg ccagggttccc cacgaacgtg cgggtgcgtga 120
cgggcgaggg                                     130

```

```

<210> 123
<211> 424
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(424)
<223> n = A,T,C or G

```

```

<400> 123
gtcgacgaga tgtggagtgg ctaaaagaag cctgtgttcc tgagaactta gaggaccagg 60
acctctattc caggcttgga cacctacatt tagactatta tatgaggaag caatcaactt 120
ctcacttggt tcaaccactt tcacttgcag tcaaacctga attgtaagtg aaattgcttt 180
cctgatagca aacctgttgg attttctcca gaatccctgg gccactttta gcagtcagat 240
tcgtctaata ctcctttaa gatggtggca gtgaaactgg tacatgggac ctgactgggc 300
tttgtttgca actttctgat aatttataat tatttcaaaa taaaaaaatt ttaaaaataa 360
aaaaaaaaaa aaagggcggc cgctcggagt ctagagggcc cgtttaaacc cgntgatcag 420
cctc                                     424

```

```

<210> 124
<211> 548
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(548)
<223> n = A,T,C or G

```

```

<400> 124
cctttttttt tttttttctc tagtaatgac tttattcatg aatctataat ggaattcaaa 60
atagcaaaga acatgaaaat gttcanatta atatttatta accaaatgca tcanaaaata 120
catctatttt cacatatcaa aagtgcctaa aatgcatgtg anaatataaa tattctccac 180
tttgnngaac ttcaagataa tgaaaaattg cttaatacac ttggccacaa aaactcatta 240
cactgcaaat ncagaanaaa taaaataact cattacattg cagatncaaa agaaatcaaa 300
tgtaactggc aaaataacca tttcatggct aatctttngg naaagncta ttttcacact 360
gaaaaaaaga anttagaaaa gattaaaaat tttaaattct gaaccatcat tctnaaagtc 420
tgaagcgttt tctttagtat tcactatggt catcacattc atgtgtntccc aacatgagac 480
taaacactat ctcaaaatct taaaaaatct ttccatncac anattatttc ctggaagnta 540
aaaattat                                     548

```

```

<210> 125
<211> 562
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(562)
<223> n = A,T,C or G

```

```

<400> 125
gtcgacgctc ctaacaaaga agatatcttg aaaatttcag aggatgagcg catggagctc 60

```

46

```

agtaagagct ttcgagtata ctgtattatc cttgtaaaac ccaaagatgt gagtcttttg 120
gctgcagtaa aggagacttg gaccaaacac tgtgacaaaag cagagttctt cagttctgaa 180
aatgtttaaag tgtttgagtc aattaatatg gacacaaatg acatgtgggtt aatgatgaga 240
aaagcttaca aatacgctt tgataagtat agagaccaat acaactgggtt cttccttgca 300
cgccccacta cgtttgctat cattgaaaac ctaaagtatt ttttgttaaa aaaggatcca 360
tcacagcctt tctatctagg ccacactata aaatctggag accttgaata tgtgggtatg 420
gaaggaggaa ttgtcttaag tgtagaatca atgaaaagac ttaacagcct tctcaatatc 480
ccagaaaagt gtcctgaaca gggagggatg atttggaaga tatctgaaga taaacagcta 540
gcagnttgcc tgaaatatgc tg 562

```

```

<210> 126
<211> 131
<212> DNA
<213> Homo sapien

```

```

<400> 126
cccctcgccc gtcacgcacc gcacgttcgt ggggaacctg gcgctaaacc attcgtagac 60
gacctgcttc tgggtcgggg tttcgtagct agcagagcag ctccctcgct gogatctatt 120
gaaaggtcga c 131

```

```

<210> 127
<211> 512
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(512)
<223> n = A,T,C or G

```

```

<400> 127
gtcgacgtcc ggcttcggag cgggagtgtt cgttgtgccg gcgactaaaa agagaattaa 60
atatgggtga tgttgagaaa ggcaagaaga tttttattat gaagtgttcc cagtgccaca 120
ccgttgaaaa gggaggcaag cacaagactg ggccaaatct ccatgggtctc tttgggcgga 180
agacagggtca ggcccctgga tactcttaca cagccgccaa taagaacaaa ggcacatctc 240
ggggagagga tacactgatg gagtatttgg agaatcccaa gaagtacatc cctggaacaa 300
aaatgatctt tgtcggcatt aagaagaagg aagaaagggc agacttaata gcttatctca 360
aaaaagctac taatgagtaa taattggcca ctgccttatt tattacaaaa cagaaatgtc 420
tcatgacttt tttatgtgta ccatccttta atagatctca tacaccagan tttcagatca 480
tgaatgactg acagaatatt ttgttgggca gt 512

```

```

<210> 128
<211> 483
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(483)
<223> n = A,T,C or G

```

```

<400> 128
gtcgacgttt ttgtgatact gacacatccc ccctttcaga acaccctctg cccttggatt 60
ctgtgcacag gaagctagtt gctcccctga atacactctt tcttccttgt aatacagcct 120
ctgattttga gccaagaat aaagactaca gttctcagac tccttcgcaa ataaattttg 180
tgactaaact ctagtcaaca gtaagtgtca tgtagcagct cctgggaatc tcctttaaaa 240
agagagcttg tttataccta ttgtcatctc tgttcttctg tgccccttct tccattttgc 300
tgccctgaaa gcagatgtga tggctggaat tccagtcacc attttggacc atgaggacaa 360

```

```

caccctanag atgtggagtg gctaaaagaa gcctgtgttc ctgagaactt anaggaccan 420
gacctctatt ccaggcttgn acacctanat ttanactatt atatgaggaa gcaatcaact 480
tct 483

```

```

<210> 129
<211> 326
<212> DNA
<213> Homo sapien

```

```

<400> 129
gtcgaccttt tatctgtcta tccatccatc atcatttgaa ggcctaatat atgccaaagta 60
ctcacatggt atgcattgag acataaaaaa gactgtctat aacctcaata agtattaaaa 120
atcccattat taccataaag gttcatctta tttcattttt agggaataaa attacatgtc 180
tatgaaatth caattttaag cactattgtt tttcatgacc ataattttatt tttaaaaata 240
aattaaaggt taatttatat catgtatgta tttctaataa ttaaaaatgt gttcaatccc 300
tgaaaaaaa aaaaaaaaa aaaaaa 326

```

```

<210> 130
<211> 276
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(276)
<223> n = A,T,C or G

```

```

<400> 130
gtcgacggac accagctgcg gaanttgcgg ctttggcaga ttgaaatcat ggcaggtcca 60
gaaagtgatg cgcaatacca gttcactggt attaaaaaat atttcaactc ttatactctc 120
acaggtagaa tgaactgtgt actggccaca tatggaagca ttgcattgat tgtcttatat 180
ttcaagttaa ggtccaaaaa aactccagct gtgaaagcaa cataaatgga ttttaactg 240
tctacggttc ttaacctcat ctgttaagtt cccatg 276

```

```

<210> 131
<211> 482
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(482)
<223> n = A,T,C or G

```

```

<400> 131
cctttttttt ttttttttaa attttaaggt tattttttatt tacaactttt gaaaaatgta 60
catttttttt tacatggggt acttgtgcaa agtttagattt ggaagtgata aatgcataaa 120
aggngacaat agaacattan acaaaacatt tacaagcctt gtcccatact gctacttaaa 180
ggtactatat atctaaaagt ataaatatoc aaaaaaagat cgcanacatt ggctttaagg 240
ttctcanatg ctgaaaggga anaaattaaa gcatgcagca ataactcagg atttgagtgg 300
aaaatagttt gccacanata tgctatgctc ctttccttga attcattaaa actctaaaat 360
aaagatggac aattgagttt attcacttag ggcagcactg atccttttaa aagattaaag 420
gagctccaac tttccctagc tnaaaaactc acnatngttt ccattcctct gctcccacac 480
ct 482

```

```

<210> 132
<211> 428
<212> DNA

```

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(428)

<223> n = A,T,C or G

<400> 132

```
cctttttttt tttttttgtc taaaaggcaa aaaactacaa acagcccaag tcctgagctc      60
cccaagacct ggatcctcca ctgtccccc gaaaccggc aggaggcggg atggggagca      120
caanagggtg gttcttaaaa aagtcacccc tggatgggaa agctcttcat cttctgccgc      180
cttctntgct ctcccgtgct tgccgaggag agagatggan aggaccgggg ctatgccggc      240
aaactcaact tcttcccctt taggactttg gngatataga ggtanaanaa atcgagtan      300
aggactgtct ggaccaggcc tgccacaatg gcnatgaggt cgaagaancc ctcgaaangg      360
taagcgccan anccagttga anagatanag cgtggcggtg aacgcctagc gcaaacaagt      420
agnngctg                                     428
```

<210> 133

<211> 537

<212> DNA

<213> Homo sapien

<400> 133

```
gtcgacccca aaccactccc accttactac cagacaacct tagccaaacc atttacccaa      60
ataaagtata ggcatagaa attgaaacct ggcgcaatag atatagtacc gcaagggaaa      120
gatgaaaaat tataaccaag cataatatag caaggactaa ccctatacc ttctgcataa      180
tgaattaaact agaaataact ttgcaaggag agccaaagct aagacccccg aaaccagacg      240
agctacctaa gaacagctaa aagagcacac ccgtctatgt agcaaaatag tgggaagatt      300
tataggtaga ggcgacaaac ctaccgagcc tggatgtagc tgggtgtcca agatagaatc      360
ttaattcaac tttaaatttg ccacagaac cctctaaatc cccttgtaaa tttactgtt      420
agtccaaaga ggaacagctc tttggacact agggaaaaaac cttgtagaga gagtaaaaaa      480
ttaaacaccc atagtaggcc taaaagcagc caccaattaa gaaagcgttc aagctca      537
```

<210> 134

<211> 535

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(535)

<223> n = A,T,C or G

<400> 134

```
gtcgactcct ctcatatggt ggcttttaga agatccttgg ccaggagggt gatgccagct      60
atcttgcttc tgaatatctt acctgggatg gagtgatagt aacaccttca gaaaaggctt      120
atgagaagcc accagagaag aaggaaggag aggaagaaga ggagaatata gaagaaccac      180
ctcaaggaga ggaagaagaa agcatggaaa ctcaaggagt acattccctt cactcctttt      240
cctacccaag ggggaagact ggagcctaag ctgcctgcta ctgggcttta catggtgaca      300
gacatttccg tgggataggg aagatagcag gaagaaaagt aaactccata gaagtgtcat      360
tccactgggt tttgatattg gcttagctgc cagtctccca tttgtgacct atgccatcca      420
tctataatgg aggatacca ctttcttcc taatatctta taatctccaa ctctgaaaa      480
acccctctct caactaatac tttgctgttg aaatgttng aaatgttaag tgtct      535
```

<210> 135

<211> 114

<212> DNA

<213> Homo sapien

```

<220>
<221> misc_feature
<222> (1)...(114)
<223> n = A,T,C or G

<400> 135
gtcgacctca gcgtcattca gaannnggaa agaatacaat gtaactcaag aaaggatgaa      60
aatacccttt cttcccatcc acgtgtttcc atctcaatcc tcacagggtc ctgg              114

<210> 136
<211> 354
<212> DNA
<213> Homo sapien

<400> 136
agaagcgaga tgacgaaggg aacgtcatcg tttggaaagc gtcgcaataa gacgcacacg      60
ttgtgccgcc gctgtggctc taaggcctac caccttcaga agtcgacctg tggcaaatgt      120
ggctaccctg ccaagcgcaa gagaaagtat aactggagtg ocaaggctaa aagacgaaat      180
accaccggaa ctggtcgaat gaggcaceta aaaattgtat accgcagatt caggcatgga      240
ttcctgtaag gaacaacacc taaaccaag agggcagctg ttgcagcatc cagttcatct      300
taagaatgtc aacgattagt catgcaataa atgttctggt tttaaaaaat aaaa          354

<210> 137
<211> 347
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(347)
<223> n = A,T,C or G

<400> 137
gtcgacggcg agattacgag gcgaggctcg cgcgcccgcc cccgccctgg cccccagtgc      60
ccaccgggtc ggccgggcac agccatgacg aaggcgatcc taatcttcaa caaccacggg      120
aagccgcggc tctccaagtt ctaccagccc tacagtgaag atacacaaca gcaaatcatc      180
agggagactt tccatttggg atctaagaga gatgaaaatg tttgtaattt cctagaagga      240
ggattattaa ttggaggatc tgacaacaaa ctgatttata gacattatgc aacgttatat      300
tttgtcttct gtgnnggatt cttnanaaag tgaacttggc attttag                    347

<210> 138
<211> 434
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(434)
<223> n = A,T,C or G

<400> 138
cctttttttt tttttttggt taaatgactt actgtgtaat tttatttcat attacacaaa      60
tgtaaatcaa atgctgagta gacatgcaga tgacaagcag tatatgacaa actctgaana      120
aatagttaca tgtagagttt ctcanathtt tagtgtatct aanaattaac tgaagagttt      180
gttaagaatg caggcttaaa ggccaatcca cagattataa tttcatacaa acaggatgga      240
gcctaanaac ctgtaaatta ttaacaact gattaaaaat agagagggtt ctatgaagtt      300
aggnntgtcc ttatttctta tttgaactgg acaagtagaa ggataatagg taggaccaag      360

```

tgagcattat cagaatcaaa gtagaggcaa taacaagcca aggtgtttta ncctanctaa 420
agaagctcgt cgac 434

<210> 139
<211> 553
<212> DNA
<213> Homo sapien

<400> 139
gtcgacctga ctataacagt gcctactatg ttaacattag atgaacaagt gaattagagg 60
atTTTTaaat gtgtatccat cagtgtatgg acacactccc tctaacttct tcaaaaaaca 120
aaaattcctg gtagagctaa gtggTTTTta gaagtttgggt tttggtaact gatttctacg 180
agataattga acactTTTTa aaatagttga tcattatgtc aaacagccct caacagtaaa 240
cttaaattag gtagaattat agtaagctgg aagagaaaat gttcccaaag agcatttagtc 300
cctttctggc accttattac agatgaataa attgagactc acagaaatta aatgacttag 360
ccccagttat ccaactaact ccttaatgtg aggccatgat taggaatagg cttctagtat 420
tcagtcccat attattttga ctgtgtaata ccacgtgccca ctttgatttt aaagtcaaat 480
ctcggcttga actgtatggg gaaaaaaaa atctccagct ggctctgctg aatccccaga 540
ggggccctcc act 553

<210> 140
<211> 450
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(450)
<223> n = A,T,C or G

<400> 140
gtcgacgccg gtgagttggg tgccggtgga gtcgtgttgg tcctcagaat ccccgcgtag 60
ccgctgcctc ctccctaccct cgccatgttt cttaccgggt ctgagtacga caggggcgtg 120
aatacttttt ctcccgaagg aagattatTT caagtggaat atgccattga ggctatcaag 180
cttggtttota cagccattgg gatccagaca tcagagggtg tgtgcctagc tgtggagaag 240
agaattactt cccactgat ggagcccagc agcattgaga aaattgtaga gattgatgct 300
cacataggtt gtgccatgag tgggctaatt gctgatgcta agactttaat tgataaagcc 360
agagtggaga cacagaacca ctggttcacc tacaatgaga caatgaacag nggagagtgt 420
gacccaagct gngtccaatc tgnctttgca 450

<210> 141
<211> 140
<212> DNA
<213> Homo sapien

<400> 141
acacacccct ccctcacaca gggctcgacc gccgctggca gttccagggc taaggatttc 60
ctgcaattac ttgtggagaa ggagttcata gctgggctcc tggaggggag atagagcttc 120
tctttcgttc ccgggtcgac 140

<210> 142
<211> 591
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(591)

51

<223> n = A,T,C or G

<400> 142

```
gtcgacctgg acttgacgtg taaacagaga cgctgcaaat tgcttggtga cgggtgtaggc      60
cgctgcaggc caccatgaac cggcttcggg atgactacga cccctacgag gttgaagagc      120
ctagcgacga ggagccggct ttgagcagct ctgaggatga agtggatgtg cttttacatg      180
gaactcctga ccaaaaacga aaactcatca gagaatgtct taccggagaa agtgaatcat      240
ctagtgaaga tgaatttgaa aaggagatgg aagctgaatt aaattctacc atgaaaacaa      300
tgaggagcaa gttatcctct ctgggaactg gatcttcctc aggaaatgga aaagttgcaa      360
cagctccgac aaggctactac gatgatatat attttgattc tgattccgag gatgaagaca      420
gagcagtaca ggtgaccaag aaaaaaaga agaaacaaca caagattcca acaaatgacg      480
aattactgta tgatcctgaa aaagataaca gagatcaggc ctgggttgat gcacagngaa      540
aggggttacc atggtttggg ancacaggag atcacgtcaa caacagcctg t              591
```

<210> 143

<211> 538

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(538)

<223> n = A,T,C or G

<400> 143

```
gtcgacaaat aagaagacac cttcagcatc ttaaactaga ataaataaaa gaaggggtggc      60
ctcctagaat ttaagtcagg agggaggtgg tgggcaatgg atgacaagct ctactttgaa      120
gaggttgaat ttcagctgac cactactaaa gcagtacaag cttttccttt cagcaagtgt      180
cttcccagaa atgtgatagc aatttttagg aagaatttgg caaacataat gtttagcaga      240
tttgcacaaa atgctataag ctcaaatttt tttttttttt tttttnggca gcacactcag      300
ccctccaagg ggaagtggat tatttttctt gcaagtgcac tancanggga ggtattaagg      360
acagcaacat tccttcctgt ataaaaaaat aaataaataa aagaagaaag gattattgag      420
gcctctcttg ctgnatgtaa tgtacttcan gatgttggta naaaagatat caacctanaa      480
taagnttcac aanaatacat ttggtttcac ngaaagttta aagtcaatct ggacattc      538
```

<210> 144

<211> 401

<212> DNA

<213> Homo sapien

<400> 144

```
gtcgacctgt tccctttttg ggctgtctc cccatgtata tgttgagggg ttggacttca      60
gggcctgtga gaggccttcc aacttagact ttctcccag gagcataaat tcagtgaatc      120
tacgtgactc tcagtgatgg catcattgoc taatatccac ccagcttctg cttgaaaact      180
tccagagact ggttcacatg ggggtataaa agcccaggcc ccttgcccca acttgggaca      240
actatgaaga gtttcagct ccacagctcc ctgaggggct ggccgaggcc tttgtggggt      300
ttgcctcaca acccaattta tccctctggc caattctgct tcaatcactc cctgccagggt      360
gttgaccttg aatgtactcc cccaataaac ctctgcaag c              401
```

<210> 145

<211> 367

<212> DNA

<213> Homo sapien

<400> 145

```
cctttttttt ttttttttag ttagaaatta caagtttatt tttatatattt gaaaaaggca      60
taatagaaaa caaaaataaa caaccaggca tatcaatatt tgtgacatac acatacacac      120
aaaaatgaat ataggaaata acacgaagaa aaagcatagt atgttttgaa accaacgtgg      180
```

```

ggcatgaaca gatttttggat gaaatacaac taaagggtttt aagtgtctat gtaatgttcg      240
agatattacg atcactctta tcctactagc aaaaatttagc aaactaggct ttaaaacatg      300
attcctgttg ttttagcagg atttattttg gtaatgatcc tgcttcctta taaacaacta      360
cgtcgac                                           367

```

```

<210> 146
<211> 395
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(395)
<223> n = A,T,C or G

```

```

<400> 146
gtcgacaaga aagccccctt aatgttttta actgatgata tttttttaag cttaccaata      60
taagtatttt taaaggttct atttttcaaa gtcataacaa tgattgttct tgttttctct      120
catagaatag actgccatcg gataaagagt ggtccctagc ttctattttt ccaagtaaat      180
aagtagaaca tgttcttggg attataccat taaatgttaa ttttcttgaa gaagaaagat      240
tgttgtctgc caagatttta tgttagcgc cggattgagg cagaaaacgg aagcaccagg      300
tttaacactg ggatgacttg ggttgtgttc ctggagggtt gaagngggcc ttccccgcct      360
tttgaggggg aaaactgact gntttgaaca catat                                           395

```

```

<210> 147
<211> 455
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(455)
<223> n = A,T,C or G

```

```

<400> 147
gtcgactaaa aactggaacg gtgaagggtga cagcagtcgg ttggagcgag catcccccaa      60
agttcacaat gtggccgagg actttgattg cacattgttg tttttttaat agtcattcca      120
aatatgagat gcgttggttac aggaagtccc ttgccatcct aaaagccacc ccacttctct      180
ctaaggagaa tggcccagtc ctctcccaag tccacacagg ggaggtgata gcattgcttt      240
cgtgtaaatt atgtaatgca aaattttttt aatcttcgcc ttaatacttt tttattttgt      300
tttattttga atgatgagcc ttcgtgcccc cccttcccc ttttttgtcc cccaacttga      360
gatgtatgaa ggcttttggg ctccctggga gtgggtggan gcagccaggg cttacctgta      420
cactggactt gagaccagtt gaaataaaag tgcac                                           455

```

```

<210> 148
<211> 518
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(518)
<223> n = A,T,C or G

```

```

<400> 148
gtcgacctca cgccttcgcc gtagcatctt tcgcagcgga ccgaagagaa gaaaagtagg      60
ccagagccga actctcttcc tgccaagatg tctattgggtg tgccgattaa agtactgcat      120
gaggccgagg gccacattgt gacatgtgag acgaacaccg gtgagggtata tcgggggaag      180

```

```

ctcattgaag cagaggacaa catgaactgc cagatgtcca acatcacagt cacatacaga      240
gatggccgag tggcacagct ggagcaggta tacatccgtg gcagcaaaat cgcgtttctg      300
atthttgctg acatgctgaa gaacgcaccc atgttaaaga gcatgaaaaa taaaaaccaa      360
ggctcagggg ctggccgagg aaaagctgct attctcaagg cccaagtggc cgcaagagga      420
agaggacgtg gaatgggacg tggaaacatc tttcaaaagc gaagggataa ttttctaagt      480
tgaacagaac tttgtccttt tttctttcan gttatctg      518

```

```

<210> 149
<211> 442
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(442)
<223> n = A,T,C or G

```

```

<400> 149
cctttttttt ttttttttct tttcataaaa tttttacttt atgaattaaa tacattgaga      60
aacagnghaa atatatthac agtcatttga agngggcact actaacatat ttaattthaa      120
aaaatcittg ctgtttcttt gcctgtttct ttcaaagaga atthttaaata tgactthtagc      180
ttthaaaaaa tacaatangg aaataattac attcttaata tgaaaacatt ttacaacgta      240
tcaccatggg caattaatte tgaatatcac ttaaaagtth atgtthaaaat gtaaaagngaa      300
tatttccttt ctgtttanaa aatcaaaaag attatctcat taaaaacacc ttnggnccta      360
agacttatga tctgaanatg nccttttgaa aagnatcttc catggctaca actaaaaaan      420
accggtaac acttgtagac gg      442

```

```

<210> 150
<211> 341
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(341)
<223> n = A,T,C or G

```

```

<400> 150
gttnacotat tattacccca tgatacagtt tagaaaacaa attcatgcac taagtaaatg      60
gaccaaactg taagtcactg ctttttgctc cagagttggc tgctttgatt actcctacac      120
ttaactagtc aactthtaag aaaaaaattt ttttttctgt gaaggaaatt aagtgccat      180
tttcanagag ctaaaagcaa tcaaggcatc tactgtgtta ttttcctatc catgtngact      240
catgtthtaag gttgactagg aagacataat cattggctgc taataacaaa tngatttctt      300
ttnataaaaa attthaaaga gtntntaatg ctttatttta t      341

```

```

<210> 151
<211> 459
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(459)
<223> n = A,T,C or G

```

```

<400> 151
gtcgaccagg tcttgaccct ggtcaacaag agaataggcc tttaccgtca ctttgacgag      60
accgtcaata ggtacaagca atccggggac atctccaccc tcaacagtgg caagaagagc      120

```

54

```

ctggagactg aacacaaggc cttgaccagt gagattgcac tgctgcagtc caggctgaag 180
acagagggct ctgatctgtg cgacagagtg agcgaaatgc agaagctgga tgcacaggtc 240
aaggagctgg tgctgaagtc ggcgggtggag gctgagcgcc tgggtggctgg caagctcaag 300
aaagacacgt acattgagaa tgagaagctc atctcaggaa agcgccagga gctggtcacc 360
aagatcgacc acatcctgga tgccctgtag cccctgcccg catcctncag ggggccagg 420
gtgcctgcac tttgctgtgg gnangcagat tgggtggtgta 459

```

```

<210> 152
<211> 242
<212> DNA
<213> Homo sapien

```

```

<400> 152
gtcgacccaa gggtcacagga gcattgcgtc gctgatgggg ttgaagtttg gtttggttct 60
tgtttcagcc caatatgtag agaacatttg aaacagtcctg cacctttgat acggtattgc 120
atttccaaag ccaccaatcc attttgtgga ttttatgtgt ctgtggctta ataatacatag 180
taacaacaat aatacctttt tctccatttt gcttgccagga aacatacctt aagttttttt 240
tg 242

```

```

<210> 153
<211> 57
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(57)
<223> n = A,T,C or G

```

```

<400> 153
cctttttttt tttttttttt ttccacatca ctcaggtttt atngaattta taaaatt 57

```

```

<210> 154
<211> 437
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(437)
<223> n = A,T,C or G

```

```

<400> 154
cctttttttt ttttttttgt aatncagttt taatttatTT tcatcacttt ttcttcataa 60
tccagatatt ttaaaatgca aagaaaatta actttcaatg atatgttcag ggactggcac 120
taaaaaaaaa tttcagactg caaatgagtt atacaaatga aaatatcaaa tggagatcca 180
gttatcaaaa tgaaagcact caacatatta aaagttcaca agtatttgta ttgagacat 240
tacaaaagtc agcttgctaa ctgttgatgat tttaaagaac tattgcanaa gtctgaanaa 300
aatanattta ttagttaact tataaagaga ttaaagaggc tgaaacaagt nttaaaaaana 360
aatttgngcc tttattanaa tgttaggcgt cnacgcggcc gctcnngtct anagggcccg 420
tttaaaccgg ctgatca 437

```

```

<210> 155
<211> 518
<212> DNA
<213> Homo sapien

```

```

<400> 155

```

55

```

gtcgacgtga gccacagtca cgccactgca ttctatcctg ggcaacagat ggagaccttg      60
tctcaaaaaa aaaaaattcc tgacatcgct atgtattccc aactttatca tttgtctgcc      120
tgtttagttt tgacttatgt tttttttttt tccccctgt ggacatgtag ttgacggaaa      180
tcgtgaagga actttaatat tttatttaaa tttcccaaaa ctaatcatgc cttatgtgac      240
taatcttcag tgataaatatt tcatctactg atatattttc ttgaggtgtg taattttcag      300
tataccttaa tcatttggta taaaaaagag agagggtttt gatatatgaa tgctgttctt      360
gtaaaaatca atcttgacac tttattttta actttttatt ggtaatgaca gtgggttttg      420
tacatcatga ttttcaattt aggatatctg tctaatttgt tttttcagag taactatatt      480
ggaattcaat aaaaatattc aaaatttttc ttaaaaaa      518

```

<210> 156

<211> 600

<212> DNA

<213> Homo sapien

<400> 156

```

gtcgacgttt atttaagtcc atgtttcact gtttgcaact tgcattgaac aatgggttta      60
ttcgtgatg taaacggttc gagtgaagaa ttaatgcagt aagtatgaca acacatacac      120
acttgccctc ccccatctcc agaagagggg agcagagtcc gagcttatct aaatatgaat      180
gtggccacaa agctgtggaa ggtgacaaag cttaaacacc tttgccctgg ctctgcattg      240
tcacctagag agcaagaggt ctatagaaac atcatgtcac atgaaacgat tctctgcttt      300
ttggttctga acttgaagtc cctaaactgc aaaatctaag agttgggtgg ttattaaaaa      360
gcttttaaaa agttaactgt ggcaccaatt ctaatgtaat ccaacttgtg actgtttttt      420
tttgttttgt tttgtttttg tgtgtgtgtg tgtgtggcac tgggaaaagt ggaaacaaac      480
atgtattgaa atacatattg gaaataaaaa tggtttgagc gtcagtgata ttctccaga      540
atgtacttat cttacctogc atgtactgta gtcactcagt atttgtatat gttgctagaa      600

```

<210> 157

<211> 542

<212> DNA

<213> Homo sapien

<400> 157

```

gtcgacggct gggaagtcag ttcgttctct cctctcctct cttcttgttt gaacatgggtg      60
cggactaaag cagacagtgt tccaggcaact tacagaaaag tgggtggctgc tcgagccccc      120
agaaaggtgc ttggttcttc cacctctgcc actaattcga catcagtttc atcgaggaaa      180
gctgaaaata aatatgcagg agggaaacccc gtttgctgtc gcccaactcc caagtggcaa      240
aaaggaattg gagaattctt taggttgtcc cctaaagatt ctgaaaaaga gaatcagatt      300
cctgaagagg caggaagcag tggcttagga aaagcaaaga gaaaagcatg tcctttgcaa      360
cctgatcaca caaatgatga aaaaagaatag aactttctca ttcatctttg aataacgtct      420
ccttgtttac cctgggtattc tagaatgtaa atttacataa atgtgtttgt tccaattagc      480
tttgttgaac aggcatttaa ttaaaaaatt taggtttaa tttagatggt caaaagtagt      540
tg      542

```

<210> 158

<211> 526

<212> DNA

<213> Homo sapien

<400> 158

```

cacctcaggc tgtggctctt tgggcttctt cctaattgcag aagaagttgc ccagcagcaa      60
aatcagggag gaggtgagca cctcggcccc cgccaggatg aacacgtaca tgtagacgtg      120
ggtcgcatcc aggagtttgc ctcccgaagg gggcccgaag agcacggcca ccgcctccat      180
cagcagcacc aggccaatgg cactggagaa cttgtaggag atgccaaaaga agatgcagaa      240
gaccacgagg ccgcccgtagt cgcccgcgct agagcccgcc aggtccgcga ggccgttgaa      300
gaacatggag aagctgaaga ggtagacgga gtagggccgc accttcccaa gcccgcgac      360
gaagcccgcg gccggccgcg cgaagatgtc aatgaagccc aggatggtga gcaggaggc      420
ggccttggtg tcgggcacgc ccaggtcctt ggcgtagctc accacgaaca cgggcgggac      480

```

56

gaagagcccc agcaccatga ccgaggcggc cacggcgtaa agcaca 526

<210> 159
 <211> 306
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(306)
 <223> n = A,T,C or G

<400> 159
 cctttttttt tttttttttt ttttttngga tgtatnngaa attttttcta tatanatcat 60
 gtgtgacttc cataaagaaa aataaacacc tatncacagt ttacctataa tgtgtaatgt 120
 taatgaaaag aatcaaagaa agatgttcgt tcattaactc tctaaatnaa attgtttttc 180
 catttttacc aacttgatac cttaatcaag ncactcttgt tcttccttaa gtgcaaata 240
 attttttggt tgggttgggg gacaacacaa aatacaaac tgggttggtat tcaatgaaag 300
 gcccaa 306

<210> 160
 <211> 528
 <212> DNA
 <213> Homo sapien

<400> 160
 ctgaagagcg gcttgctctt cacatcctca ggactcaggg gctggtccct gagcacgtgg 60
 aaacaaggac tttgcacagc accttccagc ccaacatttc ccagggaata cttcagatgt 120
 ggggtgatgt tttccccaag agtttggggc caccaggccc tcctttcaac atcacacccc 180
 ggaaagccaa gaaatactac ctgctgtgta tcatctggaa caccaaggac gttatcttgg 240
 acgagaaaag catcacagga gaggaatga gtgacatcta cgtcaaagc tggattcctg 300
 gcaatgaaga aaacaacagc aaaacagatg tccattacag atctttggat ggtgaaggga 360
 attttaactg gcgatttggt ttcccgtttg actaccttcc agccgaacaa ctctgtatcg 420
 ttgcgaaaaa agagcatttc tggagtattg accaaacgga atttcgaatc ccaccaggc 480
 tgatcattca gatatgggac aatgacaagt tttctctgga tgactact 528

<210> 161
 <211> 527
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(527)
 <223> n = A,T,C or G

<400> 161
 cctttttttt ttttttttgg tcttacaact ctattgtaaa ctatactaga ctatagaggg 60
 acttctacat ctttcaagat gtgtttaata aaggctctgt tataataact tttgaggcat 120
 gaatctagca aatagtactt tatacaatgt cccttgcctt taccaactca taaatattaa 180
 gtgtttttca gtgacttatg tttggatgtg gtagtgctga tcagggccat gtgctgatgt 240
 cctggagagc aaaatcaatc caaagnggng ctgctatttg tgacagaaca tgttttattt 300
 ctgagccccg gagacaaaag gaaaattgat atgggggagc gggaaatagg agaactatta 360
 aatgtagtga agaaatttca caggtctaaa ggaactatta aaagggaagg taaagtagat 420
 tctatactat aaaacagaat cctacctctg ataaaagaca aatcagcctg aatttttgaa 480
 taatcaatag gattcaaaat gactattttc aattgcaatc tcattct 527

<210> 162

<211> 77
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(77)
 <223> n = A,T,C or G

<400> 162
 cctttttttt tttttttttt ttnntttttt tttttttttt ttttagggaa anaaatctgg 60
 gttcctttta tttttga 77

<210> 163
 <211> 645
 <212> DNA
 <213> Homo sapien

<400> 163
 gtcgacaaac aatgaatagt ttttcattgt accatgaaat atccagaaca tacttatatg 60
 taaagtatta tttatttgaa tctacaaaaa acaacaaata atttttaaat ataaggattt 120
 tcctagatat tgcacgggag aatatacaaa tagcaaaatt gaggccaagg gccaaagagaa 180
 tatccgaact ttaatttcag gaattgaatg ggtttgctag aatgtgatat ttgaagcatc 240
 acataaaaaat gatgggacaa taaattttgc cataaagtca aatttagctg gaaatcctgg 300
 atttttttct gttaaactctg gcaaccctag tctgctagcc aggatccaca agtccttggt 360
 ccactgtgcc ttggtttctc ctttatttct aagtggaaaa agtattagcc accatcttac 420
 ctcacagtga tgttgtgagg acatgtggaa gcactttaag ttttttcac ataacataaa 480
 ttattttcaa gtgtaactta ttaacctatt tattatttat gtatttattt aagcatcaaa 540
 tatttgtgca agaatttggg aaaatagaag atgaatcatt gattgaatag ttataaagat 600
 gttatagtaa atttatttta ttttagatat taaatgatgt tttat 645

<210> 164
 <211> 434
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(434)
 <223> n = A,T,C or G

<400> 164
 gtcgaccgga cgcggcggca ttaaaccggt gcaggcgtag cagagtggtc gttgtctttc 60
 taggtctcag ccggtcgtcg cgacgttcgc ccgctcgctc tgaggctcct gaagccgaaa 120
 ccagctagac tttcctcctt cccgcctgcc tgtagcggcg ttgttgccac tccgccacca 180
 tgttcgaggg gcgcctggtc cagggtoca tcctcaagaa ggtgttgagg gcaactcaagg 240
 acctcatcaa cgaggcctgc tgggatatta gctccagcgg tgtaaacctg cagagcatgg 300
 actcgtocca cgtctctttg gtgcagctca ccctgcggtc tgagggttn gacacctacc 360
 gctgcgaccg caacctggcc atgggcgtga acctaccag tatgtncaaa atactaaaat 420
 gcgccngcaa tgaa 434

<210> 165
 <211> 388
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature

<222> (1)...(388)

<223> n = A,T,C or G

<400> 165

gtcgaccatt	catatatata	tgcatatata	tgtgaagctc	catatctctg	ttgctttaaa	60
gaagtaaaac	cttccattta	aataagatga	catgcntaan	ataacaaagc	ttccttgatt	120
tccttttct	gtgtaattna	atagatttgt	tgactagtgc	ttgggcacat	tataaatcag	180
ngttatttgc	tcttgagacc	atcttttaaa	aaaaattttg	gcagtgcagc	gttgaattta	240
tcttgaattt	atcatgtgtg	tgtatttctg	aagcagctac	atagcagaac	attttaagag	300
attctgttag	cccacatgtt	catgttggtt	gctgctgaat	ggtaaatatt	aaataaaatt	360
accagattaa	tcttaaaaaa	aaaaaaaa				388

<210> 166

<211> 443

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(443)

<223> n = A,T,C or G

<400> 166

gtcgaccttg	ctttcttaaa	aaacaaaaaa	actactgtca	gtattaatac	tgagccagac	60
tggcatctac	agatttcaga	tctatcattt	tattgattct	taagcttgta	ttaaaaacta	120
ggcaatatca	tcatggatac	ataggagaag	acacatttac	aatcattcat	tgggcctttt	180
atctgtctat	ccatccatca	tcatttgaag	gcctaataa	tgccaagtac	tcacatggta	240
tgcatgaga	cataaaaaag	actgtctata	acctcaataa	gtattaaaaa	ttccattatt	300
accataaagg	ntcatcttat	ttcattttta	gggaataaaa	ttacatgtct	atgaaatttc	360
aattttaagc	actattgntt	ttcatgacca	taattttatt	ttaaaaataa	attaaagggt	420
aattataaaa	aaaaaaaaaa	aag				443

<210> 167

<211> 608

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(608)

<223> n = A,T,C or G

<400> 167

gtcgactgcg	cctctccgaa	cgcaacatga	aggtgctcct	tgccgcgcgc	ctcatcgcg	60
ggtccgtctt	cttctgctg	ctgcccggac	cttctgcggc	cgatgagaag	aagaaggggc	120
ccaaagtcac	cgtcaagggtg	tattttgacc	tacgaattgg	agatgaagat	gtaggccggg	180
tgatctttgg	tctcttcgga	aagactgttc	caaaaacagt	ggataatttt	gtggccttag	240
ctacaggaga	gaaaggattt	ggctacaaa	acagcaaatt	ccatcgtgta	atcaaggact	300
tcatgatoca	gggcggagac	ttcaccaggg	gagatggcac	aggaggaaag	agcatctacg	360
gtgagcgctt	ccccgatgag	aacttcaaac	tgaagcacta	cgggcctggc	tgggtgagca	420
tggccaacgc	aggcaaagac	accaacggct	cccagttott	catcacgaca	gtcaagacag	480
cctggctaga	tggcaagcat	gtggtgtttg	gcaaagttct	agagggcatg	gangtggtgc	540
ggaangtgga	gagcaccaag	acagacagcc	gggataaacc	cntgaangat	gtgatcatcg	600
cagactgc						608

<210> 168

<211> 569

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(569)

<223> n = A,T,C or G

<400> 168

gtcgacgcgg	ncggccggac	agactgacgt	gtgagctgca	tcgcgggagg	cgcatggngg	60
ggatggcgct	ggcgcgggcc	tggaagcaga	tgctctgggt	ctactaccag	tacctgctgg	120
tcacggcgct	ctacatgctg	gagccctggg	agcggaagg	gttcaattcc	atgctgggtt	180
ccattgtggg	gatggcacta	tacacaggat	acgtcttcat	gccccagcac	atcatggcga	240
tattgcaacta	ctttgaaatc	gtacaatgac	caagatgcga	ccaggatcag	aggtttcttg	300
gggaagaccc	accctacgaa	ggttggaatga	gaccatcaga	tgtgataaga	aactcttcta	360
gatgtcaaca	taaccaacct	tataaagact	aaaattcatg	agtagaacag	gaaaatcatc	420
ctgactcatg	tggtgtgttc	tttattttta	attttncaaa	gaggctcttg	tatagcagtt	480
ttttgtctat	tttaacattg	taagtcattt	tgtnttttga	natcantatt	ttcttaacct	540
ttgtgactgt	ttcaatatta	cccccgng				569

<210> 169

<211> 216

<212> DNA

<213> Homo sapien

<400> 169

gtcgacgcgg	aacccatcta	taaagtaagg	cacactcgta	atggttgaat	tgtgttctgg	60
ttaatttctt	aaaggacttc	acagttgcac	ttatgaaaat	gattttatat	tgaaatgata	120
tttgcataag	aaaaagcatg	tgattaatgt	catattgctt	gagtgttcat	ctgtgaatgt	180
gaaaaataag	ctgttttttt	ttattagata	tttgca			216

<210> 170

<211> 284

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(284)

<223> n = A,T,C or G

<400> 170

cctttttttt	tttttttgaa	atggancttc	tgaatcgaaa	agttttttcac	tttaaagtgt	60
ggatgagtg	tacaaaaaca	ctnngcatct	tagggcaagt	gtcgctgagc	acctgcttcc	120
ccatattctc	agcannatca	tttcagttct	tagcaatctg	gcaggcaaaa	ggaaagtctg	180
attttgntng	aattngcatt	ttcctgatta	ccancaaact	antttaagct	taatgggcac	240
ntnntatttc	tattctctga	actgccatt	tttctaccat	tcag		284

<210> 171

<211> 541

<212> DNA

<213> Homo sapien

<400> 171

cagacagcac	tgtgttggcg	tacaggtctt	tgcgatgtc	cacgtcacac	ttcatgatgg	60
agttgaagg	agtttctgtg	atgccacagg	actccatgcc	caggaaggaa	ggctggaaga	120
gtgcctcagg	gcagcggaac	cgctcattgc	caatggtgat	gacctggccg	tcaggcagct	180
cgtagctctt	ctccaggagg	gagctggaag	cagccgtggc	catctcttgc	tcgaagtcca	240
gggcgacgta	gcacagcttc	tccttaatgt	cacgcacgat	ttcccgtctg	gccgtggtgg	300

60

tgaagctgta	gccgcgctcg	gtgaggatct	tcatgaggta	gtcagtcagg	tcccggccag	360
ccaggtccag	acgcaggatg	gcatggggga	gggcataccc	ctcgtagatg	ggcacagtgt	420
gggtgacccc	gtcaccggag	tccatcacga	tgccagtggg	acggccagag	gcgtacaggg	480
atagcacagc	ctggatagca	acgtacatgg	ctgggggtgt	gaaggctctca	aacatgatct	540
g						541

<210> 172
 <211> 573
 <212> DNA
 <213> Homo sapien

<400> 172						
gtcgactttc	aacaaatcct	gaagtctttc	tgtgaagtga	ccagttctga	actttgaaga	60
taaataattg	ctgtaaattc	cttttgattt	tctttttcca	ggttcatggt	ccttggtaat	120
ttcattcatg	gaaaaaatc	ttattataat	aacaacaaag	atttgatat	ttttgacttt	180
atatttcctg	agctctcctg	actttgtgaa	aaaggggtga	tgaaaatgca	ttccgaatct	240
gtgaggggccc	aaaacagaat	ttaggggtgg	gtgaaagcac	ttgtgcttta	gctttttcat	300
attaaatata	tattatattt	aaacattcat	ggcatagatg	atgatttaca	gacaatttaa	360
aagttcaagt	ctgtactgtt	acagtttgag	aattgtagat	aacatcatac	ataagtcatt	420
tagtaacagc	ctttgtgaaa	tgaacttggt	tactattgga	gataaccaca	cttaataaag	480
aagagacagt	gaaagtacca	tcataattaa	cctaaatttt	tgttatagca	gagtttcttg	540
tttaaaaaaa	aataaaatca	tctgaaaagc	aaa			573

<210> 173
 <211> 545
 <212> DNA
 <213> Homo sapien

<400> 173						
gtcgacctgg	gctggacgtg	gttttgtctg	ctgcgcccgc	tcttcgcgct	ctcgtttcat	60
tttctgcagc	gcgccagcag	gatggcccac	aagcagatct	actactcgga	caagtacttc	120
gacgaacact	acgagtacog	gcatgttatg	ttaccagag	aactttccaa	acaagtacct	180
aaaactcatc	tgatgtctga	agaggagtgg	aggagacttg	gtgtccaaaca	gagtctaggc	240
tgggttcatt	acatgattca	tgagccagaa	ccacatatcc	ttctcttttag	acgacctott	300
ccaaaagatc	aacaaaaatg	aagtttatct	ggggatcgtc	aaatcttttt	caaatttaaat	360
gtatatgtgt	atataaggta	gtattcagtg	aatacttgag	aaatgtacaa	atctttcatc	420
catacctgtg	catgagctgt	attcttcaca	gcaacagagc	tcagttaaat	gcaactgcaa	480
gtaggttact	gtaagatggt	taagataaaa	gttcttccag	tcagtttttc	tcttaagtgc	540
ctggt						545

<210> 174
 <211> 469
 <212> DNA
 <213> Homo sapien

<400> 174						
gtcgacaaaag	aatcacagct	ttctctccat	gttttattaa	cacacagaaa	aatactttga	60
aaaatatatacc	atttctcaaa	aatgaaatgt	atgatttgct	acaaatggcc	atatgaaaaa	120
tatgatacct	gcttatTTTT	gactcagggt	gcattcaatt	tttatactaa	ctgaaaatta	180
catgattgcg	ttttgtttta	aaagtgaaaa	aaagtaataa	ctgcttttag	ccttgtaata	240
ttgaatgcgt	caattggctc	ccctgtaga	atgttgaatg	gctatcactg	gtgacagatg	300
ttctgtacat	cgagtaata	ctgcttatat	aattgtgata	attttccgct	tcttatttgt	360
catttttagt	gatttaaaaa	tcccttgatg	actccctgaa	aaatgactga	tgtttttctt	420
atattaagta	atttctgctg	gtaaagtgtg	agtcttttaa	taattttctt		469

<210> 175
 <211> 108
 <212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(108)

<223> n = A,T,C or G

<400> 175

cctttttttt	ttttttttng	aaattnaagt	aacttnatnn	aaattcaaaa	acaatnctta	60
aaactgnntt	tagagtcaag	acccttttgt	attataaaaa	tcacaagt		108

<210> 176

<211> 426

<212> DNA

<213> Homo sapien

<400> 176

gtcgactgtt	tagaagttat	acacagagag	aaggggaaaa	gaaactccat	caatcaagct	60
aaaggcagca	aaggaaaatt	tgaaaagaag	caacgagact	gtttaacaaa	gaacatcaaa	120
taagatgatg	gaactagaag	aaaaacacca	atgtccttaa	ttatataaaa	acatcaatgt	180
ccttaattat	ataaatTTTT	aaccctcaat	tgggttaaaa	aatcagattt	gtactaagag	240
atgtatcttt	aaaagcaaaa	gaaagaataa	aaagatcaac	aagtaaaaca	aagtaggagt	300
cagaattaat	attagacaaa	ataaaggtga	aaaatactaa	atgcaagaaa	taatatttta	360
gatgacaaaa	atgtatgagc	cataaaaaag	tcatgagttt	ttataaacct	aaaatatagc	420
gtcgac						426

<210> 177

<211> 538

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(538)

<223> n = A,T,C or G

<400> 177

cctttttttt	tttttttttt	tttttttgga	ngnattingaa	attttttcta	tatanatcat	60
gtgtgacttc	cataaagaaa	aataaacacc	tatacacagt	ttacctaata	tgtgtaatgt	120
taatgaaaag	aatcaaagaa	agatgttcgt	tcattaaactc	tntaaatcaa	attgtttttc	180
cattttttacc	aacttgatac	cttaaatcaag	tcactcttgt	tcttccttaa	gtgcaaatga	240
attttttggt	tgggttgagg	gacaacacaa	aatacaaac	tgggttggt	tcactgaaag	300
gccaananaa	gggccttant	ctaggaagta	nagngtgana	tgatacaccc	acaggctggn	360
gcattctggn	ccacacaaan	acgtgctgnt	ccccgccta	ctgntnaaaa	cagntctggt	420
ttgctnanat	gctgctgntg	caacctgcag	gtccatgana	agaacaactc	cctggttggt	480
tacanccccn	gagtgttttg	ngaatttgca	cctacatttc	ccatgtgata	tggtactca	538

<210> 178

<211> 566

<212> DNA

<213> Homo sapien

<400> 178

gtcgacttgg	aagcagggtt	atttattata	tacttgcaat	tgaatataag	atacagacat	60
atatatgtgt	tatgtatttc	tagaaatgca	cataacatat	atttgcctat	tgtttaaatgt	120
tttttccaga	tatttattac	agaagggcat	ggagggatac	ctacttattc	ttcattatga	180
gaacaattaa	aggcatttat	tagataggaa	attaacagat	catctgcttc	tataacttta	240
ttagctacat	taaaataggca	gtgagcaata	atttaaaaa	tcaccattat	ataaaaataat	300

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aaataacaaa gtaaaagtta atgttataaa aataaactga tagtaaggaa aatctaaatg 360
ggcatgatcc catttttagaa gaccaaataa ttaatagggt tgtcatgtta taatagacaa 420
ttgtctaatt atttctgtgt ttttatttag tgggtagcag aagttgttca gaagagcaga 480
aatatgtaga aaacatctct aaatttttgg caatttgaaa tagcaattct gaggcacaca 540
gctcatctac aaaaatcttt tgcaga 566

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<210> 179
<211> 277
<212> DNA
<213> Homo sapien

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<220>
<221> misc_feature
<222> (1)...(277)
<223> n = A,T,C or G

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<400> 179
gncgacggga aaggaatatt atggcannaa gctgagcaag caattctggt ggaaagtcaa 60
acctgtcagt gctccacacc agggctgtgg tcctcccaga catgcatagg aatggccaca 120
ggtttacact gccttcccag caattataag cacaccagat tcagggagac tgaccaccaa 180
gggatagtgt aaaaggacat tttctcagtt ggggtccatca gcagtttttc ttctgtcatt 240
tattgnngaa aactatngtt tcattttcttc ttttata 277

```

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<210> 180
<211> 349
<212> DNA
<213> Homo sapien

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<220>
<221> misc_feature
<222> (1)...(349)
<223> n = A,T,C or G

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<400> 180
cctttttttt tttttttttt tttttttttt tttttttttt ttagnataag gaaaagctac 60
aaacctcaag gntgttttat ttaaaccaaa taatntgagc aagacatain tacattaaaa 120
acaaatgaac acattaaaat ttcactatnt tacaatctaa attctagcaa catatacaaa 180
tactgagnga ctacagtaca tgccgnggta ananaagtac attntgggan aatatnactg 240
acnctcaaac catttttatt tccaatatgt atttcaatac atgtttgttt ccacttttcc 300
cagngccaca cacacnncna cacaaaaaca aaacaaaaaca aaaaaaac 349

```

```

<210> 181
<211> 435
<212> DNA
<213> Homo sapien

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<220>
<221> misc_feature
<222> (1)...(435)
<223> n = A,T,C or G

```

```

<400> 181
cctttttttt ttttttttga catttacagg tatttatttg agtaagagct cataaaatat 60
atttttataa tatgcacaag aaaaaataca tttgaatgaa taaaaataa aatgacagga 120
ggtgacagaa tttagtgttt ataatgagg tcataaagaa ctttaataat tcanagaana 180
agttcaaagt gtatttaaaa gttgagaccc tgctttacaa tattttataa ttttaaaaaa 240
aggcgtttaa aggtgatagg tgacttaata attttccact ttcaaatagg gtttctagac 300
actgttatga agctgctatg tactaataat actttgcttg ccaaagtgtt tgggttttgt 360

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tggtgtttgt	ttgtttgttt	gtttttgggt	catgaacaac	agtgtctaga	aaccctttt	420
caaaatgggg	tcgac					435

<210> 182
 <211> 328
 <212> DNA
 <213> Homo sapien

<400> 182						
gtcgaccatt	gtatcttttt	cttttctatc	cctttacatt	tactctttca	gaatccttat	60
gttttactgt	tttcagaaaa	cttagttttt	aaaatattct	gctaatacatt	tttcatataa	120
gtttacatta	aataagtctt	ttaaagttta	ttataattaa	ataaagttta	ttttcacatg	180
tgttttcata	tctactgtct	cagaactttc	tccttgccct	atttttccta	ttttatcccc	240
tttttgcatc	ttttgagttg	actttttatg	atttttattt	tctctcttta	ctagtttgga	300
tattatctac	cccactaata	ttctttca				328

<210> 183
 <211> 491
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(491)
 <223> n = A,T,C or G

<400> 183						
cctttttttt	tttttttttt	tttttttttt	ttacaaacct	caaggttggt	ttattttaa	60
caaataatct	gagcaagaca	tatatacatt	aaaaacaaat	gaacacatta	aaatttcact	120
attttacaat	ctaaattcta	gcaacatata	caaataactga	gtgactacag	tacatgccga	180
ggtaagataa	gtacattctg	gganaatatc	actgacgctc	aaaccatttt	tattttccat	240
atgtatttca	atacatgttt	gtttccactt	ttcccagngc	cacacacaca	cacacaaaaa	300
caaaaacaaa	caaaaaaaaa	cagtcacaag	ttggattaca	ttanaattgg	ngccacagtt	360
gacttttaaa	gcattttaat	aaccacccaa	ctcttanatt	ttgcagttta	gggacttcaa	420
gttcanaacc	aaaaagcana	gaatcgtttc	atgtgacatg	atgtttctat	agacctcttg	480
ctctctaggt	c					491

<210> 184
 <211> 478
 <212> DNA
 <213> Homo sapien

<400> 184						
gtcgacggct	gctgttggtt	gggggcccgc	ccgctcctaa	ggcaggaaga	tggtggccgc	60
aaagaagacg	aaaaagtcgc	tggagtcgat	caactctagg	ctccaactcg	ttatgaaaag	120
tgggaagtac	gtcctggggg	acaagcagac	tctgaagatg	atcagacaag	gcaaagcgaa	180
attggtcatt	ctcgctaaca	actgccagc	tttgaggaaa	tctgaaatag	agtactatgc	240
tatgttggct	aaaactgggtg	tccatcacta	cagtggcaat	aatattgaac	tgggcacagc	300
atgcggaaaa	tactacagag	tgtgcacact	ggctatcatt	gatccaggtg	actctgacat	360
cattagaagc	atgccagaac	agactggtga	aaagtaaac	ttttcaccta	caaaatttca	420
cctgcaaac	ttaaacctgc	aaaattttcc	tttaataaaa	tttgcttggt	ttaaaaaa	478

<210> 185
 <211> 596
 <212> DNA
 <213> Homo sapien

<220>

64

<221> misc_feature
 <222> (1)...(596)
 <223> n = A,T,C or G

<400> 185
 gtcgacggac gaggagtgcg gcactgatga gtactgcgct agtcccaccc gcggagggga 60
 cgcgggcggtg caaatctgtc tcgcctgcag gaagcgccga aaacgctgca tgcgtcacgc 120
 tatgtgctgc cccgggaatt actgcaaaaa tggaatatgt gtgtcttctg atcaaaatca 180
 tttccgagga gaaattgagg aaaccatcac tgaaagcttt ggtaatgac atagcacctt 240
 ggatgggtat tccagaagaa ccaccttgct ttcaaaaatg tatcacacca aaggacaaga 300
 aggttctgtt tgtctccggt catcagactg tgcctcagga ttgtgttggt ctagacactt 360
 ctggtccaag atctgtaaac ctgtcctgaa agaaggtaa gtgtgtacca agcataggag 420
 aaaaggctct catggactag aaatattcca gcgttggtac tgtggagaag gtctgtcttg 480
 ccgatacag aaagatcacc atcaagccag taattcttct aggccttcaca cttgncagag 540
 aactaaacc agctatccaa atgcagtga ctccttttat ataatagatg ctatga 596

<210> 186
 <211> 314
 <212> DNA
 <213> Homo sapien

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

<400> 186
 gtcgactgcc tatttaaatgt agctaataaa gttatagaag cagatgatct gttaatattcc 60
 tatctaataa atgcctttaa ttgttctcat aatgaagaat aagtaggtat cctccatgc 120
 cttctgttaa taaatatctg gaaaaaacat taaacaatag gcaaatatat gttatgtgca 180
 tttctagaaa tacataacac atatatatgt ctgtatctta tattcaattg caagtatata 240
 ataaataaac ctgcttccaa acaacaaaaa aaaaaaaaaa aaaaaaaaaan naaaaaaaaa 300
 aaaaaaaaaa aaaa 314

<210> 187
 <211> 331
 <212> DNA
 <213> Homo sapien

<220>
 <221> misc_feature
 <222> (1)...(331)
 <223> n = A,T,C or G

<400> 187
 cctttttttt tttttttatt cctcagngct tttgatttta attccttttg catatctaaa 60
 tgtcagaaag tgaatatata catacagaat tcaaaacacc ttcctaaaat gggtattatt 120
 ggccantcat tnacatcttt attttgaaag tctgaattgn caaatagtgc taaagtgcac 180
 tcttgagct aataaatagc agcatttggt tataaaacct taagaaattc agaccagggc 240
 tgganaagtc acaataaaaa atcagacatg atctanatat agtcttccct aatcatctaa 300
 gacaaacact tgtgtgaatt agtttataag g 331

<210> 188
 <211> 567
 <212> DNA
 <213> Homo sapien

<400> 188

65

```

gtcgacgctg aagaaggaaa agaaatgtgt gaaactcata ggagttcccg ctgacgctga      60
ggccttaagt gaaagaagtg gaaacacccc taactctccc aggttagctg ctgaatcaaa      120
gcttcaaaaca gaagttaaag aaggaaaaga aacttcaagc aaattggaaa aagaaacttg      180
taagaaatta caccctattc tatatgtgtc ttctaaatct actccagaga cccagtgtcc      240
tcaacagtaa agacttgtct ttaataagag tacggtgcca cttgcctcaa aagttactat      300
ggtgcttaag attgtcttga tctgacatat atcaccttct gggttattta ctcattgtgc      360
caggacctgg cattttcatg tgcctttgac caagtgttca gaatttgctt gactctaacc      420
tgagagctt cttaagtgat gccccttcat ggagcttcta tgacagtga taaactatta      480
attgaaggaa aatgttataa ttaatgtatc tatttgctgc attgtatatg gattaaatga      540
taaaaaacaa gtaatctacc ctcagag                                     567

```

```

<210> 189
<211> 130
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(130)
<223> n = A,T,C or G

```

```

<400> 189
cctttttttt tttttttttt tttttttttt tttttttttt tttttatcnc ctaagnanat      60
tttaatatata attttgaaca gttataaaaa anaaanangg cttttgggtc aataacanaa      120
cataacaaaa                                     130

```

```

<210> 190
<211> 426
<212> DNA
<213> Homo sapien

```

```

<400> 190
gtcgaccaac ttcccacata tatttactaa gatgattaag acttacattt tctgcacagg      60
tctgcaaaaa caaaaattat aaactagtcc atccaagaac caaagtttgt ataaacagggt      120
tgctataagc ttggtgaaat gaaaatggaa catttcaatc aaacatttcc tatataacaa      180
ttattatatt tacaatttgg ttcttgcaat atttttctta tgtccaccct tttaaaaaatt      240
attatttgaa gtaatttatt tacaggaaat gttaatgaga tgtattttct tatagagata      300
tttcttacag aaagctttgt agcagaatat atttgcagct attgactttg taatttagga      360
aaaatgtata ataagataaa atctattaaa tttttctcct ctaaaaactg aaaaaaaaaa      420
aaaaaag                                     426

```

```

<210> 191
<211> 550
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(550)
<223> n = A,T,C or G

```

```

<400> 191
cctttttttt tttttttttt tttttttttt tttagttnng gatatgacct ttattgaact      60
tatccaccan agnggaaata atgtctgtac aaaaccaaatt gtttgttact ataactttotg      120
catcacaatt aaaatccaaa cagtttttta aaaacagtca actcaatcaa aaccactac      180
ttcanaatca atagcttntt tgaagccaca gtaacactta aatatggtta anactcgaat      240
gcanaaattt ggttggttgg aaagctaatt aaacttccaa cttgctcaaa tagaattaca      300
aaaaggcaaa atttgtgttt tcacananat acagnccact ggaatcacca aactggaca      360

```

```

gctgttanag tatttanagt cctganataa caaggaatcc aggcntcctt taaacagtct 420
tctgttgnc tttcttccca atcananatt tgtggatgtg tggaatgaca cncaccag 480
caattgtagc cttgatgann gaatccaatt cttcatctcc acgaatagca agttgcaagt 540
gacgaggggt 550

```

```

<210> 192
<211> 299
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(299)
<223> n = A,T,C or G

```

```

<400> 192
cctttttttt tttttttgaa attnnaaatt ttattacaaa aactttttat tgctataaga 60
aaaatatgta ttaattctac aaaataacat tcagattatg ttctaattca attattcaat 120
acaattttat ctcttgtaaa taagagaaac ttatttagaa tataaaatta taacctaatg 180
acaaagctct agtaaattgn gaactacacc tctacaccgg gcttaaatgc atcctgatta 240
atgatttctt catacatgtc acttatttta tccaaaaaag gatttgagtt ctgcgcgac 299

```

```

<210> 193
<211> 536
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(536)
<223> n = A,T,C or G

```

```

<400> 193
tttttttttt ttttttttat tctnncaatt tttatttctc ttacatgctc aaagaagcca 60
agcaaatcca ggtatacatg tatatgtttt aattttacag gagagagaaa gaggtataag 120
gcaagaatta actacatttt catttcacta tttctttatg agctctatth tgctgctaag 180
ttcaagtthc aaaaaaatta ttaattcctc tgctatgtta tcttgctcca attcacaaaa 240
taacagggat ttcccatgt gactcaaaag caagaatctt actcctaaat aacataaaca 300
gcaatatgtg tgactactgt cattcattaa cttcgatggt gaagtthcatt aaactgacca 360
ttaaaagaac atttgaacaa ttccaaaagg gagcaaggat aaatctccaa atcacccaat 420
agacaaggaa cccagagatg acatacagng tgctcacttc caccactgc cactgagaac 480
actgattgct ctcttcaaac acagagcgaa gaatgggcct catgtcacat ggggca 536

```

```

<210> 194
<211> 566
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(566)
<223> n = A,T,C or G

```

```

<400> 194
gtcgactgca ctattaccca gggcagatat tatgagaaac tgtttcttct ctaagggttt 60
atggcagact ttgctttttt aacatgtgag aaatgaattt tttattttgt gatttatgtg 120
atctcttttg ctgagtgaag gaaaggagaa attgttgcta ttgtcagcat cttaaaggta 180

```

67

```

tttccagtca aggcaaggct aagtgccttg tgatagtatt aagcaagtca tgttttgaat      240
ggattacctg tagtgactca ttggaatgat ataattatac aagtaatgcc aaaaaccaag      300
tcaaagccta attaaccaaa gcactcattt aaaaatcatc atgtttggac ctatctggac      360
ctctcagcac tgtaaaatag ttttggtttt gtggcatatg aatagctgtt taacaaatca      420
aagtttagctn tttgcttctc agcttttttg ggcaatacaa gttaagttct taatggggag      480
acattatcat ggcattgactt aagggaacat tggtttgtga aggaaaaaca gattatctaa      540
agccatctct atgtttctgt tcagat                                     566

```

```

<210> 195
<211> 217
<212> DNA
<213> Homo sapien

```

```

<400> 195
gtcgacataa ataaatggaa gaaatatcat gttcatgggc ttcaaaagtc aacagtaaag      60
atgccatttt ttctaaatt gatctacagg ttcagtgcaa ttccctccga atctcaccag      120
ggtttttggg agacataaac aagtttattc taaaatttgt atggaaaggc acaggtcctg      180
gaataactaa agcaacctta caaaaaaaaa aaaaaag                                     217

```

```

<210> 196
<211> 391
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(391)
<223> n = A,T,C or G

```

```

<400> 196
gtcgacggac agacttagga gttttgttta gagcagttaa catctgaagt gtctaatagca      60
ttaacttttg taaggtactg aatacttaat atgtgggaaa cccttttgcg tggtccttag      120
gcttacaatg tgcactgaat cgtttcatgt aagaatccaa agtggacacc attaacaggt      180
ctttgaaata tgcattgact ttatatattc tatatttgta actttgcatg ttcttggttt      240
gttatataaa aaaattgtaa atgtttaata tctgactgaa attaaacgag cgaagatgag      300
caccacaaaa aaaaaaaaaa aaaaaaaaaa aaannnnaaa aaaaaaaann aaaaaaaaaa      360
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa a                                     391

```

```

<210> 197
<211> 445
<212> DNA
<213> Homo sapien

```

```

<400> 197
gtcgactgga tctttatgtc aatgtgtaca tagtacaagc ttttttactg gaattgaggt      60
ttaaaaccac aactgccct tttggtggtg tgcctgttgg gccaaaaatt gggtgataat      120
gtagtgtcac tttctcagct caatgcagtt tctacttttt cttatgggaa aatttttcat      180
aaaacctttt tgcacacaaa ccaggggtg ttttttgcaa tatccttgtt atcctcgtag      240
tgtgccaagt cagaggcttt ctcttgccct tttcctgctg tgttctcagg cctcccaagg      300
gctgtttgac tcaacagttc acatccttgc ttgtgttttg gagaatgtgg ggggtggggg      360
cagagttcaa ggtgtctgtt cccttttccct gtgaactcct tctagtccct atttggggag      420
ggtggtctga aacagatttt tgctg                                     445

```

```

<210> 198
<211> 463
<212> DNA
<213> Homo sapien

```

```

<220>
<221> misc_feature
<222> (1)...(463)
<223> n = A,T,C or G

<400> 198
gtcgacgtca gtattaatac tgagccagac tggcatctac agatttcaga tctatcattt      60
tattgattct taagcttgta ttaaaaacta ggcaatatca tcatggatac ataggagaag      120
acacatttac aatcattcat tgggcctttt atctgtctat ccatccatca tcatttgaag      180
gcctaataata tgccaagtac tcacatggta tgcattgaga cataaaaaag actgtctata      240
acctcaataa gtattaaaaa tcccattatt acccataagg ttcattcttat ttcattttta      300
gggaataaaa ttacatgtct atgaaatttc aatttttaagc actattgttt ttcattgacca      360
taatttatatt ttaaaaaataa attaaagggtt aatttatatgc atgtatgtat ttctaataat      420
taaaaaatgtg ttcaatccct ganaaaaaaaa aaaaaaaaaa aaa                      463

<210> 199
<211> 129
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(129)
<223> n = A,T,C or G

<400> 199
gtcgaccggc gggcagctgc agcttctgct gctgaggccg ggattgctac gactgggact      60
gaagactcag acgatgccct gctgaagatg accatcagcc ancaagagtt tggccgnact      120
gggttcctt                                     .                      129

<210> 200
<211> 523
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(523)
<223> n = A,T,C or G

<400> 200
cctttttttt tttttttttt ttttttnaat cttttattta aagtccatgc taataatgng      60
tttacatttt tacagttaca ttatgataga aactgttgga tttttttaat atctaaaaca      120
atggcccaact gaanaaagga acaattaact ctttaattta ttccttagga taaatacca      180
naaattttaac agctagggca gacttntaat acaataccga aagtccttcc aaaaaccaag      240
nggttgccaa cttatgtccc ttagcattat aacattcttg agccaatagt gtaaaaatac      300
gctgacaatt ttataggcaa acattactca aggtatctta ctttccactt attactaaag      360
taattaaccc ctaaacagat gctcctcaac agngggacta catcctggta aacctatcat      420
aagttgaaac tatcaagttg aaatgcattt agtaccctga taaacctatc ataaagttga      480
aaatttgtaa attgaaccag tgtaaatcag aggccatntt act                      523

<210> 201
<211> 532
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature

```

69

<222> (1)...(532)

<223> n = A,T,C or G

<400> 201

```

cctttttttt tttttttaca cttgagctta gccaaaaggc tgagaagcga ttttttttta      60
aaagctgttc tttaccatgg tttaaacgct aaaatgcata gctataaaaa caaaacactg      120
agctaactcg attacatcca gcttttgcac tcaatagccc ttgaccctcc agtcataagc      180
aagcctgtca ttcgcccagc cctgctatac attctcatta tagtttcggt tcaaatccag      240
tgttacagaa acaaaacacc aagccctcaa tcatgctatg cgtatcttta tgtgtgcatg      300
tcttatgtat gtttaaaata aacattttta aatgttttag gccaggcttg gnggctcatt      360
cagtttttagt ttgctttttt tttgccattc tttgttattt tnggaataag taaaacattt      420
aaataacttaa gtcacatctg tataaaaagt atattcatag gaaggaattt aacaatttta      480
ataaaactta ttagcatatc aatgagtttc aagatacacc tgaaactaaa tt              532

```

<210> 202

<211> 114

<212> DNA

<213> Homo sapien

<400> 202

```

ctccttggtg tggctcttct tgagtgaatg tcacaaggcc ggtgacagga gggggtggag      60
gtgaggggac aaagtagagg ccgagggtca gtgccttttg agaaagtcca gaga          114

```

<210> 203

<211> 304

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(304)

<223> n = A,T,C or G

<400> 203

```

gtcgaccttt ttttccaac ttcttgcttt ctattggatt gttagggatt tctgtttttc      60
actttatttc tctctgctta tttgaaagct atacagcatg gttttctttc tttagggatc      120
actcttcac tttacttttt aaagatggat aaattttata catttaaaaa atttaactctg      180
tatttgatc ttcttctga gtggacctta gcatgttata aatgctcact gaataattct      240
cattgttaat tagagtttgg ttttatntt ttaaanncaa tgtacttact tattcttagn      300
gtaa

```

<210> 204

<211> 581

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(581)

<223> n = A,T,C or G

<400> 204

```

cngcgttggt aggtgagcnn tttcagaagc gcgatcccag gacacgtcgg gaagcaagca      60
tcnnttttagc tgcttggaag gaggacaaa gacggctaaa anntcatttg gaaatatctc      120
taaatatttg ttaccatgta taagctgcta aagagaaatt gggcccaaca aaactaattg      180
aataattgag gcagatttgt gtgtatcatc aaattctatc cagaagttga agaactgtga      240
tttaaagatt gtgtgcattt aataagagga tgacctttca gtttaatttc actatagaag      300

```

```

accatctgga aaatgaatta acaccatta gagatggagc tttgaccctg gattcctcaa 360
aagagctgtc agtctcagaa agtcaaaaag gagaagagag ggacagaaaa tgttctgcag 420
aacaatttga cttgcctcag gatcacttgt gggaacataa gtcaatggaa aatgcagctc 480
cctctcaaga cacagacagt ccactcagtg cagccagcag ttcaaggaac ttggagccac 540
atggaaaaca gccctccttg agagctgccca aagagcatgc t 581

```

```

<210> 205
<211> 409
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(409)
<223> n = A,T,C or G

```

```

<400> 205
gccctgaaga acagtgcctg gatgtggtga ccactggat ccaggaaggt gaagaagggc 60
gtccaaagga tgaccgccac ctccgtggct gtggctacct tcccggctgc ccgggctcca 120
atggtttcca caacaacgac accttccact tctgaaatg ctgcaacacc accaaatgca 180
acgaggggccc aatcctggag cttgaaaatc tgccgcagaa tggccgccag tgttacagct 240
gcaagggggaa cagcaccat ggatgtcct ctgaagagac tttcctcatt gactgccggg 300
gccccatgaa tcaatgtctg gtagccacgc gngcgacgtc acagagacnc ggaaaaacca 360
aagctatatn ggtaaagagg ctgtgcaacc cgctctcaat gtgccaaca 409

```

```

<210> 206
<211> 561
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(561)
<223> n = A,T,C or G

```

```

<400> 206
gtntcatggg aaaggacatg tctctcgaag aaaggttata aaccctgaga tatgaggggt 60
tttttgagac atccgagcct gtttcgttcc gggntgggan caggaataac octgacttct 120
gagctttcat aacccagga tcctccagaa aatttgcggc gcgctgaggg aaaaccttgc 180
tgaagctgta cattggaatg cgtttacagt cattgtaatg gaagcaaat acatgaagga 240
aaaactgtta tttgtatccc tgcttattgc acctgacgac tagttgcaga tggttttgtt 300
tacctaagaa aacttgtgat ataaatgaaa aaaacacctg ttttcctaga gtcattggtt 360
acaaatatgc ttcgtctaag agctatattgt ccattctcct ggagagtgtt tcaatttcga 420
cccatcagtt gtgaaccact aattattcag atgaataagt gtacagatga ggagcaaattg 480
tttggtttta ttgaaagaaa caaagccata ctttcagaaa agcaagtggg atgtgcattt 540
gatatgcttt ggaagcttca a 561

```

```

<210> 207
<211> 461
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(461)
<223> n = A,T,C or G

```

```

<400> 207

```

```

ggtnntttcca gccaatgtga ccttttaaac ctatgaaggt ntnatgcaca gttcgtgtca 60
acaggaaatg atggatgtca agcaattcat tgataaactc ctacctcaa ttgattgacg 120
tactaagag gccttgtgta gaagtacacc agcatcattg tagtagagtg taaacctttt 180
cccatgccca gtcttcaa at tcta atgtt ttgcagtgtt aaaatgtttt gcaaatacat 240
gccgataaca cagatcaa at aatatctcct catgagaa at ttatgatcct ttaagtttct 300
atacatgtat tcttataaga cgaccagga tctactatat tagaatagat gaagcaggta 360
gcttcttttt tctcaa atgt aattcagcaa aataatacag tactgccacc agatttttta 420
ttacatcatt tgaaaattag cagtatgctt aatgaaaatt t 461

```

```

<210> 208
<211> 296
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(296)
<223> n = A,T,C or G

```

```

<400> 208
gatgaacatc catccnaatt nogaagagcc tatattatac cctcttcaag aatttgcattg 60
gcatcaatat ctacaggaga aaaaaaggga actcaaaaat gaaacctggg aatattcttc 120
ctctgtgatt tcttttgta atgttcagtt tctgggtgat gcattggatc tgcagaaatg 180
ggcccacgag gtgtgggata tagttgacat taaacctct gcactttatg acgcactcac 240
tgaggatttt tccgctaagt tottaagaga caccaagcat gatttcgtgt ttttgg 296

```

```

<210> 209
<211> 282
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc_feature
<222> (1)...(282)
<223> n = A,T,C or G

```

```

<400> 209
gcataataaa tgctttgagc ttcttgacta tcatatacct aaagaaagt catcagagaa 60
tnatatctct gacttttnc tgactggcaa aaagcnagct ttatcttgct ttataggatg 120
cttagtttgc cactncaact caaaccaatg ggacagtcnt anatggngng acagtgttna 180
ancncaccaa aaggntncnt ttccntgggg ccancnctgt cntnancctc nctaancat 240
ttgnanaatt ttaancncnn gttaantaaa aaaaaaaaa aa 282

```

```

<210> 210
<211> 1445
<212> DNA
<213> Homo sapiens

```

```

<400> 210
ggcgttgatga ggtgagcttt ttcagaagcg cgatcccagg acacgtcggg aagcaagcat 60
ccccagagct gcttggaag aggaccaa agctctaaaa agtcatttgg aaatatctct 120
aaatatttgc taccatgtat aagctgctaa agagaaattg ggccaacaa aactaattga 180
ataattgagg cagatttgtg tgtatcatca aattctatcc agaagttgaa gaatctgaat 240
ttaaagattg tgtgcattta ataagaggat gacctttcag tttaatttca ctatagaaga 300
ccatctggaa aatgaattaa caccatttag agatggagct ttgacctgg attcctcaa 360
agagctgtca gtctcagaaa gtcaaaaagg agaagagagg gacagaaaat gttctgcaga 420

```

```

acaatttgac ttgcctcagg atcacttggt ggaacataag tcaatggaaa atgcagctcc 480
ctctcaagac acagacagtc cactcagtc agccagcagt tcaaggaaact tggagccaca 540
tggaacacag ccctccttga gagctgcaa agagcatgct atgcctaaag atttaaagaa 600
gatgttagaa aataaagtca tagaaacatt accaggtttc cagcatgtta agttatcagt 660
agtgaacacc atcttgttga aagagaactt ccctggagaa aacatagttt caaaaagctt 720
ttcttctcac tctgatctga ttacagggtt ttatgaggga ggcttaaaaa tctgggaatg 780
tacctttgac ctcttggtt atttcacaaa ggccaaagt aaatttgctg ggaaaaaagt 840
cttgatctt gggttggtt caggtttact aggtataact gcattcaagg gaggtccaa 900
agaaattcac tttcaagatt ataacagtat ggtgattgat gaagtaacct tacctaagt 960
agtagctaac tccactttgg aagatgaaga aaatgatgta aatgagccag atgtgaaaag 1020
atgcaggaaa ccaaaagtaa cacaactata taaatgccga ttttttctg gtgagtggc 1080
tgagttttgt aagcttgtag taagtagtga aaaactttt gtaaaatag atctcattct 1140
cacctcagaa accatttaca acccagatta ttatagtaat ttgcaccaga ctttccttag 1200
actgttaagt aaaaatggac gtgtactttt ggccagcaaa gcacattatt ttggtgtagg 1260
tggagggtt catctcttc agaagttgt agaagaaaga gatgtttta agaccagaat 1320
actcaaaata attgatgaag gattgaagag gttcataatt gaaataactt ttaagtttcc 1380
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aaaaa 1445

```

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<210> 211
<211> 414
<212> DNA
<213> Homo sapiens

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<400> 211
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ttaaatagga taaatgccga aaaatttaag actggcaaaa tatacttggc taaatactgt 180
gcgtctctat taaataccat gtttcagaag aattattaat gacatgagaa tatgctcaaa 240
atacatattg atatgtgcaa atacatattg caaagtaaga ttatagaatg atcctagtct 300
aaaaatgtca catatatatg tatttaaaaa aaaaggcagt taagatttac aacaaaatgt 360
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```

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<210> 212
<211> 720
<212> DNA
<213> Homo sapiens

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<400> 212
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taacctaca gttaacatta taatcaatgg tgaatcattg agtactttcc ttctaagatc 120
agaaacagtt caaagtccac tctcaccatt tctattcaac attgtactgg aatcccagcc 180
agtgcagtaa taccaataat aaaaaattaa agtcataaag attgaaaagg atgaagtaaa 240
gctatttcaa ttctatttag aagtatttag aaaccccaaa gaatctacaa aaaactaata 300
gaaataagtg aatatatgaa ggtcttacta tacaagatca acatatcaaa agcagtggta 360
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agttgacttt ctgtgtaaat caaccttggt tcccaggaaa aaactccaat tgatcatgat 540
gtgttatcct ttttatacat tgctgtattc aatatgctaa tatattttatt tttgtgtct 600
atttcatgag ggatatcagt atgtaattgt ttttcttgt tatatctttg ttggttttat 660
taatcaacat tatgctaact tcatacaata tattggaaca tgctccctcc ttttattttc 720

```

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<210> 213
<211> 1114
<212> DNA
<213> Homo sapiens

```

```

<400> 213

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gtaaaggaga cttggaccaaa acactgtgac aaagcagagt tcttcagttc tgaaaatgtt 180
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tacaaatacg cttttgataa gtatagagac caatacaact ggttcttcct tgcacgcccc 300
actacgtttg ctatcattga aaacctaaag ttttttttgt taaaaaagga tccatcacag 360
cctttctatc taggccacac tataaaatct ggagaccttg aatatgtggg tatggaagga 420
ggaattgtct taagtgtaga atcaatgaaa agacttaaca gccttctcaa tatcccagaa 480
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<210> 214

<211> 1495

<212> DNA

<213> Homo sapiens

<400> 214

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gtaacggatg gtgcgccaac gtgagaggaa acccggtgcgc ggctgcgctt tctgtgtccc 60
aagcggttct agacgcggtat gaagtgcata acaacttctc ccatagagga gttgtgtgca 120
agttccagtt tataccaaac agtaatcaga ttccattgga agctaaagat tttgagagcc 180
ttttgtacta tatgcaacta acttgatttc aagcttgga acttttaaaa aaacatttaa 240
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tttcagagga tgagcgcatg gagctcagta agagctttcg agtatactgt attatccttg 480
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taatttgggtg gcactgggtat aaccacccat taaagtcagt agtacatttt taaatgaggg 1380
tggttttttt ctttaaaaca catgaacatt gtaaatgtgt tggaaaaaag tgttttaaga 1440
ataataattt tgcaataaaa ctattaataa atattatatg tgataaattc taacc 1495

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<210> 215

<211> 838

<212> DNA

<213> Homo sapiens

<400> 215

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gtgcttggtt cttccacctc tgccactaat tgcacatcag tttcatcgag gaaagctgaa 180
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gaggcaggaa gcagtggcgt aggaaaagca aagagaaaag catgtccttt gcaacctgat 360
cacacaaatg atgaaaaaga atagaacttt ctcatcctc tttgaataac gtctccttgt 420
ttaccctggt attctagaat gtaaatttac ataaatgtgt ttgttccaat tagcttttgt 480
gaacaggcat ttaattaaaa aatttaggtt taaatttaga tgttcaaaag tagttgtgaa 540
atttgagaat ttgtaagact aattatggta acttagctta gtattcaata taatgcattg 600
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gttctaatta caagtatgtt gtatttgaga tttgcttaga ttgttgtagt gctgccattt 720
ttattgggtg ttgattattg gaatgggtgc atattgtcac tcttctact tgctttaaaa 780
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<210> 216
 <211> 938
 <212> DNA
 <213> Homo sapiens

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<400> 216
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ggtcgcatcc aggagtttgc ctcccgaagg gggcccgacg agcacggcca ccgcctccat 180
cagcagcacc aggccaatgg cactggagaa cttgtaggag atgccaaga agatgcagaa 240
gaccacgagg ccgctgtagt cgcccgcctg agagcccggc aggtccgaga ggccgttgaa 300
gaacatggag aagctgaaga ggtagacgga gtagggccgc accttccaa gcccgcgcac 360
gaagcccgcg gccggccgcg cgaagatgtc aatgaagccc aggatggtga gcaggaaggc 420
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gaagagcccc agcaccatga ccgaggcggc cacggcgtaa agcacaagc cgcggtccc 540
gaagacgctc aggtctagca ggcgcggga gggtcgcggc ggcccagc ccggttggc 600
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caggatgagg aagccgcccc gccagccgta gcggctctgc agcagctgcc ccagcgggct 720
cagggcacac aggaagacag ggctacctgc tgccgccagc ccgttgacca tggggcgccg 780
cttgctgaag tagcggttca gcatgatgag cgagggtg agttgagt ccaaacc 840
ccccgtgatg acccagtggt tgaggtagac ctggatgatg ctccggcaaa aggacgcagc 900
caccatgccc agcgacgcaa agagaccccc cacaagca 938

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<210> 217
 <211> 1982
 <212> DNA
 <213> Homo sapiens

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<400> 217
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gggctgggc cgtgtcttcc ggctgttctg tcatcactgg cttctcctac gccttcccca 180
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tgggtgtcac ggccagccg ggctcggggc cgccgcgacc ctcccgcgcc ctgctagacc 720
tgagcgtctt ccgggacgcg ggctttgtgc tttacgccgt ggccgcctcg gtcattgtgc 780
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ctggaagatg gaaataaacc tgcgtgtggg tggagtgttc tcgtgccgaa ttcaaaaagc 1980
tt
1982

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<210> 218

<211> 592

<212> DNA

<213> Homo sapiens

<400> 218

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tacaaatatg ctctgtctaa gagctatttg tccattctcc tggagagtgt ttcaatttcg 420
accatcagat tgtgaaccac taattattca gatgaataag tgtacagatg aggagcaaat 480
gtttggtttt attgaaagaa acaaagccat actttcagaa aagcaagtgg gatgtgcatt 540
tgatatgctt tggaaagctt aaaagcagaa gaccagcctg ttaaaaaatg ct 592

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<210> 219

<211> 650

<212> DNA

<213> Homo sapiens

<400> 219

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gagcatgtaa gagaaataaa aattgaaaga ataaaaaaa aaaaaaaaaa 650

```

<210> 220

<211> 782

<212> DNA

<213> Homo sapiens

<400> 220

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tcactaagag gccttgtgta gaagtacacc agcatcattg tagtagagtg taaacctttt 180
cccattgcca gtcttcaaat ttctaattgt ttgcagtgtt aaaatgtttt gcaaatacat 240
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gcttcttttt tctcaaatgt aattcagcaa aataatacag tactgccacc agatttttta 420
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attgtcaaga aaaagtaaaa tcgttctctt caattaatgg cccttttatt ttgggaccag 720
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aa

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<210> 221

<211> 2417

<212> DNA

<213> Homo sapiens

<400> 221

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cgctgcccgc catcgtgccc gccgcccgga aggccaccgc tgcggtgatt ttccctgcatg 120
gattgggaga tactgggcac ggatgggcag aagcctttgc aggtatcaga agttcacata 180
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atcattttta attgtcaaaa tttccagatt actggtaaaa attatttgaa aacaaactta 1980

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aatttaattc tgaaaaaa                2417

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<210> 222

<211> 1466

<212> DNA

<213> Homo sapiens

<400> 222

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cactgaggat ttttccgcta agttcttaag agacaccaag catgatttctg tgtttttgga 360
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acaaggaggg gatatagtgt atggaaaagg agataatgga gagtcgattt atggccaac 600
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