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(54) COMPOSITIONS FOR THE TREATMENT AND DIAGNOSIS OF BREAST CANCER AND METHODS FOR THEIR USE

(75) Inventors: **Jiang Yuqiu**, San Diego, CA (US); **Davin C. Dillon**, Issaquah, WA (US); **Jennifer L. Mitcham**, Redmond, WA (US); **Jiangchun Xu**, Bellevue, WA (US)

Correspondence Address:
SEED INTELLECTUAL PROPERTY LAW GROUP PLLC
701 FIFTH AVE
SUITE 6300
SEATTLE, WA 98104-7092 (US)

(73) Assignee: **Corixa Corporation**, Seattle, WA

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(57) ABSTRACT

Compounds and methods for the treatment and diagnosis of breast cancer are provided. The inventive compounds include polypeptides containing at least a portion of a breast tumor antigen. Vaccines and pharmaceutical compositions for immunotherapy of breast cancer comprising such polypeptides, or polynucleotides encoding such polypeptides, are provided, together with polynucleotides for preparing the inventive polypeptides. The inventive polypeptides may be used to generate antibodies useful for the diagnosis and monitoring of breast cancer.

SYN18C6 Northern Blot

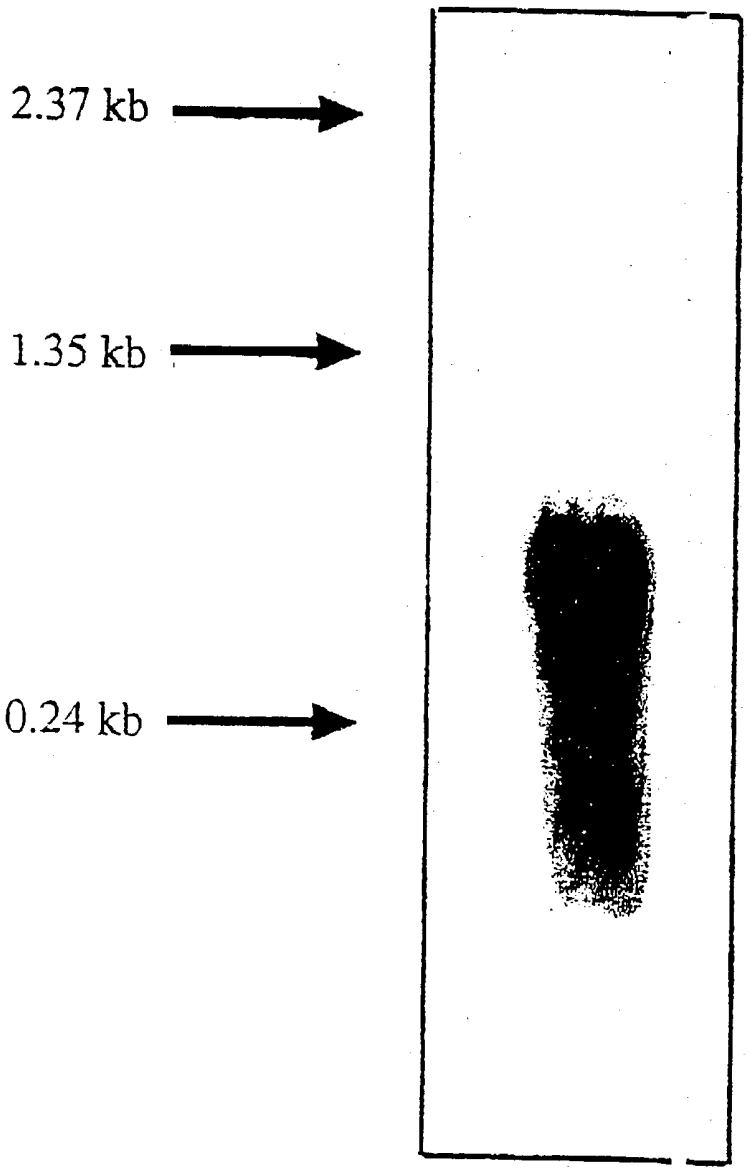

Fig. 1

COMPOSITIONS FOR THE TREATMENT AND DIAGNOSIS OF BREAST CANCER AND METHODS FOR THEIR USE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. application Ser. No. 09/222,575, filed Dec. 28, 1998.

TECHNICAL FIELD

[0002] The present invention relates generally to compositions and methods for the treatment of breast cancer. The invention is more particularly related to polypeptides comprising at least a portion of a protein that is preferentially expressed in breast tumor tissue and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides may be used in vaccines and pharmaceutical compositions for treatment of breast cancer.

BACKGROUND OF THE INVENTION

[0003] Breast cancer is a significant health problem for women in the United States and throughout the world. Although advances have been made in detection and treatment of the disease, breast cancer remains the second leading cause of cancer-related deaths in women, affecting more than 180,000 women in the United States each year. For women in North America, the life-time odds of getting breast cancer are one in eight.

[0004] No vaccine or other universally successful method for the prevention or treatment of breast cancer is currently available. Management of the disease currently relies on a combination of early diagnosis (through routine breast screening procedures) 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 breast cancer is often selected based on a variety of prognostic parameters, including an analysis of specific tumor markers. See, e.g., Porter-Jordan and Lippman, *Breast Cancer* 8:73-100 (1994). However, the use of established markers often leads to a result that is difficult to interpret, and the high mortality observed in breast cancer patients indicates that improvements are needed in the treatment, diagnosis and prevention of the disease.

[0005] Accordingly, there is a need in the art for improved methods for the treatment and diagnosis of breast cancer. The present invention fulfills these needs and further provides other related advantages.

SUMMARY OF THE INVENTION

[0006] The present invention provides compounds and methods for the treatment and diagnosis of breast cancer. In one aspect, isolated polypeptides are provided comprising at least an immunogenic portion of a breast tumor antigen or a variant thereof, wherein the antigen comprises an amino acid sequence encoded by a polynucleotide having a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NO: 1-61, 63-175, 178 and 180; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions. In specific embodiments, the inventive polypeptides comprise an amino acid sequence selected from the group consisting of SEQ ID NO: 62, 176, 179 and 181.

[0007] In related aspects, isolated polynucleotides encoding the above polypeptides are provided. In specific embodiments, such polynucleotides comprise a sequence selected from the group consisting of sequences provided in SEQ ID NO: 1-61, 63-175, 178 and 180. The present invention further provides expression vectors comprising the above polynucleotides, together with host cells transformed or transfected with such expression vectors. In preferred embodiments, the host cells are selected from the group consisting of *E coli*, yeast and mammalian cells.

[0008] In another aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, an inventive polypeptide and a known breast tumor antigen.

[0009] The present invention also provides pharmaceutical compositions comprising at least one of the above polypeptides, or a polynucleotide encoding such a polypeptide, and a physiologically acceptable carrier, together with vaccines comprising at least one such polypeptide or polynucleotide in combination with a non-specific immune response enhancer. Pharmaceutical compositions and vaccines comprising one or more of the above fusion proteins are also provided.

[0010] In yet another aspect, methods are provided for inhibiting the development of breast cancer in a patient, comprising administering an effective amount of at least one of the above pharmaceutical compositions and/or vaccines.

[0011] The polypeptides disclosed herein may be usefully employed in the diagnosis and monitoring of breast cancer. In one aspect of the present invention, methods are provided for detecting breast cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that is capable of binding to one of the above polypeptides; and (b) detecting in the sample a protein or polypeptide that binds to the binding agent. In preferred embodiments, the binding agent is an antibody, most preferably a monoclonal antibody.

[0012] In related aspects, methods are provided for monitoring the progression of breast cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that is capable of binding to one of the above polypeptides; (b) determining in the sample an amount of a protein or polypeptide that binds to the binding agent; (c) repeating steps (a) and (b); and comparing the amounts of polypeptide detected in steps (b) and (c).

[0013] Within related aspects, the present invention provides antibodies, preferably monoclonal antibodies, that bind to the inventive polypeptides, as well as diagnostic kits comprising such antibodies, and methods of using such antibodies to inhibit the development of breast cancer.

[0014] The present invention further provides methods for detecting breast cancer comprising: (a) obtaining a biological sample from a patient; (b) contacting the sample with a first and a second oligonucleotide primer in a polymerase chain reaction, at least one of the oligonucleotide primers being specific for a polynucleotide that encodes one of the above polypeptides; and (c) detecting in the sample a DNA

sequence that amplifies in the presence of the first and second oligonucleotide primers. In a preferred embodiment, at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide comprising a sequence selected from the group consisting of SEQ ID NO: 1-61, 63-175, 178 and 180.

[0015] In a further aspect, the present invention provides a method for detecting breast cancer in a patient comprising: (a) obtaining a biological sample from the patient; (b) contacting the sample with an oligonucleotide probe specific for a polynucleotide that encodes one of the above polypeptides; and (c) detecting in the sample a DNA sequence that hybridizes to the oligonucleotide probe. Preferably, the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide comprising a sequence selected from the group consisting of SEQ ID NO: 1-61, 63-175, 178 and 180.

[0016] In related aspects, diagnostic kits comprising the above oligonucleotide probes or primers are provided.

[0017] 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 DRAWING AND SEQUENCE IDENTIFIERS

[0018] **FIG. 1** shows the results of a Northern blot of the clone SYN18C6 (SEQ ID NO: 40).

[0019] SEQ ID NO: 1 is the determined cDNA sequence of JBT2.

[0020] SEQ ID NO: 2 is the determined cDNA sequence of JBT6.

[0021] SEQ ID NO: 3 is the determined cDNA sequence of JBT7.

[0022] SEQ ID NO: 4 is the determined cDNA sequence of JBT10.

[0023] SEQ ID NO: 5 is the determined cDNA sequence of JBT13.

[0024] SEQ ID NO: 6 is the determined cDNA sequence of JBT14.

[0025] SEQ ID NO: 7 is the determined cDNA sequence of JBT15.

[0026] SEQ ID NO: 8 is the determined cDNA sequence of JBT16.

[0027] SEQ ID NO: 9 is the determined cDNA sequence of JBT17.

[0028] SEQ ID NO: 10 is the determined cDNA sequence of JBT22.

[0029] SEQ ID NO: 11 is the determined cDNA sequence of JBT25.

[0030] SEQ ID NO: 12 is the determined cDNA sequence of JBT28.

[0031] SEQ ID NO: 13 is the determined cDNA sequence of JBT32.

[0032] SEQ ID NO: 14 is the determined cDNA sequence of JBT33.

[0033] SEQ ID NO: 15 is the determined cDNA sequence of JBT34.

[0034] SEQ ID NO: 16 is the determined cDNA sequence of JBT36.

[0035] SEQ ID NO: 17 is the determined cDNA sequence of JBT37.

[0036] SEQ ID NO: 18 is the determined cDNA sequence of JBT51.

[0037] SEQ ID NO: 19 is the determined cDNA sequence of JBTT1.

[0038] SEQ ID NO: 20 is the determined cDNA sequence of JBTT7.

[0039] SEQ ID NO: 21 is the determined cDNA sequence of JBTT11.

[0040] SEQ ID NO: 22 is the determined cDNA sequence of JBTT14.

[0041] SEQ ID NO: 23 is the determined cDNA sequence of JBTT18.

[0042] SEQ ID NO: 24 is the determined cDNA sequence of JBTT19.

[0043] SEQ ID NO: 25 is the determined cDNA sequence of JBTT20.

[0044] SEQ ID NO: 26 is the determined cDNA sequence of JBTT21.

[0045] SEQ ID NO: 27 is the determined cDNA sequence of JBTT22.

[0046] SEQ ID NO: 28 is the determined cDNA sequence of JBTT28.

[0047] SEQ ID NO: 29 is the determined cDNA sequence of JBTT29.

[0048] SEQ ID NO: 30 is the determined cDNA sequence of JBTT33.

[0049] SEQ ID NO: 31 is the determined cDNA sequence of JBTT37.

[0050] SEQ ID NO: 32 is the determined cDNA sequence of JBTT38.

[0051] SEQ ID NO: 33 is the determined cDNA sequence of JBTT47.

[0052] SEQ ID NO: 34 is the determined cDNA sequence of JBTT48.

[0053] SEQ ID NO: 35 is the determined cDNA sequence of JBTT50.

[0054] SEQ ID NO: 36 is the determined cDNA sequence of JBTT51.

[0055] SEQ ID NO: 37 is the determined cDNA sequence of JBTT52.

[0056] SEQ ID NO: 38 is the determined cDNA sequence of JBTT54.

[0057] SEQ ID NO: 39 is the determined cDNA sequence of SYN17F4.

[0058] SEQ ID NO: 40 is the determined cDNA sequence of SYN18C6.

[0059] SEQ ID NO: 41 is the determined cDNA sequence of SYN19A2.

[0060] SEQ ID NO: 42 is the determined cDNA sequence of SYN19C8.

[0061] SEQ ID NO: 43 is the determined cDNA sequence of SYN20A12.

[0062] SEQ ID NO: 44 is the determined cDNA sequence of SYN20G6.

[0063] SEQ ID NO: 45 is the determined cDNA sequence of SYN20G6-2.

[0064] SEQ ID NO: 46 is the determined cDNA sequence of SYN21B9.

[0065] SEQ ID NO: 47 is the determined cDNA sequence of SYN21B9-2.

[0066] SEQ ID NO: 48 is the determined cDNA sequence of SYN21C10.

[0067] SEQ ID NO: 49 is the determined cDNA sequence of SYN21G10.

[0068] SEQ ID NO: 50 is the determined cDNA sequence of SYN21G10-2.

[0069] SEQ ID NO: 51 is the determined cDNA sequence of SYN21G11.

[0070] SEQ ID NO: 52 is the determined cDNA sequence of SYN21G11-2.

[0071] SEQ ID NO: 53 is the determined cDNA sequence of SYN21H8.

[0072] SEQ ID NO: 54 is the determined cDNA sequence of SYN22A10.

[0073] SEQ ID NO: 55 is the determined cDNA sequence of SYN22A10-2.

[0074] SEQ ID NO: 56 is the determined cDNA sequence of SYN22A12.

[0075] SEQ ID NO: 57 is the determined cDNA sequence of SYN22A2.

[0076] SEQ ID NO: 58 is the determined cDNA sequence of SYN22B4.

[0077] SEQ ID NO: 59 is the determined cDNA sequence of SYN22C2.

[0078] SEQ ID NO: 60 is the determined cDNA sequence of SYN22E10.

[0079] SEQ ID NO: 61 is the determined cDNA sequence of SYN22F2.

[0080] SEQ ID NO: 62 is a predicted amino acid sequence for SYN18C6.

[0081] SEQ ID NO: 63 is the determined cDNA sequence of B723P.

[0082] SEQ ID NO: 64 is the determined cDNA sequence for B724P.

[0083] SEQ ID NO: 65 is the determined cDNA sequence of B770P.

[0084] SEQ ID NO: 66 is the determined cDNA sequence of B716P.

[0085] SEQ ID NO: 67 is the determined cDNA sequence of B725P.

[0086] SEQ ID NO: 68 is the determined cDNA sequence of B717P.

[0087] SEQ ID NO: 69 is the determined cDNA sequence of B771P.

[0088] SEQ ID NO: 70 is the determined cDNA sequence of B722P.

[0089] SEQ ID NO: 71 is the determined cDNA sequence of B726P.

[0090] SEQ ID NO: 72 is the determined cDNA sequence of B727P.

[0091] SEQ ID NO: 73 is the determined cDNA sequence of B728P.

[0092] SEQ ID NO: 74-87 are the determined cDNA sequences of isolated clones which show homology to known sequences.

[0093] SEQ ID NO: 88 is the determined cDNA sequence of 13053.

[0094] SEQ ID NO: 89 is the determined cDNA sequence of 13057.

[0095] SEQ ID NO: 90 is the determined cDNA sequence of 13059.

[0096] SEQ ID NO: 91 is the determined cDNA sequence of 13065.

[0097] SEQ ID NO: 92 is the determined cDNA sequence of 13067.

[0098] SEQ ID NO: 93 is the determined cDNA sequence of 13068.

[0099] SEQ ID NO: 94 is the determined cDNA sequence of 13071.

[0100] SEQ ID NO: 95 is the determined cDNA sequence of 13072.

[0101] SEQ ID NO: 96 is the determined cDNA sequence of 13073.

[0102] SEQ ID NO: 97 is the determined cDNA sequence of 13075.

[0103] SEQ ID NO: 98 is the determined cDNA sequence of 13078.

[0104] SEQ ID NO: 99 is the determined cDNA sequence of 13079.

[0105] SEQ ID NO: 100 is the determined cDNA sequence of 13081.

[0106] SEQ ID NO: 101 is the determined cDNA sequence of 13082.

[0107] SEQ ID NO: 102 is the determined cDNA sequence of 13092.

[0108] SEQ ID NO: 103 is the determined cDNA sequence of 13097.

[0109] SEQ ID NO: 104 is the determined cDNA sequence of 13101.

[0110] SEQ ID NO: 105 is the determined cDNA sequence of 13102.

[0111] SEQ ID NO: 106 is the determined cDNA sequence of 13119.

[0112] SEQ ID NO: 107 is the determined cDNA sequence of 13131.

[0113] SEQ ID NO: 108 is the determined cDNA sequence of 13133.

[0114] SEQ ID NO: 109 is the determined cDNA sequence of 13135.

[0115] SEQ ID NO: 110 is the determined cDNA sequence of 13139.

[0116] SEQ ID NO: 111 is the determined cDNA sequence of 13140.

[0117] SEQ ID NO: 112 is the determined cDNA sequence of 13146.

[0118] SEQ ID NO: 113 is the determined cDNA sequence of 13147.

[0119] SEQ ID NO: 114 is the determined cDNA sequence of 13148.

[0120] SEQ ID NO: 115 is the determined cDNA sequence of 13149.

[0121] SEQ ID NO: 116 is the determined cDNA sequence of 13151.

[0122] SEQ ID NO: 117 is the determined cDNA sequence of 13051

[0123] SEQ ID NO: 118 is the determined cDNA sequence of 13052

[0124] SEQ ID NO: 119 is the determined cDNA sequence of 13055

[0125] SEQ ID NO: 120 is the determined cDNA sequence of 13058

[0126] SEQ ID NO: 121 is the determined cDNA sequence of 13062

[0127] SEQ ID NO: 122 is the determined cDNA sequence of 13064

[0128] SEQ ID NO: 123 is the determined cDNA sequence of 13080

[0129] SEQ ID NO: 124 is the determined cDNA sequence of 13093

[0130] SEQ ID NO: 125 is the determined cDNA sequence of 13094

[0131] SEQ ID NO: 126 is the determined cDNA sequence of 13095

[0132] SEQ ID NO: 127 is the determined cDNA sequence of 13096

[0133] SEQ ID NO: 128 is the determined cDNA sequence of 13099

[0134] SEQ ID NO: 129 is the determined cDNA sequence of 13100

[0135] SEQ ID NO: 130 is the determined cDNA sequence of 13103

[0136] SEQ ID NO: 131 is the determined cDNA sequence of 13106

[0137] SEQ ID NO: 132 is the determined cDNA sequence of 13107

[0138] SEQ ID NO: 133 is the determined cDNA sequence of 13108

[0139] SEQ ID NO: 134 is the determined cDNA sequence of 13121

[0140] SEQ ID NO: 135 is the determined cDNA sequence of 13126

[0141] SEQ ID NO: 136 is the determined cDNA sequence of 13129

[0142] SEQ ID NO: 137 is the determined cDNA sequence of 13130

[0143] SEQ ID NO: 138 is the determined cDNA sequence of 13134

[0144] SEQ ID NO: 139 is the determined cDNA sequence of 13141

[0145] SEQ ID NO: 140 is the determined cDNA sequence of 13142

[0146] SEQ ID NO: 141 is the determined cDNA sequence of 14376

[0147] SEQ ID NO: 142 is the determined cDNA sequence of 14377

[0148] SEQ ID NO: 143 is the determined cDNA sequence of 14383

[0149] SEQ ID NO: 144 is the determined cDNA sequence of 14384

[0150] SEQ ID NO: 145 is the determined cDNA sequence of 14387

[0151] SEQ ID NO: 146 is the determined cDNA sequence of 14392

[0152] SEQ ID NO: 147 is the determined cDNA sequence of 14394

[0153] SEQ ID NO: 148 is the determined cDNA sequence of 14398

[0154] SEQ ID NO: 149 is the determined cDNA sequence of 14401

[0155] SEQ ID NO: 150 is the determined cDNA sequence of 14402

[0156] SEQ ID NO: 151 is the determined cDNA sequence of 14405

[0157] SEQ ID NO: 152 is the determined cDNA sequence of 14409

[0158] SEQ ID NO: 153 is the determined cDNA sequence of 14412

[0159] SEQ ID NO: 154 is the determined cDNA sequence of 14414

[0160] SEQ ID NO: 155 is the determined cDNA sequence of 14415

[0161] SEQ ID NO: 156 is the determined cDNA sequence of 14416

[0162] SEQ ID NO: 157 is the determined cDNA sequence of 14419

[0163] SEQ ID NO: 158 is the determined cDNA sequence of 14426

[0164] SEQ ID NO: 159 is the determined cDNA sequence of 14427

[0165] SEQ ID NO: 160 is the determined cDNA sequence of 14375

[0166] SEQ ID NO: 161 is the determined cDNA sequence of 14378

[0167] SEQ ID NO: 162 is the determined cDNA sequence of 14379

[0168] SEQ ID NO: 163 is the determined cDNA sequence of 14380

[0169] SEQ ID NO: 164 is the determined cDNA sequence of 14381

[0170] SEQ ID NO: 165 is the determined cDNA sequence of 14382

[0171] SEQ ID NO: 166 is the determined cDNA sequence of 14388

[0172] SEQ ID NO: 167 is the determined cDNA sequence of 14399

[0173] SEQ ID NO: 168 is the determined cDNA sequence of 14406

[0174] SEQ ID NO: 169 is the determined cDNA sequence of 14407

[0175] SEQ ID NO: 170 is the determined cDNA sequence of 14408

[0176] SEQ ID NO: 171 is the determined cDNA sequence of 14417

[0177] SEQ ID NO: 172 is the determined cDNA sequence of 14418

[0178] SEQ ID NO: 173 is the determined cDNA sequence of 14423

[0179] SEQ ID NO: 174 is the determined cDNA sequence of 14424

[0180] SEQ ID NO: 175 is the determined cDNA sequence of B726P-20

[0181] SEQ ID NO: 176 is the predicted amino acid sequence of B726P-20

[0182] SEQ ID NO: 177 is a PCR primer

[0183] SEQ ID NO: 178 is the determined cDNA sequence of B726P-74

[0184] SEQ ID NO: 179 is the predicted amino acid sequence of B726P-74

[0185] SEQ ID NO: 180 is the determined cDNA sequence of B726P-79

[0186] SEQ ID NO: 181 is the predicted amino acid sequence of B726P-79

DETAILED DESCRIPTION OF THE INVENTION

[0187] As noted above, the present invention is generally directed to compositions and methods for the treatment and diagnosis of breast cancer. The inventive compositions are generally isolated polypeptides that comprise at least a portion of a breast tumor antigen. Also included within the present invention are molecules (such as an antibody or fragment thereof) that bind to the inventive polypeptides. Such molecules are referred to herein as "binding agents." In particular, the subject invention discloses polypeptides comprising at least a portion of a human breast tumor antigen, or a variant thereof, wherein the breast tumor antigen includes an amino acid sequence encoded by a polynucleotide including a sequence selected from the group consisting of: nucleotide sequences recited in SEQ ID NO: 1-61, 63-175, 178 and 180, the complements of said nucleotide sequences, and variants thereof. As used herein, the term "polypeptide" encompasses amino acid chains of any length, including full length proteins, wherein the amino acid residues are linked by covalent peptide bonds. Thus, a polypeptide comprising a portion of one of the above breast antigens may consist entirely of the portion, or the portion may be present within a larger polypeptide that contains additional sequences. The additional sequences may be derived from the native protein or may be heterologous, and such sequences may be immunoreactive and/or antigenic.

[0188] As used herein, an "immunogenic portion" of a human breast tumor antigen is a portion that is capable of eliciting an immune response in a patient inflicted with breast cancer and as such binds to antibodies present within sera from a breast cancer patient. Such immunogenic portions generally comprise at least about 5 amino acid residues, more preferably at least about 10, and most preferably at least about 20 amino acid residues. Immunogenic portions of the proteins described herein may be identified in antibody binding assays. Such assays may generally be performed using any of a variety of means known to those of ordinary skill in the art, as described, for example, in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1988. For example, a polypeptide may be immobilized on a solid support (as described below) and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ^{125}I-labeled Protein A. Alternatively, a polypeptide may be used to generate monoclonal and polyclonal antibodies for use in detection of the polypeptide in blood or other fluids of breast cancer patients. Methods for preparing and identifying immunogenic portions of antigens of known sequence are well known in the art and include those summarized in Paul, *Fundamental Immunology*, 3rd ed., Raven Press, 1993, pp. 243-247.

[0189] The term "polynucleotide(s)," as used herein, means a single or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases and includes DNA and corresponding RNA molecules, including HnRNA and mRNA molecules, both sense and anti-sense strands, and comprehends cDNA, genomic DNA and recombinant DNA, as well as wholly or partially synthesized polynucleotides. An HnRNA molecule contains introns and corresponds to a polynucleotide in a generally one-to-one manner. An mRNA

molecule corresponds to an HnRNA and polynucleotide from which the introns have been excised. A polynucleotide may consist of an entire gene, or any portion thereof. Operable anti-sense polynucleotides may comprise a fragment of the corresponding polynucleotide, and the definition of "polynucleotide" therefore includes all such operable anti-sense fragments.

[0190] The compositions and methods of the present invention also encompass variants of the above polypeptides and polynucleotides. Such variants include, but are not limited to, naturally occurring allelic variants of the inventive sequences.

[0191] A polypeptide "variant," as used herein, is a polypeptide that differs from the recited polypeptide only in conservative substitutions and/or modifications, such that the antigenic properties of the polypeptide are retained. In a preferred embodiment, variant polypeptides differ from an identified sequence by substitution, deletion or addition of five amino acids or fewer. Such variants may generally be identified by modifying one of the above polypeptide sequences, and evaluating the antigenic properties of the modified polypeptide using, for example, the representative procedures described herein. Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity (determined as described below) to the identified polypeptides.

[0192] As used herein, a "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. In general, the following groups of amino acids represent conservative changes: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his.

[0193] Variants may also, or alternatively, contain other modifications, including the deletion or addition of amino acids that have minimal influence on the antigenic properties, secondary structure and hydropathic nature of the polypeptide. For example, a polypeptide may be conjugated to a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

[0194] A nucleotide "variant" is a sequence that differs from the recited nucleotide sequence in having one or more nucleotide deletions, substitutions or additions. Such modifications may be readily introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis as taught, for example, by Adelman et al. (*DNA,* 2:183, 1983). Nucleotide variants may be naturally occurring allelic variants, or non-naturally occurring variants. Variant nucleotide sequences preferably exhibit at least about 70%, more preferably at least about 80% and most preferably at least about 90% identity (determined as described below) to the recited sequence.

[0195] The breast tumor antigens provided by the present invention include variants that are encoded by DNA sequences which are substantially homologous to one or more of the DNA sequences specifically recited herein. "Substantial homology," as used herein, refers to DNA sequences that are capable of hybridizing under moderately stringent conditions. Suitable moderately stringent conditions include prewashing in a solution of 5×SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50° C.-65° C., 5×SSC, overnight or, in the event of cross-species homology, at 45° C. with 0.5×SSC; followed by washing twice at 65° C. for 20 minutes with each of 2×, 0.5× and 0.2×SSC containing 0.1% SDS. Such hybridizing DNA sequences are also within the scope of this invention, as are nucleotide sequences that, due to code degeneracy, encode an immunogenic polypeptide that is encoded by a hybridizing DNA sequence.

[0196] Two nucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acid residues in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

[0197] Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, Wis.), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M. O. (1978) A model of evolutionary change in proteins—Matrices for detecting distant relationships. In Dayhoff, M. O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Resarch Foundaiton, Washington D.C. Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, Calif.; Higgins, D. G. and Sharp, P. M. (1989) Fast and sensitive multiple sequence alignments on a microcomputer *CABIOS* 5:151-153; Myers, E. W. and Muller W. (1988) Optimal alignments in linear space *CABIOS* 4:11-17; Robinson, E. D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) The neighbor joining method. A new method for reconstructing phylogenetic trees *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, Calif.; Wilbur, W. J. and Lipman, D. J. (1983) Rapid similarity searches of nucleic acid and protein data banks *Proc. Natl. Acad., Sci. USA* 80:726-730.

[0198] 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 sequence in the comparison window may comprise additions or deletions (i.e. gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in

both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (i.e. the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

[0199] The breast tumor antigens of the present invention, and polynucleotides encoding such antigens, may be isolated from breast tumor tissue using any of a variety of methods well known in the art. DNA sequences corresponding to a gene (or a portion thereof) encoding one of the inventive breast tumor antigens may be isolated from a breast tumor cDNA library using a subtraction technique as described in detail below. Examples of such DNA sequences are provided in SEQ ID NO: 1-61, 63-175, 178 and 180. Partial DNA sequences thus obtained may be used to design oligonucleotide primers for the amplification of full-length DNA sequences in a polymerase chain reaction (PCR), using techniques 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). Once a DNA sequence encoding a polypeptide is obtained, any of the above modifications may be readily introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis as taught, for example, by Adelman et al. (*DNA,* 2:183, 1983).

[0200] The breast tumor polypeptides disclosed herein may also be generated by synthetic or recombinant means. Synthetic polypeptides having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may be generated using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain (see, for example, Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963). Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, Calif.), and may be operated according to the manufacturer's instructions.

[0201] Alternatively, any of the above polypeptides may be produced recombinantly by inserting a DNA sequence that encodes the polypeptide into an expression vector and expressing the protein in an appropriate host. Any of a variety of expression vectors known to those of ordinary skill in the art may be employed to express recombinant polypeptides of this invention. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a polynucleotide that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line, such as CHO cells. The DNA sequences expressed in this manner may encode naturally occurring polypeptides, portions of naturally occurring polypeptides, or other variants thereof.

[0202] In general, regardless of the method of preparation, the polypeptides disclosed herein are prepared in an isolated, substantially pure, form (i.e., the polypeptides are homogenous as determined by amino acid composition and primary sequence analysis). Preferably, the polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. In certain preferred embodiments, described in more detail below, the substantially pure polypeptides are incorporated into pharmaceutical compositions or vaccines for use in one or more of the methods disclosed herein.

[0203] In a related aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, a polypeptide of the present invention and a known breast tumor antigen, together with variants of such fusion proteins.

[0204] A DNA sequence encoding a fusion protein of the present invention is constructed using known recombinant DNA techniques to assemble separate DNA sequences encoding the first and second polypeptides into an appropriate expression vector. The 3' end of a DNA sequence encoding the first polypeptide is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide so that the reading frames of the sequences are in phase to permit mRNA translation of the two DNA sequences into a single fusion protein that retains the biological activity of both the first and the second polypeptides.

[0205] A peptide linker sequence may be employed to separate the first and the second polypeptides by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene* 40:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA* 83:8258-8262, 1986; U.S. Pat. No. 4,935,233 and U.S. Pat. No. 4,751,180. The linker sequence may be from 1 to about 50 amino acids in length. Peptide sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

[0206] The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons require to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

[0207] Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. *New Engl. J. Med.,* 336:86-91 (1997)).

[0208] Polypeptides of the present invention that comprise an immunogenic portion of a breast tumor antigen may

generally be used for immunotherapy of breast cancer, wherein the polypeptide stimulates the patient's own immune response to breast tumor cells. The present invention thus provides methods for using one or more of the immunoreactive polypeptides encoded by a polynucleotide comprising a sequence of SEQ ID NO: 1-61, 63-175, 178 and 180 (or fusion proteins comprising one or more such polypeptides and/or DNA encoding such polypeptides) for immunotherapy of breast cancer in a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may be afflicted with a disease, or may be free of detectable disease. Accordingly, the above immunoreactive polypeptides (or fusion proteins or polynucleotides encoding such polypeptides) may be used to treat breast cancer or to inhibit the development of breast cancer. The polypeptides may be administered either prior to or following surgical removal of primary tumors and/or treatment by administration of radiotherapy and conventional chemotherapeutic drugs.

[0209] In these aspects, the polypeptide or fusion protein is generally present within a pharmaceutical composition and/or a vaccine. Pharmaceutical compositions may comprise one or more polypeptides, each of which may contain one or more of the inventive sequences (or variants thereof), and a physiologically acceptable carrier. The vaccines may comprise one or more such polypeptides and a non-specific immune response enhancer, wherein the non-specific immune response enhancer is capable of eliciting or enhancing an immune response to an exogenous antigen. Examples of non-specific-immune response enhancers include adjuvants, biodegradable microspheres (e.g., polylactic galactide) and liposomes (into which the polypeptide is incorporated). Pharmaceutical compositions and vaccines may also contain other epitopes of breast tumor antigens, either incorporated into a combination polypeptide (i.e., a single polypeptide that contains multiple epitopes) or present within a separate polypeptide.

[0210] Alternatively, a pharmaceutical composition or vaccine may contain DNA encoding one or more of the above polypeptides, such that the polypeptide is generated in situ. In such pharmaceutical compositions and vaccines, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter). Bacterial delivery systems involve the administration of a bacterium (such as Bacillus-Calmette-Gruerrin) that expresses an epitope of a breast tumor cell antigen on its cell surface. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., *PNAS* 86:317-321, 1989; Flexner et al., *Ann. N.Y Acad. Sci.* 569:86-103, 1989; Flexner et al., *Vaccine* 8:17-21, 1990; U.S. Pat. Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Pat. 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., *PNAS* 91:215-219, 1994; Kass-Eisler et al., *PNAS* 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 published PCT application WO 90/11092, and Ulmer et al., *Science* 259:1745-1749, 1993, reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

[0211] Routes and frequency of administration, as well as dosage, will vary from individual to individual and may parallel those currently being used in immunotherapy of other diseases. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration) or orally. Between 1 and 10 doses may be administered over a 3-24 week period. Preferably, 4 doses are administered, at an interval of 3 months, and booster administrations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of polypeptide or DNA that is effective to raise an immune response (cellular and/or humoral) against breast tumor cells in a treated patient. A suitable immune response is at least 10-50% above the basal (ie., untreated) level. In general, the amount of polypeptide present in a dose (or produced in situ by the DNA in a dose) ranges from about 1 pg to about 100 mg per kg of host, typically from about 10 pg to about 1 mg, and preferably from about 100 pg to about 1 μg. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.01 mL to about 5 mL.

[0212] While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a lipid, a wax and/or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and/or magnesium carbonate, may be employed. Biodegradable microspheres (e.g., polylactic glycolide) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Pat. Nos. 4,897,268 and 5,075,109.

[0213] Any of a variety of non-specific immune response enhancers may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a nonspecific stimulator of immune response, such as lipid A, *Bordella pertussis* or *Mycobacterium tuberculosis*. Such adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, Mich.) and Merck Adjuvant 65 (Merck and Company, Inc., Rahway, N.J.).

[0214] Polypeptides disclosed herein may also be employed in adoptive immunotherapy for the treatment of cancer. Adoptive immunotherapy may be broadly classified into either active or passive immunotherapy. In active immu-

notherapy, treatment relies on the in vivo stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (for example, tumor vaccines, bacterial adjuvants, and/or cytokines).

[0215] In passive immunotherapy, treatment involves the delivery of biologic reagents 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 lymphocytes (for example, CD8+ cytotoxic T-lymphocyte, CD4+ T-helper, gamma/delta T lymphocytes, tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells, lymphokine-activated killer cells), B cells, or antigen presenting cells (such as dendritic cells and macrophages) expressing the disclosed antigens. The polypeptides disclosed herein may also be used to generate antibodies or anti-idiotypic antibodies (as in U.S. Pat. No. 4,918,164), for passive immunotherapy.

[0216] The predominant method of procuring adequate numbers of T-cells for adoptive immunotherapy is to grow immune T-cells in vitro. Culture conditions for expanding single antigen-specific T-cells to several billion in number with retention of antigen recognition in vivo are well known in the art. These in vitro culture conditions typically utilize intermittent stimulation with antigen, often in the presence of cytokines, such as IL-2, and non-dividing feeder cells. As noted above, the immunoreactive polypeptides described herein may be used to rapidly expand antigen-specific T cell cultures in order to generate sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast or B-cells, may be pulsed with immunoreactive polypeptides or polynucleotide sequence(s) may be introduced into: antigen presenting cells, using standard techniques well known in the art. For example, antigen presenting cells may be transfected or transduced with a polynucleotide sequence, wherein said sequence contains a promoter region appropriate for inducing expression, and can be expressed as part of a recombinant virus or other expression system. Several viral vectors may be used to transduce an antigen presenting cell, including pox virus, vaccinia virus, and adenovirus. Antigen presenting cells may be transfected with polynucleotide sequences disclosed herein by a variety of means, including gene-gun technology, lipid-mediated delivery, electroporation, osmotic shock, and particulate delivery mechanisms, resulting in efficient and acceptable expression levels as determined by one of ordinary skill in the art. For cultured T-cells to be effective in therapy, the cultured T-cells must be able to grow and distribute widely and to survive long term in vivo. Studies have demonstrated that cultured T-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. *Ibid*).

[0217] The polypeptides disclosed herein may also be employed to generate and/or isolate tumor-reactive T-cells, which can then be administered to the patient. In one technique, antigen-specific T-cell lines may be generated by in vivo immunization with short peptides corresponding to immunogenic portions of the disclosed polypeptides. The resulting antigen specific CD8+ CTL clones may be isolated from the patient, expanded using standard tissue culture techniques, and returned to the patient.

[0218] Alternatively, peptides corresponding to immunogenic portions of the polypeptides may be employed to generate tumor reactive T cell subsets by selective in vitro stimulation and expansion of autologous T cells to provide antigen-specific T cells which may be subsequently transferred to the patient as described, for example, by Chang et al. (*Crit. Rev. Oncol. Hematol.,* 22(3), 213, 1996). Cells of the immune system, such as T cells, may be isolated from the peripheral blood of a patient, using a commercially available cell separation system. The separated cells are stimulated with one or more of the immunoreactive polypeptides contained within a delivery vehicle, such as a microsphere, to provide antigen-specific T cells. The population of tumor antigen-specific T cells is then expanded using standard techniques and the cells are administered back to the patient.

[0219] In other embodiments, T-cell and/or antibody receptors specific for the polypeptides disclosed herein can be cloned, expanded, and transferred into other vectors or effector cells for use in adoptive immunotherapy. In particular, T cells may be transfected with the appropriate genes to express the variable domains from tumor specific monoclonal antibodies as the extracellular recognition elements and joined to the T cell receptor signaling chains, resulting in T cell activation, specific lysis, and cytokine release. This enables the T cell to redirect its specificity in an MHC-independent manner. See for example, Eshhar, Z., *Cancer Immunol Immunother,* 45(3-4):131-6, 1997 and Hwu, P., et al, *Cancer Res,* 55(15):3369-73, 1995. Another embodiment may include the transfection of tumor antigen specific alpha and beta T cell receptor chains into alternate T cells, as in Cole, D J, et al, *Cancer Res,* 55(4):748-52, 1995.

[0220] In further embodiments, syngeneic or autologous dendritic cells may be pulsed with peptides corresponding to at least an immunogenic portion of a polypeptide disclosed herein. The resulting antigen-specific dendritic cells may either be transferred into a patient, or employed to stimulate T cells to provide antigen-specific T cells which may, in turn, be administered to a patient. The use of peptide-pulsed dendritic cells to generate antigen-specific T cells and the subsequent use of such antigen-specific T cells to eradicate tumors in a murine model has been demonstrated by Cheever et al. ("Therapy With Cultured T Cells: Principles Revisited,"*Immunological Reviews,* 157:177, 1997). Additionally vectors expressing the disclosed polynucleotides may be introduced into stem cells taken from the patient and clonally propagated in vitro for autologous transplant back into the same patient.

[0221] In one specific embodiment, cells of the immune system, such as T cells, may be isolated from the peripheral blood of a patient, using a commercially available cell separation system, such as CellPro Incorporated's (Bothell, Wash.) CEPRATE™ system (see U.S. Pat. No. 5,240,856; U.S. Pat. No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). The separated cells are stimulated with one or more of the immunoreactive polypeptides contained within a delivery vehicle, such as a microsphere, to provide antigen-specific T cells. The population of tumor antigen-specific T cells is then expanded using standard techniques and the cells are administered back to the patient.

[0222] Additionally vectors expressing the disclosed polynucleotides may be introduced into stem cells taken from the

patient and clonally propagated in vitro for autologous transplant back into the same patient.

[0223] Polypeptides of the present invention may also, or alternatively, be used to generate binding agents, such as antibodies or fragments thereof, that are capable of detecting metastatic human breast tumors. Binding agents of the present invention may generally be prepared using methods known to those of ordinary skill in the art, including the representative procedures described herein. Binding agents are capable of differentiating between patients with and without breast cancer, using the representative assays described herein. In other words, antibodies or other binding agents raised against a breast tumor antigen, or a suitable portion thereof, will generate a signal indicating the presence of primary or metastatic breast cancer in at least about 20% of patients afflicted with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without primary or metastatic breast cancer. Suitable portions of such breast tumor antigens are portions that are able to generate a binding agent that indicates the presence of primary or metastatic breast cancer in substantially all (i.e., at least about 80%, and preferably at least about 90%) of the patients for which breast cancer would be indicated using the full length antigen, and that indicate the absence of breast cancer in substantially all of those samples that would be negative when tested with full length antigen. The representative assays described below, such as the two-antibody sandwich assay, may generally be employed for evaluating the ability of a binding agent to detect metastatic human breast tumors.

[0224] The ability of a polypeptide prepared as described herein to generate antibodies capable of detecting primary or metastatic human breast tumors may generally be evaluated by raising one or more antibodies against the polypeptide (using, for example, a representative method described herein) and determining the ability of such antibodies to detect such tumors in patients. This determination may be made by assaying biological samples from patients with and without primary or metastatic breast cancer for the presence of a polypeptide that binds to the generated antibodies. Such test assays may be performed, for example, using a representative procedure described below. Polypeptides that generate antibodies capable of detecting at least 20% of primary or metastatic breast tumors by such procedures are considered to be useful in assays for detecting primary or metastatic human breast tumors Polypeptide specific antibodies may be used alone or in combination to improve sensitivity.

[0225] Polypeptides capable of detecting primary or metastatic human breast tumors may be used as markers for diagnosing breast cancer or for monitoring disease progression in patients. In one embodiment, breast cancer in a patient may be diagnosed by evaluating a biological sample obtained from the patient for the level of one or more of the above polypeptides, relative to a predetermined cut-off value. As used herein, suitable "biological samples" include blood, sera and urine.

[0226] The level of one or more of the above polypeptides may be evaluated using any binding agent specific for the polypeptide(s). A "binding agent," in the context of this invention, is any agent (such as a compound or a cell) that binds to a polypeptide as described above. As used herein, "binding" refers to a noncovalent association between two separate molecules (each of which may be free (ie., in solution) or present on the surface of a cell or a solid support), such that a "complex" is formed. Such a complex may be free or immobilized (either covalently or noncovalently) on a support material. The ability to bind may generally be evaluated by determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind" in the context of the present invention when the binding constant for complex formation exceeds about 10^3 L/mol. The binding constant may be determined using methods well known to those of ordinary skill in the art.

[0227] Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome with or without a peptide component, an RNA molecule or a peptide. In a preferred embodiment, the binding partner is an antibody, or a fragment thereof. Such antibodies may be polyclonal, or monoclonal. In addition, the antibodies may be single chain, chimeric, CDR-grafted or humanized. Antibodies may be prepared by the methods described herein and by other methods well known to those of skill in the art.

[0228] There are a variety of assay formats known to those of ordinary skill in the art for using a binding partner to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In a preferred embodiment, the assay involves the use of binding partner immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a second binding partner that contains a reporter group. Suitable second binding partners include antibodies that bind to the binding partner/polypeptide complex. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding partner after incubation of the binding partner with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding partner is indicative of the reactivity of the sample with the immobilized binding partner.

[0229] The solid support may be any material known to those of ordinary skill in the art to which the antigen may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or 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. Pat. No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the antigen and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent,

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

[0230] Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

[0231] In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a second antibody (containing a reporter group) capable of binding to a different site on the polypeptide is added. The amount of second antibody that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

[0232] More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, Mo.). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (i.e., incubation time) is that period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with breast 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.

[0233] Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include enzymes (such as horseradish peroxidase), substrates, cofactors, inhibitors, dyes, radionuclides, luminescent groups, fluorescent groups and biotin. The conjugation of antibody to reporter group may be achieved using standard methods known to those of ordinary skill in the art.

[0234] The second antibody 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 second antibody is then removed and bound second antibody is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

[0235] To determine the presence or absence of breast cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without breast cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for breast cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (i.e., sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (i.e., the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for breast cancer.

[0236] In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the antibody is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized antibody as the sample passes through the membrane. A second, labeled antibody then binds to the antibody-polypeptide complex as a solution containing the second antibody flows through the membrane. The detection of bound second antibody may then be performed as described above. In the strip test format, one end of the membrane to which antibody is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second antibody and to the area of immobilized antibody. Concentration of second antibody at the area of immobilized antibody indicates the presence of breast cancer. Typically, the concentration of second antibody at that site generates a pattern, such as a line, that can be read visually. The absence of such

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

[0237] Of course, numerous other assay protocols exist that are suitable for use with the antigens or antibodies of the present invention. The above descriptions are intended to be exemplary only.

[0238] In another embodiment, the above polypeptides may be used as markers for the progression of breast cancer. In this embodiment, assays as described above for the diagnosis of breast cancer may be performed over time, and the change in the level of reactive polypeptide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, breast cancer is progressing in those patients in whom the level of polypeptide detected by the binding agent increases over time. In contrast, breast cancer is not progressing when the level of reactive polypeptide either remains constant or decreases with time.

[0239] Antibodies for use in the above methods may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In one such technique, an immunogen comprising the antigenic polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits; sheep and goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and 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.

[0240] Monoclonal antibodies specific for the antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

[0241] 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.

[0242] Monoclonal antibodies of the present invention may also be used as therapeutic reagents, to diminish or eliminate breast tumors. The antibodies may be used on their own (for instance, to inhibit metastases) or coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ^{90}Y, ^{123}I, ^{125}I, ^{131}I, ^{186}Re, ^{188}Re, ^{211}At, and ^{212}Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, *Pseudomonas exotoxin, Shigella toxin*, and pokeweed antiviral protein.

[0243] A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (e.g., a halide) on the other.

[0244] Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

[0245] It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, Ill.), 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. Pat. No. 4,671,958, to Rodwell et al.

[0246] Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the

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

[0247] It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

[0248] 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. Pat. No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Pat. 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. Pat. Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Pat. 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. Pat. No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

[0249] 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.

[0250] Diagnostic reagents of the present invention may also comprise DNA sequences encoding one or more of the above polypeptides, or one or more portions thereof. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify breast tumor-specific cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for a polynucleotide encoding a breast tumor protein of the present invention. The presence of the amplified cDNA is then detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes specific for a polynucleotide encoding a breast tumor protein of the present invention may be used in a hybridization assay to detect the presence of an inventive polypeptide in a biological sample.

[0251] As used herein, the term "oligonucleotide primer/probe specific for a polynucleotide" means an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to the polynucleotide in question. Oligonucleotide primers and/or probes which may be usefully employed in the inventive diagnostic methods preferably have at least about 10-40 nucleotides. In a preferred embodiment, the oligonucleotide primers comprise at least about 10 contiguous nucleotides of a polynucleotide comprising a sequence selected from SEQ ID NO: 1-61, 63-175, 178 and 180. Preferably, oligonucleotide probes for use in the inventive diagnostic methods comprise at least about 15 contiguous oligonucleotides of a polynucleotide comprising a sequence provided in SEQ ID NO: 1-61, 63-175, 178 and 180. Techniques for both PCR based assays and hybridization assays are well known in the art (see, for example, Mullis et al. *Ibid*; Ehrlich, *Ibid*). Primers or probes may thus be used to detect breast tumor-specific sequences in biological samples, including blood, urine and/or breast tumor tissue.

[0252] The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1

[0253] Isolation and Characterization of Breast Tumor Polypeptides

[0254] This Example describes the isolation of breast tumor polypeptides from a breast tumor cDNA library.

[0255] A cDNA subtraction library containing cDNA from breast tumor subtracted with normal breast cDNA was constructed as follows. Total RNA was extracted from primary tissues using Trizol reagent (Gibco BRL Life Technologies, Gaithersburg, Md.) as described by the manufacturer. The polyA+RNA was purified using an oligo(dT) cellulose column according to standard protocols. First strand cDNA was synthesized using the primer supplied in a Clontech PCR-Select cDNA Subtraction Kit (Clontech, Palo Alto, Calif.). The driver DNA consisted of cDNAs from two normal breast tissues with the tester cDNA being from three primary breast tumors. Double-stranded cDNA was synthesized for both tester and driver, and digested with a combination of endonucleases (MluI, MscI, PvuII, SalI and StuI) which recognize six base pairs DNA. This modification increased the average cDNA size dramatically compared with cDNAs generated according to Clontech's protocol. The digested tester cDNAs were ligated to two different adaptors and the subtraction was performed according to Clontech's protocol. The subtracted cDNAs were subjected to two rounds of PCR amplification, following the manufacturer's protocol. The resulting PCR products were subcloned into the TA cloning vector, pCRII (Invitrogen, San Diego, Calif.) and transformed into ElectroMax *E. coli* DH10B cells (Gibco BRL Life, Technologies) by electroporation. DNA was isolated from independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division (Foster City, Calif.) Automated Sequencer Model 373A.

[0256] Sixty-three distinct cDNA clones were found in the subtracted breast tumor-specific cDNA library. The determined one strand (5' or 3') cDNA sequences for the clones

are provided in SEQ ID NO: 1-61, 72 and 73, respectively. Comparison of these cDNA sequences with known sequences in the gene bank using the EMBL and GenBank databases (Release 97) revealed no significant homologies to the sequences provided in SEQ ID NO: 14, 21, 22, 27, 29, 30, 32, 38, 44, 45, 53, 72 and 73. The sequences of SEQ ID NO: 1, 3, 16, 17, 34, 48, 57, 60 and 61 were found to represent known human genes. The sequences of SEQ ID NO: 2, 4, 23, 39 and 50 were found to show some similarity to previously identified non-human genes. The remaining clones (SEQ ID NO: 5-13, 15, 18-20, 24-26, 28, 31, 33, 35-37, 40-43, 46, 47, 49, 51, 52, 54-56, 58 and 59) were found to show at least some degree of homology to previously identified expressed sequence tags (ESTs).

[0257] To determine mRNA expression levels of the isolated cDNA clones, cDNA clones from the breast subtraction described above were randomly picked and colony PCR amplified. Their mRNA expression levels in breast tumor, normal breast and various other normal tissues were determined using microarray technology (Synteni, Palo Alto, Calif.). Briefly, the PCR amplification products were arrayed onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed, and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. Data was analyzed using Synteni provided GEMTOOLS Software. Of the seventeen cDNA clones examined, those of SEQ ID NO: 40, 46, 59 and 73 were found to be over-expressed in breast tumor and expressed at low levels in all normal tissues tested (breast, PBMC, colon, fetal tissue, salivary gland, bone marrow, lung, pancreas, large intestine, spinal cord, adrenal gland, kidney, pancreas, liver, stomach, skeletal muscle, heart, small intestine, skin, brain and human mammary epithelial cells). The clones of SEQ ID NO: 41 and 48 were found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested, with the exception of bone marrow. The clone of SEQ ID NO: 42 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested except bone marrow and spinal cord. The clone of SEQ ID NO: 43 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of spinal cord, heart and small intestine The clone of SEQ ID NO: 51 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of large intestine. The clone of SEQ ID NO: 54 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of PBMC, stomach and small intestine. The clone of SEQ ID NO: 56 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of large and small intestine, human mammary epithelia cells and SCID mouse-passaged breast tumor. The clone of SEQ ID NO: 60 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of spinal cord and heart. The clone of SEQ ID NO: 61 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of small intestine. The clone of SEQ ID NO: 72 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of colon and salivary gland.

[0258] The results of a Northern blot analysis of the clone SYN18C6 (SEQ ID NO: 40) are shown in **FIG. 1**. A predicted protein sequence encoded by SYN18C6 is provided in SEQ ID NO: 62.

[0259] Additional cDNA clones that are over-expressed in breast tumor tissue were isolated from breast cDNA subtraction libraries as follows. Breast subtraction libraries were prepared, as described above, by PCR-based subtraction employing pools of breast tumor cDNA as the tester and pools of either normal breast cDNA or cDNA from other normal tissues as the driver. cDNA clones from breast subtraction were randomly picked and colony PCR amplified and their mRNA expression levels in breast tumor, normal breast and various other normal tissues were determined using the microarray technology described above. Twenty-four distinct cDNA clones were found to be over-expressed in breast tumor and expressed at low levels in all normal tissues tested (breast, brain, liver, pancreas, lung, salivary gland, stomach, colon, kidney, bone marrow, skeletal muscle, PBMC, heart, small intestine, adrenal gland, spinal cord, large intestine and skin). The determined partial cDNA sequences for these clones are provided in SEQ ID NO: 63-87. Comparison of the sequences of SEQ ID NO: 74-87 with those in the gene bank as described above, revealed homology to previously identified human genes. No significant homologies were found to the sequences of SEQ ID NO: 63-73.

[0260] Three DNA isoforms for the clone B726P (partial sequence provided in SEQ ID NO: 71) were isolated as follows. A radioactive probe was synthesized from B726P by excising B726P DNA from a pT7Blue vector (Novagen) by a BamHI/XbaI restriction digest and using the resulting DNA as the template in a single-stranded PCR in the presence of [α-32P]dCTP. The sequence of the primer employed for this PCR is provided in SEQ ID NO: 177. The resulting radioactive probe was used to probe a directional cDNA library and a random-primed cDNA library made using RNA isolated from breast tumors. Eighty-five clones were identified, excised, purified and sequenced. Of these 85 clones, three were found to each contain a significant open reading frame. The determined cDNA sequence of the isoform B726P-20 is provided in SEQ ID NO: 175, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 176. The determined cDNA sequence of the isoform B726P-74 is provided in SEQ ID NO: 178, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 179. The determined cDNA sequence of the isoform B726P-79 is provided in SEQ ID NO: 180, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 181.

Example 2

[0261] Isolation and Characterization of Breast Tumor Polypeptides Obtained by PCR-Based Subtraction Using SCID-Passaged Tumor RNA

[0262] Human breast tumor antigens were obtained by PCR-based subtraction using SCID mouse passaged breast tumor RNA as follows. Human breast tumor was implanted in SCID mice and harvested on the first or sixth serial passage, as described in patent application Ser. No. 08/556,659 filed Nov. 13, 1995, U.S. Pat. No. _____. Genes found to be differentially expressed between early and late passage

SCID tumor may be stage specific and therefore useful in therapeutic and diagnostic applications. Total RNA was prepared from snap frozen SCID passaged human breast tumor from both the first and sixth passage.

[0263] PCR-based subtraction was performed essentially as described above. In the first subtraction (referred to as T9), RNA from first passage tumor was subtracted from sixth passage tumor RNA to identify more aggressive, later passage-specific antigens. Of the 64 clones isolated and sequenced from this subtraction, no significant homologies were found to 30 of these clones, hereinafter referred to as: 13053, 13057, 13059, 13065, 13067, 13068, 13071-13073, 13075, 13078, 13079, 13081, 13082, 13092, 13097, 13101, 13102, 13131, 13133, 13119, 13135, 13139, 13140, 13146-13149, and 13151, with the exception of some previously identified expressed sequence tags (ESTs). The determined cDNA sequences for these clones are provided in SEQ ID NO: 88-116, respectively. The isolated cDNA sequences of SEQ ID NO: 117-140 showed homology to known genes.

[0264] In a second PCR-based subtraction, RNA from sixth passage tumor was subtracted from first passage tumor RNA to identify antigens down-regulated over multiple passages. Of the 36 clones isolated and sequenced, no significant homologies were found to nineteen of these clones, hereinafter referred to as: 14376, 14377, 14383, 14384, 14387, 14392, 14394, 14398, 14401, 14402, 14405, 14409, 14412, 14414-14416, 14419, 14426, and 14427, with the exception of some previously identified expressed sequence tags (ESTs). The determined cDNA sequences for these clones are provided in SEQ ID NO: 141-159, respectively. The isolated cDNA sequences of SEQ ID NO: 160-174 were found to show homology to previously known genes.

Example 3

[0265] Synthesis of Polypeptides

[0266] Polypeptides may be synthesized on an Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

[0267] From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

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atcctctacc tttcctgtcc ccagaggtat gagatagacc ccctggcctg gttcctgcac 120

tgtgctaggc ccacagtgga cacttccacc ttaatggaga ataggcccca tggagtggag 180

gtccctcctc catggcctgc aacccaatga ctatgggggt gacacaagtg acctctgccc 240

tgtgatggct caacaccatc acacgcaact gtccagacaa gccccctcaa cgggctgctg 300

t 301

<210> SEQ ID NO 15
<211> LENGTH: 259
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 15

gtcttgaaag tatttattgt ttaataattc tttctcccct cagccccatc cggccactct 60

ctctttctgc ttttctgatc atcctaaagg ctgaatacat cctcctcctg tgtggaggac 120

acgaagcaat actaaaatca atacactcga tcaggtcttc atcagatacc acgtcactgt 180

gggtagagtg ctaattttca acaaatgtgg tgttcttagg gccccacaag gtagtccttt 240

ctcaaggtcg ctgggccac 259

<210> SEQ ID NO 16
<211> LENGTH: 301
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 16

cgaggttgtt cacattttca aataaataat actccccgta agtaataact gcaaccaatc 60

agtgttattc agtgctatgc ctccttgtaa tgggtagtta ttaattattt tcagagcttt 120

ctggaaatac tgtcctaact ggctatgttt aggatctttg ttatctctga agacaaagaa 180

agaactagga ctcttaattt tggggtgctt cttgactctt agttgggaaa ctgaaaatat 240

ttccaacctt ttacccacgt caatggcata ttctgggaat caccaccacc accaccacta 300

c 301

<210> SEQ ID NO 17
<211> LENGTH: 301
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 17

gcccgggcag gtctggggcc tagggtggct ctttgcaaag ctgaggggca agctaaggaa 60

gccaggcagg tcaggggccc tttcggcctt ctcaagcctc cacctgagtt ctcgtcaatg 120

ccagtctccc tggtatgatt ggggacatta tcagagaaac atctaatagc gcacatctgg 180

gcacccacac tctgcttcag ttgcatccat cctcccaccc caaattcaac tcctgaccca 240

atacaaaaga ctttttaac caggatttct tcttgcagga aagctgactt ggaaacacgg 300

g 301

<210> SEQ ID NO 18
<211> LENGTH: 301
<212> TYPE: DNA

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<213> ORGANISM: Homo sapien

<400> SEQUENCE: 18

attacaggca cgtgccacca cacctagcta atttttgagc atggggctca aaggaactgc 60

tctctggggc atgtcagatt tcggatttgg ggctgcacac tgatactctc taagtggtgg 120

aggaacttca tcccactgaa attcctttgg catttggggt tttgtttttc tttttttcct 180

tcttcatcct cctccttttt taaaagtcaa cgagagcctt cgctgactcc accgaagaag 240

tgcaccactg gggaccaccc agtgccaggc gcccgtccag ggacacacac agtcttcact 300

g 301

<210> SEQ ID NO 19
<211> LENGTH: 301
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 19

agaatctctg cactgtcatc aggtacaaca aaagatcaaa cccctgtccc gatgttaact 60

ttttaactta aaagaatgcc agaaaaccca gatcaacact ttccagctac gagccgtcca 120

caaaggccac ccaaaggcca gtcagactcg tgcagatctt atttttaat agtagtaacc 180

acaatacaca gctctttaaa gctgttcata ttcttccccc attaaacacc tgccccgggc 240

ggccaagggc gaattctgca gatatccatc acactggcgg ccgctcgagc atgcatctag 300

a 301

<210> SEQ ID NO 20
<211> LENGTH: 290
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 20

aggtttttt ttttttttt ttttttttt tttttccctt tcaattcatt taatttcaac 60

aatctgtcaa aaaacagcca ataaacaaat actgaattac attctgctgg gttttttaaa 120

ggctctaaac tataaaaaca tcttgtgtct cccaccctga ccaccctgct acttttccat 180

ataccacagg ccacccataa acacaaagcc agggggtgaa gctgacatgg tctatttgga 240

gccagtaaac aggagggcga taagtcctga taagcactta tggacaatat 290

<210> SEQ ID NO 21
<211> LENGTH: 301
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 21

agaaaggtaa ctgccagcca ggcttgcatt gtttagccag aaattgctgc ttggttctag 60

actctttaaa aaaaaaaaat acccagggtt tgtcatcatt ttcagaggca gagtgccaaa 120

tatcacccaa agctcttgtg tctttttttt acccccttat tttattttta tttattaatt 180

ttttgtgcaa acatcaaatg tcactggtgt tcacagaagg ctttttgac tagccttaaa 240

ttcctgagtc aaaagattaa tcagattttc aggcagtgtt taatcaggtg ctttgtcctg 300

t 301

<210> SEQ ID NO 22

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<211> LENGTH: 301
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 22

gacgccatgc accctccggt aaccagcagc cgcctgtcca tcccccaaga ccggaaaggc 60

agcagcagcc cccgggagcc cagggctgtc ctcggtgcat ctggctgcag agggaaattg 120

atgaccttac acagcaacta gcggccatgc agtccttcac tgacaagttc caggaccttt 180

gaagttggag ccagcgtccg gagctgcagc caagcgagtt tcctccttat cctccttagc 240

cagggctttt tctcttccgc tgcatttgcc cccttcccaa cgcaattcaa agcagttgtg 300

a 301

<210> SEQ ID NO 23
<211> LENGTH: 381
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 23

cgaggtccag acagtggacc aagagatacg ctacataaat tggggtttca caattcttac 60

attatttgtc tgtcacagaa gagagctgct tatgattttg aaggggtcag ggagggtggg 120

agttggtaaa gagtagggta tttctataac agatattatt cagtcttatt tcctaagatt 180

ttgttgtaac ttaaggtatc ttgctacagt agacagaatt ggtaatagca acttttaaaa 240

ttgtcattag ttctgcaata ttagctgaaa tgtagtacag aaaagaatgt acatttagac 300

atttgggttc agttgcttgt agtctgtaaa tttaaaacag cttaatttgg tacaggttac 360

acatatggac ctcccgggcg g 381

<210> SEQ ID NO 24
<211> LENGTH: 214
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 24

aatgatgtaa aaattaatca acagggctgc cacttgcgaa tcccctccaa ggatgctgtg 60

caaagggtct cattggtcct gatgaataat cttgtgactg tacatattcc tgggtgcatg 120

tccacaaata ctgaggtata gcctgcatgc cactaaaaat aacaaaggtt tcaggggtgg 180

aaacattgtc caccacactg tcatgaccat cttt 214

<210> SEQ ID NO 25
<211> LENGTH: 302
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 25

gggggcactg agaactccct ctggaattct tgggggtgt tggggagaga ctgtgggcct 60

ggagataaaa cttgtctcct ctaccaccac cctgtaccct agcctgcacc tgtcctcatc 120

tctgcaaagt tcagcttcct tccccaggtc tctgtgcact ctgtcttgga tgctctgggg 180

agctcatggg tggaggagtc tccaccagag ggaggctcag gggactggtt gggccaggga 240

tgaatatttg agggataaaa attgtgtaag aagccaaaga aattggtagt agggggggaga 300

ac 302

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<210> SEQ ID NO 26
<211> LENGTH: 301
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 26

ttggagaacg cgctgacata ctgctcggcc acagtcagtg aagctgctgc atctccatta 60

tgttgtgtca gagctgcagc caggattcga atagcttcag ctttagcctt ggccttcgcc 120

agaactgcac tggcctctcc tgctgcctga tttatctgtg cagccttttc tgcttcggag 180

gccaggatct gggcctgttt cttcccttct gccacattga tggccgactc tcgggtcccc 240

tcagactcta gaactgtggc ccgtttccgc cgctctgcct ccacctgcat ctgcatagac 300

t 301

<210> SEQ ID NO 27
<211> LENGTH: 301
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 27

aaatcagtca tcacatctgt gaaaagagtg ctagttataa caaatgagat cacaaatttg 60

accattttat tagacaccct ctattagtgt taacagacaa agatgaaggt taagttgaaa 120

tcaaattgaa atcatcttcc ctctgtacag attgcaatat ctgataatac cctcaacttt 180

cttggtgcaa attaattgcc tggtactcac agtccagtgt taacaggcaa taatggtgtg 240

attccagagg agaggactag gtggcaggaa aataaatgag attagcagta tttgacttgg 300

a 301

<210> SEQ ID NO 28
<211> LENGTH: 286
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 28

ttttttttg cacaggatgc acttattcta ttcattctcc cccacccttc ccatatttac 60

atccttagag gaagagaggg gtaaggtgat aaagtaactg aaggaccgca agacgggtat 120

gtcccttgtt caccaaatgg tcaaagggtc aaagatcgga ggaggtcagg gggtaacgca 180

ggaacaggtg agggcgtttc gccctctctc cctctcccct tttcaacctc ttaatcactg 240

gctaactcgc gacctcatgg gttaattcgt aagcttacac gcgttg 286

<210> SEQ ID NO 29
<211> LENGTH: 301
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 29

gtcatgttct tgctcttcct tctttacaca tttgagttgt gccttctgtt cttaaagaga 60

ttttcctttg ttcaaaggat ttattcctac catttcacaa atccgaaaat aattgaggaa 120

acaggttaca tcattccaat tttgccttgg gtttgaagag tctctcatgg tggcacagtc 180

ctccagggta gctatgttgt tgggctcccc tacatcccag aagctcagag actttgtcaa 240

aggtgtgccg tccacccatt gccactgacc ctcgacaacc tggtctgaca gtccaataaa 300

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a 301

<210> SEQ ID NO 30
<211> LENGTH: 332
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 30

gagcagaatt gatgcctatg gctccaagtc aaatactgct aatctcattt attttcctgc 60

cacctagtcc tctcctctgg aatcacacca ttattgcctg ttaacactgg actgtgagta 120

ccaggcaatt aatttgcacc aagaaagttg agggtattat cagatattgc aatctgtaca 180

gagggaagat gatttcaatt tgatttcaac ttaaccttca tctttgtctg ttaacactaa 240

tagagggtgt ctaataaaat ggtcaaattt gtgatctcat ttgttataac tagcactctt 300

ttcacagatg tgatgactga tttccagcag ac 332

<210> SEQ ID NO 31
<211> LENGTH: 141
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 31

aaaggctatc aagtactttg aaggacagga aggaatgaac acacccaggt ggacgtttgg 60

tttcatttgc aggggttcag ggagggttgc aggggttcag ggagggctct tgtcccacaa 120

ccgggggaag ggagagggca c 141

<210> SEQ ID NO 32
<211> LENGTH: 201
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 32

gagctgatct cacagcacat acagaatgat gctactatgt agaccctcac tcccttggga 60

aatctgtcat ctaccttaaa gagagaaaaa agatggaaca taggcccacc tagtttcatc 120

catccaccta cataaccaac atagatgtga ggtccactgc actgatagcc agactgcctg 180

gggtaaacct tttcagggag g 201

<210> SEQ ID NO 33
<211> LENGTH: 181
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 33

tttcaaaaca ctcatatgtt gcaaaaaaca catagaaaaa taaagtttgg tgggggtgct 60

gactaaactt caagtcacag acttttatgt gacagattgg agcagggttt gttatgcatg 120

tagagaaccc aaactaattt attaaacagg atagaaacag gctgtctggg tgaaatggtt 180

c 181

<210> SEQ ID NO 34
<211> LENGTH: 151
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 34

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atgtcctgca cagtatagct tggacctctg ggcctgaacc agggtgagca tcaaggcccc 60

catttctcct caccacgggg tcgcttgtca gctccaagaa ccagtctggc cccactgaga 120

acttttcagt cgagggcctg atgaatcttg g 151

<210> SEQ ID NO 35
<211> LENGTH: 291
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 35

tctttagggc aaaatcatgt ttctgtgtac ctagcaatgt gttcccattt tattaagaaa 60

agctttaaca cgtgtaatct gcagtcctta acagtggcgt aattgtacgt acctgttgtg 120

tttcagtttg tttttcacct ataatgaatt gtaaaaacaa acatacttgt ggggtctgat 180

agcaaacata gaaatgatgt atattgtttt ttgttatcta tttattttca tcaatacagt 240

attttgatgt attgcaaaaa tagataataa tttatataac aggttttctg t 291

<210> SEQ ID NO 36
<211> LENGTH: 201
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 36

ctgatacaat tataataacg gttccctgaa ccttttagag tgcaattaag aacaaaaact 60

aaattttgtt tacatgaata tggaataaat acaataatca aaatatgact ctccctaaaa 120

gtgaaacaca caagccaatc cggaactgct gtgcgaaaga taaaatcgag aaaggcaagg 180

tttcggtagg aggacgcgat g 201

<210> SEQ ID NO 37
<211> LENGTH: 121
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 37

catcacactg gcggccgctc gagcatgcat ctagagggcc caattcgccc tataatgagt 60

cgtattacaa ttcactggcc gtcgttttac aacgtcgtga ctgggaaaac cctggcgtta 120

c 121

<210> SEQ ID NO 38
<211> LENGTH: 200
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 38

aaacatgtat tactctatat ccccaagtcc tagagcatga cctgcatgtt ggagatgttg 60

tacagcaatg tatttatcca gacatacata tatgatattt agagacacag tgattctttt 120

gataacacca cacatagaac attataatta cacacaaatt tatggtaaaa gaattaatat 180

gctgtctggt gctgctgtta 200

<210> SEQ ID NO 39
<211> LENGTH: 760
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

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<400> SEQUENCE: 39

gcgtggtcgt cggccgaggt cctgggctag acctaatggt ttattattgg tggagagaaa 60

gatctggaaa tacttgaggt tattacatac tagattagct tctaatgtga accatttttc 120

ttttaacagt gatcaaatta ttatttcgaa gttaatcgtt cccttggtgg ctgcatacac 180

atcgcattaa caaacatact gttgtatttt ttcccagttt tgtttggcta tgccaccaca 240

gtcatcccca gggtctatac atactatgtt tcaactgtat tatttgccat ttttggcatt 300

agaatgcttc gggaaggctt aaagatgagc cctgatgagg gtcaagagga actggaagaa 360

gttcaagctg aattaaagaa gaaagatgaa gaagtaagcc atggcactgt tgatctggac 420

caaaaaggca ctcaactagg aataaacact ctacagaggt ttctcagtgg ccccatctgt 480

gtgatatgcg gggctacaca aaaatagctt cttttgcttt gttctgttct tatacctgtc 540

tgtgatctga cttggggttg gtgtgaatgt agtagagaaa ggaagctgac agatgaatac 600

tgaacacagg taatcagttt ccttaattag gttgattata agctcctgaa aagcaggaac 660

tgtattttat aattttacct gtttctcccg tggtgtctag gatagtaagt gagcagagca 720

gtaaatactg tttggtttgt tcagacctgc ccgggcggcc 760

<210> SEQ ID NO 40
<211> LENGTH: 452
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 40

aatcactaaa gatattgact agagaatgct gtgtgctatt tcaattacat ttgtttttct 60

tttattaaca ggaattttga ttcttcaagg aagtggctca atttcaattt caggtgacca 120

ggtttatcgt gacttttcct tcttgtttac ttttcgctag gaaggggagt tgtaggggca 180

gattcaggta ttggaatagg aaaattacgt ctaaaccatg gaaatcttgg aaatggaatt 240

ggtggaagtg ggcgaaatgg atatgggtaa gggaacacaa aaaaccctga agctaattca 300

tcgctgtcac tgatacttct tttttctcgt tcctggtctt gagagactgg gaaaccaaca 360

gccactgcca agatggctgt gatcaggagg agaactttct tcatctcaaa cgtttcagtc 420

agttctttct ctcacctcgg ccgcgaccac gc 452

<210> SEQ ID NO 41
<211> LENGTH: 676
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 41

aatctttgaa tgccaagtct cttctgtact ttcttttatt aacatcatag tctttgcatc 60

aagatacata gcaatgatag caggtttctt tttaaagctt agtattaata ttaaatattt 120

ttccccattt aaattttaca ttacttgcca agaaaaaaaa aaaattaaaa ctcaagttac 180

ttgaagcctg gacacacttc catgattagc cgggctaggt aaaagttggt ggctttattc 240

ttcctgctct ataagcagat ccaggcccta gaaagatggg accagggtat ataattgttt 300

ttgaaaagtg tgctacaaaa atggatggcc tgttataagc caggatacaa agttaaggat 360

gggggtaagg gagggacatt ttcttccaga agaaaagaca gaatttctga agagtcccag 420

tccataattt tcccaaaatg gttggaggag agggtaaaat ctcaacatga gtttcaaagt 480

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actgtctctg tgaggggccg gtagatgcct tgctgaggag ggatggctaa tttggaccat 540

gccccatccc cagctaggag aatggaaatg gaaactttaa ttgcccagtg ggtgtgaaag 600

tgggctgaag cttggttggt actgaattct ctaagaggtt tcttctagaa acagacaact 660

cagacctgcc cgggcg 676

<210> SEQ ID NO 42
<211> LENGTH: 468
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 42

agcgtggtcg cggccgaggt ttggccggga gcctgatcac ctgccctgct gagtcccagg 60

ctgagcctca gtctccctcc cttggggcct atgcagaggt ccacaacaca cagatttgag 120

ctcagccctg gtgggcagag aggtagggat ggggctgtgg ggatagtgag gcatcgcaat 180

gtaagactcg ggattagtac acacttgttg attaatggaa atgtttacag atccccaagc 240

ctggcaaggg aatttcttca actccctgcc ccccagccct ccttatcaaa ggacaccatt 300

ttggcaagct ctatgaccaa ggagccaaac atcctacaag acacagtgac catactaatt 360

aaaaccccct gcaaagccca gcttgaaacc ttcacttagg aacgtaatcg tgtcccctat 420

cctacttccc cttcctaatt ccacagacct gcccgggcgg ccgctcga 468

<210> SEQ ID NO 43
<211> LENGTH: 408
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 43

atcatatcaa aacactatct tcccatctgt ttctcaatgc ctgctacttc ttgtagatat 60

ttcatttcag gagagcagca gttaaacccg tggattttgt agttaggaac ctgggttcaa 120

acctctttcc actaattggc tatgtctctg gacagttttt ttttttttt ttttttttaa 180

acccttttctg aactttcact ttctatggct acctcaaaga attgttgtga ggcttgagat 240

aatgcatttg taaagggtct gccagatagg aagatgctag ttatggattt acaaggttgt 300

taaggctgta agagtctaaa acctacagtg aatcacaatg catttacccc cactgacttg 360

gacataagtg aaaactagcc cgaagtctct ttttcaaatt acttacag 408

<210> SEQ ID NO 44
<211> LENGTH: 160
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 44

tggtcgcggc cgaggtcttg tgtgccctgt ggtccagggg accaagaaca acaagatcca 60

ctctctgtgc tacaatgatt gcaccttctc acgcaacact ccaaccagga ctttcaacta 120

caacttctcc gctttggcaa acaccgtcac tcttgctgga 160

<210> SEQ ID NO 45
<211> LENGTH: 231
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 45

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cgagcggccg cccgggcagg tctggggagg tgattccatc cagagtcata tctgttgtca 60

ccccaataag tcgatcagca aggctgacag gctgtgagga aaccccggcc ttgtagcctg 120

tcacctctgg ggggatgatg actgcctggc agacgtaggc tgtgatagat ttgggagaaa 180

acctgactca ccctcaggaa tccggaggtc ggtgacattg tcggtgcaca c 231

<210> SEQ ID NO 46
<211> LENGTH: 371
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 46

cccgggcagg tctgtgtaac atgccaaggc tttgcacttt ctgcagagca gttttttatt 60

ttccttatca ggtacaggtt ttggtttttc ttgactatct ctgatgaatt tttcatgagt 120

ctgtatatgc agaatctttt ccctaaatac tgcttcgtcc catgtctgaa ggcgtaaaat 180

aaagtcattc atcatttttt ctttgtacat gtttatttgt tctttttcaa ttacaccaag 240

cattactagt cagaaggaag cacttgctac ctcttgctct tcctctgcct ctggtttgga 300

tcattttgat gacattgccc acattactca tgaaggatga caagattgca ctgtgcaatg 360

tcaattgcct t 371

<210> SEQ ID NO 47
<211> LENGTH: 261
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 47

gccctgtttt tatacacttc acatttgcag aaatataatg atgccctcat tatcagtgag 60

catgcacgaa tgaaagatgc tctggattac ttgaaagact tcttcagcaa tgtccgagca 120

gcaggattcg atgagattga gcaagatctt actcagagat ttgaagaaaa gctgcaggaa 180

ctagaaagtg tttccaggga tcccagcaat gagaatccta aacttgaaga cctctgcttc 240

atcttacaag aagagtacca c 261

<210> SEQ ID NO 48
<211> LENGTH: 701
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 48

cgagcggccc ccgggcaggt ccaattagta caagtctcat gatataatca ctgcctgcat 60

acatatgcac agatccagtt agtgagtttg tcaagcttaa tctaattggt taagtctcaa 120

agagattatt attcttgatg tttgctttgt attggctaac aaatgtgcag aggtaataca 180

tatgtgatgt ccgatgtctc tgtctttttt tttgtcttta aaaaataatt ggcagcaact 240

gtatttgaat aaaatgattt cttagtatga ttgtaccgta atgaatgaaa gtggaacatg 300

tttctttttg aaagggagag aattgaccat ttattattgt gatgtttaag ttataactta 360

ttgagcactt ttagtagtga taactgtttt taaacttgcc taataccttt cttgggtatt 420

gtttgtaatg tgacttattt aacccccttt tttgtttgtt taagttgctg ctttaggtta 480

acagcgtgtt ttagaagatt taaatttttt tcctgtctgc acaattagtt attcagagca 540

agagggcctg attttataga agccccttga aaagaggtcc agatgagagc agagatacag 600

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tgagaaatta tgtgatctgt gtgttgtggg aagagaattt tcaatatgta actacggagc 660

tgtagtgcca ttagaaactg tgaatttcca aataaatttg a 701

<210> SEQ ID NO 49
<211> LENGTH: 270
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 49

agcggccgcc cgggcaggtc tgatattagt agctttgcaa ccctgataga gtaaataaat 60

tttatgggcg ggtgccaaat actgctgtga atctatttgt atagtatcca tgaatgaatt 120

tatggaaata gatatttgtg cagctcaatt tatgcagaga ttaaatgaca tcataatact 180

ggatgaaaac ttgcatagaa ttctgattaa atagtgggtc tgtttcacat gtgcagtttg 240

aagtatttaa attaaccact cctttcacag 270

<210> SEQ ID NO 50
<211> LENGTH: 271
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 50

atgcatttat ccatatgaac ttgattattc tgaattactg actataaaaa ggctattgtg 60

aaagatatca cactttgaaa cagcaaatga attttcaatt ttacatttaa ttataagacc 120

acaataaaaa gttgaacatg cgcatatcta tgcatttcac agaagattag taaaactgat 180

ggcaacttca gaattatttc atgaagggta caaacagtct ttaccacaat tttcccatgg 240

tcttatcctt caaaataaaa ttccacacac t 271

<210> SEQ ID NO 51
<211> LENGTH: 241
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 51

tggtcgcggc cgaggtgtga ggagatgaac tttgtgttaa tgggggggcac tttaaatcga 60

aatggcttat ccccaccgcc atgtaagtta ccatgcctgt ctcctccctc ctacacattt 120

ccagctcctg ctgcagttat tcctacagaa gctgccattt accagccctc tgtgattttg 180

aatccacgag cactgcaggc cctccacagc gttactaccc agcaggcact cagctcttca 240

t 241

<210> SEQ ID NO 52
<211> LENGTH: 271
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 52

tccaagactt aaaacttagg aaacacctat gatgccactt taactggaag taatggagac 60

atctgattcc aaattcacat tttaaatgcc tatttgcaat cagcaaagag ccaggtatgc 120

tgcatgctgc ttgctgtaag ttacgatttg gcttcactag ctcaaatttt ttcactccac 180

caaaagataa ggcacaggcc cgtttgtcca atcaagtttg ctgaaaatac tgcagcctga 240

gtgtagacaa acttcccctg aatttgctag a 271

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<210> SEQ ID NO 53
<211> LENGTH: 493
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 53

ttagcgtggt cgcggtccga ggtctggcct gactagctca ctctgaagag tgtctttcac 60

atggattaac caaaaaatgc attactgcct ttggcacact gtcttgaata ttctttctga 120

caatgagaaa atatgattta atggagtcgt tcaataacct cacaatctcg ctgttccgag 180

cagatagttt tcgtgccaac aggaactggc acatctagca ggttcacggc atgacctttt 240

tgtggactgg ctggcataat tggaatgggt tttgattttt cttctgctaa taactcttca 300

agcttttgaa gttttcaagc attcctctcc agttgcctgt ggttggttct tgaacaccat 360

ctccaacccc accacctcca gatgcaacct tgtctcgtga tacagacctg cccgggcggc 420

cctcaagggc gaattctgca gatatccatc acactggcgg ccgctcgagc atgcatctag 480

agggcccaat tcg 493

<210> SEQ ID NO 54
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 54

cgtggtcgcg gccgaggtct gtttgcttgt tggtgtgagt ttttcttctg gagactttgt 60

actgaatgtc aataaactct gtgattttgt taggaagtaa aactgggatc tatttagcca 120

ctggtaagct tctgaggtga aggattcagg gacatctcgt ggaacaaaca ctccccactg 180

gactttctct ctggagatac ccttttgaat atacaatggc cttggctcac taggtttaaa 240

tacaaacaag tctgaaaccc actgaagact gagagattgc agcaatattc tctgaattag 300

gatcgggttc cataactcta a 321

<210> SEQ ID NO 55
<211> LENGTH: 281
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 55

ttgcaaatga aactgtggat gtataataag aaaacacaag ggtttattct taacactaaa 60

attaacatgc cacacgaaga ctgcattaca gctctctgtt tctgtaatgc agaaaaatct 120

gaacagccca ccttggttac agctagcaaa gatggttact tcaaagtatg gatattaaca 180

gatgactctg acatatacaa aaaagctgtt ggctggacct gtgactttgt tggtagttat 240

cacaagtatc aagcaactaa ctgttgtttc tccgaagatg g 281

<210> SEQ ID NO 56
<211> LENGTH: 612
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 56

gcgtggtcgc ggccgaggtc ctgtccgggg gcactgagaa ctccctctgg aattcttggg 60

gggtgttggg gagagactgt gggcctggag ataaaacttg tctcctctac caccaccctg 120

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taccctagcc tgcacctgtc ctcatctctg caaagttcag cttccttccc caggtctctg 180

tgccactctg tcttggatgc tctggggagc tcatgggtgg aggagtctcc accagaggga 240

ggctcagggg actggttggg ccagggatga atatttgagg gataaaaatt gtgtaagagc 300

caaagaattg gtagtagggg gagaacagag aggagctggg ctatgggaaa tgatttgaat 360

aatggagctg ggaatatggc tggatatctg gtactaaaaa agggtcttta agaacctact 420

tcctaatctc ttccccaatc caaaccatag ctgtctgtcc agtgctctct tcctgcctcc 480

agctctgccc caggctcctc ctagactctg tccctgggct agggcagggg aggagggaga 540

gcagggttgg gggagaggct gaggagagtg tgacatgtgg ggagaggacc agacctgccc 600

gggcggccgt cg 612

<210> SEQ ID NO 57
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 57

gtcgcggccg aggtcctgag cgtcacccta gttctgcccc tttttagctg tgtagacttg 60

gacaagacat ttgacttccc tttctccttg tctataaaat gtggacagtg gacgtctgtc 120

acccaagaga gttgtgggag acaagatcac agctatgagc acctcgcacg gtgtccagga 180

tgcacagcac aatccatgat gcgttttctc cccttacgca ctttgaaacc catgctagaa 240

aagtgaatac atctgactgt gctccactcc aacctccagc gtggatgtcc ctgtctgggc 300

ccttttctg ttttttattc tatgttcagc accactggca ccaaatacat tttaattcac 360

cga 363

<210> SEQ ID NO 58
<211> LENGTH: 750
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 58

cgtggtcgcg gccgaggtct aattccacct gactggcaga acctgcgccc ctcgcctaac 60

ctgcgccctt ctcccaactc gcgtgcctca cagaacccag gtgctgcaca gccccgagat 120

gtggcccttc ttcaggaaag agcaaataag ttggtccaag tacttgatgc ttaaggaata 180

cacaaaggtg cccatcaagc gctcagaaat gctgagagat atcatccgtg aatacactga 240

tgtttatcca gaaatcattg aacgtgcatg ctttgtccta gagaagaaat ttgggattca 300

actgaaagaa attgacaaag aagaacacct gtatattctc atcagtaccc ccgagtccct 360

ggctggcata ctgggaacga ccaaagacac acccaagctc ggtctcttct tggtgattct 420

gggtgtcatc ttcatgaatg gcaaccgtgc cagtgaggct gtcttttggg aggcactacg 480

caagatggga ctgcgtcctg gggtgagaca tcccctccct tggagatcta aggaaacttc 540

tcacctatga gtttgtaaag cagaaatacc tggactacag acgagtgccc aacagcaacc 600

ccccggagta tgagttcctc tggggcctcc gtccctacca tgagactagc aagatgaaaa 660

tgctgagatt cattgcagag gttcagaaaa gagaccctcg tgactggact gcacagttca 720

tggaggctgc agatgaggac ctgcccgggc 750

<210> SEQ ID NO 59

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<211> LENGTH: 505
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 59

tggccgcccg ggcaggtcca gtctacaagc agagcactct catggggagc accagatgag 60

ttccagccgc agttctttta taagctttaa gtgcctcatg aagacgcgag gatctcttcc 120

aagtgcaacc tggtcacatc agggcacatt cagcagcaga agtctgtttc cagtatagtc 180

cttggtatgg ctaaattcca ctgtcccttt ctcagcagtc aataatccat gataaattct 240

gtacaacact gtagtcaata acagcagcac cagacagcat attaattctt ttaccataaa 300

tttgtgtgta attataatgt tctatgtgtg gtgttatcaa aagaatcact gtgtctctaa 360

atatcatata tgtatgtctg gataaataca ttgctgtaca acatctccaa catgcaggtc 420

atgctctaag acttggggat atagagtaat acatgtttcg tggacctcgg ccgcgaccac 480

gctaagggcg aattctgcag atatc 505

<210> SEQ ID NO 60
<211> LENGTH: 520
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 60

cgtggtcgcg gccgaggtcc tcaggacaag gaaacaggta tcagcatgat ggtagcagaa 60

accttatcac caaggtgcag gagctgactt cttccaaaga gttgtggttc cgggcagcgg 120

tcattgcctg cccttgctgg agggctgatt ttagtgttgc ttattatgtt ggccctgagg 180

atgcttcgaa gtgaaaataa gaggctgcag gatcagcggc aacagatgct ctcccgtttg 240

cactacagct ttcacggaca ccattccaaa aaggggcagg ttgcaaagtt agacttggaa 300

tgcatggtgc cggtcagtgg gcacgagaac tgctgtctga cctgtgataa aatgagacaa 360

gcagacctca gcaacgataa gatcctctcg cttgttcact ggggcatgta cagtgggcac 420

gggaagctgg aattcgtatg acggagtctt atctgaacta cacttactga acagcttgaa 480

ggacctgccc gggcggccgc tcgaaagggg cgaattctgc 520

<210> SEQ ID NO 61
<211> LENGTH: 447
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 61

agagaggtgt ttttattctt tggggacaaa gccgggttct gtgggtgtag gattctccag 60

gttctccagg ctgtagggcc cagaggctta atcagaattt tcagacaaaa ctggaacctt 120

tctttttttcc cgttggttta tttgtagtcc ttgggcaaac caatgtcttt gttcgaaaga 180

gggaaaataa tccaaacgtt tttcttttaa ctttttttttt aggttcaggg gcacatgtgt 240

aggcttgcta tataggtaaa ttgcatgtca ccagggtttg ttgtacagat tatttcatca 300

tccagataaa aagcatagta ccagataggt agtttttttga tcctcaccct ccttccatgc 360

tccgacctca ggtaggcccc agtgtctgac ctgcccggcg gcccgctcga aagggccaat 420

tctgcagata tccatcacac tggccgg 447

<210> SEQ ID NO 62

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<211> LENGTH: 83
<212> TYPE: PRT
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 62

Lys Lys Val Leu Leu Leu Ile Thr Ala Ile Leu Ala Val Ala Val Gly
 1   5   10   15

Phe Pro Val Ser Gln Asp Gln Glu Arg Glu Lys Arg Ser Ile Ser Asp
            20   25   30

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

Phe Arg Pro Leu Pro Pro Ile Pro Phe Pro Arg Phe Pro Trp Phe Arg
    50   55   60

Arg Asn Phe Pro Ile Pro Ile Pro Ser Ala Pro Thr Thr Pro Leu Pro
65   70   75   80

Ser Glu Lys

<210> SEQ ID NO 63
<211> LENGTH: 683
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 63

acaaagattg gtagctttta tatttttta aaaatgctat actaagagaa aaaacaaaag 60

accacaacaa tattccaaat tataggttga gagaatgtga ctatgaagaa agtattctaa 120

ccaactaaaa aaaatattga aaccactttt gattgaagca aaatgaataa tgctagattt 180

aaaaacagtg tgaaatcaca ctttggtctg taaacatatt tagctttgct tttcattcag 240

atgtatacat aaacttattt aaaatgtcat ttaagtgaac cattccaagg cataataaaa 300

aaagwggtag caaatgaaaa ttaaagcatt tattttggta gttcttcaat aatgatrcga 360

gaaactgaat tccatccagt agaagcatct ccttttgggt aatctgaaca agtrccaacc 420

cagatagcaa catccactaa tccagcacca attccttcac aaagtccttc cacagaagaa 480

gtgcgatgaa tattaattgt tgaattcatt tcagggcttc cttggtccaa ataaattata 540

gcttcaatgg gaagaggtcc tgaacattca gctccattga atgtgaaata ccaacgctga 600

cagcatgcat ttctgcattt tagccgaagt gagccactga acaaaactct tagagcacta 660

tttgaacgca tctttgtaaa tgt 683

<210> SEQ ID NO 64
<211> LENGTH: 749
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(749)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 64

ctgttcattt gtccgccagc tcctggactg gatgtgtgaa aggcatcaca tttccatttt 60

cctccgtgta aatgttttat gtgttcgcct actgatccca ttcgttgctt ctattgtaaa 120

tatttgtcat ttgtatttat tatctctgtg ttttccccct aaggcataaa atggtttact 180

gtgttcattt gaacccattt actgatctct gttgtatatt tttcatgcca ctgctttgtt 240

ttctcctcag aagtcgggta gatagcattt ctatcccatc cctcacgtta ttggaagcat 300

-continued

gcaacagtat ttattgctca gggtcttctg cttaaaactg aggaaggtcc acattcctgc 360

aagcattgat tgagacattt gcacaatcta aaatgtaagc aaagtaagtc attaaaaata 420

caccctctac ttgggcttta tactgcatac aaatttactc atgagccttc ctttgaggaa 480

ggatgtggat ctccaaataa agatttagtg tttattttga gctctgcatc ttancaagat 540

gatctgaaca cctctccttt gtatcaataa atagccctgt tattctgaag tgagaggacc 600

aagtatagta aaatgctgac atctaaaact aaataaatag aaaacaccag gccagaacta 660

tagtcatact cacacaaagg gagaaattta aactcgaacc aagcaaaagg cttcacggaa 720

atagcatgga aaaacaatgc ttccagtgg 749

<210> SEQ ID NO 65
<211> LENGTH: 612
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 65

acagcagcag tagatggctg caacaacctt cctcctaccc cagcccagaa aatatttctg 60

ccccacccca ggatccggga ccaaaataaa gagcaagcag gccccttca ctgaggtgct 120

gggtagggct cagtgccaca ttactgtgct ttgagaaaga ggaaggggat ttgtttggca 180

ctttaaaaat agaggagtaa gcaggactgg agaggccaga gaagatacca aaattggcag 240

ggagagacca tttggcgcca gtcccctagg agatgggagg agggagatag gtatgagggt 300

aggcgctaag aagagtagga ggggtccact ccaagtggca gggtgctgaa atgggctagg 360

accaacagga cactgactct aggtttatga cctgtccata cccgttccac agcagctggg 420

tgggagaaat caccattttg tgacttctaa taaaataatg ggtctaggca acagttttca 480

atggatgcta aaacgattag gtgaaaagtt gatggagaat tttaattcag gggaattagg 540

ctgataccat ctgaaaccat ttggcatcat taaaaatgtg acaacctggt ggctgccagg 600

gaggaagggg ag 612

<210> SEQ ID NO 66
<211> LENGTH: 703
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 66

tagcgtggtc gcggccgagg tacattgatg ggctggagag cagggttggc agcctgttct 60

gcacagaacc aagaattaca gaaaaaagtc caggagctgg agaggcacaa catctccttg 120

gtagctcagc tccgccagct gcagacgcta attgctcaaa cttccaacaa agctgcccag 180

accagcactt gtgttttgat tcttcttttt tccctggctc tcatcatcct gcccagcttc 240

agtccattcc agagtcgacc agaagctggg tctgaggatt accagcctca cggagtgact 300

tccagaaata tcctgaccca caaggacgta acagaaaatc tggagaccca agtggtagag 360

tccagactga gggagccacc tggagccaag gatgcaaatg gctcaacaag gacactgctt 420

gagaagatgg gagggaagcc aagacccagt gggcgcatcc ggtccgtgct gcatgcagat 480

gagatgtgag ctggaacaga ccttcctggc ccacttcctg atcacaagga atcctgggct 540

tccttatggc tttgcttccc actgggattc ctacttaggt gtctgccctc aggggtccaa 600

atcacttcag gacaccccaa gagatgtcct ttagtctctg cctgaggcct agtctgcatt 660

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tgtttgcata tatgagaggg tacctgcccg ggcggccgct cga 703

<210> SEQ ID NO 67
<211> LENGTH: 1022
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 67

cttgagaaag caggattgtt ttaagttcca agatttaaca aacttactgt tcagcatcat 60

attcaagcct aaaaggaaga taggattttc aagatatatt tccaacttct ttaacatggc 120

accatggatg aactgtttct cagcactgtg ctgcttcact tggaattaag gatgaattgg 180

gaggagacag tatgacatag gtgggtaggt tgggtggtga ggggaaccag ttctaatagt 240

cctcaactcc actccagctg ttcctgttcc acacggtcca ctgagctggc ccagtccctt 300

tcactcagtg tgtcaccaaa ggcagcttca aggctcaatg gcaagagacc acctataacc 360

tcttcacctt ctgctgcctc tttctgctgc cactgactgc catggccatc tgctatagcc 420

gcattgtcct cagtgtgtcc aggccccaga caaggaaggg gagccatggt gagactccaa 480

ttcccaggcc ttaatcctta accctagacc tgttgcctct agcatcattt atttatctac 540

ctacctaata gctatctacc agtcattaaa ccatggtgag attctaacca tgtctagcac 600

ctgatgctag agataatttt gttgaatccc ttcaattata aacagctgag ttagctggac 660

aaggactagg gaggcaatca gtattattta ttcttgaaca ccatcaagtc tagacttggt 720

ggcttcatat ttctatcata atccctgggg gtaagaaatc atatagcccc aggttgggaa 780

ggggaaaacg gtttgcaaca ttctcctcct tgtaggaggc gagctctgtc tcactagcta 840

tgcccctcca tcaattcacc ctatactcag atcagaagct gagtgtctga attacagtat 900

attttctaaa ttcctagccc ctgctggtga atttgccctc ccccgctcct ttgacaattg 960

tccccgtgtt cgtctccggg ccctgagact ggccctgctt atcttgctga ccttcatcct 1020

ct 1022

<210> SEQ ID NO 68
<211> LENGTH: 449
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 68

ccagatccat tttcagtggt ctggatttct ttttatttttc ttttcaactt gaaagaaact 60

ggacattagg ccactatgtg ttgttactgc cactagtgtt caagtgcctc ttgttttccc 120

agagatttcc tgggtctgcc agaggcccag acaggctcac tcaagctctt taactgaaaa 180

gcaacaagcc actccaggac aaggttcaaa atggttacaa cagcctctac ctgtcgcccc 240

agggagaaag gggtagtgat acaagtctca tagccagaga tggttttcca ctccttctag 300

atattcccaa aaagaggctg agacaggagg ttattttcaa ttttattttg gaattaaata 360

ctttttttccc tttattactg ttgtagtccc tcacttggat atacctctgt tttcacgata 420

gaaataaggg aggtctagag cttctattc 449

<210> SEQ ID NO 69
<211> LENGTH: 387
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(387)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 69

gcccttagcg tgggtcgcgg cncgangtct ggagcntatg tgatncctat ggtncncagg 60

cnnatactgc tantctcatt tattctcctg cnacctantc ctctnctctg gaatcacacc 120

attattgcct gttaacactg gactgtgagt accangcaat taatttgcac caanaaagtt 180

gagggtatta tcanatattg caatctgtac agagggaaga tgatttcaat ttgatttcaa 240

cttaaccttc atctttgtct gttaacacta atagagggtg tctaataaaa tggcaaattt 300

gngatctcat tnggtataac tacactcttt ttcacagatg tgatgactga atttccanca 360

acctgcccgg gcggncgntc naagggc 387

<210> SEQ ID NO 70
<211> LENGTH: 836
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 70

tattccattt acaaaataaa ttcagccctg cactttcttt agatgccttg atttccagaa 60

tggagcttag tgctactgaa taccctggcc acagagccac ctcaggatat tcttttctcc 120

accctagttt atttatttat agatatctgt ttacaaagtc tgtagtaaat cctgatgctg 180

accatctgaa atgtactttt tttctgaatg ctgtttcaat ctaaaatagc agcttttgag 240

aaaacaatga tgtaaattcc ttatgataaa aggatgattc tatatattct ttaatgatat 300

taaatatgcc gaagccaagc acacagtctt tctaaagtgt gtgtatgttt gtgtgaatgt 360

gaatgatact gatcttatat ctgttaaaag ttgttttaaa aagctgtggc atcccattgt 420

tcatatttgc caagtcttct gtaaagatgt ctaggacgaa atattttatg tgctaatgca 480

tgtatttgta aaccagattt gtttaccact caaaattaac ttgttttctt catccaaaaa 540

agtttatttc ttccacgtac ttaaattttc tgtgtgggta taatatagct ttctaatttt 600

tttctttcac aaaggcaggt tcaaaattct gttgaaagaa aaatgctttc tgaaactgag 660

gtataacacc agagcttgct gtttaaagga ttatatgatg tacatcagtt ctataaatgt 720

gctcagcagt ttaacatgtg aatcctgttt taaagtgctc agatttcaac tgtgtaagcc 780

attgatataa cgctgtaatt aaaaatgttt atatgaaaaa aaaaaaaaaa aaaaaa 836

<210> SEQ ID NO 71
<211> LENGTH: 618
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 71

gttgcagtga gctcaagtgt tgggtgtatc agctcaaaac accatgtgat gccaatcatc 60

tccacaggag caatttgttt acctttttt tctgatgctt tactaacttc atcttttaga 120

tttaaatcat tagtagatcc tagaggagcc agtttcagaa aatatagatt ctagttcagc 180

accacccgta gttgtgcatt gaaataatta tcattatgat tatgtatcag agcttctggt 240

tttctcattc tttattcatt tattcaacaa ccacgtgaca aacactggaa ttacaggatg 300

aagatgagat aatccgctcc ttggcagtgt tatactatta tataacctga aaaaacaaac 360

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aggtaatttt cacacaaagt aatagatatc atgacacatt taaaataggg cactactgga 420

acacacagat aggacatcca ggttttgggt caatattgta gacttttgg tggatgagat 480

atgcaggttg atrccagaag gacaacaaaa acatatgtca gatagaaggg aggagcaaat 540

gccaagagct ggagctgagg aagatcactg tgaaattcta tgtagtctag ttggctggat 600

gctagagcaa agaggtgg 618

<210> SEQ ID NO 72
<211> LENGTH: 806
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 72

tctacgatgg ccatttgctc attgtctttc ctctgtgtgt agtgagtgac cctggcagtg 60

tttgcctgct cagagtggcc cctcagaaca acagggctgg ccttggaaaa accccaaaac 120

aggactgtgg tgacaactct ggtcaggtgt gatttgacat gagggccgga ggcggttgct 180

gacggcagga ctggagaggc tgcgtgcccg gcactggcag cgaggctcgt gtgtccccca 240

ggcagatctg ggcactttcc caacccaggt ttatgccgtc tccagggaag cctcggtgcc 300

agagtggtgg gcagatctga ccatccccac agaccagaaa caaggaattt ctgggattac 360

ccagtccccc ttcaacccag ttgatgtaac cacctcattt tttacaaata cagaatctat 420

tctactcagg ctatgggcct cgtcctcact cagttattgc gagtgttgct gtccgcatgc 480

tccgggcccc acgtggctcc tgtgctctag atcatggtga ctcccccgcc ctgtggttgg 540

aatcgatgcc acggattgca ggccaaattt cagatcgtgt ttccaaacac ccttgctgtg 600

ccctttaatg ggattgaaag cacttttacc acatggagaa atatattttt aatttgtgat 660

gcttttctac aaggtccact atttctgagt ttaatgtgtt tccaacactt aaggagactc 720

taatgaaagc tgatgaattt tcttttctgt ccaaacaagt aaaataaaaa taaaagtcta 780

tttagatgtt gaaaaaaaaa aaaaaa 806

<210> SEQ ID NO 73
<211> LENGTH: 301
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(301)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 73

actctggtaa gcttgttgtt gtccaagtga agctccctca gatgaggcgt gttggccana 60

gagccattgt caacagcaga gatgctgttg aaactcaatc ccaacttagc caaattattc 120

agtcctttca ggctagctgc atcaactctg ctgattttgt tgccatcaag atgtaattcc 180

gtaagggaag gaggaagacc ttgaggaatg ctggygatat tggyatcagc aatgcggatg 240

tasgaagagc ttcttcmttc cctggaaagc cccattttca atyccttgag ctcttcakcg 300

g 301

<210> SEQ ID NO 74
<211> LENGTH: 401
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

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<400> SEQUENCE: 74

agtttacatg atccctgtaa cagccatggt ctcaaactca gatgcttcct ccatctgcca 60

agtgtgttct ggatacagag cacatcgtgg cttctggggt cacactcagc ttaggctgtg 120

ggtccacaga gcactcatct ggctgggcta tggtggtggt ggctctactc aagaagcaaa 180

gcagttacca gcacattcaa acagtgtatt gaacatcttt taaatatcaa agtgagaaac 240

aagaaggcaa cataataatg ttatcagaaa gatgttagga agtaaggaca gctgtgtaaa 300

gcttgaggct gaaaagtagc ttgccagctt catttctttg gtttcttggg tagtgggccg 360

ccggaacagc aagatgtgag gttctggttc atggatcata t 401

<210> SEQ ID NO 75
<211> LENGTH: 612
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 75

ttatttttca atttttattt tggttttctt acaaaggttg acattttcca taacaggtgt 60

aagagtgttg aaaaaaaaat tcaaattttt ggggagcgag ggaaggagtt aatgaaactg 120

tattgcacaa tgctctgatc aatccttctt tttctctttt gcccacaatt taagcaagta 180

gatgtgcaga agaaatggaa ggattcagct ttcagttaaa aaagaagaag aagaaatggc 240

aaagagaaag ttttttcaaa tttctttctt ttttaattta gattgagttc atttatttga 300

aacagactgg gccaatgtcc acaaagaatt cctggtcagc accaccgatg tccaaaggtg 360

caatatcaag gaagggcagg cgtgatggct tatttgtttt gtattcaatg attgtctttc 420

cccattcatt tgtcttttta gagcagccat ctacaagaac agtgtaagtg aacctgctgt 480

tgccctcagc aacaagttca acatcattag agccctgtag aatgacagcc tttttcaggt 540

tgccagtctc ctcatccatg tatgcaatgc tgttcttgca gtggtaggtg atgttctgag 600

aggcatagtt gg 612

<210> SEQ ID NO 76
<211> LENGTH: 844
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 76

ggctttcgag cggccgcccg ggcaggtctg atggttctcg taaaaacccc gctagaaact 60

gcagagacct gaaattctgc catcctgaac tcaagagtgg agaatactgg gttgacccta 120

accaaggatg caaattggat gctatcaagg tattctgtaa tatggaaact ggggaaacat 180

gcataagtgc caatcctttg aatgttccac ggaaacactg gtggacagat tctagtgctg 240

agaagaaaca cgtttggttt ggagagtcca tggatggtgg ttttcagttt agctacggca 300

atcctgaact tcctgaagat gtccttgatg tgcagcykgc attccttcga cttctctcca 360

gccgagcttc ccagaacatc acatatcact gcaaaaatag cattgcatac atggatcagg 420

ccagtggaaa tgtaaagaag gccctgaagc tgatggggtc aaatgaaggt gaattcaagg 480

ctgaaggaaa tagcaaattc acctacacag ttctggagga tggttgcacg aaacacactg 540

gggaatggag caaaacagtc tttgaatatc gaacacgcaa tgctgttcct tgacattgca 600

ccaccaatgt ccagaggtgc aatgtcaagg aacggcaggc gagatggctt atttgttttg 660

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tattcaatga ttgtcttgcc ccattcattt gtctttttgg agcagccatc gactaggaca 720

gagtaggtga acctgctgtt gccctcagca acaagttcca catcgttgga accctgcaga 780

agcacagcct tgttcaarct gcccgtctcc tcatccagat acctcggccg cgaccacgct 840

aatc 844

<210> SEQ ID NO 77
<211> LENGTH: 314
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 77

ccagtcctcc acttggcctg atgagagtgg ggagtggcaa gggacgtttc tcctgcaata 60

gacacttaga tttctctctt gtgggaagaa accacctgtc catccactga ctcttctaca 120

ttgatgtgga aattgctgct gctaccacca cctcctgaag aggcttccct gatgccaatg 180

ccagccatcc tggcatcctg gccctcgagc aggctgcggt aagtagcgat ctcctgctcc 240

agccgtgtct ttatgtcaag cagcatcttg tactcctggt tctgagcctc catctcgcat 300

cggagctcac tcag 314

<210> SEQ ID NO 78
<211> LENGTH: 548
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 78

accaagagcc aagtgttaca caggatattt taaaaataaa atgtttttgg aatcctcacc 60

tcccatgcta tcttctaaga taactacaaa tattcttcaa agatttaact gagttctgcc 120

aaggacctcc caggactcta tccagaatga ttattgtaaa gctttacaaa tcccaccttg 180

gccctagcga taattaggaa atcacaggca aacctcctct ctcggagacc aatgaccagg 240

ccaatcagtc tgcacattgg ttttgttaga tactttgtgg agaaaaacaa aggctcgtga 300

tagtgcagct ctgtgcctac agagagcctc ccttttggtt ctgaaattgc tgatgtgaca 360

gagacaaagc tgctatgggt ctaaaacctt caataaagta actaatgaca ctcaaggtcc 420

tgggactctg agacagacgg tggtaaaacc cacagctgcg attcacattt ccaatttatt 480

ttgagctctt tctgaagctg ttgcttccta cctgagaatt cccatttaga gagctgcaca 540

gcacagtc 548

<210> SEQ ID NO 79
<211> LENGTH: 646
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 79

accccgtcac tatgtgaata aaggcagcta gaaaatggac tcaattctgc aagccttcat 60

ggcaacagcc catattaaga cttctagaac aagttaaaaa aaatcttcca tttccatcca 120

tgcatgggaa aagggcttta gtatagttta ggatggatgt gtgtataata ataaaatgat 180

aagatatgca tagtgggggа ataaagcctc agagtccttc cagtatgggg aatccattgt 240

atcttagaac cgagggattt gtttagattg ttgatctact aatttttttc ttcacttata 300

tttgaatttt caatgatagg acttattgga aattggggat aattctgttg tggtattaaa 360

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taatattcat tttttaaaaa ctcatcttgg tattgagtta gtgcattgac ttccaatgaa 420

ttgacataag cccatatttc attttaacca gaaacaaaaa ctagaaaatg ttactcccta 480

aataggcaac aatgtatttt ataagcactg cagagattta gtaaaaaaca tgtatagtta 540

ctttagaaac aacttctgac acttgagggt tacccaatgg tctccttccc attctttata 600

tgaggtaaat gcaaaccagg gagccaccga ataaacagcc ctgagt 646

<210> SEQ ID NO 80
<211> LENGTH: 276
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(276)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 80

gtctgaatga gcttcnctgc gagatgganc ancataaccc agaantccaa aancntanng 60

aacgnnaaaa cccgntngaa caagnaaacn gcaactnacg gccgcctgnt gnagggcgag 120

gacgcccacc tctcctcctc ccagttctcc tctggatcgc agncatccan agatgtgacc 180

tcttccagcc gccaaatccg caccaaggtc atggatgtgc acgatggcaa ggtgggtgtc 240

cacccacgaa caggtccttc gcaccaagaa ctgagg 276

<210> SEQ ID NO 81
<211> LENGTH: 647
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 81

gtcctgcctt tcatcttttc tttaaaaaaa ataaatgttt acaaaacatt tccctcagat 60

tttaaaattc atggaagtaa taaacagtaa taaaatatgg atactatgaa aactgacaca 120

cagaaaaaca taaccataaa atattgttcc aggatacaga tattaattaa gagtgacttc 180

gttagcaaca cgtagacatt catacatatc cggtggaaga ctggtttctg agatgcgatt 240

gccatccaaa cgcaaatgct tgatcttgga gtaggrtaat ggccccagga tcttgcagaa 300

gctctttatg tcaaacttct caagttgatt gacctccagg taatagtttt caaggttttc 360

attgacagtt ggtatgtttt taagcttgtt ataggacaga tccagctcaa ccagggatga 420

cacattgaaa gaatttccag gtattccact atcagccagt tcgttgtgag ataaacgcag 480

atactgcaat gcattaaaac gcttgaaata ctcatcaggg atgttgctga tcttattgtt 540

gtctaagtag agagttagaa gagagacagg gagaccagaa ggcagtctgg ctatctgatt 600

gaagctcaag tcaaggtatt cgagtgattt aagaccttta aaagcag 647

<210> SEQ ID NO 82
<211> LENGTH: 878
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 82

ccttctttcc ccactcaatt cttcctgccc tgttattaat taagatatct tcagcttgta 60

gtcagacaca atcagaatya cagaaaaatc ctgcctaagg caaagaaata taagacaaga 120

ctatgatatc aatgaatgtg ggttaagtaa tagatttcca gctaaattgg tctaaaaaag 180

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aatattaagt gtggacagac ctatttcaaa ggagcttaat tgatctcact tgttttagtt 240

ctgatccagg gagatcaccc ctctaattat ttctgaactt ggttaataaa agtttataag 300

atttttatga agcagccact gtatgatatt ttaagcaaat atgttattta aaatattgat 360

ccttcccttg gaccaccttc atgttagttg ggtattataa ataagagata caaccatgaa 420

tatattatgt ttatacaaaa tcaatctgaa cacaattcat aaagatttct cttttatacc 480

ttcctcactg gccccctcca cctgcccata gtcaccaaat tctgttttaa atcaatgacc 540

taagatcaac aatgaagtat tttataaatg tatttatgct gctagactgt gggtcaaatg 600

tttccatttt caaattattt agaattctta tgagtttaaa atttgtaaat ttctaaatcc 660

aatcatgtaa aatgaaactg ttgctccatt ggagtagtct cccacctaaa tatcaagatg 720

gctatatgct aaaaagagaa aatatggtca agtctaaaat ggctaattgt cctatgatgc 780

tattatcata gactaatgac atttatcttc aaaacaccaa attgtcttta gaaaaattaa 840

tgtgattaca ggtagagaac ctcggccgcg accacgct 878

<210> SEQ ID NO 83
<211> LENGTH: 645
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 83

acaaacattt tacaaaaaag aacattacca atatcagtgg cagtaagggc aagctgaaga 60

ataaatagac tgagtttccg ggcaatgtct gtcctcaaag acatccaaac tgcgttcagg 120

cagctgaaac aggcttcttt cccagtgaca agcatatgtg gtcagtaata caaacgatgg 180

taaatgaggc tactacatag gcccagttaa caaactcctc ttctcctcgg gtaggccatg 240

atacaagtgg aactcatcaa ataatttaaa cccaaggcga taacaacgct atttcccatc 300

taaactcatt taagccttca caatgtcgca atggattcag ttacttgcaa acgatcccgg 360

gttgtcatac agatacttgt ttttacacat aacgctgtgc catcccttcc ttcactgccc 420

cagtcaggtt tcctgttgtt ggaccgaaag gggatacatt ttagaaatgc ttccctcaag 480

acagaagtga gaaagaaagg agaccctgag gccaggatct attaaacctg gtgtgtgcgc 540

aaaagggagg gggaaggcag gaatttgaaa ggataaacgt ctcctttgcg ccgaggaatc 600

aggaagcgtg actcacttgg gtctgggacg ataccgaaat ccggt 645

<210> SEQ ID NO 84
<211> LENGTH: 301
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(301)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 84

tctgatgtca atcacaactt gaaggatgcc aatgatgtac caatccaatg tgaaatctct 60

cctcttatct cctatgctgg agaaggatta gaaggttatg tggcagataa agaattccat 120

gcacctctaa tcatcgatga gaatggagtt catgggctgg tgaaaaatgg tatttgaacc 180

agataccaag ttttgtttgc cacgatagga atagctttta tttttgatag accaactgtg 240

aacctacaag acgtcttgga caactgaagn ttaaatatcc acanggttt attttgcttg 300

-continued

g 301

<210> SEQ ID NO 85
<211> LENGTH: 296
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(296)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 85

agcgtgggtc gcggcncgan gtagagaacc gactgaaacg tttgagatga agaaagttct 60

cctcctgatc acagccatct tggcagtggc tgttggtttc ccagtctctc aagaccagga 120

acgagaaaaa agaagtatca gtgacagcga tgaattagct tcagggtttt ttgtgttccc 180

ttacccatat ccatttcgcc cacttccacc aattccattt ccaagatttc catggtttan 240

acgtaatttt cctattccaa tacctgaatc tgcccctaca actccccttc ctagcg 296

<210> SEQ ID NO 86
<211> LENGTH: 806
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 86

tctacgatgg ccatttgctc attgtctttc ctctgtgtgt agtgagtgac cctggcagtg 60

tttgcctgct cagagtggcc cctcagaaca acagggctgg ccttggaaaa accccaaaac 120

aggactgtgg tgacaactct ggtcaggtgt gatttgacat gagggccgga ggcggttgct 180

gacggcagga ctggagaggc tgcgtgcccg gcactggcag cgaggctcgt gtgtccccca 240

ggcagatctg ggcactttcc caacccaggt ttatgccgtc tccagggaag cctcggtgcc 300

agagtggtgg gcagatctga ccatccccac agaccagaaa caaggaattt ctgggattac 360

ccagtccccc ttcaacccag ttgatgtaac cacctcattt tttacaaata cagaatctat 420

tctactcagg ctatgggcct cgtcctcact cagttattgc gagtgttgct gtccgcatgc 480

tccgggcccc acgtggctcc tgtgctctag atcatggtga ctccccccgcc ctgtggttgg 540

aatcgatgcc acggattgca ggccaaattt cagatcgtgt ttccaaacac ccttgctgtg 600

ccctttaatg ggattgaaag cacttttacc acatggagaa atatattttt aatttgtgat 660

gcttttctac aaggtccact atttctgagt ttaatgtgtt tccaacactt aaggagactc 720

taatgaaagc tgatgaattt tcttttctgt ccaaacaagt aaaataaaaa taaaagtcta 780

tttagatgtt gaaaaaaaaa aaaaaa 806

<210> SEQ ID NO 87
<211> LENGTH: 620
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 87

tttttgcatc agatctgaaa tgtctgagag taatagtttc tgttgaattt ttttttgttc 60

atttttctgc acagtccatt ctgtttttat tactatctag gcttgaaata tatagtttga 120

aattatgaca tccttcctct ttgttatttt cctcatgatt gctttggcta ttcaaagttt 180

attttagttt catgtaaatt tttgaattgt attttccatt attgtgaaaa tagtaccact 240

-continued

gcaattttaa taggaagttt attgaatcta tagattactt tggataatat ggcacttcaa 300

taatattcat gttttcaatt catagacaaa atattttaaa atttatttgt atcttttcta 360

atttttcctt tttttattgt aaagatttac ctccttggtt aatattttcc tcagaaattt 420

attatttaag gtatagtcaa taaaattttc ttcctctatt ttgtcagata gtttaagtgt 480

atgaaaccat agatatactt gtatgttaat tttatatttt gctaatttac tgagtgtatt 540

tattagttta gagaggtttt aatgtactgt ttatggtttt ttaaatataa gattacttat 600

tttttaaaaa aaaaaaaaaa 620

<210> SEQ ID NO 88
<211> LENGTH: 308
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(308)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 88

tagctgtgnt cagcaggccg aggtttttt ttttttgag atggagtctc gccctgtcac 60

ccaggctgga gtgcagtggc ctgatctcag ctcactgcaa gctccacctc ctggattcac 120

gctattctcc tgcctcagcc tcccaagtag ctgggactac aggcgcccgc caccacgccc 180

agctaattnt ttgnattttt agtacnagat gcggtttcat cgtgttagcc agcatggnct 240

cgatctcctg acctcgtgaa ctgcccgcct cggcctccca aagacctgcc cgggcnggcc 300

gctcgaaa 308

<210> SEQ ID NO 89
<211> LENGTH: 492
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(492)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 89

agcggccgcc cgggcaggtc tgttaagtaa catacatatc accttaataa aaatcaagat 60

gaaatgtttt agaaactatt ttatcaaaag tggctctgat acaaagactt gtacatgatt 120

gttcacagca gcactattaa tgccaaaaag tagacaaaac ctaaatgtcc attaactgat 180

aagcaaaatg tggtatatcc atacaatgga atattatgta gcccacaaca tggcatggag 240

tactacaaca tggatgagcc tcaaaaacgt tatgctaaat gaaaaaagtc agatatagga 300

aaccacatgt catatgatcc catttatatg aaatagccag aaaaggcaag tcatagaaac 360

aagatagatc ggaaaatggg ttggaggact acaaatggca ccagggatct ttgaagttga 420

tggaaatggt ctaaaatcag actgtggntg tggttgaaca agtctgtaaa tttaccaaaa 480

tgcgttaata ca 492

<210> SEQ ID NO 90
<211> LENGTH: 390
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature

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<222> LOCATION: (1)...(390)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 90

tcgagcggcc gcccgggcag gtacaagctt ttttttttt ttttttttt ttttctaaca 60

gttctctgtt ttattgcaat acagcaaagt ctggttaata ttaagngata tcaacataaa 120

gtattggtga ggagtctttt gtgacatttt ttaccatccc accttaaata tttctgtgca 180

aaanaatcca catcattgtt tggtancana ggatctctta aaaagttccc taanacactg 240

agggcataaa accaaacaaa ataaaataag gagtgatagg ctaaagcagt atcttcccct 300

ccatccacat ttgncaagca ttatattcta accaaaaaat gatcacacca ggccatgcaa 360

aactgtccaa tattaccgag aaaaaaccct 390

<210> SEQ ID NO 91
<211> LENGTH: 192
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 91

agcgtggtcg cggccgaggt ctgtcaatta atgctagtcc tcaggattta aaaaataatc 60

ttaactcaaa gtccaatgca aaaacattaa gttggtaatt actcttgatc ttgaattact 120

tccgttacga aagtccttca catttttcaa actaagctac tatatttaag gcctgcccgg 180

gcggccgctc ga 192

<210> SEQ ID NO 92
<211> LENGTH: 570
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(570)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 92

agcgtggtcg cggccgaggt ctgacaacta acaaagaagc aaaaactggc atcttggaca 60

tcctagtatt acacttgcaa gcaattagaa cacaaggagg gccaaggaaa aagtttagct 120

ttgaatcact tccaaatcta ctgattttga ggttccgcag tagttctaac aaaacttttc 180

agacaatgtt aactttcgat taagaaagaa aaaaacccca aacatcttca ggaattccat 240

gccaggttca gtctcttcca gtgagcccgc ttgctaaaag tccacgtgca ccattaatta 300

gctgggctgg cagcaccatg taaaaagaag cctattcacc accaaccaca cagactagac 360

atgtaaagta ggatcaagta atggatgaca accatggtcg tggaatatgg tcaatgagag 420

tcagaaaagt acaggcacca gtacaagcag cagataacag aattgacggg ccaaaggata 480

aaaataggct tatttaaata ggatgctaca gaacacatnc acttctaatt ggaagctgct 540

ttacactggg tggcattgna ccatatgcat 570

<210> SEQ ID NO 93
<211> LENGTH: 446
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(446)
<223> OTHER INFORMATION: n = A,T,C or G

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<400> SEQUENCE: 93

tcgagcggcc gcccgggcag gtccaggttt ttatttagtt gtgtaatctt ggacaagtta 60

cctaactttt ttgagtctga atatatttaa tctgcaaaat gagaatcatg ataatacgtc 120

ataggcttaa ttaggaggat taaatgaaat aatttatagg tggtgccatg gttacataca 180

agtattagta gttaattctt ttcctttgtt tacttttata gtataggttg gatgaaggtt 240

ccagtatagg caaaaatact acttgggggt aaagtagagt gtgatacttt atttgaaatg 300

ttccctgaat ctgatcttta ctttttgnta ctgctgcact acccaaatcc aaattttcat 360

cccaacattc ttggatttgt gggacagcng tagcagcttt tccaatataa tctatactac 420

atcttttctt actttggtgc ttttg 446

<210> SEQ ID NO 94
<211> LENGTH: 409
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 94

cgagcggccg cccgggcagg tccatcagct cttctgctta gaatacgagg cagacagtgg 60

agaggtcaca tcagttatcg tctatcaggg tgatgaccca agaaaggtga gtgagaaggt 120

gtcggcacac acgcctctgg atccacccat gcgagaagcc ctcaagttgc gtatccagga 180

ggagattgca aagcgccaga gccaacactg accatgttga aggcgttctc tccaggctgg 240

attcactgca ctcggaagaa ttctgcccag ggaatttagt gtgggggtac caggaccagt 300

ttgtcttgat cttgagaccc ccagagctgc tgcatccata gggtgttgca ggactacacc 360

tggcctgcct tgcagtcatt ctttcttata tgttgaccca tttgcccaa 409

<210> SEQ ID NO 95
<211> LENGTH: 490
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(490)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 95

tcgagcggcc gcccgggcag gtcctacttg tttgcagctt ccacacactg cacctaccta 60

ctacctctct tccatgctta actgggttta gaaaggtgag ctatgcgtag aagaactact 120

tgggatattc aagtgctgta tttgaacgat aagcctatag ataacagtct gaagctgcaa 180

gggagacttt gttagtacac tactataaac aggtaaacta cctgtttgta cttgatatag 240

tgcatatgaa atgactgatt taatacaaaa ctacagaaca tgcaaaattt tttctgagat 300

gttaagtatt acttcagtgg agaacaaaac ttacttaacc tttcgctaat gcatgtagta 360

ccagaaagca aacatggttt tagcttcctt tactcaaaat atgaacatta agtggttgtg 420

aattttgtct gccaagtggt tcagaaaata cattataaat aacctaagtt aaaaaaaaga 480

aactgngaac 490

<210> SEQ ID NO 96
<211> LENGTH: 223
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

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<400> SEQUENCE: 96

agcgtggtcg cggccgaggt ctggaagccc accctaggac ttgaatggca ccttgtcctt 60

tctctgccag taatgcaatc caacacaata tgctacaggg aaaacagaat ttccacggtg 120

ccgccctctg gtacaaggga aacagcacgc aaagcaaaag gccacagagg gctccctgag 180

aatccagtac aactaagcga ggacctgccc gggcggccgc tcg 223

<210> SEQ ID NO 97
<211> LENGTH: 527
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(527)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 97

tcgagcggcc gcccgggcag gtctgtgcag gagacactga agtgggtagt gtccataatc 60

tttttagcct gttgctgaaa ttccagttgt actccttcaa accaaaatgc ttacaggatc 120

atgggaaagc ctcggttgca gaaatcaaga caggcaagtg ggaagataac tcggctttga 180

ggttaaacag atctgggttc aaagcatagt ttcactctct gtcttgtgaa gtgtcctggg 240

tgaagtcatt tcctctcttg aatttcagag aggatgaaaa tataaaaagt ataataacta 300

tcttcataat ctttgtgagg attaaagaag acgaagtgtg tgaaaagcta agcacagagc 360

aggcattcta caataagtag ttattatttt tggaaccatc ccgnccctag ccccagccca 420

attaccttct cttagnctct tcatatcgaa ngccgtaatc ttgaccttct cttgcnactg 480

gattggtgct ggttgatgcc caaacttccc gagatgctgt ctgggaa 527

<210> SEQ ID NO 98
<211> LENGTH: 514
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(514)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 98

tcgagcggcc gcccgggcag gtctggctcc catggccctt ggggtggcct gactctgtca 60

ctattcctaa aaccttctag gacatctgct ccaggaagaa ctttcaacac caaaattcat 120

ctcaatttta cagatgggaa aagtgattct gagaccagac cagggtcagg ccaaggtcat 180

ccagcatcag tggctgggct gagactgggc ccagggaacc ctgtctgctc ctctttttcc 240

cagagctgtg agttctctag ccaaggctgc actcttgagg gagagccagg aagcatagct 300

gaggccatga caacctcact cttcacctga aaatttaacc cgtggcagag gatccaggca 360

catataggct tcggagccaa acaggacctc ggccgcgacc acgctaagcc gaattccagc 420

acactggcgg ccgttactag tggatcccga gcttnggtac caagcttggc gtaatcatgg 480

gcatagctgg ttcctggggt gaaaatggta tccg 514

<210> SEQ ID NO 99
<211> LENGTH: 530
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(530)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 99

tcgagcggcc gcccgggcag gtctgaagaa acaggtataa atttggcagc cagtaatttt 60

gacagggaag ttacagcttg catgacttta aatatgtaaa tttgaaaata ctgaatttcg 120

agtaatcatt gtgctttgtg ttgatctgaa aaatataaca ctggctgtcg aagaagcatg 180

ttcaaaaata tttaattcac ttcaaaatgt catacaaatt atggtggttt ctatgcaccc 240

ctaaagcttc aagtcattta gctcaggtac atactaaagt aatatattaa ttcttccagt 300

acagtggtgt ttcataccat tgacatttgc ataccctaga ataatttaag aaagacatgt 360

gtaatattca caatgttcag aaaagcaagc aaaaggtcaa ggaacctgct ttggttcttc 420

tggagatggn ctcatatcag cttcataaac attcattcta caaaatagta agctaaccat 480

ttgaacccca atttccagat taagcatatt ttctcataaa tnatgaagcc 530

<210> SEQ ID NO 100
<211> LENGTH: 529
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 100

agcgtggtcg cggccgaggt ccaggcacgg tggcttatgt gtgtaatccc agcacttggg 60

gaggctgagg gaggtggatc acttgagtcc aggagtttga gaccagtctg ggcaacatgg 120

cgaaacttca tcactaccaa agaagaaaaa aattagccag gtgtggtggt gtatgcctgt 180

agtcccagat actctggtgg ctgaggtgag aggatagctt gagcccagga aattgaggct 240

gcagtgaact atgattgcac tactgtgctc cagcttgggc aacagagtga gatcttgtct 300

ccaaaagtcc ttgaaggatt ttaggaagtt gttaaaagtc ttgaaacgat gtttgggggc 360

atgttagggt tcttgaatgt ttaattcctc taataactgc ttattcaaga gaagcatttc 420

tgactgggtg cggggcagtg gcttcatgcc ccataatccc agtactttgg gaggctgaag 480

caggaacatt gcttgagccc aggacttcaa gaacagcctg ggtaacata 529

<210> SEQ ID NO 101
<211> LENGTH: 277
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 101

tcgagcggcc gcccgggcag gtcgcaggaa gaggatggaa actgaggagt ccaggaagaa 60

gagggaacga gatcttgagc tggaaatggg agatgattat attttggatc ttcagaagta 120

ctgggattta atgaatttgt ctgaaaaaca tgataagata ccagaaatct gggaaggcca 180

taatatagct gattatattg atccagccat catgaagaaa ttggaagaat tagaaaaaga 240

agaagagctg agaacagacc tcggccgcga ccacgct 277

<210> SEQ ID NO 102
<211> LENGTH: 490
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 102

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gcgtggtcgc ggccgaggtc tgacggcttt gctgtcccag agccgcctaa acgcaagaaa 60

agtcgatggg acagttagag gggatgtgct aaagcgtgaa atcagttgtc cttaattttt 120

agaaagattt tggtaactag gtgtctcagg gctgggttgg ggtccaaagt gtaaggaccc 180

cctgccctta gtggagagct ggagcttgga gacattaccc cttcatcaga aggaattttc 240

ggatgttttc ttgggaagct gttttggtcc ttggaagcag tgagagctgg gaagcttctt 300

ttggctctag gtgagttgtc atgtgggtaa gttgaggtta tcttgggata aagggtcttc 360

tagggcacaa aactcactct aggtttatat tgtatgtagc ttatattttt tactaaggtg 420

tcaccttata agcatctata aattgacttc tttttcttag ttgtatgacc tgccccgggc 480

ggccgctcga 490

<210> SEQ ID NO 103
<211> LENGTH: 490
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 103

gagcggccgc ccgggcaggt ccaaaccagc ttgctcataa gtcattaacc aaatccatta 60

taggtaattt gttcagttca atgtttacaa ttcttatgga aaaaattagc aacacacaca 120

tttaaaacgt gtgcatttac ctttgcgtga gtgcttaaaa tacatatttc tatttcaaga 180

tgacatttaa aaattattct aatatatcag cagcaaaaat ataatttgca attacaaaaa 240

actaaactag aatccttaag ttattctcat gtttacagtt gtgattcttt aataaatact 300

attatgcagc tctattgttt aagctttctg gatttggttt aaacacatgc atatatattg 360

tcaattgtgg gaagctttac aagttatatt ccatgcactt tttggacaga gttctaacag 420

agccagccag tccacaaaac aggcaagaca aaagttgaat taactggggc aaaataggac 480

tcttatgcaa 490

<210> SEQ ID NO 104
<211> LENGTH: 489
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 104

cgtggtcgcg gccgaggtcc aggctggtct cgaactcctg accttgtgat ctgcccgcct 60

cggcctccca aagtgttggg attacaggca tgagccactg cgcccgaccg agttgaacat 120

ttaatgtcag actaggccag agtttctcaa tctttttatt ctcacttccc aaaggagccg 180

ttggagattt tcccctcaat ctctctcctt catgaaattt cataccacaa atatagtatg 240

ttttatttat gtactgtgac cctttgaagg atcacaaacc aatataatag tttttctttt 300

taacccgtca aggaccaagt ttttgccoct gttggaaatg cataaactgg actgatgaat 360

tggtatagat ggcttttatc atgaggatca gaaaaacttg aaattccttg gctacgacac 420

tccatattta tcaccgtata gggaggacct tggtatgggg aagtagaaac acttctacac 480

tttacagca 489

<210> SEQ ID NO 105
<211> LENGTH: 479
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

-continued

<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(479)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 105

gcgtggtcgc ggccgaggtc tgactggctt cagccccaga agttgagctg gcctttagac 60

aaaataattg cacctccctc tgctgcttat tcccttccgt ttttcatttg agtgtgaaca 120

gttagataaa atctgtggct gnctcttcca ccttgctcta gtttccattg ctgtgagcag 180

gccctcctat gccccgcatt tagctacaat gctgtggact cacttgattc tttttctccg 240

agctttgtct agaaatatgt gaaggtgagg ttaagtgctt ctctgtgtag atccacttag 300

ccctgtctgc tgtctcgatg ggcgttgctt cgtctctcct ctcttccatc ctttccattt 360

gcttctcacc accttctggc ttcttttctt aatgcaataa aggcagtttc taacaaagaa 420

agaatgtggg ctttggagtt agacagacct ggntttaaat tctgcttctg gctctccaa 479

<210> SEQ ID NO 106
<211> LENGTH: 511
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 106

tcgcggccga ggtccaaaac gtggattcca atgacctgcc ttgagcccgc ggttgccagg 60

agttggacct gcagtagtat gggaagctca cggcctaaat accgactgcc ctctgacccc 120

accgtccagc gattctagaa catttctagt aggaaagaca tagcaaggga ttttcatgat 180

tgggaaatac tgggagacaa gctgaagatt tgttaagggc tatgcttctg tcatctttta 240

ggtatttaag gctactcctt tagctagcta ctttgagctg tttaaagtga ctatctccct 300

acacagagtt acacaatgag catctctgaa agagaatatt accctggatt tccaaagatg 360

tactctaaca ggatgaccag gcaaaaggtg acccgggggа ggagtctgtt ataacactcg 420

gacccacatg ttctcaaggc acttcagaac tttgggaaat cattttgtac cggatcctca 480

gaaagcattt atggaaatac acatccttta g 511

<210> SEQ ID NO 107
<211> LENGTH: 451
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 107

ggccgcccgg gcaggtccag aatatcaaat caaaaggtca caaatgttca cttcctcctc 60

caccctctta catattggat cttcaattgc aatagggagt gtaagatggg cattttagag 120

acgtagttgc atcagcagaa gcaaacccat cttatacaaa tgggttttgg ggataggaaa 180

aggctgctaa aaattcacaa gtcaccattc cccagaagca atgaatagcc gtagaagacc 240

aaggaagatc aacaagtttc caaagtgcta aagccagaga tttggccctt ccaaaatacc 300

accaggacgc ctggacccgt gggctctccg catgtcacca ctgactgcca ggatgctgct 360

gcacctccct tccttgagac acaacagaga gacagtgaag tcacccaaga ctgggatcat 420

cagaggctcc tcatgcttgc tacagagaag c 451

<210> SEQ ID NO 108
<211> LENGTH: 461

-continued

<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 108

ccgcccgggc aggtcctgaa aacattcaga ctaatcaaaa tggtactact gtaacttctt 60

ataatacata atataaaagt ttttgaaaga tatagacaca attaacccct aaacaacaca 120

ctatctgatt ctcaaaagca atggctattt aacaagatgt aaaaggacaa taacatatca 180

aagaactttc acacacctaa agatagcatt tagcagcaag ttagtcagac aaaacaaaca 240

caaatatttt cacatttcct atgtttgttt ttaactttac ttcataaagc cactgataat 300

tgaggtttct ttcaagtata agatttctaa aattaaaaac tgtttttgac atatttttat 360

aaagaaataa aaagcaaaac gcaatccaac tatttatatg agtccctctt ctccaacagc 420

tttagatggt tttctgagta ctttttttaca cagaatattt t 461

<210> SEQ ID NO 109
<211> LENGTH: 441
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 109

ggccgcccgg gcaggtctga ttataagaga aagaaatcca gtgacacgag ggcaggcagg 60

ccccgctctg ctctgatcga gaaaagcttc ctgatgtcag ggagatggaa ctgccaccat 120

cagaaccatg gcactttggg tgaaggtgtg tcagcgacca agggggcagg aaatgggcag 180

tgactaaggg ggcaggaaac aggcaggcac atggcaaggt tctcccagcc catcagccca 240

gtgatggcct cgattttgaa gctgcactac tgtctgaaaa gcacaattac tggtgactct 300

taacaaactt cagcatactg gggaaggaga ctgtcaagta actgaattgg aaagatgaaa 360

aagaaccatc tctaaaagtt gatgcttgtc agaagaataa cctcctttgt gcaagtcttg 420

caacatcttc attcaaccac a 441

<210> SEQ ID NO 110
<211> LENGTH: 451
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(451)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 110

ggtcgcggcc gaggtctggg gaaggggtga gaatccctgg gccttgccca gtcctgagct 60

ctgggtgtct gcagggaagc acagtggtga gttagtgtta aagaaagcat ccagagaggt 120

aagaggggct tgggtagcac cctttgcctc tgtcacttcc gcaaaaactt cttgttgagg 180

aggaagatga gaaggttgac attgactttg gccttgttga agagtttcat gacagccaca 240

ccctcatact ggagctgcan gagatcctga tagtgaagct tgaaatcgct ccatgtccac 300

acccaggaac ttggcattta cttcaaactt tcctgcctca tctcccggcg tgatgtcaaa 360

natgacgttt cttgaagtga gaggcgggaa agatcttcaa tttccaccaa agacaccctt 420

tttccaggaa gcttgagcaa caagtgtaat g 451

<210> SEQ ID NO 111
<211> LENGTH: 407

-continued

<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(407)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 111

ggccgacgtt cgacctgact tctttngagc agntgncact acccgtcttg aggaatgccg 60

actgcagaca gtggcccang gcaaagagtg tgcgtcatcg atganattgg naagatggag 120

ctcttcagtc agnttttcat tcaagctgnt cgtcagacgc tgtctacccc agggactata 180

atcctnggca caatcccagt tcctanagga aagccactgn ctcttgtaga agaaatcana 240

cacanaaagg atgtgaacng tgtttaatgt caccaaggga aaacatgaaa ccaccttctg 300

ccagatatcg ggacgttgcg tgcagatcaa gcacgnaagt gaagacgcgt gcattccttg 360

ccttccgtga acgantgccc agntcaagaa gancctgatg gaaccct 407

<210> SEQ ID NO 112
<211> LENGTH: 401
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(401)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 112

tcgcggccga ggtcggccga ggtctgacat ctgttgtctg tgataaccac ttctgtattg 60

cgtcttaacc acttctgtat tgtgtggttt taactgccta aggcggcaat gggcagtggg 120

ccccctttccc ttaggatggg tatcaattca acaatattta taaggcattt actgtgtgct 180

aagcatttgg aagacccagg ctacaaaata agacatagtt cctgccctcc aggccagcag 240

agggaggcac aaatacccag gaatctctga tgggtgtgaa gtgcggtcgt gggccacaga 300

aaatgaccgt catggagacc ctgctaaagg tcggaccctg agcccaaagg ggtattcaga 360

agnggagatg attttggccc cactcataga tgggtggcaa a 401

<210> SEQ ID NO 113
<211> LENGTH: 451
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 113

gtcgcggccg aggtccatat taaaaagtcc atcataaaca aagactcctc ctcatggtat 60

gaatatgctc catatgccca taatggtgca taacggactt agaaattcca atgagtctta 120

gggttgaaat ttccaatgac ctgagcaagg cagctcccta tagcttctgg ataacatttt 180

acacccagag ttcaggctta aacagaccta tcaacacaat tattttcgga ttgtctgtct 240

agaaaacggc aatgctcaaa ggaatataaa taagggtggg gggacatatg cttccagcct 300

ggcctttctc catgtggtaa aaaacaatgg aatggctgtg ttaatttttt tttaatcttt 360

tctgaccttt actatgtttg gtaatggaaa taagtcaggg aaaacaaaat gaacaggtct 420

catcacttaa ttaatactgg gttttcttct t 451

<210> SEQ ID NO 114
<211> LENGTH: 441

-continued

<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 114

ggccgcccgg gcaggtccat cctgtcagag atgggagaag tcacagacgg aatgatggat 60

acaaagatgg ttcactttct tacacactat gctgacaaga ttgaatctgt tcatttttca 120

gaccagttct ctggtccaaa aattatgcaa gaggaaggtc agcctttaaa gctacctgac 180

actaagagga cactgttgtt tacatttaat gtgcctggct caggtaacac ttacccaaag 240

gatatggagg cactgctacc cctgatgaac atggtgattt attctattga taaagccaaa 300

aagttccgac tcaacagaga aggcaaacaa aaagcagata agaaccgtgc ccgagtagaa 360

gagaacttct tgaaacttga cacatgtgca aagacaggaa gcagcacagt ctcggcggga 420

ggaagaaaaa aagaacagag a 441

<210> SEQ ID NO 115
<211> LENGTH: 431
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(431)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 115

gccgcccggg caggtccatt ggcggtgaca aaaggaaaag aagcaaagag actcagtcca 60

taatgctgat tagttagaag aaagggctag gattgagaaa gtaccaggaa cttttaatta 120

tttaaaagag aatgctgact gttaatgttt taaatcttac tgttcaaatg tactaatatg 180

aatttttacc ctttgtgcat gaatattcta aacaactaga agacctccac aatttagcag 240

ttatgaaagt taaacttttt attataaaaa ttctaaacct tactgctcct ttaccaggaa 300

catgacacac tatttancat cagttgcata cctcgccaat agtataattc aactgtcttg 360

cccgaacaat catctccatc tggaagacgt aagcctttag aaacacattt ttctattaat 420

ttctctagaa c 431

<210> SEQ ID NO 116
<211> LENGTH: 421
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 116

gtcgcggccg aggtccagaa atgaagaaga agtttgcaga tgtatttgca aagaagacga 60

aggcagagtg gtgtcaaatc tttgacggca cagatgcctg tgtgactccg gttctgactt 120

ttgaggaggt tgttcatcat gatcacaaca aggaaccggg gctcgtttat caccagtgag 180

gagcaggacg tgagcccccg ccctgcacct ctgctgttaa acaccccagc catcccttct 240

ttcaaaaggg atcctttcat aggagaacac actgaggaga tacttgaaga atttggattc 300

agcccgcgaa gagatttatc aagcttaact cagataaaat cattgaaagt aataaggtaa 360

aagctaagtc tctaacttcc aggcccacgg ctcaagtgaa tttcgaatac tgcatttaca 420

g 421

<210> SEQ ID NO 117
<211> LENGTH: 489

-continued

<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 117

agcgtggtcg cggccgaggt aaggctgcga ggttgtggtg tctgggaaac tccgaggaca 60

gagggctaaa tccatgaagt ttgtggatgg cctgatgatc cacagcggag accctgttaa 120

ctactacgtt gacactgctg tgcgccacgt gttgctcaga cagggtgtgc tgggcatcaa 180

ggtgaagatc atgctgccct gggacccaac tggtaagatt ggccctaaga agcccctgcc 240

tgaccacgtg agcattgtgg aacccaaaga tgagatactg cccaccaccc ccatctcaga 300

acagaagggt gggaagccag agccgcctgc catgccccag ccagtcccca cagcataaca 360

gggtctcctt ggcagacctg cccgggcggc cgctcgaaag cccgaattcc agcacactgg 420

cggccgttac tagtggatcc cagctcggta ccaagcttgg cgtaatcatg gtcatagctg 480

gtttcctgt 489

<210> SEQ ID NO 118
<211> LENGTH: 489
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 118

tcgagcggcc gcccgggcag gtattgaata cagcaaaatt ctatatacaa agtgacctgg 60

acctgctgct tcaaaacatg atcctttctt actaatatct tgatagtcgg tccatagagc 120

attagaaagc aattgactct taaataaaca gaaaagtgcc taatgcacat taaatgaatg 180

gcctaactac tggaacttta gtagttctat aaggtgatta acataggtag gatccagttc 240

ctatgacagg ctgctgaaga acagatatga gcatcaagag gccattttgt gcactgccac 300

cgtgatgcca tcgtgtttct ggatcataat gttcccatta tctgattcta gacacaccac 360

aggaatatca gtggggtcag aggttagctt agctgcttgc tgggctagaa cagatatcac 420

tccagcatgc tcatctgaca gggtcccgcg gcaacccaga ttaagtcctt gtgaatctgt 480

gcacaggga 489

<210> SEQ ID NO 119
<211> LENGTH: 181
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 119

taggttccag agacttttgg cccaggagga atatttactt ttagctctgg acatcattac 60

aaaaaggaat atttcccaaa cctcttcaga ccgagaatac atgggtaaaa ttattaaata 120

gttgtataat aaaaataatt ttttccttaa aaaaaaaaaa aacctcggcc gcgaccacgc 180

t 181

<210> SEQ ID NO 120
<211> LENGTH: 489
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(489)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 120

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gcgtggtcgc ggccgaggtc catttaaaac aaagaaaaat actaaagcca ctagtaaaca 60

tctgatgtgc aaaatacaac atcctctagt tggctttatg ccattattac ataagctcca 120

aatagctcat cttaaattaa aaagaaaaag tggctgtccc atctctgctg cataaatcag 180

attttttttt aaaggtttag agtactttaa ggaagggaag ttcaaaactg ccagtgaaat 240

tcacagagaa tacaaattta gcaatttaat ttcccaaagc tctttgaaga agcaagagag 300

tctctcttct taatgcagtg ttctcccaag aggaactgta attttgcttg gtacttatgc 360

tgggagatat gcaaaatgtg tttttcaatg tttgctagaa tataatggtt cctcttcagt 420

gnctggttca tcctggaact catgggttaa gaaggacttc ttggagccga actgcccggg 480

cgggccntt 489

<210> SEQ ID NO 121
<211> LENGTH: 531
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 121

cgagcggccg cccgggcagg tggccagcgc tggtcccgca gacgccgaga tggaggaaat 60

atttgatgat gcgtcacctg gaaagcaaaa ggaaatccaa gaaccagatc ctacctatga 120

agaaaaaatg caaactgacc gggcaaatag attcgagtat ttattaaagc agacagaact 180

ttttgcacat ttcattcaac ctgctgctca gaagactcca acttcacctt tgaagatgaa 240

accagggcgc ccacgaataa aaaaagatga gaagcagaac ttactatccg ttggcgatta 300

ccgacaccgt agaacagagc aagaggagga tgaagagcta ttaacagaaa gctccaaagc 360

aaccaatgtt tgcactcgat ttgaagactc tccatcgtat gtaaaatggg gtaaactgag 420

agattatcag gtcccgagga ttaaactggc tcatttcttt gtatgagaat ggcatcaatg 480

gtatccttgc agatgaaatg ggcctaggaa agactcttca acaatttctc t 531

<210> SEQ ID NO 122
<211> LENGTH: 174
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 122

tcgagcggcc gcccgggcag gtctgccaac agcagaggcg gggcctccgg catcttcaaa 60

gcacctctga gcaggctcca gccctctggc tgcgggaggg gtctggggtc tcctctgagc 120

tcggcagcaa agcagatgtt atttctctcc cgcgacctcg gccgcgacca cgct 174

<210> SEQ ID NO 123
<211> LENGTH: 531
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(531)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 123

agcgtggtcg cggccgaggt cctcaaccaa gagggttgat ggcctccagt caagaaactg 60

tggctcatgc cagcagagct ctctcctcgt ccagcaggcg ccatgcaagg gcaggctaaa 120

agacctccag tgcatcaaca tccatctagc anagagaaaa ggggcactga agcagctatg 180

-continued

tctgccaggg gctaggggct cccttgcaga cagcaatgct acaataaagg acacagaaat 240

gggggaggtg ggggaagccc tatttttata acaaagtcaa acagatctgt gccgttcatt 300

cccccagaca cacaagtaga aaaaaaccaa tgcttgtggt ttctgccaag atggaatatt 360

cctccttcct aanttccaca catggccgtt tgcaatgctc gacagcattg cactgggctg 420

cttgtctctg tggtctgggc accagtagct tgggccccat atacacttct cagttcccac 480

anggcttatg gccnangggc angctccaat tttcaagcac cacgaaggaa g 531

<210> SEQ ID NO 124
<211> LENGTH: 416
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 124

tcgagcggcc gcccgggcag gtccatctat actttctaga gcagtaaatc tcataaattc 60

acttaccaag cccaggaata atgactttta aagccttgaa tatcaactaa gacaaattat 120

gccaattctg atttctcaca tatacttaga ttacacaaag ataaagcttt agatgtgatc 180

attgtttaat gtagacttat ctttaaagtt tttaattaaa aactacagaa gggagtaaac 240

agcaagccaa atgatttaac caaatgattt aagagtaaaa ctcactcaga aagcattata 300

cgtaactaaa tatacatgag catgattata tacatacatg aaactgcaat tttatggcat 360

tctaagtaac tcatttaagt acatttttgg catttaaaca aagatcaaat caagct 416

<210> SEQ ID NO 125
<211> LENGTH: 199
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(199)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 125

agcgtggtcg cggccgaggt gctttttttt ttttttttt ttttttttt gctattctaa 60

aggggaaggc ccctttttat taaacttgta cattttactt tccttctttc anaatgctaa 120

taaaaaactt ttgtttatac ttaaaaaaac cataaatcan acaaacaaaa gaaacgattc 180

caacatcact tctgngatg 199

<210> SEQ ID NO 126
<211> LENGTH: 490
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 126

cgtggtcgcg gccgaggtcc agttgctcta agtggattgg atatggttgg agtggcacag 60

actggatctg ggaaaacatt gtcttatttg cttcctgcca ttgtccacat caatcatcag 120

ccattcctag agagaggcga tgggcctatt tgtttggtgc tggcaccaac tcgggaactg 180

gcccaacagg tgcagcaagt agctgctgaa tattgtagag catgtcgctt gaagtctact 240

tgtatctacg gtggtgctcc taagggacca caaatacgtg atttggagag aggtgtggaa 300

atctgtattg caacacctgg aagactgatt gacttttag agtgtggaaa aaccaatctg 360

agaagaacaa cctaccttgt ccttgatgaa gcagatagaa tgcttgatat gggctttgaa 420

-continued

ccccaaataa ggaagattgt ggatcaaata agacctgata ggcaaactct aatgtggagt 480

gcgacttggc 490

<210> SEQ ID NO 127
<211> LENGTH: 490
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 127

cgtggtcgcg gccgaggtcg gccgaggtct ggagatctga gaacgggcag actgcctcct 60

caagtgggtc cctgacccct gacccccgag cagcctaact gggaggcacc ccccagcagg 120

ggcacactga cacctcacac ggcagggtat tccaacagac ctgaagctga gggtcctgtc 180

tgttagaagg aaaactaaca agcagaaagg acagccacat caaaaaccca tctgtacatc 240

accatcatca aagaccaaaa gtaaataaaa ccacaaagat gggaaaaaaa cagaacagaa 300

aaactggaaa ctctaaaaag cagagcacct ctcctcttcc aaaggaacgc agttcctcac 360

cagcaatgga acaaagctgg atggagaatg actttgacga gctgagaaaa gaacgcttca 420

gacgatcaaa ttactctgag ctacgggagg acattcaaac caaaggcaaa gaagttgaaa 480

actttgaaaa 490

<210> SEQ ID NO 128
<211> LENGTH: 469
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(469)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 128

cgtggtcgcg gccgaggtgc ttttttttnt ttttttnttt ttttttnttt tgctgattta 60

ttttttctnt ttattgttac atacaatgta taaacacata aaacanaaaa cagtagggat 120

cctctaggat ctctagggan acagtaaagt anaaagaggt ctcanaaaca ttttttaaa 180

gtacaagaca ttcagngctc ggcccaaagg cgtaaaaggt ttanagccag canatagctg 240

nactaaaggc tccgtctntn tccccanagc caggacaacc ccagggagct ntccattagc 300

agccagtcca cgcaggcagg atgctgcgga aaaagctcta tgctganaac attccccttg 360

atggaaagaa gggcaacaca aaaggggtaa ctaanagctc cttcctctcg tgagggcgac 420

aactgaggaa cagaaaagga gtgtcccatg tcacttttga ccccctccc 469

<210> SEQ ID NO 129
<211> LENGTH: 419
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 129

gcgtggtcgc ggccgaggtc tgattttcat ttaaatattt cagagctata gcatttgcct 60

ccatgctcaa atccacacca ttggggctta agccgctcat gccaacatta gcaaatgaca 120

tgcagtttaa tccagagatc actgcttctg ggctgatgca tgccaacaca ctggcgtgat 180

ccacgttatg tgcatttttc ttcactttag tgggagaatc aatttttact ccaaggcttc 240

ttagttgctt aagagttgca ttaaggacac aatctttgtc caccagtctt gaatgatgtg 300

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tttttttctt tgtatggtaa acgttttggg ttctggtgca ttcatgactg ataattactg 360

ctttggtaga cggctgctca agtttccttg gaggaactat ttaataggtg ggttacttg 419

<210> SEQ ID NO 130
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 130

agcgtggtcg cggccgaggt ccatctgagg agataaccac atcactaaca aagtgggagt 60

gaccccgcag agcacgctgt ggaattccat agttggtctc atccctggtc agtttccaca 120

tgatgatggt cttatctcga gaggcggaga ggatcatgtc cgggaactgc ggggtagtag 180

cgatctgggt tacccagccg ttgtggccct tgagggtgcc acgaagggtc atctgctcag 240

tcatggcggc ggcgagagcg tgtgtcgctg cagcgacgag gatggcactg gatggcttag 300

agaaactagc accacaacct ctcctgccgc acctgcccgg gcggcccgct cgaa 354

<210> SEQ ID NO 131
<211> LENGTH: 474
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(474)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 131

cgagcggccg cccgggcagg tctggcagca gcttcctctg gaataattga cagctttgtg 60

ctgcctgact aaaatttgaa atgacaaccg ctgaatgtaa aatgatgtac ctacaatgag 120

agagatttag gaatactatc tgtcaatcca tagatgtaga aacaaaacaa actacagaat 180

gaaaacaaac ttattttaaa ccaaagaaac aaatgtatcc aaaatatagt ccatgatata 240

tttgattact agtataacca cagttgaaaa cttaaaaaaa aaaattgaca ttttttgtaa 300

tgggtactaa tggatttata aaaggtttct gtttccaaag atgttattgg ggtccacata 360

ttccttgaag acttcagcat cccaaagccc gacatcagag atactttcct ttagccattg 420

nttcccgtaa cttgcccact ccatggtgat gtgacaggct tcccttcatt agca 474

<210> SEQ ID NO 132
<211> LENGTH: 474
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(474)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 132

ggccgaggtg gggaattcat gtggaggtca gagtggaagc aggtgtgaga gggtccagca 60

gaaggaaaca tggctgccaa agtgtttgag tccattggca agtttggcct ggccttagct 120

gttgcaggag gcgtggtgaa ctctgcctta tataatgtgg atgctgggca cagagctgtc 180

atctttgacc gattccgtgg agtgcaggac attgtggtag gggaagggac tcattttctc 240

atcccgtggg tacagaaacc aattatcttt gactgccgtt ctcgaccacg taatgtgcca 300

gtcatcactg gtagcaaaga tttacagaat gtcaacatca cactgcgcat cctcttccgg 360

-continued

cctgtcgcca gccagcttcc tcgcatcttc accagcatcg ganaggacta tgatgaaccg 420

tgtgctgccg tccatcacaa ctgagatcct caagtcagtg gtggctcgct ttga 474

<210> SEQ ID NO 133
<211> LENGTH: 387
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 133

tgctcgagcg gccgccagtg tgatggatat ctgcagaatt cggcttagcg tggtcgcggc 60

cgaggtctgc gggcccctta gcctgccctg cttccaagcg acggccatcc cagtagggga 120

ctttcccaca ctgtgccttt acgatcagcg tgacagagta gaagctggag tgcctcacca 180

cacggcccgg aaacagcggg aagtaactgg aaagagcttt aggacagctt agatgccgag 240

tgggcgaatg ccagaccaat gatacccaga gctacctgcc gccaacttgt tgagatgtgt 300

gtttgactgt gagagagtgt gtgtttgtgt gtgtgttttg ccatgaactg tggccccagt 360

gtatagtgtt tcagtggggg agaactg 387

<210> SEQ ID NO 134
<211> LENGTH: 401
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 134

ggccgcccgg gcaggtctga tgaagaacac gggtgtgatc cttgccaatg acgccaatgc 60

tgagcggctc aagagtgttg tgggcaactt gcatcggctg ggagtcacca acaccattat 120

cagccactat gatgggcgcc agttccccaa ggtggtgggg ggctttgacc gagtactgct 180

ggatgctccc tgcagtggca ctggggtcat ctccaaggat ccagccgtga agactaacaa 240

ggatgagaag gacatcctgc gcttgtgctc acctccagaa ggaagttgct cctgagtgct 300

attgactctt gtcaatgcga ccttcaagac aggaggctac ctggtttact gcacctgttc 360

tatcacagtg agacctctgc catggcagaa cagggaagc t 401

<210> SEQ ID NO 135
<211> LENGTH: 451
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 135

ggtcgcggcc gaggtctgtt cctgagaaca gcctgcattg gaatctacag agaggacaac 60

taatgtgagt gaggaagtga ctgtatgtgg actgtggaga aagtaagtca cgtgggccct 120

tgaggacctg gactgggtta ggaacagttg tactttcaga ggtgaggtgt cgagaaggga 180

aagtgaatgt ggtctggagt gtgtccttgg ccttggctcc acagggtgtg ctttcctctg 240

gggccgtcag ggagctcatc ccttgtgttc tgccagggtg gggtaccggg gtttgacact 300

gaggagggta acctgctggc tggagcggca gaacagtggc cttgatttgt cttttggaag 360

attttaaaaa ccaaaaagca taaacattct ggtccttcac aatgctttct ctgaagaaat 420

acttaacgga aggacttctc cattcaccat t 451

<210> SEQ ID NO 136
<211> LENGTH: 411

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<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 136

ggccgcccgg gcaggtctga atcacgtaga atttgaagat caagatgatg aagccagagt 60

tcagtatgag ggttttcgac ctgggatgta tgtccgcgtt gagattgaaa atgttccctg 120

tgaatttgtg cagaactttg acccccttta ccccattatc ctgggtggct tgggcaacag 180

tgagggaaat gttggacatg tgcaggtggg tccctttgct gcgtatttgg tgcctgaggc 240

tctgtggatt tcccctccat caatcatctt accctctcat ccccctcaga tgcgtctgaa 300

gaaacatctc tggtataaga aaatcctcaa gtcccaagat ccaatcatat tttctgtagg 360

gtggaggaag tttcagacca tcctgctcta ttatatccga agaccacaat g 411

<210> SEQ ID NO 137
<211> LENGTH: 211
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(211)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 137

cggccgcccg ggcaggtcgg ttggtgcggc ctccattgtt cgtgttttaa ggcgccatga 60

ggggtgacag aggccgtggt cgtggtgggc gctttggttc cagaggaggc ccaggaggag 120

ggttcaggcc ctttgcacca catatcccat ttgacttcta tttgtgtgaa atggcctttc 180

cccggntcaa gccagcacct cgatgaaact t 211

<210> SEQ ID NO 138
<211> LENGTH: 471
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 138

gccgcccggg caggtctggg ctggcgactg gcatccaggc cgtaactgca aatctatgct 60

aggcggggtc tcccttctgt gtgttcaagt gttctcgact tggattctta actattttaa 120

aaaatgcact gagtttgggt taaaaaccaa ccaccaaaat ggatttcaac acagctctaa 180

agccaagggc gtggccggct ctcccaacac agcgactcct ggaggccagg tgcccatggg 240

cctacatccc ctctcagcac tgaacagtga gttgattttt ctttttacaa taaaaaaagc 300

tgagtaatat tgcataggag taccaagaaa ctgcctcatt ggaaacaaaa actatttaca 360

ttaaataaaa agcctggccg caggctgcgt ctgccacatt tacagcacgg tgcgatgcac 420

acggtgacca aaccacggag gcaagcttct ggcactcaca ccacgacccg c 471

<210> SEQ ID NO 139
<211> LENGTH: 481
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(481)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 139

gtcgcggccg aggtctgttc tttagctcag atttaaacct gctgtctctt ctttatttgc 60

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agaatgaatt cccagttcct gagcagttca agaccctatg gaacgggcag aagttggtca 120

ccacagtgac agaaattgct ggataagcga agtgccactg ggttctttgc cctcccttca 180

caccatggga taaatctgta tcaagacggt tcttttctag atttcctcta ccttttgct 240

cttaaaactg cttctctgct ctgagaagca cagctacctg ccttcactga aatatacctc 300

aggctgaaat ttggggtggg atagcaggtc agttgatctt ctgcaggaag gtgcagcttt 360

tccatatcag ctcaaccacg ccgncagtcc attcttaagg aactgccgac taggactgat 420

gatgcatttt agcttttgag cttttggggg gtattctacc aaccaacagt ccatttggaa 480

a 481

<210> SEQ ID NO 140
<211> LENGTH: 421
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(421)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 140

gtcgcggccg aggtttccca tttaagaaaa atagatcttg agattctgat tcttttccaa 60

acagtcccct gctttcatgt acagcttttt ctttacctta cccaaaattc tggccttgaa 120

gcagttttcc tctatggctt tgcctttctg attttctcag aggctcgagt ctttaatata 180

accccaaatg aaagaaccaa ggggaggggt gggatggcac tttttttgt tggtcttgtt 240

ttgttttgtt ttttggttgg ttgggttccg ttatttttta agattagcca ttctctgctg 300

ctatttccct acataatgtc aatttttaac cataattttg acatgattga gatgtacttg 360

aggctttttt gntttaattg agaaaagact ttgcaatttt ttttttagga tgagcctctc 420

c 421

<210> SEQ ID NO 141
<211> LENGTH: 242
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(242)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 141

cgantngccc gcccgggcan gtctgtctaa ntttntcang gaccacgaac agaaactcgt 60

gcttcaccga anaacaatat cttaaacatc gaanaattta aatattatga aaaaaaacat 120

tgcaaaatat aaaataaata nnaaaaggaa aggaaacttt gaaccttatg taccgagcaa 180

atccaggtct agcaaacagt gctagtccta nattacttga tntacaacaa cacatgaata 240

ca 242

<210> SEQ ID NO 142
<211> LENGTH: 551
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(551)
<223> OTHER INFORMATION: n = A,T,C or G

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<400> SEQUENCE: 142

agcgtggtcg cggcncgang tccacagggc anatattctt ttagtgtctg gaattaaaat 60

gtttgaggtt tangtttgcc attgtctttc caaaaggcca aataattcan atgtaaccac 120

accaagtgca aacctgtgct ttctatttca cgtactgttg tccatacagt tctaaataca 180

tgtgcagggg attgtagcta atgcattaca cagtcgttca gtcttctctg cagacacact 240

aagtgatcat accaacgtgt tatacactca actagaanat aataagcttt aatctgaggg 300

caagtacagt cctgacaaaa gggcaagttt gcataataga tcttcgatca attctctctc 360

caaggggccc gcaactaggc tattattcat aaaacacaac tgaanagggg attggtttta 420

ctggtaaatc atgtgntgct aaatcatttt ctgaacagtg gggtctaaat cantcattga 480

tttagtggca gccacctgcc cggcggccgn tcgaagccca attctgcaga tatccatcac 540

actggcggcc g 551

<210> SEQ ID NO 143
<211> LENGTH: 515
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(515)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 143

cgagnggccc gcccgggcag gtatcttcac aaactcaaca aaggcactac atgagacttc 60

acattcccct agtccaatag ctgacaaatt tttgcaacgt tctgcaatgc gaattaactc 120

ttcatcaagt ggccgtaatc catttgcaca cactactagt tcaaccagtc tagggcatgt 180

cattcccaca cggccaagca catctttgct tactgatctc ccaaagtaca gatgggtggc 240

aggtatttca tagcgaaaga aggggtcaaa ttcttcttca tataanaaaa aatacatcac 300

taagttcact ttgggtgaat gtctgatgaa agcatcccag ctactcttct gaatagtatg 360

gaagtgtgtc tgtccaggat tctcactgac tacatcaatg cgcaaatgtt ctaatcgaac 420

atgtttttca gaagacaatg caagtaacaa ctcatcactc aataagtggt aagttcaggg 480

ctagttctct taagccgnga cactgatcag cacac 515

<210> SEQ ID NO 144
<211> LENGTH: 247
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(247)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 144

tgcattctct ntggatgcan acctgcccgt tggtagggac tntgctcaca cggaacatgg 60

acggttacac ctgtgccgtg ggtgacgtcc accagcttct ggatcatctc ggcgngggtg 120

ttgtggaagg gcagactatc cacctccatg cncacgatgc ccganacgcc actccggact 180

ntgtgctgca ccaanatgcc cagcattnta tcttcaagca nagcacttat cagggtcctt 240

ggcacac 247

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<210> SEQ ID NO 145
<211> LENGTH: 309
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(309)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 145

cgtgggtcgc ggcccgangt ctgctgtaac aaaacaccat agtctgggca gctcatagac 60

aatggaattt tatttctcac gcttctggag gctggattcc aagatcaagg ttccaggaga 120

ctcagtgtct ggcaaggtct cggtttctgc ctcanagatg gtgccatctg gctgtgtcct 180

cacaagtagg aaggtgcaag aagctcccct caggctctgt ctgtaagaca ctgatcccat 240

tcatganggg gaaacgtaat gacctaatca gcccccagag accccacttc taacaccatc 300

accttgggg 309

<210> SEQ ID NO 146
<211> LENGTH: 486
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(486)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 146

agcgtgggtc gcggcncgac gtcctgtcca tatttcacag cccgagaact aatacaagat 60

gctgacatca tattttgtcc ctacaactat cttctanatg cacaaataag ggaaagtatg 120

gatttaaatc tgaaagaaca ggttgtcatt ttanatgaag ctcataacat cgaggactgt 180

gctcgggaat cagcaagtta cagtgtaaca gaagttcagc ttcggtttgc tcgggatgaa 240

ctanatagta tggtcaacaa taatataagg aaganagatc atgaacccct acgagctgtg 300

tgctgtagcc tcattaattg gntagaagca aacgctgaat atcttgnana angagantat 360

gaatcagctt gtaaaatatg gagtggaaat gaaatgctct taactttaca caaaatgggt 420

atcaccactg ctacttttcc cattttgcng gtaagatatn ttttctacct gngaaacgta 480

tttaag 486

<210> SEQ ID NO 147
<211> LENGTH: 430
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(430)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 147

gccgcccggg cangttcgac attacntnga gttccatgat gtacaattct ttcacgaaaa 60

acaatgaatg caagaatttg aggatctcct tactcctccc ttttacagat ggtctctcaa 120

tcccttcttc ttcctcttca tcttcatctt cttctgaacg cgctgccggg taccacggct 180

ttctttgtct ttatcgtgag atgaaggtga tgcttctgtt tcttctacca taactgaaga 240

aatttcgctg caagtctctt gactggctgt ttctccgact tcgcctttnt gtcaaacgng 300

agtcttttta cctcatgccc ctcagcttca cagcatcttc atctggatgt tnatttctca 360

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aagggctcac tgaggaaact tctgattcan atgtcgaana gcactgtgaa gttttctctt 420

cattttgctg 430

<210> SEQ ID NO 148
<211> LENGTH: 483
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(483)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 148

cccgggcagg tctgtgttgn tttncaaccg gtgtcctccc cagcgtccag aananggaaa 60

tgtggagcgg gtgatgatga cccctcgctg tcctgtcacc tcctgcacag cttcgtatgt 120

gggtctggtc tgggaccacc cgtacaggtt gtgcacgttg tagtgctcca cgggggagct 180

gtccggcagg atctgctgac tctccatgca cagagtcttg ctgctcaggc ccttgtccct 240

agattccaaa tatggcatat agggtggggt tatttagcat ttcattgctg cagcccctga 300

cagatccatc cacaaaattt gatggctcat tcatatcaat ccacaatcca tcaaacttca 360

agctcttctc tggntctcga nggtttgcat agaactcttc tatctctttc ttccaccacg 420

canacctcgg ncgcgaccac gctaagccga attctgcana tatccatcac actggcggcc 480

gct 483

<210> SEQ ID NO 149
<211> LENGTH: 439
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(439)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 149

ctttcacgaa nacaatgaat gcaagaattt gaggatctcc ttactcctcc cttttacaga 60

tggtctctca atcccttctt cttcctcttc atcttcatct tcttctgaac gcgctgccgg 120

gtaccacggc tttctttgtc tttatcgtga gatgaaggtg atgcttctgt ttcttctacc 180

ataactgaag aaatttcgct gcaagtctct tgactggctg tttctccgac ttcgcctttt 240

tgcaaacgtg agtcttttta cctcatgccc ctcagcttcc acagcatctt catctggatg 300

ttcatttctc aaagggctca ctgaggaaac ttctgactca catgtcgaag aagcactgng 360

agtttctctt catttgctgc aaanttgctc tttgctggct gngctctcag accacccatt 420

tggctgcatg ggggctgac 439

<210> SEQ ID NO 150
<211> LENGTH: 578
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(578)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 150

ggcncgcccg ggcangtcca ctccactttt gagctctgag ggaatacctt caggagggac 60

-continued

agggtcaggg agtcctggca gctccgcagc agagattcac attcattcag agacttgttg 120

tccagtgcaa tgccattgat cgcaacgatc ctgtctccca cagcaaggga cccttcttta 180

gcggcagggc ttccaggcag cacagcggca gcatacactc cattctccag actgatgcca 240

ctgtctttct gtccactgan gttgatgtgc agcggcgtga ccaccttccc acccagggac 300

ttcctccgcc gcacgaccat gttgatgggc cccctnccca ttgaggagcg ccttgatggc 360

ctgcttcttg nccttggtga tgaagtccac atcggtgatt ctcacagcca gtcattgacc 420

cttaagcggn catcagcaat gcttcctttg gccactttag ngacaaatat gccacagtcc 480

ccgggaaaca agggtcattc acaccttctg gcatatcaaa cacctcggcc gggancacta 540

agccgaattc tgcagatatc catcacactg gngggccg 578

<210> SEQ ID NO 151
<211> LENGTH: 503
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(503)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 151

cgagcggccc gcccgggcag gtctgggaga tcagcgactg ctgccacgtg cccagaaatg 60

gctcgtcctt tcactacagc ggaatgcaat gagggtgggt gagaagatga tgggtcggtt 120

atttcattcc ttttcttttt acaacttcac tttcagagac ttcagcgttc catgtctgct 180

gtgctgtgga acccagagtg ctcttgcctg gatggctgag aatcccttgg accctggaag 240

cacctactcc atgatggccc ggtatagtgc aggctcaata taatcttccc ggtatcttga 300

gttgataact cgttgccgtt tcttttcttg cttaacctct ttctctgtga aaatctcatt 360

gaagcgcatg tctgaagcta ctgacagtct anatttgact ctcttgggaa gctcttcatc 420

cagtgtgtat acatcatctc tcttaaccac aagttggagc catncttaaa cttcacctgg 480

tacatttgga tagggtggga ggc 503

<210> SEQ ID NO 152
<211> LENGTH: 553
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(553)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 152

agcgtggtcg cggcccgagg tccactgagc tccgccttcc ccgggctccc tgaggaagca 60

gagtcctgac ttccaggaag gacaggacac agaggcaaga actcagcctg tgaggctctg 120

ggtggctcct gaggccagag gacgccttcc gcgatccatg gctcagcatc gtccttctgg 180

cttcccagcc ccgggccgaa cgttcgggtt aataagcaga gcagttattc ggctcctggc 240

aggagctccc ccgttagttt ccacgttgtg agcacattca tacttaagac tgnttctctt 300

tgtgttttaa gcgtctgtct ctgtagtaaa ctgaaatgtt aacagaaatg cagacctgcc 360

cgggcggccg ctcgaaagcc gaattctgca gatatccatc acactggcgg ccgctcgagc 420

atgcatctag anggcccaat tcgccctata gtgagtcgna ttacaattca ctgggccgcg 480

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ntttacaacg tcgtgactgg gaaaaccctg cggtacccac ttaatcgcct tgcagnacat 540

ccccctttcg cca 553

<210> SEQ ID NO 153
<211> LENGTH: 454
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(454)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 153

tcgagcggct cgcccgggca ggtccaccta gcatggctcc tctaaacacg caactcagcg 60

aggggacccc cttcacctct ggcaagagag ctgggtagat cagaaacttg gtgacacctg 120

gctagcacag agcaggctca cttgtcttgg tcccactacc cagattcctg cagacattgc 180

aaaccaaatg aaggttgntg aatgacccct gtccccagcc acttgttttg gtatcatctg 240

ctctgcagtg gaatgcctgt gtgtttgagt tcactctgca tctgtatatt tgagtataga 300

aaccgantca agtgatctgt gcatncagac acactggggc acctgancac agaacaaatc 360

accttaacga tctggaatga aactgnganc antgcccgcc tgggtgggtc tgganaaact 420

gccgncttct tgttggacct tggccgcacc acct 454

<210> SEQ ID NO 154
<211> LENGTH: 596
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(596)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 154

agcgtggtcg cggcccgang gcggcctcct gantganggg aagggacgtg ggggcggcca 60

cggcaggatt aacctccatt tcagctaatc atgggagaga ttaaagtctc tcctgattat 120

aactggttta naggtacagt tccccttaaa aagattattg tggatgatga tgacagtaag 180

atatggtcgc tctatgacgc gggcccccga agtatcaggt gtcctctcat attcctgccc 240

cctgtcagtg gaactgcaga tgtctttttc cggcagattt tggctctgac tggatggggt 300

taccgggtta tcgctttgca gtatccagtt tattgggacc atctcgagtt cttgtgatgg 360

attcacaaaa cttttanacc atttacaatt ggataaagtt catcttttg gcgcttcttt 420

gggangcttt ttggcccana aatttgctga atacactcac aaatctccta gaagccattc 480

cctaatcctc tgcaattcct tcagngacac ctctatcttc aaccaacttg gactggaaac 540

agctttggct gatgcctgca tttatgctca aaaaatagtt cttggaaatt ttcatc 596

<210> SEQ ID NO 155
<211> LENGTH: 343
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(343)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 155

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ctcganttgg cncgcccggg cangtctgcc tggtttttga ccgngcgagc tatttagnct 60

ctggctctgt ttccggagct caaggnaaaa atcttgaana actcgagcag cttctgtgga 120

tagccttggg tacacatact gccgagcata gccaatgtac tttctcaata gctggtgggg 180

aatgggatct attgtttctc caggaaccac ctttagtctt tctgataatg gcttctcaga 240

aactacttca agtacggaag tatttgaatc ttgactatnc atacgagcta ctgtggcact 300

gctaatgggn tctctgctnt ccagctctta ttgcaatcac atg 343

<210> SEQ ID NO 156
<211> LENGTH: 556
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(556)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 156

tcgagcggcc cgcccgggca ggtctggcac cacncagatc gattaactgg ctcatctgat 60

ctcgtggccc ccaccctgga actgacttag cacaaaagga cacctcaatt ccttatgatt 120

tcatctccga cccaaccaat caacaccctt gactcactgg ccttcccct cccaccaaat 180

tatccttaaa aactctgatc cccgaatgct cagggagatc gatttgagta ctaataagac 240

tccagtctcc tgcacaagca gctctgtgta ctcttcctct attgcaattc ctgtcttgat 300

aaatcggctc tgtgtaggcg gcggaagaag tgaacctgtt gggcggttac cacctctgtc 360

gtgtgtgaca gttgntttga atctctaatt gctcagtaca gatccacatg caggttaagt 420

aagaagcttt tgaagaaaat ggaaagtctt aagtgatggc ttccaagaaa tcaaacctac 480

attaattagg gaacaacgga ctttacgtat cacaaatgaa gagactgacn aagtaaatca 540

acttggcctt ttctta 556

<210> SEQ ID NO 157
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(333)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 157

ggtccacaaa aatatatnaa ataagctgga tatataaaan caaacactta acatngncan 60

cattccttca gttattcaaa ctcactgata nctaacnggg agnagttggn attctggaag 120

acttcctaag ctaaaagtat atttacatat ttacaacaca ngtaaatata acngaagaac 180

tacttcaaat aangnngaaa ttccagaatt ctanagattt atagctatag ntnacaanta 240

tcaccaattg gtttgcaatc aanngnccag cactacttat gannaangtt taactannaa 300

accaaaaggg gagaaaacct ggnagggaaa nat 333

<210> SEQ ID NO 158
<211> LENGTH: 629
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature

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<222> LOCATION: (1)...(629)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 158

tcgagcggcc gcccgggcag gtctggtaca tttgtgcgag gtccggcact ctgttctcat 60

ccagtaagtg gtcgagccct ttctgcagaa ttgctgttaa atgttctcct aatagctgtt 120

tctccacaca agcaatcagt ggtttctgtg tgctgtggtc caagtaagtg attactctgt 180

ctccctcttc ttctaagcgt ttacttacat ggttaagata ttctggaacc tctctttcct 240

gcattaacct ttggccttcg gcagcatata agcaattagt ctcttccaaa aatttcagtt 300

caaatgaatc tttatacacc tgcaggtcag acagcatgcc caggnaggct ccgcaacagg 360

ctccggtcca cggcctcgcc gctcctctcg cgctcgatca gcagtaggat tccatcaatg 420

gttttactct gaaccatttt atcactaata atatgggttc taaacagttc taatcccata 480

tcccagatgg agggcagcgt ggagttctgc agcacatagg tgcggtccaa gaacaggaag 540

atgcttctga tcatgaatca tttgnctggc aatggtcctg ccagcacgtg gtaatctttc 600

ttttaaaaat aaacccttat ctaaacgtc 629

<210> SEQ ID NO 159
<211> LENGTH: 629
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(629)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 159

tcgagcggcc gcccgggcag gttctagagg ganaatctgg ctgatttggg aataaaatat 60

aatcgaatat tcaacaccat gaagataaat cttattttgg aaatctactg accttaatac 120

cccaagcttg ccctgaatac tttgattgga attggaatat atcaaaaaag gttagtattt 180

ttgttgtagt taggatacta aaaggatatt agttacccaa gagatccaat ttgtttttct 240

gatgaatagt gttcagtaaa atgaagcagt cttaagagtg actaataatt tcaaagtgat 300

ttttcgtcta ttcttaatat tttttaatta tttatttta agagttttat accttgagca 360

gatacaatga tccgctttag tgagaggaca atttctgatt gattgttttc tcttcaggcc 420

atctcacctc ttcattctct tgttacattt gaagcagttg atataatggg tttatacttt 480

aaaagataga catggtgcca tgaagtttgg ggaagttggg tgaattatcc cattctagtt 540

acagangagc tttccttaaa tgccctttac ttctangttt ggtcaagaag tcattttctg 600

agtaaaagtt attttcatat atgttgggg 629

<210> SEQ ID NO 160
<211> LENGTH: 519
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(519)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 160

tcgagcggcg cgcccgggca ggtctgctgg gattaatgcc aagttnttca gccataaggt 60

agcgaaatct agcagaatcc agattacatc cacttccaat cacgcggtgt ttgggtaatc 120

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cacttagttt ccagataaca tacgtaagaa tgtccactgg gttggaaacc acaattatga 180

tgcaatcagg actgtacttg acgatctgag gaataatgaa tttgaagaca ttaacatttc 240

tctgcaccag attgagccga ctctcccctt cttgctgacg gactcctgca gttaccacta 300

caatcttana attgggcggg tcacagaata atctttatct gccacaattt taggtgctga 360

agaaataagc tcccatgctg cagatccatc atttctnctt taagcttatc ttccaaaaca 420

tccacaagan caangttcat cagccagaga ctttcccaga atgctgatag nacacgccat 480

accaacttgt ccaacancca ctacagcgat cttattggt 519

<210> SEQ ID NO 161
<211> LENGTH: 446
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(446)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 161

cgagnggccc gcccgggcag gtccagtaag cntttnacga tgatgggaaa ggttatgcaa 60

ggtcccagcg gtacaacgag ctgtttctac atcatttgta ttctgcatgg tacgtacaat 120

agcagacacc atctgaggag aacgcatgat agcgtgtctg gaagcttcct ttttagaaag 180

ctgatggacc ataactgcag ccttattaac caccacctgg tcctcgtcat ttagcagttt 240

tgtcagttca gggattgcac gtgtggcang ttctgcatca tcttgatagt taatcaagtt 300

tacaactggc atgtttcagc atctgcgatg ggctcagcaa acgctggaca ttantgggat 360

gagcagcatc aaactgtgta natgggatct gcatgccctc atctaatgtc tcagggaaca 420

tagcagctcg taccctctga gctcga 446

<210> SEQ ID NO 162
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(354)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 162

agcgtngtcg cggcccgang tcctgggaag cctttnttgc tgagcctcac agcctctgtc 60

aggcggctgc ggatccagcg gtccaccagg ctctcatggc ctccgggctg ggaggngggt 120

gagggcacaa aacccttccc aaggccacga anggcaaact tggtggcatt ccanagcttg 180

ttgcanaagt ggcggnaacc cagtatccgg ttcacatcca ggntgatgtc acgaccctgg 240

gacatgtang cacataatcc aaaccggaga gcatcggtgc cacattcacg aatccccgct 300

gggaagtcag ctttctgccc ttctttggcc ttctccacct cgctgggatc cagg 354

<210> SEQ ID NO 163
<211> LENGTH: 258
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(258)
<223> OTHER INFORMATION: n = A,T,C or G

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<400> SEQUENCE: 163

ttttcncca agtcctcttg ccgngggatc tngactgcaa tttaagacac ttctaattag 60

ttatacccag gccctgcaaa attgctgggt ttatataata tattcttgct gcacgaagat 120

ttattattct gttggatgat tctattttaa ttntatttat tctggccaaa aaagaacctt 180

ctccgctcgt caagagangc caatntgtct tgaaggacaa gagaaagatg ctaacacaca 240

ctttcttctt cttgagga 258

<210> SEQ ID NO 164
<211> LENGTH: 282
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(282)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 164

ggaacatatt acttttaaat tacttgggtc aatgaaacat ttaataaaaa catttgcttc 60

tctatataat acgtatgtat aaaataagcc ttttcanaaa ctctggttct cataatcctc 120

tataaatcan atgatctgac ttctaagagg aacaaattac agnaaggggt atacattnat 180

gaatactggt agtactagag ganngacgct aaaccactct actaccactt gcggaactct 240

cacagggtaa atgacaaagc caatgactga ctctaaaaac aa 282

<210> SEQ ID NO 165
<211> LENGTH: 462
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(462)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 165

gcccgggcan gtcctgtaat cccagctact cangangctg agtcatgana atcgcctgaa 60

tccgggaggt agaggccgca gcgagcaaag attaagccac tgcactccag tctgggtgac 120

agagtgagaa tctgtctgtt gctcctctgg cattggtctg aaatgggttt gtagaacatg 180

ccacagaagg accagcanca gcaacaaatg gatttgtgga angcgtagct ccaaatggag 240

cangcacact tgatgaagca cgctgtgtct gtgcagangc aaccactggc actgttccaa 300

aaacattgct gctagcatta cttgtggaag tatacgcatt actggaggtg gctgcanaac 360

tgaaaacgct gtctagttct gccanagctg catacttgnc tgaanatgca cttgactgac 420

tgggaactga accacanaac caacaggacc tttacctgtg ga 462

<210> SEQ ID NO 166
<211> LENGTH: 365
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(365)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 166

cgtgggtcgc ggcncgangt ctgaaaccaa tccagaacta aacatcagca cacaaaaaat 60

-continued

accaggatag atggaatcaa aagactctga agccaaaagg aggctaggga gagcaactga 120

acttagcaag ctgaggactt cagtgtccat catccgatcc tgccctgtaa caacaggtct 180

atatgataga gatattccat ctgagctgga ggccattatc cttagcaaac taacacagaa 240

cagaaaacca aatacatgtt ctcatttaga agtaggagct aaatgatgag aactcaagga 300

cacaaagaaa ggaacaacag acactggggc ctacttgagg gtggagggtg ggaggaggga 360

gaaga 365

<210> SEQ ID NO 167
<211> LENGTH: 364
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(364)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 167

agcgtggtcg cggcgcgang tccagcccta gcttgcctgt gactccgcct tcactgggtg 60

ctctctctaa aagttgctga ctctttactg tatctcccaa ttcccactcc attggttcca 120

taaggggagg ggtgtctcac tcaacatggt gttcctggta ccaagaactg gctgacgaag 180

ctgggtgccg tggctcatgc ctgtaatccc agcacttttg ggaggccaag aagggcggat 240

cacctgaggt ctggagttca agatcagcct gaccaacatg atgaaaccaa gtctccacta 300

aaaatataaa acaattagcc aggcatggtg gtgggtgcct gnaatcccag ctactgggga 360

ngct 364

<210> SEQ ID NO 168
<211> LENGTH: 447
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(447)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 168

cccgggcagg tcaaaaccca aaacctttca ttttagccca aaccagctca tgattaggta 60

tacaaggata acagaaccag ttgtcaggac gagcatttga caagtaaaag caattcttgc 120

aaagctgcag ttcatccagc tcatggcatg tgtctttata tagcatcctc gcaatgtcag 180

cttgctcact gtctgctcca tagaaaatca cggtattgtg gagaagcaat tgggcatcag 240

ctttgaactc ttcataactt cggtatttcc cttcattcac tttctcttga atggtgggaa 300

cgtccacaga cctcggccgc gaccacgcta agcccgaatt ctgcagatat ccatcacact 360

ggcggccgtt cgagcatggc atctagaagg cccaattcgc ctatagngag tcgnattacc 420

aattcactgg ccgtcgnttt acaacgc 447

<210> SEQ ID NO 169
<211> LENGTH: 524
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(524)
<223> OTHER INFORMATION: n = A,T,C or G

-continued

<400> SEQUENCE: 169

cgantngcgc gcccgggcag gtctgagcag cctttctgnn tgctggacta ttgggattgg 60

gttcatccaa cagagactgt atggatgtta gaatggaaga cacatcatag gttggactcc 120

aacggttctg aagtatgtcc agacatatac taccatctgc atagactaag aacaaagaag 180

taggtacatt aaacgtaaca agaccactaa ggttttaaca ttatagacaa aacanaaata 240

gtcaaganta ctttgctttt gaagtttaaa gattcctatg ttgcttccca gttaactgcc 300

taaaaagata agncataacc accactagtg aaataatcan gatgatcaga gaatgtcana 360

tgtgatcagt ataaaactgg angatattna gtgtcatcct ttggaaaagg ctgccctatn 420

atccaggaaa tcanaaacat tnttgaacag ggnccctagc tatccacaga catgtgggaa 480

attcattccc caaatngtag gctggatccc ctatctgaaa taac 524

<210> SEQ ID NO 170
<211> LENGTH: 332
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(332)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 170

tcgancggcn cgcccgggca ggtgacaaac ctgttattga agatgttggt tctgatgagg 60

aanaanatca gaagggatgg tgacaagaan aanaanaaga agattaagga aaagtacatc 120

gatcaagaag agctcaacaa aacaaagccc atctggacca gaaatcccga cgatattact 180

aatgangagt acggagaatt ctataanagc ttgaccaatg actgggaaga tcacttggca 240

gtgaagcatt tttcagttga nggacagttg gaattcagag cccttctatn tgtcccacga 300

cgtgctcctt ttgatctgtt tganancaga aa 332

<210> SEQ ID NO 171
<211> LENGTH: 334
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(334)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 171

cgagnggcnc gcccgggcag gtctgttgat agcgacttaa cagaaaagtc tagacaaaca 60

taagcataaa aaattacagt ctttctaccc ttgggaatgg ggagaaaaag gaatctctac 120

cccaagacca gaaataataa gtcctgtttc tggtcctgaa catccagaat tatggaggct 180

ttggcctgac accacattan aatttggtct ggaaatcaaa ctttaganac angagatcgt 240

aagccatttt atactatcga cctaaattcc agtctaacgg ttcctttaca aagttgcgga 300

aagccctctt atatgctagc tgtaggaaat atag 334

<210> SEQ ID NO 172
<211> LENGTH: 439
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature

-continued

<222> LOCATION: (1)...(439)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 172

agcgtggtcg cggcccgang tctgcctata aaactagact tctgacgctg ggctccagct 60

tcattctcac aggtcatcat cctcatccgg gagagcagtt gtctgagcaa cctctaagtc 120

gtgctcatac tgtgctgcca aagctgggtc catgacaact tctggtgggg cgagagcagg 180

catggcaaca aattccaagt tagggtctcc aatgagcttc ctagcaagcc agaggaaggg 240

cttttcaaag ttgtagttac ttttggcaga aatgtcgtag tactgaagat tcttctttcg 300

gtggaagaca atggatttcg ccttcacttt ctgccttaat atccactttg gtgccacaca 360

acacaatggg gatgntttca cacacttngn accanatctc tatgccagnt aggccatttt 420

ggaagnactt cganggtac 439

<210> SEQ ID NO 173
<211> LENGTH: 599
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(599)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 173

cgatnggccg cccgggcagg tcctgtaaaa naggaaattc agacatcgta cgactcgtaa 60

ttgaatgtgg agctgactgc aatattttgt caaagcacca gaatagtgcc ctgcactttg 120

cgaagcagtc taacaatgtg cttgtgtacg acttgctgaa gaaccattta gagacacttt 180

caagagtagc agaagagaca ataaaggatt actttgaagc tcgccttgct ctgctagaac 240

cagtttttcc aatcgcatgt catcgactct gtgagggtcc agatttttca acagatttca 300

attaccaacc cccacagaac ataccagaag gctctggcat cctgctgttt atcttccatg 360

caaacttttt gggtaaagaa gttattgctc ggctctgtgg accgtgtagt gtacaagctg 420

tagttctgaa tgataaattt cagcttcctg tttttctggg tctcgctctg ttgtccaggc 480

tggagtgcag tggcgcggat tacagctcac tggagtcttg acttcccagg cacaagcaat 540

cctcccacct cagcctccta actacctggg actaaaaatg caccgccacc acattccgg 599

<210> SEQ ID NO 174
<211> LENGTH: 458
<212> TYPE: DNA
<213> ORGANISM: Homo sapien
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)...(458)
<223> OTHER INFORMATION: n = A,T,C or G

<400> SEQUENCE: 174

tcgatttggc cgcccgggca ggtccatgcn gnttntgccc attcccatgg ngcccgacaa 60

ncccatcccc gaggccgaca tccccatgtt catgttcatg cccaccatgc cctggctcat 120

ccctgcgctg ttccccagag gggccattcc catggtgccc gtcattacac cgggcatgtt 180

cataggcatg ggtcccccca ggagagggtt agnttgaggc cggacaggaa gcatgtttga 240

tggagaactg aggttcacag nctccaaaac tttgagtcat cacattcata ggctgctgca 300

tattctgtct gctgaatcca ttgtatncag tgatggcctg ctggggnttt ggaaggctng 360

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cataccaggt agtaagntcg tctaggctga tgtttacacc tggggtcaga ccaagtanga 420

gggcaaggtt ttgctgactg attttctgga cccatatc 458

<210> SEQ ID NO 175
<211> LENGTH: 1206
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 175

ggcacgagga agttttgtgt actgaaaaag aaactgtcag aagcaaaaga aataaaatca 60

cagttagaga accaaaaagt taaatgggaa caagagctct gcagtgtgag gtttctcaca 120

ctcatgaaaa tgaaaattat ctcttacatg aaaattgcat gttgaaaaag gaaattgcca 180

tgctaaaact ggaaatagcc acactgaaac accaatacca ggaaaaggaa aataaatact 240

ttgaggacat taagatttta aaagaaaaga atgctgaact tcagatgacc ctaaaactga 300

aagaggaatc attaactaaa agggcatctc aatatagtgg gcagcttaaa gttctgatag 360

ctgagaacac aatgctcact tctaaattga aggaaaaaca agacaaagaa atactagagg 420

cagaaattga atcacaccat cctagactgg cttctgctgt acaagaccat gatcaaattg 480

tgacatcaag aaaaagtcaa gaacctgctt tccacattgc aggagatgct tgtttgcaaa 540

gaaaaatgaa tgttgatgtg agtagtacga tatataacaa tgaggtgctc catcaaccac 600

tttctgaagc tcaaaggaaa tccaaaagcc taaaaattaa tctcaattat gccggagatg 660

ctctaagaga aaatacattg gtttcagaac atgcacaaag agaccaacgt gaaacacagt 720

gtcaaatgaa ggaagctgaa cacatgtatc aaaacgaaca agataatgtg aacaaacaca 780

ctgaacagca ggagtctcta gatcagaaat tatttcaact acaaagcaaa aatatgtggc 840

ttcaacagca attagttcat gcacataaga aagctgacaa caaaagcaag ataacaattg 900

atattcattt tcttgagagg aaaatgcaac atcatctcct aaaagagaaa aatgaggaga 960

tatttaatta caataaccat ttaaaaaacc gtatatatca atatgaaaaa gagaaagcag 1020

aaacagaagt tatataatag tataacactg ccaaggagcg gattatctca tcttcatcct 1080

gtaattccag tgtttgtcac gtggttgttg aataaatgaa taaagaatga gaaaaccaga 1140

agctctgata cataatcata atgataatta tttcaatgca caactacggg tggtgctgct 1200

cgtgcc 1206

<210> SEQ ID NO 176
<211> LENGTH: 317
<212> TYPE: PRT
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 176

Met Gly Thr Arg Ala Leu Gln Cys Glu Val Ser His Thr His Glu Asn
1 5 10 15

Glu Asn Tyr Leu Leu His Glu Asn Cys Met Leu Lys Lys Glu Ile Ala
20 25 30

Met Leu Lys Leu Glu Ile Ala Thr Leu Lys His Gln Tyr Gln Glu Lys
35 40 45

Glu Asn Lys Tyr Phe Glu Asp Ile Lys Ile Leu Lys Glu Lys Asn Ala
50 55 60

Glu Leu Gln Met Thr Leu Lys Leu Lys Glu Glu Ser Leu Thr Lys Arg

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65 70 75 80

Ala Ser Gln Tyr Ser Gly Gln Leu Lys Val Leu Ile Ala Glu Asn Thr
85 90 95

Met Leu Thr Ser Lys Leu Lys Glu Lys Gln Asp Lys Glu Ile Leu Glu
100 105 110

Ala Glu Ile Glu Ser His His Pro Arg Leu Ala Ser Ala Val Gln Asp
115 120 125

His Asp Gln Ile Val Thr Ser Arg Lys Ser Gln Glu Pro Ala Phe His
130 135 140

Ile Ala Gly Asp Ala Cys Leu Gln Arg Lys Met Asn Val Asp Val Ser
145 150 155 160

Ser Thr Ile Tyr Asn Asn Glu Val Leu His Gln Pro Leu Ser Glu Ala
165 170 175

Gln Arg Lys Ser Lys Ser Leu Lys Ile Asn Leu Asn Tyr Ala Gly Asp
180 185 190

Ala Leu Arg Glu Asn Thr Leu Val Ser Glu His Ala Gln Arg Asp Gln
195 200 205

Arg Glu Thr Gln Cys Gln Met Lys Glu Ala Glu His Met Tyr Gln Asn
210 215 220

Glu Gln Asp Asn Val Asn Lys His Thr Glu Gln Gln Glu Ser Leu Asp
225 230 235 240

Gln Lys Leu Phe Gln Leu Gln Ser Lys Asn Met Trp Leu Gln Gln Gln
245 250 255

Leu Val His Ala His Lys Lys Ala Asp Asn Lys Ser Lys Ile Thr Ile
260 265 270

Asp Ile His Phe Leu Glu Arg Lys Met Gln His His Leu Leu Lys Glu
275 280 285

Lys Asn Glu Glu Ile Phe Asn Tyr Asn Asn His Leu Lys Asn Arg Ile
290 295 300

Tyr Gln Tyr Glu Lys Glu Lys Ala Glu Thr Glu Val Ile
305 310 315

<210> SEQ ID NO 177
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Made in the Lab

<400> SEQUENCE: 177

ccaatcatct ccacaggagc 20

<210> SEQ ID NO 178
<211> LENGTH: 1665
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 178

gcaaactttc aagcagagcc tcccgagaag ccatctgcct tcgagcctgc cattgaaatg 60

caaaagtctg ttccaaataa agccttggaa ttgaagaatg aacaaacatt gagagcagat 120

cagatgttcc cttcagaatc aaaacaaaag aaggttgaag aaaattcttg ggattctgag 180

agtctccgtg agactgtttc acagaaggat gtgtgtgtac ccaaggctac acatcaaaaa 240

gaaatggata aaataagtgg aaaattagaa gattcaacta gcctatcaaa aatcttggat 300

-continued

acagttcatt cttgtgaaag agcaagggaa cttcaaaaag atcactgtga acaacgtaca 360

ggaaaaatgg aacaaatgaa aaagaagttt tgtgtactga aaaagaaact gtcagaagca 420

aaagaaataa aatcacagtt agagaaccaa aaagttaaat gggaacaaga gctctgcagt 480

gtgaggtttc tcacactcat gaaaatgaaa attatctctt acatgaaaat tgcatgttga 540

aaaaggaaat tgccatgcta aaactggaaa tagccacact gaaacaccaa taccaggaaa 600

aggaaaataa atactttgag gacattaaga ttttaaaaga aaagaatgct gaacttcaga 660

tgaccctaaa actgaaagag gaatcattaa ctaaaagggc atctcaatat agtgggcagc 720

ttaaagttct gatagctgag aacacaatgc tcacttctaa attgaaggaa aaacaagaca 780

aagaaatact agaggcagaa attgaatcac accatcctag actggcttct gctgtacaag 840

accatgatca aattgtgaca tcaagaaaaa gtcaagaacc tgctttccac attgcaggag 900

atgcttgttt gcaaagaaaa atgaatgttg atgtgagtag tacgatatat aacaatgagg 960

tgctccatca accactttct gaagctcaaa ggaaatccaa aagcctaaaa attaatctca 1020

attatgccgg agatgctcta agagaaaata cattggtttc agaacatgca caaagagacc 1080

aacgtgaaac acagtgtcaa atgaaggaag ctgaacacat gtatcaaaac gaacaagata 1140

atgtgaacaa acacactgaa cagcaggagt ctctagatca gaaattattt caactacaaa 1200

gcaaaaatat gtggcttcaa cagcaattag ttcatgcaca taagaaagct gacaacaaaa 1260

gcaagataac aattgatatt cattttcttg agaggaaaat gcaacatcat ctcctaaaag 1320

agaaaaatga ggagatattt aattacaata accatttaaa aaaccgtata tatcaatatg 1380

aaaaagagaa agcagaaaca gaaaactcat gagagacaag cagtaagaaa cttcttttgg 1440

agaaacaaca gaccagatct ttactcacaa ctcatgctag gaggccagtc ctagcattac 1500

cttatgttga aaatcttacc aatagtctgt gtcaacagaa tacttatttt agaagaaaaa 1560

ttcatgattt cttcctgaag cctgggcgac agagcgagac tctgtctcaa aaaaaaaaaa 1620

aaaaaaagaa agaaagaaat gcctgtgctt acttcgcttc ccagg 1665

<210> SEQ ID NO 179
<211> LENGTH: 179
<212> TYPE: PRT
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 179

Ala Asn Phe Gln Ala Glu Pro Pro Glu Lys Pro Ser Ala Phe Glu Pro
 1   5   10   15

Ala Ile Glu Met Gln Lys Ser Val Pro Asn Lys Ala Leu Glu Leu Lys
            20   25   30

Asn Glu Gln Thr Leu Arg Ala Asp Gln Met Phe Pro Ser Glu Ser Lys
        35   40   45

Gln Lys Lys Val Glu Glu Asn Ser Trp Asp Ser Glu Ser Leu Arg Glu
    50   55   60

Thr Val Ser Gln Lys Asp Val Cys Val Pro Lys Ala Thr His Gln Lys
65   70   75   80

Glu Met Asp Lys Ile Ser Gly Lys Leu Glu Asp Ser Thr Ser Leu Ser
                85   90   95

Lys Ile Leu Asp Thr Val His Ser Cys Glu Arg Ala Arg Glu Leu Gln
            100   105   110

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Lys Asp His Cys Glu Gln Arg Thr Gly Lys Met Glu Gln Met Lys Lys
        115                 120                 125

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

Ser Gln Leu Glu Asn Gln Lys Val Lys Trp Glu Gln Glu Leu Cys Ser
145                 150                 155                 160

Val Arg Phe Leu Thr Leu Met Lys Met Lys Ile Ile Ser Tyr Met Lys
                165                 170                 175

Ile Ala Cys
```

<210> SEQ ID NO 180
<211> LENGTH: 1681
<212> TYPE: DNA
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 180

```
gatacagtca ttcttgtgaa agagcaaggg aacttcaaaa agatcactgt gaacaacgta     60

caggaaaaat ggaacaaatg aaaaagaagt tttgtgtact gaaaaagaaa ctgtcagaag    120

caaaagaaat aaaatcacag ttagagaacc aaaaagttaa atgggaacaa gagctctgca    180

gtgtgagatt gactttaaac caagaagaag agaagagaag aaatgccgat atattaaatg    240

aaaaaattag ggaagaatta ggaagaatcg aagagcagca taggaaagag ttagaagtga    300

aacaacaact tgaacaggct ctcagaatac aagatataga attgaagagt gtagaaagta    360

atttgaatca ggtttctcac actcatgaaa atgaaaatta tctcttacat gaaaattgca    420

tgttgaaaaa ggaaattgcc atgctaaaac tggaaatagc cacactgaaa caccaatacc    480

aggaaaagga aaataaatac tttgaggaca ttaagatttt aaaagaaaag aatgctgaac    540

ttcagatgac cctaaaactg aaagaggaat cattaactaa aagggcatct caatatagtg    600

ggcagcttaa agttctgata gctgagaaca caatgctcac ttctaaattg aaggaaaaac    660

aagacaaaga aatactagag gcagaaattg aatcacacca tcctagactg gcttctgctg    720

tacaagacca tgatcaaatt gtgacatcaa gaaaaagtca agaacctgct ttccacattg    780

caggagatgc ttgtttgcaa agaaaaatga atgttgatgt gagtagtacg atatataaca    840

atgaggtgct ccatcaacca ctttctgaag ctcaaaggaa atccaaaagc ctaaaaatta    900

atctcaatta tgccggagat gctctaagag aaaatacatt ggtttcagaa catgcacaaa    960

gagaccaacg tgaaacacag tgtcaaatga aggaagctga acacatgtat caaaacgaac   1020

aagataatgt gaacaaacac actgaacagc aggagtctct agatcagaaa ttatttcaac   1080

tacaaagcaa aaatatgtgg cttcaacagc aattagttca tgcacataag aaagctgaca   1140

acaaaagcaa gataacaatt gatattcatt ttcttgagag gaaaatgcaa catcatctcc   1200

taaaagagaa aaatgaggag atatttaatt acaataacca tttaaaaaac cgtatatatc   1260

aatatgaaaa agagaaagca gaaacagaaa actcatgaga gacaagcagt aagaaacttc   1320

ttttggagaa acaacagacc agatctttac tcacaactca tgctaggagg ccagtcctag   1380

cattacctta tgttgaaaaa tcttaccaat agtctgtgtc aacagaatac ttattttaga   1440

agaaaaattc atgatttctt cctgaagcct acagacataa aataacagtg tgaagaatta   1500

cttgttcacg aattgcataa aagctgccca ggatttccat ctaccctgga tgatgccgga   1560

gacatcattc aatccaacca gaatctcgct ctgtcactca ggctggagtg cagtgggcgc   1620
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-continued

aatctcggct cactgcaact ctgcctccca ggttcacgcc attctctggc acagcctccc 1680

g 1681

<210> SEQ ID NO 181
<211> LENGTH: 432
<212> TYPE: PRT
<213> ORGANISM: Homo sapien

<400> SEQUENCE: 181

Asp Thr Val His Ser Cys Glu Arg Ala Arg Glu Leu Gln Lys Asp His
1 5 10 15

Cys Glu Gln Arg Thr Gly Lys Met Glu Gln Met Lys Lys Lys Phe Cys
20 25 30

Val Leu Lys Lys Lys Leu Ser Glu Ala Lys Glu Ile Lys Ser Gln Leu
35 40 45

Glu Asn Gln Lys Val Lys Trp Glu Gln Glu Leu Cys Ser Val Arg Leu
50 55 60

Thr Leu Asn Gln Glu Glu Glu Lys Arg Arg Asn Ala Asp Ile Leu Asn
65 70 75 80

Glu Lys Ile Arg Glu Glu Leu Gly Arg Ile Glu Glu Gln His Arg Lys
85 90 95

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

Ile Glu Leu Lys Ser Val Glu Ser Asn Leu Asn Gln Val Ser His Thr
115 120 125

His Glu Asn Glu Asn Tyr Leu Leu His Glu Asn Cys Met Leu Lys Lys
130 135 140

Glu Ile Ala Met Leu Lys Leu Glu Ile Ala Thr Leu Lys His Gln Tyr
145 150 155 160

Gln Glu Lys Glu Asn Lys Tyr Phe Glu Asp Ile Lys Ile Leu Lys Glu
165 170 175

Lys Asn Ala Glu Leu Gln Met Thr Leu Lys Leu Lys Glu Glu Ser Leu
180 185 190

Thr Lys Arg Ala Ser Gln Tyr Ser Gly Gln Leu Lys Val Leu Ile Ala
195 200 205

Glu Asn Thr Met Leu Thr Ser Lys Leu Lys Glu Lys Gln Asp Lys Glu
210 215 220

Ile Leu Glu Ala Glu Ile Glu Ser His His Pro Arg Leu Ala Ser Ala
225 230 235 240

Val Gln Asp His Asp Gln Ile Val Thr Ser Arg Lys Ser Gln Glu Pro
245 250 255

Ala Phe His Ile Ala Gly Asp Ala Cys Leu Gln Arg Lys Met Asn Val
260 265 270

Asp Val Ser Ser Thr Ile Tyr Asn Asn Glu Val Leu His Gln Pro Leu
275 280 285

Ser Glu Ala Gln Arg Lys Ser Lys Ser Leu Lys Ile Asn Leu Asn Tyr
290 295 300

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

Arg Asp Gln Arg Glu Thr Gln Cys Gln Met Lys Glu Ala Glu His Met
325 330 335

Tyr Gln Asn Glu Gln Asp Asn Val Asn Lys His Thr Glu Gln Gln Glu

-continued

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            340                 345                 350

Ser Leu Asp Gln Lys Leu Phe Gln Leu Gln Ser Lys Asn Met Trp Leu
        355                 360                 365

Gln Gln Gln Leu Val His Ala His Lys Lys Ala Asp Asn Lys Ser Lys
    370                 375                 380

Ile Thr Ile Asp Ile His Phe Leu Glu Arg Lys Met Gln His His Leu
385                 390                 395                 400

Leu Lys Glu Lys Asn Glu Glu Ile Phe Asn Tyr Asn Asn His Leu Lys
                405                 410                 415

Asn Arg Ile Tyr Gln Tyr Glu Lys Glu Lys Ala Glu Thr Glu Asn Ser
            420                 425                 430
```

1. An isolated polypeptide comprising an immunogenic portion of a breast antigen or a variant thereof, wherein said antigen comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NO: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178 and 180; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

2. The isolated polypeptide of claim 1, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 62, 176, 179 and 181.

3. An isolated polynucleotide comprising a nucleotide sequence encoding the polypeptide of claim 1.

4. An isolated polynucleotide of claim 3, wherein the polynucleotide comprises a sequence provided in SEQ ID NO: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178 or 180.

5. An expression vector comprising a polynucleotide according to any one of claims **3** and **4**.

6. A host cell transformed with the expression vector of claim 5.

7. The host cell of claim 6 wherein the host cell is selected from the group consisting of *E. coli*, yeast and mammalian cell lines.

8. A pharmaceutical composition comprising the polypeptide of claim 1 and a physiologically acceptable carrier.

9. A vaccine comprising the polypeptide of claim 1 and a non-specific immune response enhancer.

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

11. A vaccine comprising a polynucleotide of any one of claims **3** and **4** and a non-specific immune response enhancer.

12. The vaccine of claim 11 wherein the non-specific immune response enhancer is an adjuvant.

13. A pharmaceutical composition for the treatment of breast cancer comprising a polypeptide and a physiologically acceptable carrier, the polypeptide comprising an immunogenic portion of a breast antigen, wherein said antigen comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NO: 1, 3, 16, 17, 34, 48, 57, 60, 61, 74-87, 117-140 and 160-174; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

14. A vaccine for the treatment of breast cancer comprising a polypeptide and a non-specific immune response enhancer, said polypeptide comprising an immunogenic portion of a breast antigen, wherein said antigen comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NO: 1, 3, 16, 17, 34, 48, 57, 60, 61, 74-87, 117-140 and 160-174; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

15. The vaccine of claim 14 wherein the non-specific immune response enhancer is an adjuvant.

16. A vaccine for the treatment of breast cancer comprising a polynucleotide and a non-specific immune response enhancer, the polynucleotide comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NO: 1, 3, 16, 17, 34, 48, 57, 60, 61, 74-87, 117-140 and 160-174; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

17. The vaccine of claim 16, wherein the non-specific immune response enhancer is an adjuvant.

18. A method for inhibiting the development of breast cancer in a patient, comprising administering to the patient an effective amount of the pharmaceutical composition of claims **8** or **13**.

19. A method for inhibiting the development of breast cancer in a patient, comprising administering to the patient an effective amount of the vaccine of; any one of claims **9**, **11**, **14** or **16**.

20. A fusion protein comprising at least one polypeptide according to claim 1.

21. A pharmaceutical composition comprising a fusion protein according to claim 20 and a physiologically acceptable carrier.

22. A vaccine comprising a fusion protein according to claim 20 and a non-specific immune response enhancer.

23. The vaccine of claim 22 wherein the non-specific immune response enhancer is an adjuvant.

24. A method for inhibiting the development of breast cancer in a patient, comprising administering to the patient an effective amount of the pharmaceutical composition of claim 21.

25. A method for inhibiting the development of breast cancer in a patient, comprising administering to the patient an effective amount of the vaccine of claim 22.

26. A method for detecting breast cancer in a patient, comprising:

(a) contacting a biological sample obtained from the patient with a binding agent which is capable of binding to a polypeptide, the polypeptide comprising an immunogenic portion of a breast antigen, wherein said antigen comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NO: 1-61, 63-175, 178 and 180, complements of said nucleotide sequences, and sequences that hybridize to a sequence provided in SEQ ID NO: 1-61, 63-175, 178 and 180 under moderately stringent conditions; and

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

27. The method of claim 26 wherein the binding agent is a monoclonal antibody.

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

29. A method for monitoring the progression of breast cancer in a patient, comprising:

(a) contacting a biological sample obtained from the patient with a binding agent that is capable of binding to a polypeptide, said polypeptide comprising an immunogenic portion of a breast antigen, wherein said antigen comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NO: 1-61, 63-175, 178 and 180, complements of said nucleotide sequences and sequences that hybridize to a sequence provided in SEQ ID NO: 1-61, 63-175, 178 and 180 under moderately stringent conditions;

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

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

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

30. A monoclonal antibody that binds to a polypeptide comprising an immunogenic portion of a breast antigen or a variant of said antigen, wherein said antigen comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NO: 2, 4-15, 18-33, 35-39, 40-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178 and 180; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

31. A method for inhibiting the development of breast cancer in a patient, comprising administering to the patient a therapeutically effective amount of a monoclonal antibody according to claim 30.

32. The method of claim 31 wherein the monoclonal antibody is conjugated to a therapeutic agent.

33. A method for detecting breast cancer in a patient comprising:

(a) obtaining a biological sample from the patient;

(b) contacting the sample with at least two oligonucleotide primers in a polymerase chain reaction, wherein at least one of the oligonucleotides is specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a breast antigen, said antigen comprising an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NO: 1-61, 63-175, 178 and 180, complements of said nucleotide sequences, and sequences that hybridize to a sequence of SEQ ID NO: 1-61, 63-175, 178 and 180 under moderately stringent conditions; and

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

34. The method of claim 33, wherein at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide comprising a sequence selected from SEQ ID NO: 1-61, 63-175, 178 and 180.

35. A diagnostic kit comprising:

(a) one or more monoclonal antibodies of claim 30; and

(b) a detection reagent.

36. A diagnostic kit comprising:

(a) one or more monoclonal antibodies that bind to a polypeptide encoded by a polynucleotide comprising a sequence selected from the group consisting of SEQ ID NO: 1, 3, 16, 17, 34, 48, 57, 60, 61, 74-87, 117-140 and 160-174, complements of said sequences, and sequences that hybridize to a sequence of SEQ ID NO:, 1, 3, 16, 17, 34, 48, 57, 60, 61, 74-87, 117-140 and 160-174 under moderately stringent conditions; and

(b) a detection reagent.

37. The kit of claims **35** or **36** wherein the monoclonal antibodies are immobilized on a solid support.

38. The kit of claim 37 wherein the solid support comprises nitrocellulose, latex or a plastic material.

39. The kit of claims **35** or **36** wherein the detection reagent comprises a reporter group conjugated to a binding agent.

40. The kit of claim 39 wherein the binding agent is selected from the group consisting of anti-immunoglobulins, Protein G, Protein A and lectins.

41. The kit of claim 39 wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.

42. A diagnostic kit comprising at least two oligonucleotide primers, at least one of the oligonucleotide primers being specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a breast antigen, said antigen comprising an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NO: 1-61, 63-175, 178 and 180, complements of said nucleotide sequences, and sequences that hybridize to a

sequence of SEQ ID NO: 1-61, 63-175, 178 and 180 under moderately stringent conditions.

43. A diagnostic kit of claim 42 wherein at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide having a sequence selected from SEQ ID NO: 1-61, 63-175, 178 and 180.

44. A method for detecting breast cancer in a patient, comprising:

(a) obtaining a biological sample from the patient;

(b) contacting the biological sample with an oligonucleotide probe specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a breast antigen, said antigen comprising an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NO: 1-61, 63-175, 178 and 180, complements of said nucleotide sequences, and sequences that hybridize to a sequence of SEQ ID NO: 1-61, 63-175, 178 and 180 under moderately stringent conditions; and

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

45. The method of claim 44 wherein the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide comprising a sequence selected from the group consisting of SEQ ID NO: 1-61, 63-175, 178 and 180.

46. A diagnostic kit comprising an oligonucleotide probe specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a breast antigen, said antigen comprising an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NO: 1-61, 63-175, 178 and 180, complements of said nucleotide sequences, and sequences that hybridize to a sequence of SEQ ID NO: 1-61, 63-175, 178 and 180 under moderately stringent conditions.

47. The diagnostic kit of claim 46, wherein the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide comprising a sequence selected from the group consisting of SEQ ID NO: 1-61, 63-175, 178 and 180.

48. A method for treating breast cancer in a patient, comprising the steps of:

(a) obtaining peripheral blood cells from the patient;

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

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

49. A method for treating breast cancer in a patient, comprising the steps of:

(a) obtaining peripheral blood cells from the patient;

(b) incubating the cells in the presence of at least one polynucleotide of claim 3, such that T cells proliferate; and

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

50. The method of any one of claims **48** and **49** wherein the step of incubating the T cells is repeated one or more times.

51. The method of any one of claims **48** and **49** wherein step (a) further comprises separating T cells from the peripheral blood cells, and the cells incubated in step (b) are the T cells.

52. The method of any one of claims **48** and **49** wherein step (a) further comprises separating CD4+ cells or CD8+ cells from the peripheral blood cells, and the cells proliferated in step (b) are CD4+ or CD8+ T cells.

53. The method of any one of claims **48** and **49** wherein step (b) further comprises cloning one or more T cells that proliferated in the presence of the polypeptide.

54. A composition for the treatment of breast cancer in a patient, comprising T cells proliferated in the presence of a polypeptide of claim 1, in combination with a pharmaceutically acceptable carrier.

55. A composition for the treatment of breast cancer in a patient, comprising T cells proliferated in the presence of a polynucleotide of claim 3, in combination with a pharmaceutically acceptable carrier.

56. A method for treating breast cancer in a patient, comprising the steps of:

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

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

57. A method for treating breast cancer in a patient, comprising the steps of:

(a) incubating antigen presenting cells in the presence of at least one polynucleotide of claim 3; and

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

58. The method of claims **56** or **57** wherein the antigen presenting cells are selected from the group consisting of dendritic cells and macrophage cells.

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

60. A composition for the treatment of breast cancer in a patient, comprising antigen presenting cells incubated in the presence of a polynucleotide of claim 3, in combination with a pharmaceutically acceptable carrier.

* * * * *

专利名称(译)	用于治疗和诊断乳腺癌的组合物及其使用方法		
公开(公告)号	US20030229020A1	公开(公告)日	2003-12-11
申请号	US10/441893	申请日	2003-05-16
[标]申请(专利权)人(译)	科里克萨有限公司		
申请(专利权)人(译)	Corixa公司CORPORATION		
当前申请(专利权)人(译)	Corixa公司CORPORATION		
[标]发明人	YUQIU JIANG DILLON DAVIN C MITCHAM JENNIFER L XU JIANGCHUN		
发明人	YUQIU, JIANG DILLON, DAVIN C. MITCHAM, JENNIFER L. XU, JIANGCHUN		
IPC分类号	G01N33/53 A61K A61K35/12 A61K35/14 A61K35/76 A61K38/00 A61K39/00 A61K39/39 A61K39/395 A61K48/00 A61P35/00 C07K C07K14/47 C07K14/82 C07K16/32 C07K19/00 C12N C12N1/15 C12N1/19 C12N1/21 C12N5/10 C12N9/00 C12N15/09 C12N15/12 C12Q C12Q1/68 G01N G01N33/566 G01N33/577 A61K38/17 C07H21/04 C12P21/02 C12N5/06 C07K14/705		
CPC分类号	A61K35/12 A61K38/00 A61K39/00 C12Q2600/118 C07K2319/00 C12N9/00 C12Q1/6886 C07K14/47		
外部链接	Espacenet USPTO		

摘要(译)

提供了用于治疗和诊断乳腺癌的化合物和方法。本发明化合物包括含有至少一部分乳腺肿瘤抗原的多肽。提供了用于乳腺癌免疫疗法的疫苗和药物组合物，其包含此类多肽或编码此类多肽的多核苷酸，以及用于制备本发明多肽的多核苷酸。本发明的多肽可用于产生可用于诊断和监测乳腺癌的抗体。

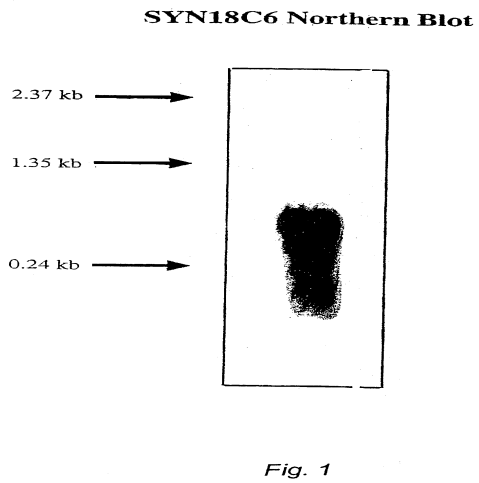

Fig. 1