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(54) **HUMAN SARCOMA-ASSOCIATED ANTIGENS**

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C07K 16/00 (2006.01)
G01N 33/53 (2006.01)

(52) **U.S. Cl.** **530/387.1**; 435/7.1

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

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(57) **ABSTRACT**

The invention relates to sarcoma-associated antigens and the nucleic acid molecules that encode them. The invention further relates to the use of the nucleic acid molecules, polypeptides and fragments thereof associated with sarcoma in methods and compositions for the diagnosis and treatment of diseases, such as cancer. More specifically, the invention relates to the discovery of a novel cancer/testis (CT) antigen, NY-SAR-35.

24 Claims, 4 Drawing Sheets

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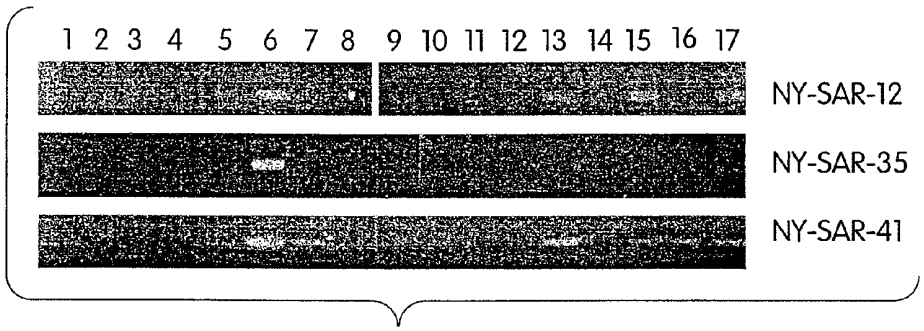
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Fig. 1A

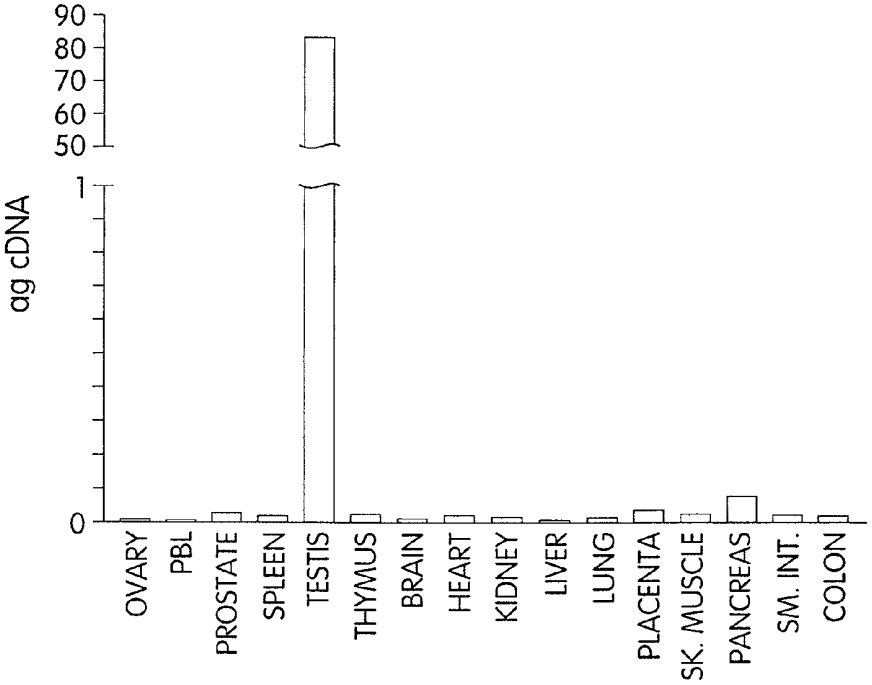
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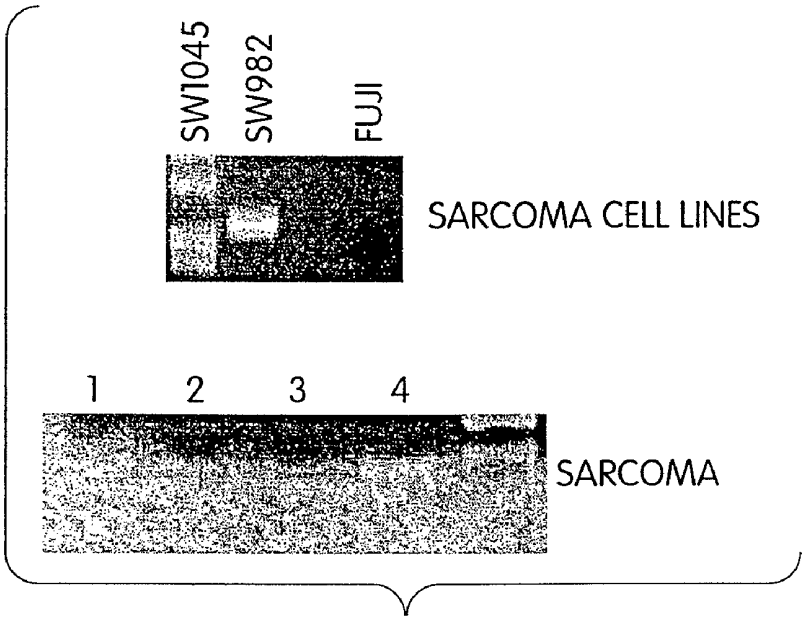
Fig. 1B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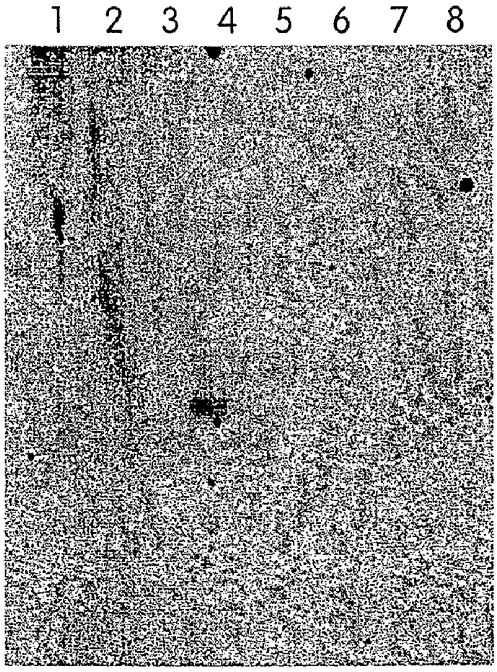
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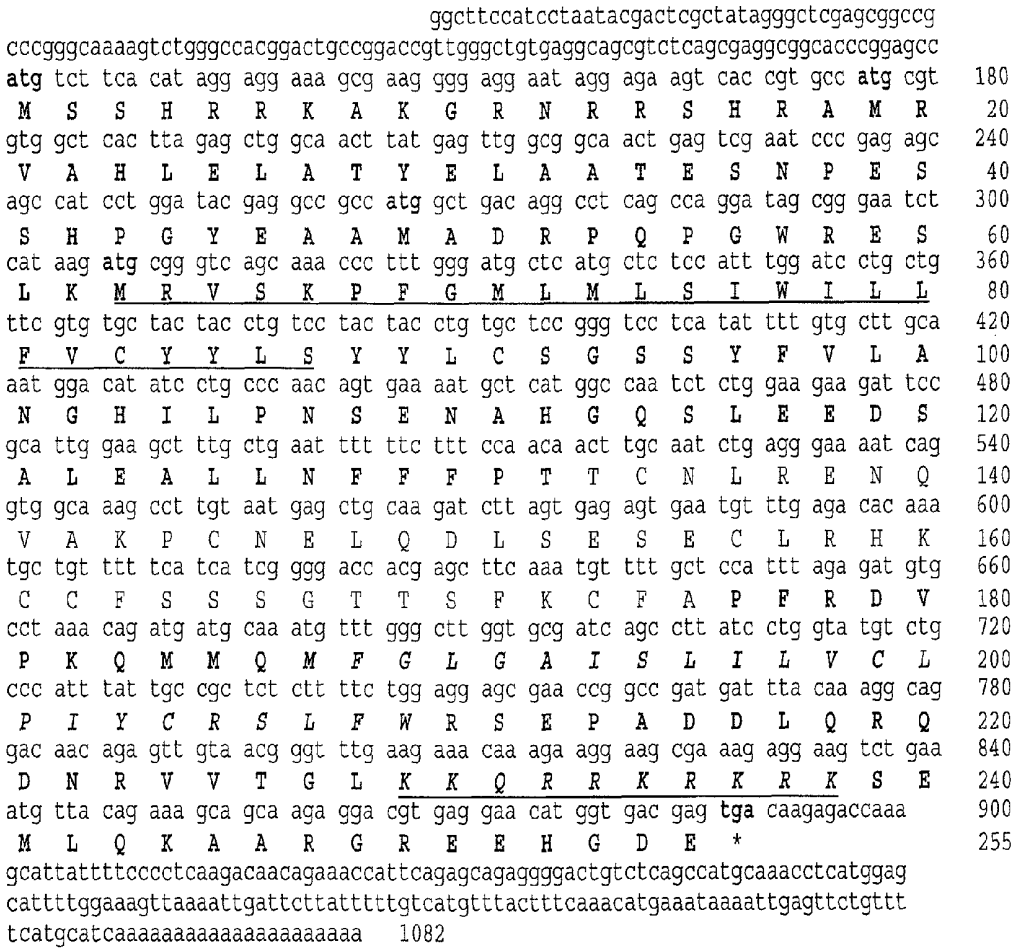
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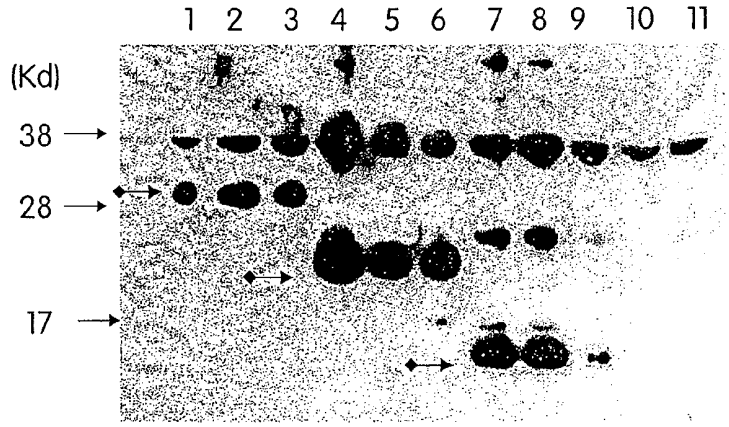
Fig. 2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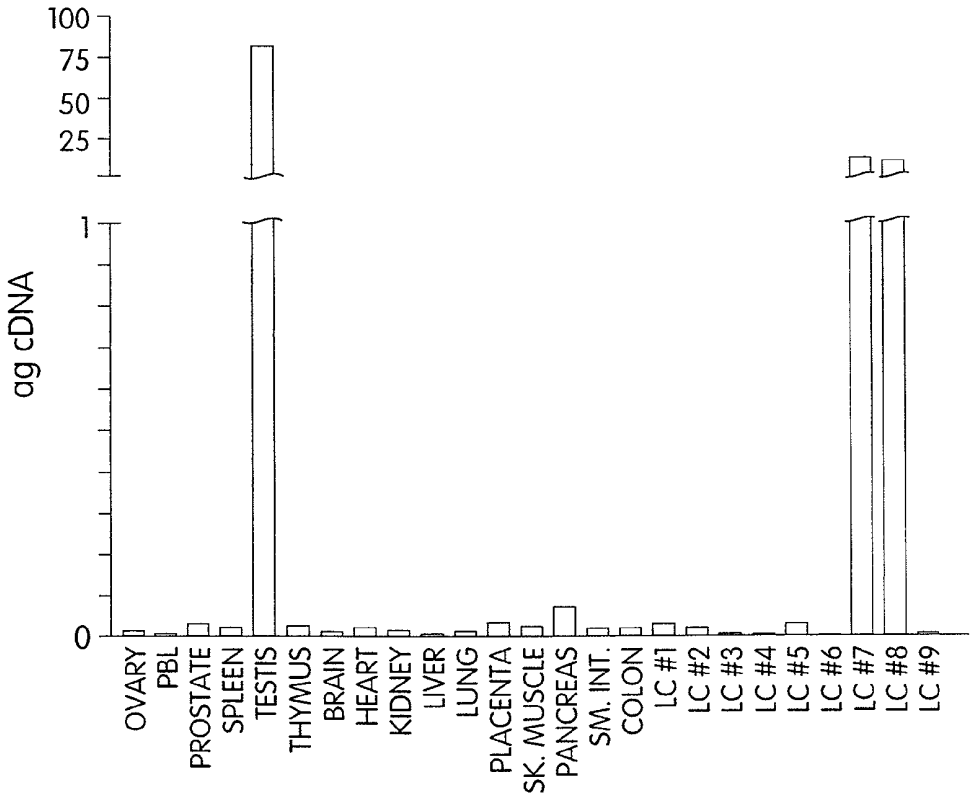
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PANCREAS
SM. INT.
COLON
LC #1
LC #2
LC #3
LC #4
LC #5
LC #6
LC #7
LC #8
LC #9

Fig. 4

HUMAN SARCOMA-ASSOCIATED ANTIGENS

RELATED APPLICATIONS

This application is a divisional of U.S. Non-Provisional patent application Ser. No. 10/529,655, filed Nov. 28, 2006, issued on Feb. 16, 2010 as U.S. Pat. No. 7,662,917, which is a national stage filing under 35 U.S.C. §371 of PCT International application PCT/US03/30870, filed Sep. 30, 2003, which was published under PCT Article 21(2) in English, which is a continuation-in-part of U.S. application Ser. No. 10/260,708, filed on Sep. 30, 2002, and issued on Jul. 14, 2009 as U.S. Pat. No. 7,560,537, the entire disclosure of each of which is incorporated herein by reference.

FIELD OF THE INVENTION

The invention relates to sarcoma-associated antigens and the nucleic acid molecules that encode them. The invention further relates to the use of the nucleic acid molecules, polypeptides and fragments thereof associated with sarcoma in methods and compositions for the diagnosis and treatment of diseases, such as cancer. More specifically, the invention relates to the discovery of a novel cancer/testis (CT) antigen, NY-SAR-35.

BACKGROUND OF THE INVENTION

The identification of human tumor antigens recognized by the autologous host is yielding new and promising target molecules for immunotherapy, diagnosis and monitoring of human cancer (van der Bruggen P, et al. 1991. A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma. Science 254:1643-47; Gaugler, B., et al. Human gene MAGE-3 codes for an antigen recognized on a melanoma by autologous cytolytic T lymphocytes. *J. Exp. Med.* 1994; 179: 921-30; Kawakami, Y., et al. Cloning of the gene for a shared human melanoma antigen recognized by autologous T cells infiltrating into tumor. *Proc. Natl. Acad. Sci. USA.* 1994; 91: 3515-19 and Chen, Y.-T., et al. A testicular antigen aberrantly expressed in human cancers detected by autologous antibody screening. *Proc. Natl. Acad. Sci. USA.* 1997; 94: 1914-18). Studies of the cellular and humoral immune response to cancer have revealed an extensive repertoire of tumor antigens recognized by the immune system, collectively termed the cancer immunome (Jager D, et al. Identification of a tissue-specific putative transcription factor in breast tissue by serological screening of a breast cancer library. Cancer Res 2001 Mar. 1; 61(5):2055-61).

The immunome is composed largely of antigens defined by T-cell epitope cloning (van der Bruggen P, et al. 1991. A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma. Science 254:1643-47; Gaugler, B., et al. Human gene MAGE-3 codes for an antigen recognized on a melanoma by autologous cytolytic T lymphocytes. *J. Exp. Med.* 1994; 179: 921-30; Kawakami, et al. Cloning of the gene for a shared human melanoma antigen recognized by autologous T cells infiltrating into tumor. *Proc. Natl. Acad. Sci. USA.* 1994; 91: 3515-19; Boel, P., et al. BAGE: a new gene encoding an antigen recognized on human melanomas by cytolytic T lymphocytes. *Immunity* 1995; 2: 167-75. (PMID: 7895173); Van den Eynde, B., et al. A new family of genes coding for an antigen recognized by autologous cytolytic T lymphocytes on a human melanoma. *J. Exp. Med.* 1995; 182: 689-98. (PMID: 7544395)), MHC peptide elution (Skipper J C, et al. An HLA-A2-restricted tyrosinase antigen on melanoma cells results from posttranslational modification and suggests a novel pathway for processing of membrane proteins. J Exp Med 1996 Feb. 1; 183(2):527-34; Cox A L, et al. Identification of a peptide recognized by five melanoma-specific human cytotoxic T cell lines. Science 1994 Apr. 29; 264(5159):716-9; Pascolo S, et al. A MAGE-A1 HLA-A A*0201 epitope identified by mass spectrometry. Cancer Res 2001 May 15; 61(10):4072-7), and serological expression cloning (SEREX, Chen, Y.-T., et al. A testicular antigen aberrantly expressed in human cancers detected by autologous antibody screening. *Proc. Natl. Acad. Sci. USA.* 1997; 94: 1914-18; Jager D, et al. Identification of a tissue-specific putative transcription factor in breast tissue by serological screening of a breast cancer library. Cancer Res 2001 Mar. 1; 61(5):2055-61; Sahin, U., et al. Human neoplasms elicit multiple specific immune responses in the autologous host. *Proc. Natl. Acad. Sci. USA* 1995; 92: 11810-13; Scanlan, M. J., et al. Characterization of human colon cancer antigens recognized by autologous antibodies. *Int. J. Cancer* 1998; 76: 652-8; Scanlan, M. J., et al. Antigens recognized by autologous antibody in patients with renal-cell carcinoma. *Int. J. Cancer* 1999; 83: 456-64; Scanlan M J, et al. Humoral immunity to human breast cancer: antigen definition and quantitative analysis of mRNA expression. Cancer Immunity 1:4 [epub]), and is catalogued in three databases: the peptide database of T-cell defined tumor antigens (authored by members of the Ludwig Institute for Cancer Research (LICR) that is available on the website of Cancer Immunity, Journal of the Academy of Cancer Immunology, cancerimmunity.org/peptidedatabase/Tcellepitopes); the SYFPEITHI database of MHC ligands and peptide motifs (available on the website of Biomedical Informatics-Heidelberg, bmi-heidelberg.com/syfpeithi/) and the cancer immunome database available on the website of the LICR (licr.org/CancerImmunomeDB, formerly licr.org/SEREX.html).

SEREX is a method of immunoscreening tumor-derived cDNA expression libraries with cancer patient sera in order to identify molecules recognized by high titered IgG antibodies (Sahin, U., et al. Human neoplasms elicit multiple specific immune responses in the autologous host. *Proc. Natl. Acad. Sci. USA* 1995; 92: 11810-13) Approximately 1000 distinct antigens have been defined by SEREX analysis, including a number of etiologically and therapeutically significant cancer antigens, such as mutational antigens (e.g. p53, LKB1, BUB1; Scanlan, M. J., et al. Characterization of human colon cancer antigens recognized by autologous antibodies. *Int. J. Cancer* 1998; 76: 652-8; Scanlan, M. J., et al. Antigens recognized by autologous antibody in patients with renal-cell carcinoma. *Int. J. Cancer* 1999; 83: 456-64; Scanlan M J, et al. Humoral immunity to human breast cancer: antigen definition and quantitative analysis of mRNA expression. Cancer Immunity 1:4 [epub]), differentiation antigens (e.g. tyrosinase, NY-BR-1, rab 38; Jager D, et al. Identification of a tissue-specific putative transcription factor in breast tissue by serological screening of a breast cancer library. Cancer Res 2001 Mar. 1; 61(5):2055-61; Sahin, U., et al. Human neoplasms elicit multiple specific immune responses in the autologous host. *Proc. Natl. Acad. Sci. USA* 1995; 92: 11810-13; Jager D, et al. Serological cloning of a melanocyte rab guanosine 5'-triphosphate-binding protein and a chromosome condensation protein from a melanoma complementary DNA library. Cancer Res 2000 Jul. 1; 60(13):3584-91), overexpressed gene products (e.g. Her2neu, TPD52, eIF4-gamma; Scanlan M J, et al. Humoral immunity to human breast cancer: antigen definition and quantitative analysis of mRNA expression. Cancer Immunity 1:4 [epub]; Chen, Y.-T., et al. Identification of human tumor antigens by serological

expression cloning. In: S. A. Rosenberg (ed.). Principles and Practice of Biologic Therapy of Cancer, pp. 557-570. Philadelphia: Lippincott Williams & Wilkins, 2000) and cancer/testis (CT) antigens (e.g. MAGE-1, NY-ESO-1, SSX-2; Chen, Y.-T., et al. A testicular antigen aberrantly expressed in human cancers detected by autologous antibody screening. *Proc. Natl. Acad. Sci. USA.* 1997; 94: 1914-18; Sahin, U., et al. Human neoplasms elicit multiple specific immune responses in the autologous host. *Proc. Natl. Acad. Sci. USA* 1995; 92: 11810-13).

CT antigens represent a group of shared, tumor-specific antigens expressed exclusively in developing germ cells of the testis and fetal ovary, as well as in placental trophoblast, and most notably, in a proportion of human cancers of diverse origins (Chen, Y.-T., et al. Identification of human tumor antigens by serological expression cloning. In: S. A. Rosenberg (ed.). Principles and Practice of Biologic Therapy of Cancer, pp. 557-570. Philadelphia: Lippincott Williams & Wilkins, 2000). These antigens elicit spontaneous cellular (Van den Eynde, B. J. and van der Bruggen, P. (1997) Curr. Opin. Immunol. 9,684-693) and humoral immune responses (Stockert, E., et al. (1998) J. Exp. Med. 187, 1349-1354) in some cancer patients. On the basis of tissue-restricted expression and immunogenicity, CT antigens are attractive targets for vaccine-based immunotherapies. In general, CT antigens are expressed in 20-40% of specimens from a given tumor type (Sahin U, et al. 1998. Expression of multiple cancer/testis antigens in breast cancer and melanoma: basis for polyvalent CT vaccine strategies. Int J Cancer 78:387-89; Scanlan M J et al. 2000. Expression of cancer-testis antigens in lung cancer: definition of bromodomain testis-specific gene (BRDT) as a new CT gene, CT9. Cancer Lett. 150:155-64; Van den Eynde B J and van der Bruggen P. 1997. T cell defined tumor antigens. Curr Opin Immunol 9:684-693). One exception to this is synovial sarcoma, in which 80% of specimens express NY-ESO-1 (Jungbluth A A, et al. 2001. Monophasic and biphasic synovial sarcomas abundantly express cancer/testis antigen NY-ESO-1 but not MAGE-A1 or CT7. Int J Cancer 94:252-6) and MAGE antigens (Antonescu C R, et al. MAGE antigen expression in monophasic and biphasic synovial sarcoma. Hum Pathol 2002 February; 33(2):225-9); the expression of which are often homogeneous throughout the tumor. Thus, identification of additional CT antigens and other genes having a tumor-associated expression profile is needed for the development of additional therapeutics and diagnostics to permit effective treatment and diagnosis of a broader group of cancer patients.

SUMMARY OF THE INVENTION

The humoral immune response of sarcoma patients to CT antigens was examined using the SEREX method. Sera from patients which showed a humoral immune response to CT antigens were subsequently used to screen cDNA libraries derived from CT-rich synovial sarcoma cell lines as well as normal testis. Although there was little overlap in the identity of clones isolated with different sarcoma sera, more than 30% of the isolated clones were previously identified during SEREX analysis of other tumor types. Approximately 60% of these antigens also reacted with sera from normal individuals. This is in conformity with other findings (Scanlan, M. J., et al. Antigens recognized by autologous antibody in patients with renal-cell carcinoma. *Int. J. Cancer* 1999; 83: 456-64 and Scanlan M J, et al. Humoral immunity to human breast cancer: antigen definition and quantitative analysis of mRNA expression. Cancer Immunity 20001; 1:4 [epub]). Thus, only a fraction of the serologically-defined immunome is associated with a cancer-related immune response. The studies described herein have led to the identification of antigens, which include antigens not before associated with cancer along with several novel gene products associated with a sarcoma-related immune response. One such novel CT antigen is NY-SAR-35, which appears to be a cell surface/secreted molecule.

According to one aspect of the invention, isolated nucleic acid molecules are provided. The isolated nucleic acid molecules are selected from the group consisting of (a) nucleic acid molecules which hybridize under high stringency conditions to a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of nucleotide sequences set forth as SEQ ID NOs: 1-14 and 97-107 and which code for a sarcoma-associated antigen, (b) nucleic acid molecules that differ from the nucleic acid molecules of (a) in codon sequence due to the degeneracy of the genetic code, and (c) complements of (a) or (b).

In some embodiments, the isolated nucleic acid molecule includes a nucleotide sequence selected from the group consisting of nucleotide sequences set forth as SEQ ID NOs: 1-14 and 97-107. In some embodiments the isolated nucleic acid molecule comprises a nucleotide sequence selected from the group consisting of nucleotide sequences set forth as SEQ ID NOs: 10, 11, 99, 102 and 104. In other embodiments the nucleic acid molecule comprises a nucleotide sequence set forth as SEQ ID NO: 10. In yet other embodiments the nucleic acid molecule comprises a nucleotide sequence set forth as SEQ ID NO: 11. In still other embodiments the nucleic acid molecule comprises a nucleotide sequence set forth as SEQ ID NO: 102. In still further embodiments the nucleic acid molecule comprises a nucleotide sequence set forth as SEQ ID NO: 104.

In some embodiments the nucleic acid molecule comprises a nucleotide sequence set forth as SEQ ID NOs: 121, 123, 125, 127, 129 or 131. In some embodiments the nucleic acid molecule comprises a nucleotide sequence set forth as SEQ ID NO: 121. In other embodiments the nucleic acid molecule comprises a nucleotide sequence set forth as SEQ ID NO: 123. In still other embodiments the nucleic acid molecule comprises a nucleotide sequence set forth as SEQ ID NO: 125. In yet other embodiments the nucleic acid molecule comprises a nucleotide sequence set forth as SEQ ID NO: 131.

According to another aspect of the invention, additional isolated nucleic acid molecules are provided. The isolated nucleic acid molecules are selected from the group consisting of: (a) unique fragments of a nucleotide sequence selected from the group consisting of nucleotide sequences set forth as SEQ ID NOs: 10, 11, 99, 102 and 104, which encodes an immunogenic peptide and (b) complements of (a). In some embodiments the isolated nucleic acid molecules are selected from the group consisting of: (a) unique fragments of a nucleotide sequence set forth as SEQ ID NO: 10, which encodes an immunogenic peptide and (b) complements of (a). In other embodiments the isolated nucleic acid molecules are selected from the group consisting of: (a) unique fragments of a nucleotide sequence set forth as SEQ ID NO: 11, which encodes an immunogenic peptide and (b) complements of (a). In yet other embodiments the isolated nucleic acid molecules are selected from the group consisting of: (a) unique fragments of a nucleotide sequence set forth as SEQ ID NO: 102, which encodes an immunogenic peptide and (b) complements of (a). In still other embodiments the isolated nucleic acid molecules are selected from the group consisting of: (a) unique fragments of a nucleotide sequence set forth as SEQ ID NO: 104, which encodes an immunogenic peptide and (b) comple-

ments of (a). In some embodiments the nucleic acid molecule comprises a nucleotide sequence set forth as SEQ ID NO: 121. In other embodiments the nucleic acid molecule comprises a nucleotide sequence set forth as SEQ ID NO: 123. In still other embodiments the nucleic acid molecule comprises a nucleotide sequence set forth as SEQ ID NO: 125. In yet other embodiments the nucleic acid molecule comprises a nucleotide sequence set forth as SEQ ID NO: 131.

In certain embodiments, the isolated nucleic acid molecule includes a nucleotide sequence that is at least about 90% identical to a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-14 and 97-107; preferably the nucleotide sequence is at least about 95% identical, more preferably the nucleotide sequence is at least about 97% identical, still more preferably the nucleotide sequence is at least about 98% identical, and yet more preferably the nucleotide sequence is at least about 99% identical.

According to further aspects of the invention, expression vectors that include any of the foregoing isolated nucleic acid molecules operably linked to a promoter are provided, as are host cells transformed or transfected with these expression vectors. In certain embodiments, the host cell expresses a MHC molecule, and in some of these embodiments the MHC molecule is expressed recombinantly.

According to another aspect of the invention, isolated polypeptides are provided that are encoded by the isolated nucleic acid molecules described herein. In certain embodiments, the isolated polypeptide includes an amino acid sequence as set forth in SEQ ID NOs: 46-60, 109-120 or a fragment thereof that is at least eight amino acids in length. In certain embodiments, the isolated polypeptides are antigenic polypeptides that are capable of eliciting antibodies to a sarcoma-associated antigen. In some embodiments the isolated polypeptide includes an amino acid sequence as set forth in SEQ ID NO: 55 or a fragment thereof that is at least eight amino acids in length. In other embodiments the isolated polypeptide includes an amino acid sequence as set forth in SEQ ID NO: 56 or a fragment thereof that is at least eight amino acids in length. In yet other embodiments the isolated polypeptide includes an amino acid sequence as set forth in SEQ ID NO: 111 or a fragment thereof that is at least eight amino acids in length. In still other embodiments the isolated polypeptide includes an amino acid sequence as set forth in SEQ ID NO: 114 or a fragment thereof that is at least eight amino acids in length. In yet other embodiments the isolated polypeptide includes an amino acid sequence as set forth in SEQ ID NO: 116 or a fragment thereof that is at least eight amino acids in length. In still other embodiments the isolated polypeptide includes an amino acid sequence as set forth in SEQ ID NO: 122. In yet other embodiments the isolated polypeptide includes an amino acid sequence as set forth in SEQ ID NO: 124. In still further embodiments the isolated polypeptide includes an amino acid sequence as set forth in SEQ ID NO: 126. In yet other embodiments the polypeptide includes the amino acid sequence set forth as SEQ ID NOs: 128, 130 or 132.

Another aspect of the invention provides binding polypeptides that selectively bind to the foregoing isolated polypeptides. In some embodiments these binding polypeptides are isolated also. In other embodiments, the binding polypeptides are antibodies or antigen-binding fragments thereof.

According to another aspect of the invention, methods of diagnosing cancer in a subject are provided. The methods include obtaining a biological sample from the subject, and determining the presence of an antibody in the biological sample that binds specifically to one or more sarcoma-associated antigens encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOs: 3, 5-8, 10-45, 99, 102, 104 and 108. The presence of such antibodies indicates that the subject has cancer. In some embodiments the one or more sarcoma-associated antigens is/are encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOs: 5-7, 10-13, 15-45, 102, 104 and 108. In still other embodiments the one or more sarcoma-associated antigens is/are encoded by a nucleotide sequence selected from the group consisting of SEQ ID NOs: 10, 11, 15, 102, 104 and 108. In some embodiments the sarcoma-associated antigens is encoded by a nucleotide sequence set forth as SEQ ID NO: 10.

In some embodiments, the step of determining the presence of an antibody includes contacting the biological sample with one or more sarcoma-associated antigens that are specifically bound by the antibody and are encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of (1) nucleotide sequences set forth as SEQ ID NOs: 3, 5-8, 10-45, 99, 102, 104 and 108 and (2) nucleotide sequences that are at least 90% identical to the nucleotide sequences of (1), and then determining the binding of the antibody to the sarcoma-associated antigen. In other embodiments, the step of determining the presence of an antibody includes contacting the biological sample with one or more sarcoma-associated antigens that are specifically bound by the antibody and are encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of (1) nucleotide sequences set forth as SEQ ID NOs: 5-7, 10-13, 15-45, 102, 104 and 108 and (2) nucleotide sequences that are at least 90% identical to the nucleotide sequences of (1), and then determining the binding of the antibody to the sarcoma-associated antigen.

In some embodiments, the nucleic acid molecule comprises a nucleotide sequence selected from the group consisting of nucleotide sequences set forth as SEQ ID NOs: 10, 11, 15, 102, 104 and 108, and in other embodiments the nucleic acid molecule includes the nucleotide sequence set forth as SEQ ID NO: 10. In other embodiments the nucleic acid molecule includes the nucleotide sequence set forth as SEQ ID NO: 121. In still other embodiments the nucleic acid molecule includes the nucleotide sequence set forth in SEQ ID NO: 123. In other embodiments the nucleic acid molecule includes the nucleotide sequence set forth in SEQ ID NO: 125. In yet other embodiments the nucleic acid molecule includes the nucleotide sequence set forth in SEQ ID NOs: 127, 129 or 131.

In other embodiments, the sarcoma-associated antigen is a polypeptide that includes the amino acid sequence of any of SEQ ID NOs: 48, 50-53, 55-90, 111, 114, 116 and 120 or a fragment thereof that is at least eight amino acids in length. In still other embodiments, the sarcoma-associated antigen is a polypeptide that includes the amino acid sequence of any of SEQ ID NOs: 50-52, 55-58, 60-90, 114, 116, 120 or a fragment thereof that is at least eight amino acids in length. In still other embodiments, the sarcoma-associated antigen is a polypeptide that includes the amino acid sequence of any of SEQ ID NOs: 55, 56, 60, 114, 116 and 120 or a fragment thereof that is at least eight amino acids in length.

In some embodiments, the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 55 or a fragment thereof that is at least eight amino acids in length. In certain embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 122. In still other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 124. In yet other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID

NO: 126. In still other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 128, 130 or 132.

In certain embodiments, the biological sample is serum. In other embodiments, the one or more sarcoma-associated antigens are produced recombinantly, and/or the one or more sarcoma-associated antigens are bound to a substrate. In some embodiments, the step of determining the binding of the antibody with the one or more sarcoma-associated antigens is performed with an ELISA-based method. In still other embodiments a serum antibody detection assay (SADA) is used.

According to still another aspect of the invention, methods for diagnosing cancer in a subject are provided. The methods include obtaining a biological sample from a subject, and determining the expression of a sarcoma-associated antigen or a nucleic acid molecule that encodes it. The nucleic acid molecule includes a nucleotide sequence selected from the group consisting of SEQ ID NOs: 3, 5-8, 10-45, 99, 102, 104 and 108 in the biological sample. The nucleic acid molecule is some embodiments includes a nucleotide sequence selected from the group consisting of SEQ ID NOs: 5-7, 10-13, 15-45, 102, 104 and 108 in the biological sample. The expression of the sarcoma-associated antigen or the nucleic acid molecule that encodes it in the sample is diagnostic for cancer in the subject.

In certain embodiments, the sarcoma-associated nucleic acid molecule comprises the nucleotide sequence selected from the group consisting of SEQ ID NOs: 10, 11, 15, 102, 104 and 108. In some embodiments the sarcoma-associated nucleic acid molecule includes the nucleotide sequence set forth as SEQ ID NO: 10. In other embodiments the nucleic acid molecule includes the nucleotide sequence set forth as SEQ ID NO: 121. In still other embodiments the nucleic acid molecule includes the nucleotide sequence set forth in SEQ ID NO: 123. In yet other embodiments the nucleic acid molecule includes the nucleotide sequence set forth in SEQ ID NO: 125. In yet other embodiments the nucleic acid molecule includes the nucleotide sequence set forth in SEQ ID NOs: 127, 129 or 131.

In other embodiments, the sarcoma-associated antigen comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 48, 50-53, 55-90, 111, 114, 116 and 120 or a fragment thereof that is at least eight amino acids in length. In yet other embodiments, the sarcoma-associated antigen comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 50-52, 55-58, 60-90, 114, 116 and 120 or a fragment thereof that is at least eight amino acids in length. The sarcoma-associated antigen in some embodiments includes an amino acid sequence selected from the group consisting of SEQ ID NOs: 55, 56, 60, 114, 116 and 120. In some embodiments the sarcoma-associated antigen includes an amino acid sequence set forth as SEQ ID NO: 55 or a fragment thereof that is at least eight amino acids in length. In certain embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 122. In still other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 124. In yet other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 126. In still further embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NOs: 128, 130 or 132.

According to yet another aspect of the invention, methods for determining onset, progression, or regression of cancer in a subject are provided. The methods include obtaining from a subject a first biological sample, determining the expression of a sarcoma-associated antigen or the nucleic acid molecule that encodes it in the first sample, obtaining from the subject a second biological sample, determining the expression of the sarcoma-associated antigen or the nucleic acid molecule that encodes it in the second sample, and comparing the expression in the first sample to the expression in the second sample as a determination of the onset, progression, or regression of the cancer. The nucleic acid molecule comprises a nucleotide sequence selected from the group consisting of (1) nucleotide sequences set forth as SEQ ID NOs: 3, 5-8, 10-45, 99, 102, 104 and 108 and (2) nucleotide sequences that are at least 90% identical to the nucleotide sequences of (1). In some embodiments the nucleic acid molecule comprises a nucleotide sequence selected from the group consisting of (1) nucleotide sequences set forth as SEQ ID NOs: 5-7, 10-13, 15-45, 102, 104 and 108 and (2) nucleotide sequences that are at least 90% identical to the nucleotide sequences of (1).

In some embodiments, the nucleic acid molecule that encodes the sarcoma-associated antigen includes a nucleotide sequence selected from the group consisting of SEQ ID NOs: 10, 11, 15, 102, 104 and 108. In other embodiments the nucleic acid molecule includes the nucleotide sequence of SEQ ID NO: 10. In yet other embodiments the nucleic acid molecule includes the nucleotide sequence set forth as SEQ ID NO: 121. In still other embodiments the nucleic acid molecule includes the nucleotide sequence set forth in SEQ ID NO: 123. In yet other embodiments the nucleic acid molecule includes the nucleotide sequence set forth in SEQ ID NO: 125. In still other embodiments the nucleic acid molecule includes the nucleotide sequence set forth in SEQ ID NOs: 127, 129 or 131. In other embodiments, the sarcoma-associated antigen includes a polypeptide sequence selected from the group consisting of polypeptide sequences set forth as SEQ ID NOs: 48, 50-53, 55-90, 111, 114, 116 and 120 or a fragment thereof that is at least eight amino acids in length. In still other embodiments, the sarcoma-associated antigen includes a polypeptide sequence selected from the group consisting of polypeptide sequences set forth as SEQ ID NOs: 50-52, 55-58, 60-90, 114, 116 and 120 or a fragment thereof that is at least eight amino acids in length. In yet other embodiments, the sarcoma-associated antigen includes a polypeptide sequence selected from the group consisting of polypeptide sequences set forth as SEQ ID NOs: 55, 56, 60, 114, 116 and 120 or a fragment thereof that is at least eight amino acids in length. In some embodiments the sarcoma-associated antigen includes the amino acid sequence of SEQ ID NO: 55 or a fragment thereof that is at least eight amino acids in length. In certain embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 122. In still other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 124. In yet other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 126. In still other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NOs: 128, 130 or 132.

In some embodiments of the foregoing methods, the step of determining the expression of the sarcoma-associated antigen or the nucleic acid molecule that encodes it includes contacting the biological sample with an agent that selectively binds to the sarcoma-associated antigen or the nucleic acid molecule that encodes it. For methods in which the agent that selectively binds is a nucleic acid molecule, it is preferred that the expression of the sarcoma-associated nucleic acid molecule is determined by nucleic acid hybridization or nucleic acid amplification; some embodiments of the methods utilize real-time RT-PCR or RT-PCR as methods of nucleic acid

amplification, or use a nucleic acid microarray as a method for nucleic acid hybridization. For methods in which the agent that selectively binds is a polypeptide, the polypeptide preferably is an antibody or antigen-binding fragment thereof. More preferably, the antibody is a monoclonal antibody, particularly a chimeric, human, or humanized antibody, a single chain antibody, or the antigen-binding fragment is a $F(ab')_2$, Fab, Fd, or Fv fragment. In certain embodiments, the antibody or antigen-binding fragment is labeled with a detectable label, preferably a fluorescent or radioactive label.

In certain embodiments of the foregoing methods, the sample is selected from the group consisting of tissue, cells, and blood. In some embodiments, the cancer is a sarcoma.

In another aspect of the invention, kits for detecting antibodies reactive to a sarcoma-associated antigen in a biological sample are provided. The kits include one or more sarcoma-associated antigens encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of nucleotide sequences set forth as SEQ ID NOs: 3, 5-8, 10-45, 99, 102, 104 and 108, and instructions for the use of the sarcoma-associated antigens in the detection of antibodies in the biological sample. In some embodiments the one or more sarcoma-associated antigens is/are encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of nucleotide sequences set forth as SEQ ID NOs: 5-7, 10-13, 15-45, 102, 104 and 108. In some embodiments, the sarcoma-associated nucleic acid molecule comprises the nucleotide sequence set forth as SEQ ID NO: 10, 11, 15, 102, 104 or 108. In other embodiments, the sarcoma-associated nucleic acid molecule comprises the nucleotide sequence set forth as SEQ ID NO: 10. In other embodiments the nucleic acid molecule includes the nucleotide sequence set forth as SEQ ID NO: 121. In still other embodiments the nucleic acid molecule includes the nucleotide sequence set forth in SEQ ID NO: 123. In yet other embodiments the nucleic acid molecule includes the nucleotide sequence set forth in SEQ ID NO: 125. In still further embodiments the nucleic acid molecule includes the nucleotide sequence set forth in SEQ ID NOs: 127, 129 or 131. In other embodiments, the sarcoma-associated antigens are bound to a substrate. In further embodiments, the kit also includes a labeling reagent and labeling reagent substrate, and/or a blocking reagent. Additional kit embodiments include secondary antibodies for detection of the antibody bound to the antigen.

In a further aspect of the invention, other kits for the diagnosis of cancer in a subject are provided. The kits include one or more binding agents that specifically bind to a sarcoma-associated antigen or the nucleic acid molecule that encodes it. In this aspect, the nucleic acid molecule includes a nucleotide sequence selected from the group consisting of SEQ ID NOs: 3, 5-8, 10-45, 99, 102, 104 and 108. In some embodiments the nucleic acid molecule includes a nucleotide sequence selected from the group consisting of SEQ ID NOs: 5-7, 10-13, 15-45, 102, 104 and 108. The kit also includes instructions for the use of the binding agents in the diagnosis of cancer. The one or more binding agents are nucleic acid molecules or polypeptides. If the latter, the polypeptides preferably are antibodies or antigen-binding fragments thereof. In other embodiments, the one or more agents are bound to a substrate. Further embodiments of the kits include one or more agents that bind specifically to a cancer-associated antigen other than those encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 10, 11, 15, 102, 104 and 108. In some embodiments, the kit is configured for diagnosis of sarcomas.

According to another aspect of the invention, methods for treating a subject with a disorder characterized by the aberrant expression of a sarcoma-associated antigen or the nucleic acid molecule that encodes it are provided. The methods include administering to a subject an effective amount of an antibody or antigen-binding fragment thereof that specifically binds to the sarcoma-associated antigen. In this aspect, the antigen includes an amino acid sequence selected from the group consisting of SEQ ID NOs: 48, 50-53, 55-90, 111, 114, 116 and 120 or a fragment thereof that is eight or more amino acids in length. In some embodiments the antigen includes an amino acid sequence selected from the group consisting of SEQ ID NOs: 50-52, 55-58, 60-90, 114, 116 and 120 or a fragment thereof that is eight or more amino acids in length. In other embodiments the antigen includes an amino acid sequence selected from the group consisting of SEQ ID NOs: 55, 56, 60, 114, 116 and 120 or a fragment thereof that is eight or more amino acids in length. In some embodiments, the antibody or antigen-binding fragment thereof specifically binds to the extracellular domain of a sarcoma-associated antigen that includes the amino acid sequence of SEQ ID NO: 55 or a fragment thereof that is eight or more amino acids in length. In certain embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 122. In still other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 124. In yet other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 126. In still other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 128, 130 or 132. In yet other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 134 or a fragment thereof that is eight or more amino acids in length.

In certain embodiments, the disorder is cancer, preferably sarcoma. In other embodiments, the antibody used in the methods is a monoclonal antibody, preferably a chimeric, human, or humanized antibody; a single chain antibody; or the antigen-binding fragment is a $F(ab')_2$, Fab, Fd, or Fv fragment.

In other embodiments, the antibody or antigen-binding fragment thereof is bound to a cytotoxic agent. Preferred cytotoxic agents include: calicheamicin, esperamicin, methotrexate, doxorubicin, melphalan, chlorambucil, ARA-C, vindesine, mitomycin C, cisplatinum, etopside, bleomycin and 5-fluorouracil. Other cytotoxic agents include radioisotopes, including those that emit α, β, and/or γ radiation. Preferred radioisotopes include: ^{225}Ac, ^{211}At, ^{212}Bi, ^{213}Bi, ^{186}Rh, ^{188}Rh, ^{177}Lu, ^{90}Y, ^{131}I, ^{67}Cu, ^{125}I, ^{123}I, ^{77}Br, ^{153}Sm, ^{166}Bo, ^{64}Cu, ^{212}Pb, ^{224}Ra and ^{223}Ra.

According to another aspect of the invention, methods for treating a subject with a disorder characterized by the aberrant expression of a sarcoma-associated antigen or a nucleic acid molecule that encodes it are provided. The methods include administering an amount of an agent that selectively binds to the sarcoma-associated antigen or the nucleic acid molecule that encodes it effective to treat the disorder. The nucleic acid molecule comprises a nucleotide sequence selected from the group consisting of (a) an isolated nucleic acid molecule comprising a nucleotide sequence that is at least 90% identical to the nucleotide sequence selected from the group consisting of SEQ ID NOs: 3, 5-8, 10-45, 99, 102, 104 and 108, and (b) nucleic acid molecules that differ from the nucleic acid molecules of (a) in codon sequence due to the degeneracy of the genetic code. In some embodiments the nucleic acid molecule comprises a nucleotide sequence selected from the group consisting of (a) an isolated nucleic acid molecule

comprising a nucleotide sequence that is at least 90% identical to the nucleotide sequence selected from the group consisting of SEQ ID NOs: 5-7, 10-13, 15-45, 102, 104 and 108, and (b) nucleic acid molecules that differ from the nucleic acid molecules of (a) in codon sequence due to the degeneracy of the genetic code. In certain embodiments the disorder is cancer, preferably sarcoma. In yet other embodiments the sarcoma-associated nucleic acid molecule comprises the nucleotide sequence selected from the group consisting of nucleotide sequences set forth as SEQ ID NOs: 10, 11, 15, 102, 104 and 108. In some embodiments the sarcoma-associated nucleic acid molecule comprises the nucleotide sequence set forth as SEQ ID NO: 10.

In other embodiments the sarcoma-associated nucleic acid molecule codes for a sarcoma-associated antigen which comprises the polypeptide sequence selected from the group consisting of polypeptide sequences set forth as SEQ ID NOs: 48, 50-53, 55-90, 111, 114, 116 and 120 or a fragment thereof that is at least eight amino acids in length. In still other embodiments the sarcoma-associated nucleic acid molecule codes for a sarcoma-associated antigen which comprises the polypeptide sequence selected from the group consisting of polypeptide sequences set forth as SEQ ID NOs: 50-52, 55-58, 60-90, 114, 116 and 120 or a fragment thereof that is at least eight amino acids in length. In some embodiments the sarcoma-associated nucleic acid molecule codes for a sarcoma-associated antigen which comprises the polypeptide sequence set forth as SEQ ID NO: 55, 56, 60, 114, 116 or 120 or a fragment thereof that is at least eight amino acids in length. In another embodiment the sarcoma-associated nucleic acid molecule codes for a sarcoma-associated antigen which comprises the polypeptide sequence set forth as SEQ ID NO: 55 or a fragment thereof that is at least eight amino acids in length. In certain embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 122. In still other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 124. In yet other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 126. In still other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NOs: 128, 130 or 132.

In certain embodiments, the binding agent is an antisense or RNAi molecule. In other embodiments, the binding agent is a polypeptide, preferably an antibody or antigen-binding fragment thereof. Preferred antibodies include monoclonal antibodies, including chimeric, human, or humanized antibodies, and single chain antibodies; preferred antigen-binding fragments include $F(ab')_2$, Fab, Fd, or Fv fragments. In other embodiments, the antibody or antigen-binding fragment is bound to a cytotoxic agent.

According to yet another aspect of the invention, methods for treating a subject with a disorder characterized by the aberrant expression of a sarcoma-associated antigen or the nucleic acid molecule that encodes it are provided. The methods include administering to the subject an amount of an agent effective to stimulate an immune response to a sarcoma-associated antigen encoded by a nucleic acid molecule comprising a nucleotide sequence that is at least 90% identical to the nucleotide sequence selected from the group consisting of SEQ ID NOs: 3, 5-8, 10-45, 99, 102, 104 and 108. In some embodiments the sarcoma-associated antigen is encoded by a nucleic acid molecule comprising a nucleotide sequence that is at least 90% identical to the nucleotide sequence selected from the group consisting of SEQ ID NOs: 5-7, 10-13, 15-45, 102, 104 and 108. In some embodiments, the disorder is cancer, particularly sarcoma. In other embodiments the sarcoma-associated nucleic acid molecule comprises the nucleotide sequence selected from the group consisting of nucleotide sequences set forth as SEQ ID NOs: 10, 11, 15, 102, 104 and 108. In some embodiments the sarcoma-associated nucleic acid molecule comprises the nucleotide sequence set forth as SEQ ID NO: 10. In other embodiments the sarcoma-associated antigen is encoded by a nucleic acid molecule comprising a nucleotide sequence set forth as SEQ ID NO: 133.

In yet other embodiments the sarcoma-associated antigen includes an amino acid sequence selected from the group consisting of SEQ ID NOs: 48, 50-53, 55-90, 111, 114, 116 and 120, or a fragment thereof that is at least eight amino acids in length. In still other embodiments the sarcoma-associated antigen includes an amino acid sequence selected from the group consisting of SEQ ID NOs: 50-52, 55-58, 60-90, 114, 116 and 120, or a fragment thereof that is at least eight amino acids in length. In some embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 55, or a fragment thereof that is at least eight amino acids in length. In certain embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 122. In still other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 124. In yet other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 126. In still other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NOs: 128, 130 or 132. In still further embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 134, or a fragment thereof that is at least eight amino acids in length.

In some embodiments, the agent that stimulates an immune response is a nucleic acid that encodes a sarcoma-associated antigen operably linked to a promoter for expressing the sarcoma-associated antigen; a polypeptide comprising the sarcoma-associated antigen; or a host cell that expresses the sarcoma-associated antigen, particularly a host cell that also expresses a MHC molecule. In some embodiments, the agent which stimulates an immune response is a peptide fragment of the sarcoma-associated antigen, or is a complex of a peptide fragment of the sarcoma-associated antigen and a MHC molecule. In other embodiments, the agent also includes an adjuvant or cytokine.

In another aspect of the invention, kits for diagnosing a disorder associated with the aberrant expression of a sarcoma-associated antigen or a nucleic acid molecule that encodes it are provided. The kits include one or more nucleic acid molecules that hybridize to the nucleic acid molecule that encodes the sarcoma-associated antigen comprising a nucleotide sequence selected from the group consisting of nucleotide sequences set forth as SEQ ID NOs: 3, 5-8, 10-45, 99, 102, 104 and 108 under high stringency conditions, and instructions for the use of the nucleic acid molecules in the diagnosis of a disorder associated with aberrant expression of the sarcoma-associated antigen or the nucleic acid molecule that encodes it. In some embodiments the one or more nucleic acid molecules that hybridize to the nucleic acid molecule that encodes the sarcoma-associated antigen comprises a nucleotide sequence selected from the group consisting of nucleotide sequences set forth as SEQ ID NOs: 5-7, 10-13, 15-45, 102, 104 and 108. In some embodiments, the one or more nucleic acid molecules are detectably labeled. In some embodiments the nucleic acid molecule that encodes the sarcoma-associated antigen comprises the nucleotide sequence set forth as SEQ ID NO: 10, 11, 15, 102, 104 or 108. In other embodiments the nucleic acid molecule that encodes the sar-

coma-associated antigen comprises the nucleotide sequence set forth as SEQ ID NO: 10. In other embodiments the nucleic acid molecule includes the nucleotide sequence set forth as SEQ ID NO: 121. In still other embodiments the nucleic acid molecule includes the nucleotide sequence set forth in SEQ ID NO: 123. In yet other embodiments the nucleic acid molecule includes the nucleotide sequence set forth in SEQ ID NO: 125. In still other embodiments the nucleic acid molecule includes the nucleotide sequence set forth in SEQ ID NOs: 127, 129 or 131.

In certain embodiments, the one or more nucleic acid molecules consist of a first primer and a second primer, wherein the first primer and the second primer are constructed and arranged to selectively amplify at least a portion of a nucleic acid molecule that encodes the sarcoma-associated antigen and comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 10, 11, 15, 102, 104 and 108. In other embodiments, the nucleic acids in the kit are bound to a substrate.

In still another aspect of the invention, methods for identifying a cancer-associated antigen are provided. The methods include obtaining a biological sample from one or more subjects, determining the reactivity of the biological sample to one or more known cancer-associated antigens, using the reactive biological sample to screen an expression library to determine the presence of cancer-associated antigens reactive with the biological sample, and isolating a clone that encodes the cancer-associated antigen from the expression library. In certain embodiments the biological sample is serum. In some embodiments the expression library is derived from a tumor, preferably from a tumor cell line.

In still other embodiments, the methods also include determining the identity of the cancer-associated antigen encoded by the isolated clone, preferably by DNA sequencing.

The invention in a further aspect provides a composition including an agent that stimulates an immune response to a sarcoma-associated antigen. In some embodiments sarcoma-associated antigens are those encoded by a nucleic acid molecule selected from the group consisting of an isolated nucleic acid molecule comprising a nucleotide sequence that is at least 90% identical to the nucleotide sequence selected from the group consisting of SEQ ID NOs: 3, 5-8, 10-45, 99, 102, 104 and 108, and nucleic acid molecules that differ from the nucleic acid molecules of (a) in codon sequence due to the degeneracy of the genetic code. In some embodiments the sarcoma-associated antigens are those encoded by a nucleic acid molecule selected from the group consisting of an isolated nucleic acid molecule comprising a nucleotide sequence that is at least 90% identical to the nucleotide sequence selected from the group consisting of SEQ ID NOs: 5-7, 10-13, 15-45, 102, 104 and 108, and nucleic acid molecules that differ from the nucleic acid molecules of (a) in codon sequence due to the degeneracy of the genetic code. In particular embodiments, the nucleic acid molecule includes a nucleotide sequence selected from the group consisting of SEQ ID NOs: 10, 11, 15, 102, 104 and 108. In some embodiments the nucleic acid molecule includes the nucleotide sequence set forth as SEQ ID NO: 10. In other embodiments the nucleic acid molecule includes the nucleotide sequence set forth as SEQ ID NO: 133.

In some embodiments, sarcoma-associated antigen comprises a polypeptide sequence selected from the group consisting of SEQ ID NOs: 48, 50-53, 55-90, 111, 114, 116 and 120 or a fragment thereof that is at least eight amino acids in length. In other embodiments, sarcoma-associated antigen comprises a polypeptide sequence selected from the group consisting of SEQ ID NOs: 50-52, 55-58, 60-90, 114, 116 and 120 or a fragment thereof that is at least eight amino acids in length. In some embodiments the sarcoma-associated antigen includes the amino acid sequence of SEQ ID NO: 55, 56, 60, 114, 116 or 120 or a fragment thereof that is at least eight amino acids in length. In other embodiments the sarcoma-associated antigen includes the amino acid sequence of SEQ ID NO: 55 or a fragment thereof that is at least eight amino acids in length. In certain embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 122. In still other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 124. In yet other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 126. In still other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NOs: 128, 130 or 132. In yet other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 134.

The agent, in some embodiments, is a nucleic acid that encodes a sarcoma-associated antigen operably linked to a promoter for expressing the sarcoma-associated antigen. In other embodiments, the agent is a polypeptide comprising the sarcoma-associated antigen. In still other embodiments, the agent is a host cell that expresses the sarcoma-associated antigen; preferably the host cell also expresses a MHC molecule. In yet other embodiments, the agent is a complex of a peptide derived from the sarcoma-associated antigen and a MHC molecule.

The composition also includes, in certain embodiments, an adjuvant or cytokine and/or one or more cytotoxic or chemotherapeutic agents. The compositions optionally includes a pharmaceutically acceptable carrier.

In another aspect of the invention, compositions are provided that include an agent that selectively binds to a sarcoma-associated antigen or a nucleic acid molecule that encodes it. The nucleic acid molecule includes a nucleotide sequence selected from the group consisting of: (a) an isolated nucleic acid molecule comprising a nucleotide sequence that is at least 90% identical to the nucleotide sequence selected from the group consisting of SEQ ID NOs: 3, 5-8, 10-13, 99, 102 and 104 and (b) nucleic acid molecules that differ from the nucleic acid molecules of (a) in codon sequence due to the degeneracy of the genetic code. In some embodiments the nucleic acid molecule includes a nucleotide sequence selected from the group consisting of: (a) an isolated nucleic acid molecule comprising a nucleotide sequence that is at least 90% identical to the nucleotide sequence selected from the group consisting of SEQ ID NOs: 5-7, 10-13, 102 and 104 and (b) nucleic acid molecules that differ from the nucleic acid molecules of (a) in codon sequence due to the degeneracy of the genetic code. In some embodiments the nucleic acid molecule includes a nucleotide sequence selected from the group consisting of SEQ ID NOs: 10, 11, 102 and 104; in other embodiments the nucleic acid molecule includes the nucleotide sequence set forth as SEQ ID NO: 10. In other embodiments the nucleic acid molecule includes the nucleotide sequence set forth as SEQ ID NO: 121. In still other embodiments the nucleic acid molecule includes the nucleotide sequence set forth in SEQ ID NO: 123. In yet other embodiments the nucleic acid molecule includes the nucleotide sequence set forth in SEQ ID NO: 125. In still other embodiments the nucleic acid molecule includes the nucleotide sequence set forth in SEQ ID NOs: 127, 129 or 131. In other embodiments, the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 55, 56, 114 or 116 or a fragment thereof that is at least eight amino acids in length. In some embodiments the sarcoma-associated anti-

gen includes the amino acid sequence set forth as SEQ ID NO: 55. In certain embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 122. In still other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 124. In yet other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NO: 126. In still other embodiments the sarcoma-associated antigen includes the amino acid sequence set forth as SEQ ID NOs: 128, 130 or 132. The agents in this aspect of the invention include nucleic acids and polypeptides, preferably antibodies or antigen-binding fragments thereof. Preferred antibodies include monoclonal antibodies (particularly chimeric, human, or humanized antibodies), and single chain antibodies; preferred antibody fragments include $F(ab')_2$, Fab, Fd, or Fv fragments.

In certain embodiments, the antibody or antigen-binding fragment is conjugated to cytotoxic or chemotherapeutic agent. In other embodiments, the composition includes one or more cytotoxic or chemotherapeutic agent. In still other embodiments, the composition includes a pharmaceutically acceptable carrier.

The use of the nucleotide and amino acid sequence as set forth as SEQ ID NOs: 133 and 134, respectively, in any of the compositions and methods described herein are also provided.

The invention also involves the use of the genes, gene products, fragments thereof, agents which bind thereto, and other compositions and molecules described herein in the preparation of medicaments. A particular medicament is for treating cancer.

These and other aspects of the invention will be described in further detail in connection with the detailed description of the invention.

BRIEF DESCRIPTION OF THE DRAWING

FIG. **1** provides the mRNA expression patterns of serologically defined sarcoma antigens. FIG. **1**A shows the results of the RT-PCR analysis of NY-SAR-12, -35, and -41 in a panel of 17 normal tissues (Lanes 1, brain; 2, kidney; 3, liver; 4, pancreas; 5, placenta; 6, testis; 7, fetal brain; 8, small intestine; 9, heart; 10, prostate; 11, adrenal gland; 12, spleen; 13, colon; 14, stomach; 15, lung; 16, bladder; and 17, ovary). FIG. **1**B provides the results of the quantitative real-time RT-PCR analysis of NY-SAR-35 in various normal tissues. FIG. **1**C shows the results of the RT-PCR analysis of NY-SAR-35 expression in sarcoma cell lines and sarcoma tissue (Lane 1, fibrosarcoma; 2, rhabdomyosarcoma; 3, leiomyosarcoma; and 4, normal testis). FIG. **1**D provides the results of the Northern blot analysis of NY-SAR-35 in various normal tissues (Lane 1, spleen; 2, thymus; 3, prostate; 4, testis; 5, ovary; 6, small intestine; 7, colon mucosa; and 8, peripheral blood leukocytes).

FIG. **2** provides the nucleotide and predicted amino acid sequence of NY-SAR-35 from each of the four ATG codons. The underlined letters indicate the signal peptide and the italicized letters indicate the transmembrane domain. The letters shown in gray represent the trefoil domain, while the letters that are underlined and italicized represent the other hydrophilic turn.

FIG. **3** provides the results of Western blot assay of recombinant NY-SAR-35 proteins in *E. coli*. Three colonies of each domain cloned plasmid were picked and cultured by IPTG induction. After a four hour induction, total proteins from each of the colonies were separated by SDS-gel electrophoresis. The protein gel was immunoblotted on a membrane with a His-epitope monoclonal antibody. Lanes 1, 2, and 3-whole protein (from the first ATG codon); Lanes 4, 5 and 6—MH7 protein; Lanes 7, 8, and 9-extracellular protein and Lanes 10 and 11-*E. coli* lysate as negative control.

FIG. **4** provides the real-time RT-PCR analysis of NY-SAR-35 mRNA in various normal tissues and non-small cell lung cancer specimens. NY-SAR-35 was expressed in normal testis (83.2 ag) at a level that was >1,000 times the level detected in all other normal tissues. In 2 of 9 cases of non-small cell lung cancer examined, the level of NY-SAR-35 expression was equivalent to 0.15 (12.5 ag) and 0.13 (10.8 ag) times the level detected in normal testis, or approximately 100 times the level detected in normal tissues.

DETAILED DESCRIPTION OF THE INVENTION

The screening of cDNA expression libraries derived from human tumors with autologous antibody (SEREX) has proven to be a powerful method for defining the structure of tumor antigens recognized by the humoral immune system, and has led to the identification of new targets for cancer immunotherapy. The current study examined the humoral immune response of sarcoma patients to CT antigens. Sera from patients which showed a humoral immune response to CT antigens were subsequently used to screen cDNA libraries derived from CT-rich sarcoma cell lines, leading to the identification of antigens not before associated with cancer along with several novel antigens associated with a sarcoma-related immune response, including a novel CT antigen, NY-SAR-35.

Sarcoma-associated antigens were identified with an optimized SEREX analysis method. Cell lines that were rich in CT antigen expression were chosen as the source of cDNA. Additionally, sera was obtained from a group of patients that were actively mounting a humoral immune response to a panel of known CT antigens. This optimized SEREX analysis led to the identification of 113 antigens reactive with serum IgG of sarcoma patients. The antigens identified were further evaluated for cancer-restricted expression and the frequency of eliciting antibody responses in normal individuals as well as cancer patients.

In the first round of immunoscreenings, twenty-four of 72 antigens (33%) were found to have a serological profile that was not restricted to cancer patients, as evidenced by their reactivity with normal sera, while 48 antigens had a cancer-related serological profile, reacting only with sera from cancer patients. Notable antigens belonging to this latter category include the CT antigens, NY-SAR-36/SSX-1, NY-SAR-43/SSX-4 and NY-SAR-35. Although the antibody response in these studies to NY-SAR-4/FH was most frequent, occurring in 5/39 (13%) sarcoma patients, no individual antigen was serodominant. NY-SAR-4 is equivalent to fumarate hydratase (FH), an enzyme of the tricarboxylic acid cycle. This serological response to NY-SAR-4/FH may be of interest given the recent finding that germ line mutations in the FH gene are associated with a predisposition to uterine and cutaneous leiomyomata, and also renal cell carcinoma (Tomlinson I P, et al. Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. Nat Genet 2002 April; 30(4):406-10).

In addition, 6 tissue-restricted antigens, LAGE-1/NY-SAR-17, SSX1/NY-SAR-36, SSX4/NY-SAR-43, NESG1/NY-SAR-12, NY-SAR-35, and NY-SAR-41 were identified. Two of these antigens, NY-SAR-35, and NY-SAR-41 are novel gene products, and a third, NESG1/NY-SAR-12 (Li Z, Yao K, Cao Y. Molecular cloning of a novel tissue-specific gene from human nasopharyngeal epithelium. Gene 1999

Sep. 3; 237(1):235-40), has not been previously studied in relation to cancer. NY-SAR-35 further represents a newly defined CT antigen expressed exclusively in normal testis, melanoma, sarcoma, lung cancer and breast cancer.

The second round of immunoscreenings performed led to the identification of 41 additional SEREX-defined sarcoma antigens, 11 of which are novel gene products (NY-SAR-77, -79, -80, -84, -88, -92, -95, -97, -104, 105 and -113). Within this group of 41 sarcoma antigens are three known testis-restricted antigens (NY-SAR-78/TSP-NY, NY-SAR-89/SSX2 and NY-SAR-99/SSX3), two differentially expressed antigens that are novel gene products (NY-SAR-92 and NY-SAR-97) and a tissue-restricted antigen that has not been previously studied in relation to cancer (NY-SAR-96/MCSP).

Table 1, below, provides a list of the sarcoma-associated antigens and their corresponding sequence identification numbers. The antigens listed include those that were found to be uncharacterized gene products as well as those sarcoma-associated antigens that exhibited cancer-restricted expression and were not found in the SEREX Database.

TABLE 1

Sarcoma-Associated Antigens (Uncharacterized Gene Products and Cancer-Related Antigens not Found in the SEREX Database)

NY-SAR-Antigen	Sequence Identification Number (nucleotide and amino acid sequence, respectively)
3	SEQ ID NOs: 1 and 46
10	SEQ ID NOs: 2 and 47
16	SEQ ID NOs: 3 and 48
22	SEQ ID NOs: 4 and 49
23	SEQ ID NOs: 5 and 50
24	SEQ ID NOs: 6 and 51
27	SEQ ID NOs: 7 and 52
28	SEQ ID NOs: 8 and 53
29	SEQ ID NOs: 9 and 54
35	SEQ ID NOs: 10 and 55
41	SEQ ID NOs: 11 and 56
48	SEQ ID NOs: 12 and 57
62	SEQ ID NOs: 13 and 58
71	SEQ ID NOs: 14 and 59
12	SEQ ID NOs: 15 and 60
4	SEQ ID NOs: 16 and 61
5	SEQ ID NOs: 17 and 62
8	SEQ ID NOs: 18 and 63
9	SEQ ID NOs: 19 and 64
20	SEQ ID NOs: 20 and 65
21	SEQ ID NOs: 21 and 66
25	SEQ ID NOs: 22 and 67
26	SEQ ID NOs: 23 and 68
30	SEQ ID NOs: 24 and 69
34	SEQ ID NOs: 25 and 70
36	SEQ ID NOs: 26 and 71
37	SEQ ID NOs: 27 and 72
38	SEQ ID NOs: 28 and 73
39	SEQ ID NOs: 29 and 74
40	SEQ ID NOs: 30 and 75
42	SEQ ID NOs: 31 and 76
43	SEQ ID NOs: 32 and 77
46	SEQ ID NOs: 33 and 78
49	SEQ ID NOs: 34 and 79
50	SEQ ID NOs: 35 and 80
51	SEQ ID NOs: 36 and 81
52	SEQ ID NOs: 37 and 82
56	SEQ ID NOs: 38 and 83
57	SEQ ID NOs: 39 and 84
59	SEQ ID NOs: 40 and 85
60	SEQ ID NOs: 41 and 86
63	SEQ ID NOs: 42 and 87
67	SEQ ID NOs: 43 and 88
69	SEQ ID NOs: 44 and 89
70	SEQ ID NOs: 45 and 90

TABLE 1-continued

Sarcoma-Associated Antigens (Uncharacterized Gene Products and Cancer-Related Antigens not Found in the SEREX Database)

NY-SAR-Antigen	Sequence Identification Number (nucleotide and amino acid sequence, respectively)
77	SEQ ID NOs: 97 and 109
79	SEQ ID NOs: 98 and 110
80	SEQ ID NOs: 99 and 111
84	SEQ ID NOs: 100 and 112
88	SEQ ID NOs: 101 and 113
92	SEQ ID NOs: 102 and 114
95	SEQ ID NOs: 103 and 115
97	SEQ ID NOs: 104 and 116
104	SEQ ID NOs: 105 and 117
105	SEQ ID NOs: 106 and 118
113	SEQ ID NOs: 107 and 119
96	SEQ ID NOs: 108 and 120

The invention relates, in part, to the sarcoma-associated antigens defined herein and the nucleic acid molecules that encode them. The invention further relates to the use of the nucleic acid molecules, polypeptides and fragments thereof associated with sarcoma in methods and compositions for the diagnosis and treatment of diseases, such as cancer.

As used herein, the term "sarcoma-associated antigens" means polypeptides that elicit specific immune responses to the polypeptide when expressed by a tumor cell and thus, include sarcoma-associated polypeptides (including proteins) and fragments of sarcoma-associated polypeptides, that are recognized by the immune system (e.g., by antibodies and/or T lymphocytes). In part, the invention relates to sarcoma-associated antigens as well as the nucleic acid molecules that encode the sarcoma-associated antigens. As used herein, the "nucleic acid molecules that encode" means the nucleic acid molecules that code for the immunogenic sarcoma-associated polypeptides or immunogenic fragments thereof. These nucleic acid molecules may be DNA or may be RNA (e.g. mRNA). The sarcoma-associated nucleic acid molecules of the invention also encompass variants of the nucleic acid molecules described herein. These variants may be splice variants or allelic variants of certain sequences provided. Variants of the nucleic acid molecules of the invention are intended to include homologs and alleles which are described further below. Further, as used herein, the term "sarcoma-associated molecules" includes sarcoma-associated antigens (polypeptides and fragments thereof) as well as sarcoma-associated nucleic acids. In all embodiments, human sarcoma-associated antigens and the encoding nucleic acid molecules thereof, are preferred.

In one aspect, the invention provides isolated nucleic acid molecules that encode the sarcoma-associated antigens defined herein. The isolated nucleic acid molecules of this aspect of the invention comprise: (a) nucleotide sequences selected from the group consisting of nucleotide sequences set forth as SEQ ID NOs: 1-14 and 97-107 (b) isolated nucleic acid molecules which hybridize under highly stringent conditions to the nucleic acid molecules of (a) and which code for a sarcoma-associated antigen, (c) nucleic acid molecules that differ from (a) or (b) due to the degeneracy of the genetic code, and (d) complements of (a), (b) or (c).

As used herein the term "isolated nucleic acid molecule" means: (i) amplified in vitro by, for example, polymerase chain reaction (PCR); (ii) recombinantly produced by cloning; (iii) purified, as by cleavage and gel separation; or (iv) synthesized by, for example, chemical synthesis. An isolated nucleic acid is one which is readily manipulable by recombi-

nant DNA techniques well known in the art. Thus, a nucleotide sequence contained in a vector in which 5' and 3' restriction sites are known or for which polymerase chain reaction (PCR) primer sequences have been disclosed is considered isolated but a nucleic acid sequence existing in its native state in its natural host is not. An isolated nucleic acid may be substantially purified, but need not be. For example, a nucleic acid that is isolated within a cloning or expression vector is not pure in that it may comprise only a tiny percentage of the material in the cell in which it resides. Such a nucleic acid is isolated, however, as the term is used herein because it is readily manipulable by standard techniques known to those of ordinary skill in the art.

The sarcoma-associated nucleic acid molecules of the invention also intended to encompass homologs and alleles which can be identified by conventional techniques. Identification of human and other organism homologs of sarcoma-associated polypeptides will be familiar to those of skill in the art. In general, nucleic acid hybridization is a suitable method for identification of homologous sequences of another species (e.g., human, cow, sheep), which correspond to a known sequence. Standard nucleic acid hybridization procedures can be used to identify related nucleic acid sequences of selected percent identity. For example, one can construct a library of cDNAs reverse transcribed from the mRNA of a selected tissue and use the nucleic acids that encode sarcoma-associated antigens identified herein to screen the library for related nucleotide sequences. The screening preferably is performed using high-stringency conditions to identify those sequences that are closely related by sequence identity. Nucleic acids so identified can be translated into polypeptides and the polypeptides can be tested for activity.

The term "high stringency" as used herein refers to parameters with which the art is familiar. Nucleic acid hybridization parameters may be found in references that compile such methods, e.g. Molecular Cloning: A Laboratory Manual, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989, or Current Protocols in Molecular Biology, F. M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. More specifically, high-stringency conditions, as used herein, refers, for example, to hybridization at 65° C. in hybridization buffer (3.5×SSC, 0.02% Ficoll, 0.02% polyvinyl pyrrolidone, 0.02% Bovine Serum Albumin, 2.5 mM NaH2PO4(pH7), 0.5% SDS, 2 mM EDTA). SSC is 0.15M sodium chloride/0.15M sodium citrate, pH7; SDS is sodium dodecyl sulphate; and EDTA is ethylenediaminetetracetic acid. After hybridization, the membrane upon which the DNA is transferred is washed, for example, in 2×SSC at room temperature and then at 0.1-0.5× SSC/0.1×SDS at temperatures up to 68° C.

There are other conditions, reagents, and so forth that can be used, which result in a similar degree of stringency. The skilled artisan will be familiar with such conditions, and thus they are not given here. It will be understood, however, that the skilled artisan will be able to manipulate the conditions in a manner to permit the clear identification of homologs and alleles of the sarcoma-associated nucleic acids of the invention (e.g., by using lower stringency conditions). The skilled artisan also is familiar with the methodology for screening cells and libraries for expression of such molecules, which then are routinely isolated, followed by isolation of the pertinent nucleic acid molecule and sequencing.

In general, homologs and alleles typically will share at least 90% nucleotide identity and/or at least 95% amino acid identity to the sequences of sarcoma-associated nucleic acids and polypeptides, respectively, in some instances will share at least 95% nucleotide identity and/or at least 97% amino acid identity, in other instances will share at least 97% nucleotide identity and/or at least 98% amino acid identity, in other instances will share at least 99% nucleotide identity and/or at least 99% amino acid identity, and in other instances will share at least 99.5% nucleotide identity and/or at least 99.5% amino acid identity. The homology can be calculated using various, publicly available software tools developed by NCBI (Bethesda, Md.) that can be obtained through the internet. Exemplary tools include the BLAST system available from the website of the National Center for Biotechnology Information (NCBI) at the National Institutes of Health. Pairwise and ClustalW alignments (BLOSUM30 matrix setting) as well as Kyte-Doolittle hydropathic analysis can be obtained using the MacVector sequence analysis software (Oxford Molecular Group). Watson-Crick complements of the foregoing nucleic acids also are embraced by the invention.

In another aspect of the invention, unique fragments are provided which include unique fragments of the nucleotide sequences of the invention and complements thereof. The invention, in a preferred embodiment, provides unique fragments of SEQ ID NO: 10, 11, 15, 102, 104 or 108 and complements thereof. In another preferred embodiment, provides unique fragments of SEQ ID NO: 10 and complements thereof. In other embodiments the unique fragment includes the nucleotide sequence set forth as SEQ ID NO: 121. In still other embodiments the unique fragments includes the sequence set forth as SEQ ID NO: 123, 125, 127, 129 or 131. A unique fragment is one that is a 'signature' for the larger nucleic acid. It, for example, is long enough to assure that its precise sequence is not found in molecules outside of the nucleic acid molecules that encode the sarcoma-associated antigens defined above. Those of ordinary skill in the art may apply no more than routine procedures to determine if a fragment is unique within the human genome. In some instances the unique fragment is at least about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 75, or 100 amino acids in length.

Unique fragments can be used as probes in Southern blot assays to identify such nucleic acid molecules, or can be used as probes in amplification assays such as those employing the polymerase chain reaction (PCR), including, but not limited to RT-PCR and RT-real-time PCR. As known to those skilled in the art, large probes such as 200 nucleotides or more are preferred for certain uses such as Southern blots, while smaller fragments will be preferred for uses such as PCR. Unique fragments also can be used to produce fusion proteins for generating antibodies or determining binding of the polypeptide fragments, or for generating immunoassay components. Likewise, unique fragments can be employed to produce nonfused fragments of the sarcoma-associated polypeptides useful, for example, in the preparation of antibodies and in immunoassays.

In screening for sarcoma-associated antigen genes, a Southern blot may be performed using the foregoing conditions, together with a detectably labeled probe (e.g. radioactive or chemiluminescent probes). After washing the membrane to which the DNA is finally transferred, the membrane can be placed against X-ray film or analyzed using a phosphorimager device to detect the radioactive or chemiluminescent signal. In screening for the expression of sarcoma-associated antigen nucleic acids, Northern blot hybridizations using the foregoing conditions can be performed on samples taken from cancer patients or subjects suspected of having a condition characterized by abnormal cell proliferation or neoplasia. Amplification protocols such as polymerase chain reaction using primers that hybridize to the sequences pre-

sented also can be used for detection of the sarcoma-associated antigen genes or expression thereof.

Identification of related sequences can also be achieved using polymerase chain reaction (PCR) and other amplification techniques suitable for cloning related nucleic acid sequences. Preferably, PCR primers are selected to amplify portions of a nucleic acid sequence believed to be conserved (e.g., a catalytic domain, a DNA-binding domain, etc.). Again, nucleic acids are preferably amplified from a tissue-specific library (e.g., testis). One also can use expression cloning utilizing the antisera described herein to identify nucleic acids that encode related antigenic proteins in humans or other species using the SEREX procedure to screen the appropriate expression libraries. (See: Sahin et al. Proc. Natl. Acad. Sci. USA 92:11810-11813, 1995).

The invention also includes degenerate nucleic acids that include alternative codons to those present in the native materials. For example, serine residues are encoded by the codons TCA, AGT, TCC, TCG, TCT and AGC. Each of the six codons is equivalent for the purposes of encoding a serine residue. Thus, it will be apparent to one of ordinary skill in the art that any of the serine-encoding nucleotide triplets may be employed to direct the protein synthesis apparatus, in vitro or in vivo, to incorporate a serine residue into an elongating sarcoma-associated polypeptide. Similarly, nucleotide sequence triplets which encode other amino acid residues include, but are not limited to: CCA, CCC, CCG, and CCT (proline codons); CGA, CGC, CGG, CGT, AGA, and AGG (arginine codons); ACA, ACC, ACG, and ACT (threonine codons); AAC and AAT (asparagine codons); and ATA, ATC, and ATT (isoleucine codons). Other amino acid residues may be encoded similarly by multiple nucleotide sequences. Thus, the invention embraces degenerate nucleic acids that differ from the biologically isolated nucleic acids in codon sequence due to the degeneracy of the genetic code.

The invention also provides modified nucleic acid molecules, which include additions, substitutions and deletions of one or more nucleotides (preferably 1-20 nucleotides). In preferred embodiments, these modified nucleic acid molecules and/or the polypeptides they encode retain at least one activity or function of the unmodified nucleic acid molecule and/or the polypeptides, such as antigenicity, receptor binding, etc. In certain embodiments, the modified nucleic acid molecules encode modified polypeptides, preferably polypeptides having conservative amino acid substitutions as are described elsewhere herein. The modified nucleic acid molecules are structurally related to the unmodified nucleic acid molecules and in preferred embodiments are sufficiently structurally related to the unmodified nucleic acid molecules so that the modified and unmodified nucleic acid molecules hybridize under stringent conditions known to one of skill in the art.

For example, modified nucleic acid molecules that encode polypeptides having single amino acid changes can be prepared. Each of these nucleic acid molecules can have one, two or three nucleotide substitutions exclusive of nucleotide changes corresponding to the degeneracy of the genetic code as described herein. Likewise, modified nucleic acid molecules that encode polypeptides having two amino acid changes can be prepared which have, e.g., 2-6 nucleotide changes. Numerous modified nucleic acid molecules like these will be readily envisioned by one of skill in the art, including for example, substitutions of nucleotides in codons encoding amino acids 2 and 3, 2 and 4, 2 and 5, 2 and 6, and so on. In the foregoing example, each combination of two amino acids is included in the set of modified nucleic acid molecules, as well as all nucleotide substitutions which code for the amino acid substitutions. Additional nucleic acid molecules that encode polypeptides having additional substitutions (i.e., 3 or more), additions or deletions (e.g., by introduction of a stop codon or a splice site(s)) also can be prepared and are embraced by the invention as readily envisioned by one of ordinary skill in the art. Any of the foregoing nucleic acids or polypeptides can be tested by routine experimentation for retention of activity or structural relation to the nucleic acids and/or polypeptides disclosed herein. As used herein the terms: "deletion", "addition", and "substitution" mean deletion, addition, and substitution changes to about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more nucleic acids of a sequence of the invention.

According to yet another aspect of the invention, an expression vector comprising any of the isolated nucleic acid molecules of the invention, preferably operably linked to a promoter is provided. In a related aspect, host cells transformed or transfected with such expression vectors also are provided. As used herein, a "vector" may be any of a number of nucleic acid molecules into which a desired sequence may be inserted by restriction and ligation for transport between different genetic environments or for expression in a host cell. Vectors are typically composed of DNA although RNA vectors are also available. Vectors include, but are not limited to, plasmids, phagemids, and virus genomes. A cloning vector is one which is able to replicate in a host cell, and which is further characterized by one or more endonuclease restriction sites at which the vector may be cut in a determinable fashion and into which a desired DNA sequence may be ligated such that the new recombinant vector retains its ability to replicate in the host cell. In the case of plasmids, replication of the desired sequence may occur many times as the plasmid increases in copy number within the host bacterium or just a single time per host before the host reproduces by mitosis. In the case of phage, replication may occur actively during a lytic phase or passively during a lysogenic phase. An expression vector is one into which a desired DNA sequence may be inserted by restriction and ligation such that it is operably joined to regulatory sequences and may be expressed as an RNA transcript. Vectors may further contain one or more marker sequences suitable for use in the identification of cells which have or have not been transformed or transfected with the vector. Markers include, for example, genes encoding proteins which increase or decrease either resistance or sensitivity to antibiotics or other compounds, genes which encode enzymes whose activities are detectable by standard assays known in the art, e.g., -galactosidase or alkaline phosphatase, and genes which visibly affect the phenotype of transformed or transfected cells, hosts, colonies or plaques, e.g., green fluorescent protein. Preferred vectors are those capable of autonomous replication and expression of the structural gene products present in the DNA segments to which they are operably joined.

As used herein, a coding sequence and regulatory sequences are said to be "operably joined" when they are covalently linked in such a way as to place the expression or transcription of the coding sequence under the influence or control of the regulatory sequences. As used herein, "operably joined" and "operably linked" are used interchangeably and should be construed to have the same meaning. If it is desired that the coding sequences be translated into a functional protein, two DNA sequences are said to be operably joined if induction of a promoter in the 5' regulatory sequences results in the transcription of the coding sequence and if the nature of the linkage between the two DNA sequences does not (1) result in the introduction of a frame-

shift mutation, (2) interfere with the ability of the promoter region to direct the transcription of the coding sequences, or (3) interfere with the ability of the corresponding RNA transcript to be translated into a protein. Thus, a promoter region is operably joined to a coding sequence if the promoter region is capable of effecting transcription of that DNA sequence such that the resulting transcript can be translated into the desired protein or polypeptide.

The precise nature of the regulatory sequences needed for gene expression may vary between species or cell types, but shall in general include, as necessary, 5' non-transcribed and 5' non-translated sequences involved with the initiation of transcription and translation respectively, such as a TATA box, capping sequence, CAAT sequence, and the like. Often, such 5' non-transcribed regulatory sequences will include a promoter region which includes a promoter sequence for transcriptional control of the operably joined gene. Regulatory sequences may also include enhancer sequences or upstream activator sequences as desired. The vectors of the invention may optionally include 5' leader or signal sequences. The choice and design of an appropriate vector is within the ability and discretion of one of ordinary skill in the art.

It will also be recognized that the invention embraces the use of the sarcoma-associated nucleic acid molecules and genomic sequences in expression vectors, as well as to transfect host cells and cell lines, be these prokaryotic, e.g., *E. coli*, or eukaryotic, e.g., CHO cells, COS cells, yeast expression systems, and recombinant baculovirus expression in insect cells. Especially useful are mammalian cells such as human, mouse, hamster, pig, goat, primate, etc. They may be of a wide variety of tissue types, including mast cells, fibroblasts, oocytes, and lymphocytes, and may be primary cells and cell lines. Specific examples include dendritic cells, peripheral blood leukocytes, bone marrow stem cells and embryonic stem cells. The expression vectors require that the pertinent sequence, i.e., those nucleic acids described supra, be operably linked to a promoter.

The invention, in one aspect, also permits the construction of sarcoma-associated antigen gene "knock-outs" and "knock-ins" in cells and in animals, providing materials for studying certain aspects of cancer and immune system responses to cancer.

Expression vectors containing all the necessary elements for expression are commercially available and known to those skilled in the art. See, e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press, 1989. Cells are genetically engineered by the introduction into the cells of heterologous DNA or RNA encoding a sarcoma-associated antigen, a mutant sarcoma-associated antigen, fragments, or variants thereof. The heterologous DNA or RNA is placed under operable control of transcriptional elements to permit the expression of the heterologous DNA in the host cell.

Preferred systems for mRNA expression in mammalian cells are those such as pcDNA1.1 and pCDM8 (Invitrogen) that contain a selectable marker (which facilitates the selection of stably transfected cell lines) and contain the human cytomegalovirus (CMV) enhancer-promoter sequences. Additionally, suitable for expression in primate or canine cell lines is the pCEP4 vector (Invitrogen), which contains an Epstein Barr virus (EBV) origin of replication, facilitating the maintenance of plasmid as a multicopy extrachromosomal element. Another expression vector is the pEF-BOS plasmid containing the promoter of polypeptide Elongation Factor 1, which stimulates efficiently transcription in vitro. The plasmid is described by Mizushima and Nagata (Nuc. Acids Res. 18:5322, 1990), and its use in transfection experiments is disclosed by, for example, Demoulin (Mol. Cell. Biol. 16:4710-4716, 1996). Still another preferred expression vector is an adenovirus, described by Stratford-Perricaudet, which is defective for E1 and E3 proteins (J. Clin. Invest. 90:626-630, 1992). The use of the adenovirus as an Adeno.P1A recombinant is described by Warnier et al., in intradermal injection in mice for immunization against P1A (Int. J. Cancer, 67:303-310, 1996).

The invention also embraces kits termed expression kits, which allow the artisan to prepare a desired expression vector or vectors. Such expression kits include at least separate portions of each of the previously discussed coding sequences. Other components may be added, as desired, as long as the previously mentioned sequences, which are required, are included.

The invention also includes kits for amplification of a sarcoma-associated antigen nucleic acid, including at least one pair of amplification primers which hybridize to a sarcoma-associated nucleic acid. The primers preferably are about 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 or 32 nucleotides in length and are non-overlapping to prevent formation of "primer-dimers". One of the primers will hybridize to one strand of the sarcoma-associated nucleic acid and the second primer will hybridize to the complementary strand of the sarcoma-associated nucleic acid, in an arrangement which permits amplification of the sarcoma-associated nucleic acid. Selection of appropriate primer pairs is standard in the art. For example, the selection can be made with assistance of a computer program designed for such a purpose, optionally followed by testing the primers for amplification specificity and efficiency.

The invention, in another aspect provides isolated polypeptides (including whole proteins and partial proteins) encoded by the foregoing sarcoma-associated nucleic acids. Examples of the amino acid sequences encoded by the foregoing sarcoma-associated nucleic acids are set forth as SEQ ID NOs: 46-90 and 109-120. The amino acids of the invention are also intended to encompass amino acid sequences that result from the translation of the nucleic acid sequences provided herein in a different reading frame. In one preferred embodiment of the invention a polypeptide is provided which comprises the polypeptide sequence set forth as SEQ ID NO: 55, 56, 60, 114, 116 or 120. In another preferred embodiment a polypeptide is provided which comprises the polypeptide sequence set forth as SEQ ID NO: 122. In still another preferred embodiment a polypeptide is provided which comprises the polypeptide sequence set forth as SEQ ID NO: 124. In still other embodiments polypeptides are provided which comprise the polypeptide sequence set forth as SEQ ID NO: 126, 128, 130 or 132. Such polypeptides are useful, for example, alone or as fusion proteins to generate antibodies, and as components of an immunoassay or diagnostic assay. Immunogenic sarcoma-associated polypeptides can be isolated from biological samples including tissue or cell homogenates, and can also be expressed recombinantly in a variety of prokaryotic and eukaryotic expression systems by constructing an expression vector appropriate to the expression system, introducing the expression vector into the expression system, and isolating the recombinantly expressed protein. Fragments of the immunogenic sarcoma-associated polypeptides (including immunogenic peptides) also can be synthesized chemically using well-established methods of peptide synthesis. Thus, fragments of the disclosed polypeptides are useful for eliciting an immune response. In one embodiment fragments of a polypeptide which comprises SEQ ID NO: 55, 56, 60, 114, 116 or 120 that are at least eight amino acids in

length and exhibit immunogenicity are provided. In one embodiment fragments of a polypeptide which comprises SEQ ID NO: 55 that are at least eight amino acids in length and exhibit immunogenicity are provided. In another embodiment a polypeptide is provided which comprises the polypeptide sequence set forth as SEQ ID NO: 122. In still another preferred embodiments a polypeptide is provided which comprises the polypeptide sequence set forth as SEQ ID NO: 124. In still other embodiments polypeptides are provided which comprise the polypeptide sequence set forth as SEQ ID NO: 126, 128, 130 or 132.

Fragments of a polypeptide preferably are those fragments that retain a distinct functional capability of the polypeptide. Functional capabilities that can be retained in a fragment of a polypeptide include interaction with antibodies or MHC molecules (e.g. immunogenic fragments), interaction with other polypeptides or fragments thereof, selective binding of nucleic acids or proteins, and enzymatic activity. One important activity is the ability to provoke in a subject an immune response. As will be recognized by those skilled in the art, the size of the fragment that can be used for inducing an immune response will depend upon factors such as whether the epitope recognized by an antibody is a linear epitope or a conformational epitope or the particular MHC molecule that binds to and presents the fragment (e.g. HLA class I or II). Thus, some immunogenic fragments of sarcoma-associated polypeptides will consist of longer segments while others will consist of shorter segments, (e.g. about 5, 6, 7, 8, 9, 10, 11 or 12 or more amino acids long, including each integer up to the full length of the sarcoma-associated polypeptide). Those skilled in the art are well versed in methods for selecting immunogenic fragments of polypeptides.

The invention embraces variants of the sarcoma-associated polypeptides described above. As used herein, a "variant" of a sarcoma-associated antigen polypeptide is a polypeptide which contains one or more modifications to the primary amino acid sequence of a sarcoma-associated polypeptide. Modifications which create a sarcoma-associated antigen variant can be made to a sarcoma-associated polypeptide 1) to reduce or eliminate an activity of a sarcoma-associated polypeptide; 2) to enhance a property of a sarcoma-associated polypeptide, such as protein stability in an expression system or the stability of protein-protein binding; 3) to provide a novel activity or property to a sarcoma-associated polypeptide, such as addition of an antigenic epitope or addition of a detectable moiety; or 4) to provide equivalent or better binding to a MHC molecule.

Modifications to a sarcoma-associated polypeptide are typically made to the nucleic acid which encodes the sarcoma-associated polypeptide, and can include deletions, point mutations, truncations, amino acid substitutions and additions of amino acids or non-amino acid moieties. Alternatively, modifications can be made directly to the polypeptide, such as by cleavage, addition of a linker molecule, addition of a detectable moiety, such as biotin, addition of a fatty acid, and the like. Modifications also embrace fusion proteins comprising all or part of the sarcoma-associated antigen amino acid sequence. One of skill in the art will be familiar with methods for predicting the effect on protein conformation of a change in protein sequence, and can thus "design" a variant sarcoma-associated polypeptide according to known methods. One example of such a method is described by Dahiyat and Mayo in *Science* 278:82-87, 1997, whereby proteins can be designed de novo. The method can be applied to a known protein to vary a only a portion of the polypeptide sequence. By applying the computational methods of Dahiyat and Mayo, specific variants of a sarcoma-associated polypeptide can be proposed and tested to determine whether the variant retains a desired conformation.

In general, variants include sarcoma-associated polypeptides which are modified specifically to alter a feature of the polypeptide unrelated to its desired physiological activity. For example, cysteine residues can be substituted or deleted to prevent unwanted disulfide linkages. Similarly, certain amino acids can be changed to enhance expression of a sarcoma-associated polypeptide by eliminating proteolysis by proteases in an expression system (e.g., dibasic amino acid residues in yeast expression systems in which KEX2 protease activity is present).

Mutations of a nucleic acid which encode a sarcoma-associated polypeptide preferably preserve the amino acid reading frame of the coding sequence, and preferably do not create regions in the nucleic acid which are likely to hybridize to form secondary structures, such a hairpins or loops, which can be deleterious to expression of the variant polypeptide.

Mutations can be made by selecting an amino acid substitution, or by random mutagenesis of a selected site in a nucleic acid which encodes the polypeptide. Variant polypeptides are then expressed and tested for one or more activities to determine which mutation provides a variant polypeptide with the desired properties. Further mutations can be made to variants (or to non-variant sarcoma-associated polypeptides) which are silent as to the amino acid sequence of the polypeptide, but which provide preferred codons for translation in a particular host. The preferred codons for translation of a nucleic acid in, e.g., *E. coli*, are well known to those of ordinary skill in the art. Still other mutations can be made to the noncoding sequences of a sarcoma-associated antigen gene or cDNA clone to enhance expression of the polypeptide. The activity of variants of sarcoma-associated polypeptides can be tested by cloning the gene encoding the variant sarcoma-associated polypeptide into a bacterial or mammalian expression vector, introducing the vector into an appropriate host cell, expressing the variant sarcoma-associated polypeptide, and testing for a functional capability of the sarcoma-associated polypeptides as disclosed herein. For example, the variant sarcoma-associated polypeptide can be tested for reaction with autologous or allogeneic sera as described in the Examples. Preparation of other variant polypeptides may favor testing of other activities, as will be known to one of ordinary skill in the art.

The skilled artisan will also realize that conservative amino acid substitutions may be made in immunogenic sarcoma-associated polypeptides to provide functionally equivalent variants, or homologs of the foregoing polypeptides, i.e., the variants retain the functional capabilities of the immunogenic sarcoma-associated polypeptides. As used herein, a "conservative amino acid substitution" refers to an amino acid substitution that does not alter the relative charge or size characteristics of the protein in which the amino acid substitution is made. Variants can be prepared according to methods for altering polypeptide sequence known to one of ordinary skill in the art such as are found in references that compile such methods, e.g. Molecular Cloning: A Laboratory Manual, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989, or Current Protocols in Molecular Biology, F. M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. Exemplary functionally equivalent variants or homologs of the sarcoma-associated polypeptides include conservative amino acid substitutions of in the amino acid sequences of proteins disclosed herein. Conservative substitutions of amino acids include substitutions made amongst amino acids within the following groups: (a) M, I, L, V; (b) F, Y, W; (c) K, R, H; (d) A, G; (e) S, T; (f) Q,

N; and (g) E, D. Therefore, one can make conservative amino acid substitutions to the amino acid sequence of the sarcoma-associated antigens disclosed herein and retain the specific antibody-binding characteristics of the antigens.

Likewise, upon determining that a peptide derived from a sarcoma-associated polypeptide is presented by an MHC molecule and recognized by antibodies or T lymphocytes (e.g., helper T cells or CTLs), one can make conservative amino acid substitutions to the amino acid sequence of the peptide, particularly at residues which are thought not to be direct contact points with the MHC molecule. For example, methods for identifying functional variants of HLA class II binding peptides are provided in a published PCT application of Strominger and Wucherpfennig (PCT/US96/03182). Peptides bearing one or more amino acid substitutions also can be tested for concordance with known HLA/MHC motifs prior to synthesis using, e.g. the computer program described by D'Amaro and Drijfhout (D'Amaro et al., *Human Immunol.* 43:13-18, 1995; Drijfhout et al., *Human Immunol.* 43:1-12, 1995). The substituted peptides can then be tested for binding to the MHC molecule and recognition by antibodies or T lymphocytes when bound to MHC. These variants can be tested for improved stability and are useful, inter alia, in vaccine compositions.

Conservative amino-acid substitutions in the amino acid sequence of sarcoma-associated polypeptides to produce functionally equivalent variants of sarcoma-associated polypeptides typically are made by alteration of a nucleic acid encoding a sarcoma-associated polypeptide. Such substitutions can be made by a variety of methods known to one of ordinary skill in the art. For example, amino acid substitutions may be made by PCR-directed mutation, site-directed mutagenesis according to the method of Kunkel (Kunkel, Proc. Nat. Acad. Sci. U.S.A. 82: 488-492, 1985), or by chemical synthesis of a gene encoding a sarcoma-associated polypeptide. Where amino acid substitutions are made to a small unique fragment of a sarcoma-associated polypeptide, such as an antigenic epitope recognized by autologous or allogeneic sera or T lymphocytes, the substitutions can be made by directly synthesizing the peptide. The activity of functionally equivalent variants of sarcoma-associated polypeptides can be tested by cloning the gene encoding the altered sarcoma-associated polypeptide into a bacterial or mammalian expression vector, introducing the vector into an appropriate host cell, expressing the altered polypeptide, and testing for a functional capability of the sarcoma-associated polypeptides as disclosed herein. Peptides that are chemically synthesized can be tested directly for function, e.g., for binding to antisera recognizing associated antigens.

The invention as described herein has a number of uses, some of which are described elsewhere herein. In one aspect of the invention a method of identifying cancer-associated antigens is provided. Novel cancer-associated antigens can be identified by obtaining a biological sample from a subject, determining the reactivity of the biological sample with one or more known cancer-associated antigens, and subsequently using the reactive biological sample to screen an expression library to identify novel cancer-associated antigens as well as proteins previously known but not previously associated with cancer.

As used herein, a "subject" is preferably a human, non-human primate, cow, horse, pig, sheep, goat, dog, cat or rodent. In all embodiments, human subjects are preferred. In some embodiments, the subject is suspected of having cancer or has been diagnosed with cancer. Cancers in which the sarcoma-associated nucleic acid or polypeptide are differentially expressed include sarcoma.

As used herein, a biological sample includes, but is not limited to: tissue, cells, or body fluid (e.g. serum, blood, lymph node fluid, etc.). The fluid sample may include cells and/or fluid. The tissue and cells may be obtained from a subject or may be grown in culture (e.g. from a cell line). As used herein, a biological sample is body fluid, tissue or cells obtained from a subject using methods well-known to those of ordinary skill in the related medical arts.

The invention in another aspect permits the isolation of the cancer-associated antigens described herein. A variety of methodologies well-known to the skilled practitioner can be utilized to obtain isolated cancer-associated antigens. The proteins may be purified from cells which naturally produce the protein by chromatographic means or immunological recognition. Alternatively, an expression vector may be introduced into cells to cause production of the protein. In another method, mRNA transcripts may be microinjected or otherwise introduced into cells to cause production of the encoded protein. Translation of mRNA in cell-free extracts such as the reticulocyte lysate system also may be used to produce the protein. Those skilled in the art also can readily follow known methods for isolating cancer-associated antigens. These include, but are not limited to, chromatographic techniques such as immunochromatography, HPLC, size-exclusion chromatography, ion-exchange chromatography, and immune-affinity chromatography.

The invention also involves diagnosing or monitoring cancer in subjects by determining the presence of an immune response to one or more sarcoma-associated antigens of the invention. In preferred embodiments, this determination is performed by assaying a bodily fluid obtained from the subject, preferably serum, blood, or lymph node fluid for the presence of antibodies against the sarcoma-associated antigens described herein. This determination may also be performed by assaying a tissue or cells from the subject for the presence of one or more sarcoma-associated antigens (or nucleic acid molecules that encode these antigens) described herein. In another embodiment, the presence of antibodies against at least one additional cancer antigen is determined for diagnosis of cancer. The additional antigen may be a sarcoma-associated antigen as described herein or may be some other cancer-associated antigen. This determination may also be performed by assaying a tissue or cells from the subject for the presence of the sarcoma-associated antigens described herein.

Measurement of the immune response against one of the sarcoma-associated antigens over time by sequential determinations permits monitoring of the disease and/or the effects of a course of treatment. For example, a sample, such as serum, blood, or lymph node fluid, may be obtained from a subject, tested for an immune response to one of the sarcoma-associated antigens, and at a second, subsequent time, another sample, may be obtained from the subject and similarly tested. The results of the first and second (or subsequent) tests can be compared as a measure of the onset, regression or progression of cancer, or, if cancer treatment was undertaken during the interval between obtaining the samples, the effectiveness of the treatment may be evaluated by comparing the results of the two tests. In preferred embodiments the sarcoma-associated antigens are bound to a substrate. In other preferred embodiments the immune response of the biological sample to the sarcoma-associated antigens is determined with ELISA. Other methods will be apparent to one of skill in the art.

Diagnostic methods of the invention also involve determining the aberrant expression of one or more of the sarcoma-associated antigens described herein or the nucleic acid mol-

ecules that encode them. Such determinations can be carried out via any standard nucleic acid assay, including the polymerase chain reaction or assaying with hybridization probes, which may be labeled, or by assaying biological samples with binding partners (e.g., antibodies) for sarcoma-associated antigens.

The diagnostic methods of the invention can be used to detect the presence of a disorder associated with aberrant expression of a sarcoma-associated molecule, as well as to assess the progression and/or regression of the disorder such as in response to treatment (e.g., chemotherapy, radiation). According to this aspect of the invention, the method for diagnosing a disorder characterized by aberrant expression of a sarcoma-associated molecule involve: detecting expression of a sarcoma-associated molecule in a first biological sample obtained from a subject, wherein differential expression of the sarcoma-associated molecule compared to a control sample indicates that the subject has a disorder characterized by aberrant expression of a sarcoma-associated molecule, such as cancer.

As used herein, "aberrant expression" of a sarcoma-associated antigen is intended to include any expression that is statistically significant from the expected amount of expression. For example, expression of a sarcoma-associated molecule (i.e., the sarcoma-associated antigen or the nucleic acid molecules that encode it) in a tissue that is not expected to express the sarcoma-associated molecule would be included in the definition of "aberrant expression". Likewise, expression of the sarcoma-associated molecule that is determined to be expressed at a significantly higher or lower level than expected is also included. Therefore, a determination of the level of expression of one or more of the sarcoma-associated antigens and/or the nucleic acids that encode them is diagnostic of cancer if the level of expression is above a baseline level determined for that tissue type. The baseline level of expression can be determined using standard methods known to those of skill in the art. Such methods include, for example, assaying a number of histologically normal tissue samples from subjects that are clinically normal (i.e. do not have clinical signs of cancer in that tissue type) and determining the mean level of expression for the samples.

The level of expression of the nucleic acid molecules of the invention or the antigens they encode can indicate cancer in the tissue when the level of expression is significantly more in the tissue than in a control sample. In some embodiments, a level of expression in the tissues that is at least about 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 150%, 200%, 250%, 300%, 400%, or 500% more than the level of expression in the control tissue indicates cancer in the tissue.

As used herein the term "control" means predetermined values, and also means samples of materials tested in parallel with the experimental materials. Examples include samples from control populations or control samples generated through manufacture to be tested in parallel with the experimental samples.

As used herein the term "control" includes positive and negative controls which may be a predetermined value that can take a variety of forms. The control(s) can be a single cut-off value, such as a median or mean, or can be established based upon comparative groups, such as in groups having normal amounts of sarcoma-associated molecules of the invention and groups having abnormal amounts of sarcoma-associated molecules of the invention. Another example of a comparative group is a group having a particular disease, condition and/or symptoms and a group without the disease, condition and/or symptoms. Another comparative group is a group with a family history of a particular disease and a group without such a family history of the particular disease. The predetermined control value can be arranged, for example, where a tested population is divided equally (or unequally) into groups, such as a low-risk group, a medium-risk group and a high-risk group or into quadrants or quintiles, the lowest quadrant or quintile being individuals with the lowest risk or lowest expression levels of a sarcoma-associated molecule of the invention that is up-regulated in cancer and the highest quadrant or quintile being individuals with the highest risk or highest expression levels of a sarcoma-associated molecule of the invention that is up-regulated in cancer.

The predetermined value of a control will depend upon the particular population selected. For example, an apparently healthy population will have a different "normal" sarcoma-associated molecule expression level range than will a population which is known to have a condition characterized by aberrant expression of the sarcoma-associated molecule. Accordingly, the predetermined value selected may take into account the category in which an individual falls. Appropriate ranges and categories can be selected with no more than routine experimentation by those of ordinary skill in the art. Typically the control will be based on apparently healthy individuals in an appropriate age bracket. As used herein, the term "increased expression" means a higher level of expression relative to a selected control.

The invention involves in some aspects diagnosing or monitoring cancer by determining the level of expression of one or more sarcoma-associated nucleic acid molecules and/or determining the level of expression of one or more sarcoma-associated polypeptides they encode. In some important embodiments, this determination is performed by assaying a tissue sample from a subject for the level of expression of one or more sarcoma-associated nucleic acid molecules or for the level of expression of one or more sarcoma-associated polypeptides encoded by the nucleic acid molecules of the invention.

The expression of the molecules of the invention may be determined using routine methods known to those of ordinary skill in the art. These methods include, but are not limited to: direct RNA amplification, reverse transcription of RNA to cDNA, real-time RT-PCR, amplification of cDNA, hybridization, and immunologically based assay methods, which include, but are not limited to immunohistochemistry, antibody sandwich capture assay, ELISA, and enzyme-linked immunospot assay (EliSpot assay). For example, the determination of the presence of level of nucleic acid molecules of the invention in a subject or tissue can be carried out via any standard nucleic acid determination assay, including the polymerase chain reaction, or assaying with labeled hybridization probes. Such hybridization methods include, but are not limited to microarray techniques.

These methods of determining the presence and/or level of the molecules of the invention in cells and tissues may include use of labels to monitor the presence of the molecules of the invention. Such labels may include, but are not limited to radiolabels or chemiluminescent labels, which may be utilized to determine whether a molecule of the invention is expressed in a cell or tissue, and to determine the level of expression in the cell or tissue. For example, a fluorescently labeled or radiolabeled antibody that selectively binds to a polypeptide of the invention may be contacted with a tissue or cell to visualize the polypeptide in vitro or in vivo. These and other in vitro and in vivo imaging methods for determining the presence of the nucleic acid and polypeptide molecules of the invention are well known to those of ordinary skill in the art.

The invention, therefore, also involves the use of agents such as polypeptides that bind to sarcoma-associated antigens. Such agents can be used in methods of the invention including the diagnosis and/or treatment of cancer. Such binding agents can be used, for example, in screening assays to detect the presence or absence of sarcoma-associated antigens and can be used in quantitative binding assays to determine levels of expression in biological samples and cells. Such agents also may be used to inhibit the native activity of the sarcoma-associated polypeptides, for example, by binding to such polypeptides.

According to this aspect, the binding polypeptides bind to an isolated nucleic acid or protein of the invention, including unique fragments thereof. Preferably, the binding polypeptides bind to a sarcoma-associated polypeptide, or a unique fragment thereof.

In preferred embodiments, the binding polypeptide is an antibody or antibody fragment, more preferably, an Fab or $F(ab)_2$ fragment of an antibody. Typically, the fragment includes a CDR3 region that is selective for the sarcoma-associated antigen. Any of the various types of antibodies can be used for this purpose, including polyclonal antibodies, monoclonal antibodies, humanized antibodies, and chimeric antibodies.

Thus, the invention provides agents which bind to sarcoma-associated antigens encoded by sarcoma-associated nucleic acid molecules of the invention, and in certain embodiments preferably to unique fragments of the sarcoma-associated polypeptides. Such binding partners can be used in screening assays to detect the presence or absence of a sarcoma-associated antigen and in purification protocols to isolate such sarcoma-associated antigens. Likewise, such binding partners can be used to selectively target drugs, toxins or other molecules (including detectable diagnostic molecules) to cells which express sarcoma-associated antigens. In this manner, for example, cells present in solid or non-solid tumors which express sarcoma-associated proteins can be treated with cytotoxic compounds that are selective for the sarcoma-associated molecules (nucleic acids and/or antigens). Such binding agents also can be used to inhibit the native activity of the sarcoma-associated antigen, for example, to further characterize the functions of these molecules.

The antibodies of the present invention thus are prepared by any of a variety of methods, including administering a protein, fragments of a protein, cells expressing the protein or fragments thereof and the like to an animal to induce polyclonal antibodies. The present invention also provides methods of producing monoclonal antibodies to the sarcoma-associated molecules of the invention described herein. The production of monoclonal antibodies is according to techniques well known in the art. As detailed herein, such antibodies may be used for example to identify tissues expressing protein or to purify protein. Antibodies also may be coupled to specific labeling agents or imaging agents, including, but not limited to a molecule preferably selected from the group consisting of fluorescent, enzyme, radioactive, metallic, biotin, chemiluminescent, bioluminescent, chromophore, or colored, etc. In some aspects of the invention, a label may be a combination of the foregoing molecule types.

Significantly, as is well-known in the art, only a small portion of an antibody molecule, the paratope, is involved in the binding of the antibody to its epitope (see, in general, Clark, W. R. (1986) The Experimental Foundations of Modem Immunology Wiley & Sons, Inc., New York; Roitt, I. (1991) Essential Immunology, 7th Ed., Blackwell Scientific Publications, Oxford). The pFc' and Fc regions, for example, are effectors of the complement cascade but are not involved in antigen binding. An antibody from which the pFc' region has been enzymatically cleaved, or which has been produced without the pFc' region, designated an F(ab')2 fragment, retains both of the antigen binding sites of an intact antibody. Similarly, an antibody from which the Fc region has been enzymatically cleaved, or which has been produced without the Fc region, designated an Fab fragment, retains one of the antigen binding sites of an intact antibody molecule. Fab fragments consist of a covalently bound antibody light chain and a portion of the antibody heavy chain denoted Fd. The Fd fragments are the major determinant of antibody specificity (a single Fd fragment may be associated with up to ten different light chains without altering antibody specificity) and Fd fragments retain epitope-binding ability in isolation.

Within the antigen-binding portion of an antibody, as is well-known in the art, there are complementarity determining regions (CDRs), which directly interact with the epitope of the antigen, and framework regions (FRs), which maintain the tertiary structure of the paratope (see, in general, Clark, 1986; Roitt, 1991). In both the heavy chain Fd fragment and the light chain of IgG immunoglobulins, there are four framework regions (FR1 through FR4) separated respectively by three complementarity determining regions (CDR1 through CDR3). The CDRs, and in particular the CDR3 regions, and more particularly the heavy chain CDR3, are largely responsible for antibody specificity.

It is now well-established in the art that the non-CDR regions of a mammalian antibody may be replaced with similar regions of nonspecific or heterospecific antibodies while retaining the epitopic specificity of the original antibody. This is most clearly manifested in the development and use of "humanized" antibodies in which non-human CDRs are covalently joined to human FR and/or Fc/pFc' regions to produce a functional antibody. See, e.g., U.S. Pat. Nos. 4,816,567, 5,225,539, 5,585,089, 5,693,762, and 5,859,205.

Fully human monoclonal antibodies also can be prepared by immunizing mice transgenic for large portions of human immunoglobulin heavy and light chain loci. Following immunization of these mice (e.g., XenoMouse (Abgenix), HuMAb mice (Medarex/GenPharm)), monoclonal antibodies can be prepared according to standard hybridoma technology. These monoclonal antibodies will have human immunoglobulin amino acid sequences and therefore will not provoke human anti-mouse antibody (HAMA) responses when administered to humans.

Thus, as will be apparent to one of ordinary skill in the art, the present invention also provides for F(ab')2, Fab, Fv, and Fd fragments; chimeric antibodies in which the Fc and/or FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; chimeric F(ab')2 fragment antibodies in which the FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; chimeric Fab fragment antibodies in which the FR and/or CDR1 and/or CDR2 and/or light chain CDR3 regions have been replaced by homologous human or non-human sequences; and chimeric Fd fragment antibodies in which the FR and/or CDR1 and/or CDR2 regions have been replaced by homologous human or non-human sequences. The present invention also includes so-called single chain antibodies.

Thus, the invention involves polypeptides of numerous size and type that bind specifically to sarcoma-associated antigens. These polypeptides may be derived also from sources other than antibody technology. For example, such polypeptide binding agents can be provided by degenerate peptide

libraries which can be readily prepared in solution, in immobilized form or as phage display libraries. Combinatorial libraries also can be synthesized of peptides containing one or more amino acids. Libraries further can be synthesized of peptides and non-peptide synthetic moieties.

The sarcoma-associated antigens of the invention can be used to screen peptide libraries, including phage display libraries, to identify and select peptide binding partners of the sarcoma-associated antigens of the invention. Such molecules can be used, as described, for screening assays, for diagnostic assays, for purification protocols or for targeting drugs, toxins and/or labeling agents (e.g., radioisotopes, fluorescent molecules, etc.) to cells which express sarcoma-associated molecules such as cancer cells which have aberrant sarcoma-associated expression.

Phage display can be particularly effective in identifying binding peptides useful according to the invention. Briefly, one prepares a phage library (using e.g. m13, fd, or lambda phage), displaying inserts from 4 to about 80 amino acid residues using conventional procedures. The inserts may represent, for example, a completely degenerate or biased array. One then can select phage-bearing inserts which bind to the sarcoma-associated antigen. This process can be repeated through several cycles of reselection of phage that bind to the sarcoma-associated polypeptide. Repeated rounds lead to enrichment of phage bearing particular sequences. DNA sequence analysis can be conducted to identify the sequences of the expressed polypeptides. The minimal linear portion of the sequence that binds to the sarcoma-associated polypeptide can be determined One can repeat the procedure using a biased library containing inserts containing part or all of the minimal linear portion plus one or more additional degenerate residues upstream or downstream thereof. Yeast two-hybrid screening methods also may be used to identify polypeptides that bind to the sarcoma-associated antigens.

As detailed herein, the foregoing antibodies and other binding molecules may be used to identify tissues with normal or aberrant expression of a sarcoma-associated antigen. Antibodies also may be coupled to specific diagnostic labeling agents for imaging of cells and tissues with normal or aberrant sarcoma-associated antigen expression or to therapeutically useful agents according to standard coupling procedures. As used herein, "therapeutically useful agents" include any therapeutic molecule which desirably is targeted selectively to a cell or tissue selectively with an aberrant sarcoma-associated expression.

Diagnostic agents for in vivo use include, but are not limited to, barium sulfate, iocetamic acid, iopanoic acid, ipodate calcium, diatrizoate sodium, diatrizoate meglumine, metrizamide, tyropanoate sodium and radiodiagnostics including positron emitters such as fluorine-18 and carbon-11, gamma emitters such as iodine-123, technitium-99, iodine-131 and indium-111, and nuclides for nuclear magnetic resonance such as fluorine and gadolinium. Other diagnostic agents useful in the invention will be apparent to one of ordinary skill in the art.

The antibodies of the present invention can also be used to therapeutically target sarcoma-associated antigens. In a preferred embodiment, antibodies can be used to target antigens expressed on the cell surface, such as NY-SAR-35. These antibodies can be linked not only to a detectable marker but also an antitumor agent or an immunomodulator. Antitumor agents can include cytotoxic agents and agents that act on tumor neovasculature. Detectable markers include, for example, radioactive or fluorescent markers. Cytotoxic agents include cytotoxic radionuclides, chemical toxins and protein toxins.

The cytotoxic radionuclide or radiotherapeutic isotope preferably is an alpha-emitting isotope such as ^{225}Ac, ^{211}At, ^{212}Bi, ^{213}Bi, ^{212}Pb, ^{224}Ra or ^{223}Ra. Alternatively, the cytotoxic radionuclide may a beta-emitting isotope such as ^{186}Rh, ^{188}Rh, ^{177}Lu, ^{90}Y, ^{131}I, ^{67}Cu, ^{64}Cu, ^{153}Sm or ^{166}Ho. Further, the cytotoxic radionuclide may emit Auger and low energy electrons and include the isotopes ^{125}I, ^{123}I or ^{77}Br.

Suitable chemical toxins or chemotherapeutic agents include members of the enediyne family of molecules, such as calicheamicin and esperamicin. Chemical toxins can also be taken from the group consisting of methotrexate, doxorubicin, melphalan, chlorambucil, ARA-C, vindesine, mitomycin C, cis-platinum, etoposide, bleomycin and 5-fluorouracil. Other antineoplastic agents that may be conjugated to the anti-PSMA antibodies of the present invention include dolastatins (U.S. Pat. Nos. 6,034,065 and 6,239,104) and derivatives thereof. Of particular interest is dolastatin 10 (dolavaline-valine-dolaisoleuine-dolaproine-dolaphenine) and the derivatives auristatin PHE (dolavaline-valine-dolaisoleuine-dolaproine-phenylalanine-methyl ester) (Pettit, G. R. et al., *Anticancer Drug Des.* 13(4):243-277, 1998; Woyke, T. et al., *Antimicrob. Agents Chemother.* 45(12):3580-3584, 2001), and aurastatin E and the like. Toxins that are less preferred in the compositions and methods of the invention include poisonous lectins, plant toxins such as ricin, abrin, modeccin, botulina and diphtheria toxins. Of course, combinations of the various toxins could also be coupled to one antibody molecule thereby accommodating variable cytotoxicity. Other chemotherapeutic agents are known to those skilled in the art.

Agents that act on the tumor vasculature can include tubulin-binding agents such as combrestatin A4 (Griggs et al., *Lancet Oncol.* 2:82, 2001), angiostatin and endostatin (reviewed in Rosen, *Oncologist* 5:20, 2000, incorporated by reference herein) and interferon inducible protein 10 (U.S. Pat. No. 5,994,292). A number of antiangiogenic agents currently in clinical trials are also contemplated. Agents currently in clinical trials include: 2ME2, Angiostatin, Angiozyme, Anti-VEGF RhuMAb, Apra (CT-2584), Avicine, Benefin, BMS275291, Carboxyamidotriazole, CC4047, CC5013, CC7085, CDC801, CGP-41251 (PKC 412), CM101, Combretastatin A-4 Prodrug, EMD 121974, Endostatin, Flavopiridol, Genistein (GCP), Green Tea Extract, IM-862, ImmTher, Interferon alpha, Interleukin-12, Iressa (ZD1839), Marimastat, Metastat (Col-3), Neovastat, Octreotide, Paclitaxel, Penicillamine, Photofrin, Photopoint, PI-88, Prinomastat (AG-3340), PTK787 (ZK22584), R0317453, Solimastat, Squalamine, SU 101, SU 5416, SU-6668, Suradista (FCE 26644), Suramin (Metaret), Tetrathiomolybdate, Thalidomide, TNP-470 and Vitaxin, additional antiangiogenic agents are described by Kerbel, J. Clin. Oncol. 19(18s):45s-51s, 2001, which is incorporated by reference herein Immunomodulators suitable for conjugation to the antibodies include α-interferon, γ-interferon, and tumor necrosis factor alpha (TNFα).

The coupling of one or more toxin molecules to the antibody is envisioned to include many chemical mechanisms, for instance covalent binding, affinity binding, intercalation, coordinate binding, and complexation. The toxic compounds used to prepare the immunotoxins are attached to the antibodies or antigen-binding fragments thereof by standard protocols known in the art.

In other aspects of the invention, the sarcoma-associated molecules and the antibodies and other binding molecules, as described herein, can be used for the treatment of disorders. When "disorder" is used herein, it refers to any pathological condition where the sarcoma-associated antigens are aber-

rantly expressed. An example of such a disorder is cancer, with sarcoma as a particular example. For human cancers, additional particular examples include synovial sarcoma, liposarcoma, neurosarcoma, chondrosarcoma, fibrosarcoma, Ewing sarcoma, leimyosarcoma, osteosarcoma, rhabdomyosarcoma, malignant fibrous histocytoma, DFSP, leukemia, lymphoma, gastric cancer, glioma, bladder cancer, breast cancer, ovarian cancer, renal cancer, lung cancer, colon cancer, prostate cancer, esophageal cancer, melanoma and hepatoma.

Conventional treatment for cancer may include, but is not limited to: surgical intervention, chemotherapy, radiotherapy, and adjuvant systemic therapies. In one aspect of the invention, treatment may include administering binding polypeptides such as antibodies that specifically bind to the sarcoma-associated antigen. These binding polypeptides can be optionally linked to one or more detectable markers, antitumor agents or immunomodulators as described above.

Cancer treatment, in another aspect of the invention may include administering an antisense molecules or RNAi molecules to reduce expression level and/or function level of sarcoma-associated polypeptides of the invention in the subject in cancers where a sarcoma-associated molecule is upregulated. The use of RNA interference or "RNAi" involves the use of double-stranded RNA (dsRNA) to block gene expression. (see: Sui, G, et al, Proc Natl. Acad. Sci U.S.A. 99:5515-5520, 2002). Methods of applying RNAi strategies in embodiments of the invention would be understood by one of ordinary skill in the art.

Sarcoma-associated polypeptides as described herein, can also be used in one aspect of the invention to induce or enhance an immune response. Some therapeutic approaches based upon the disclosure are premised on a response by a subject's immune system, leading to lysis of antigen presenting cells, such as cancer cells which present one or more sarcoma-associated antigens of the invention. One such approach is the administration of autologous CTLs specific to a sarcoma-associated antigen/MHC complex to a subject with abnormal cells of the phenotype at issue. It is within the ability of one of ordinary skill in the art to develop such CTLs in vitro. An example of a method for T cell differentiation is presented in International Application number PCT/US96/05607. Generally, a sample of cells taken from a subject, such as blood cells, are contacted with a cell presenting the complex and capable of provoking CTLs to proliferate. The target cell can be a transfectant, such as a COS cell. These transfectants present the desired complex of their surface and, when combined with a CTL of interest, stimulate its proliferation. COS cells are widely available, as are other suitable host cells. Specific production of CTL clones is well known in the art. The clonally expanded autologous CTLs then are administered to the subject.

Another method for selecting antigen-specific CTL clones has recently been described (Altman et al., Science 274:94-96, 1996; Dunbar et al., Curr. Biol. 8:413-416, 1998), in which fluorogenic tetramers of MHC class I molecule/peptide complexes are used to detect specific CTL clones. Briefly, soluble MHC class I molecules are folded in vitro in the presence of β_2-microglobulin and a peptide antigen which binds the class I molecule. After purification, the MHC/peptide complex is purified and labeled with biotin. Tetramers are formed by mixing the biotinylated peptide-MHC complex with labeled avidin (e.g. phycoerythrin) at a molar ratio or 4:1. Tetramers are then contacted with a source of CTLs such as peripheral blood or lymph node. The tetramers bind CTLs which recognize the peptide antigen/MHC class I complex. Cells bound by the tetramers can be sorted by fluorescence activated cell sorting to isolate the reactive CTLs. The isolated CTLs then can be expanded in vitro for use as described herein.

To detail a therapeutic methodology, referred to as adoptive transfer (Greenberg, J. Immunol. 136(5): 1917, 1986; Riddel et al., Science 257: 238, 1992; Lynch et al, Eur. J. Immunol. 21: 1403-1410, 1991; Kast et al., Cell 59: 603-614, 1989), cells presenting the desired complex (e.g., dendritic cells) are combined with CTLs leading to proliferation of the CTLs specific thereto. The proliferated CTLs are then administered to a subject with a cellular abnormality which is characterized by certain of the abnormal cells presenting the particular complex. The CTLs then lyse the abnormal cells, thereby achieving the desired therapeutic goal.

The foregoing therapy assumes that at least some of the subject's abnormal cells present the relevant HLA/cancer associated antigen complex. This can be determined very easily, as the art is very familiar with methods for identifying cells which present a particular HLA molecule, as well as how to identify cells expressing DNA of the pertinent sequences, in this case a sarcoma-associated antigen sequence. Once cells presenting the relevant complex are identified via the foregoing screening methodology, they can be combined with a sample from a patient, where the sample contains CTLs. If the complex presenting cells are lysed by the mixed CTL sample, then it can be assumed that a sarcoma-associated antigen is being presented, and the subject is an appropriate candidate for the therapeutic approaches set forth supra.

Adoptive transfer is not the only form of therapy that is available in accordance with the invention. CTLs can also be provoked in vivo, using a number of approaches. One approach is the use of non-proliferative cells expressing the complex. The cells used in this approach may be those that normally express the complex, such as irradiated tumor cells or cells transfected with one or both of the genes necessary for presentation of the complex (i.e. the antigenic peptide and the presenting MHC molecule). Chen et al. (Proc. Natl. Acad. Sci. USA 88: 110-114, 1991) exemplifies this approach, showing the use of transfected cells expressing HPV E7 peptides in a therapeutic regime. Various cell types may be used. Similarly, vectors carrying one or both of the genes of interest may be used. Viral or bacterial vectors are especially preferred. For example, nucleic acids which encode a sarcoma-associated polypeptide may be operably linked to promoter and enhancer sequences which direct expression of the sarcoma-associated antigen polypeptide in certain tissues or cell types. The nucleic acid may be incorporated into an expression vector.

Expression vectors may be unmodified extrachromosomal nucleic acids, plasmids or viral genomes constructed or modified to enable insertion of exogenous nucleic acids, such as those encoding sarcoma-associated antigen, as described elsewhere herein. Nucleic acids encoding a sarcoma-associated antigen also may be inserted into a retroviral genome, thereby facilitating integration of the nucleic acid into the genome of the target tissue or cell type. In these systems, the gene of interest is carried by a microorganism, e.g., a Vaccinia virus, pox virus, herpes simplex virus, retrovirus or adenovirus, and the materials de facto "infect" host cells. The cells which result present the complex of interest, and are recognized by autologous CTLs, which then proliferate.

A similar effect can be achieved by combining the sarcoma-associated polypeptide or a stimulatory fragment thereof with an adjuvant to facilitate incorporation into antigen presenting cells in vivo. The sarcoma-associated polypeptide is processed to yield the peptide partner of the MHC molecule while a sarcoma-associated fragment may be

presented without the need for further processing. Generally, subjects can receive an intradermal injection of an effective amount of the sarcoma-associated antigen. Initial doses can be followed by booster doses, following immunization protocols standard in the art. Preferred sarcoma-associated antigens include those found to react with allogeneic cancer antisera, shown in the examples below.

The invention involves the use of various materials disclosed herein to "immunize" subjects or as "vaccines". As used herein, "immunization" or "vaccination" means increasing or activating an immune response against an antigen. It does not require elimination or eradication of a condition but rather contemplates the clinically favorable enhancement of an immune response toward an antigen. Generally accepted animal models, can be used for testing of immunization against cancer using a sarcoma-associated nucleic acid. For example, human cancer cells can be introduced into a mouse to create a tumor, and one or more sarcoma-associated nucleic acids can be delivered by the methods described herein. The effect on the cancer cells (e.g., reduction of tumor size) can be assessed as a measure of the effectiveness of the sarcoma-associated nucleic acid immunization. Of course, testing of the foregoing animal model using more conventional methods for immunization include the administration of one or more sarcoma-associated polypeptides or fragments derived therefrom, optionally combined with one or more adjuvants and/or cytokines to boost the immune response.

Methods for immunization, including formulation of a vaccine composition and selection of doses, route of administration and the schedule of administration (e.g. primary and one or more booster doses), are well known in the art. The tests also can be performed in humans, where the end point is to test for the presence of enhanced levels of circulating CTLs against cells bearing the antigen, to test for levels of circulating antibodies against the antigen, to test for the presence of cells expressing the antigen and so forth.

As part of the immunization compositions, one or more sarcoma-associated polypeptides or immunogenic fragments thereof are administered with one or more adjuvants to induce an immune response or to increase an immune response. An adjuvant is a substance incorporated into or administered with antigen which potentiates the immune response. Adjuvants may enhance the immunological response by providing a reservoir of antigen (extracellularly or within macrophages), activating macrophages and stimulating specific sets of lymphocytes. Adjuvants of many kinds are well known in the art. Specific examples of adjuvants include monophosphoryl lipid A (MPL, SmithKline Beecham), a congener obtained after purification and acid hydrolysis of *Salmonella* minnesota Re 595 lipopolysaccharide; saponins including QS21 (SmithKline Beecham), a pure QA-21 saponin purified from *Quillja saponaria* extract; DQS21, described in PCT application WO96/33739 (SmithKline Beecham); QS-7, QS-17, QS-18, and QS-L1 (So et al., Mol. Cells 7:178-186, 1997); incomplete Freund's adjuvant; complete Freund's adjuvant; montanide; alum; CpG oligonucleotides (see e.g. Kreig et al., Nature 374:546-9, 1995); and various water-in-oil emulsions prepared from biodegradable oils such as squalene and/or tocopherol. Preferably, the antigens are administered mixed with a combination of DQS21/MPL. The ratio of DQS21 to MPL typically will be about 1:10 to 10:1, preferably about 1:5 to 5:1 and more preferably about 1:1. Typically for human administration, DQS21 and MPL will be present in a vaccine formulation in the range of about 1 μg to about 100 μg. Other adjuvants are known in the art and can be used in the invention (see, e.g. Goding, Monoclonal Antibodies: Principles and Practice, 2nd Ed., 1986). Methods for the preparation of mixtures or emulsions of polypeptide and adjuvant are well known to those of skill in the art of vaccination.

Other agents which stimulate the immune response of the subject can also be administered to the subject. For example, other cytokines are also useful in vaccination protocols as a result of their lymphocyte regulatory properties. Many other cytokines useful for such purposes will be known to one of ordinary skill in the art, including interleukin-12 (IL-12) which has been shown to enhance the protective effects of vaccines (see, e.g., Science 268: 1432-1434, 1995), GM-CSF and IL-18. Thus cytokines can be administered in conjunction with antigens and adjuvants to increase the immune response to the antigens.

There are a number of immune response potentiating compounds that can be used in vaccination protocols. These include costimulatory molecules provided in either protein or nucleic acid form. Such costimulatory molecules include the B7-1 and B7-2 (CD80 and CD86 respectively) molecules which are expressed on dendritic cells (DC) and interact with the CD28 molecule expressed on the T cell. This interaction provides costimulation (signal 2) to an antigen/MHC/TCR stimulated (signal 1) T cell, increasing T cell proliferation and effector function. B7 also interacts with CTLA4 (CD152) on T cells and studies involving CTLA4 and B7 ligands indicate that the B7-CTLA4 interaction can enhance antitumor immunity and CTL proliferation (Zheng P., et al. Proc. Natl. Acad. Sci. USA 95 (11):6284-6289 (1998)).

B7 typically is not expressed on tumor cells so they are not efficient antigen presenting cells (APCs) for T cells. Induction of B7 expression would enable the tumor cells to stimulate more efficiently CTL proliferation and effector function. A combination of B7/IL-6/IL-12 costimulation has been shown to induce IFN-gamma and a Th1 cytokine profile in the T cell population leading to further enhanced T cell activity (Gajewski et al., J. Immunol, 154:5637-5648 (1995)). Tumor cell transfection with B7 has been discussed in relation to in vitro CTL expansion for adoptive transfer immunotherapy by Wang et al., (J. Immunol., 19:1-8 (1986)). Other delivery mechanisms for the B7 molecule would include nucleic acid (naked DNA) immunization (Kim J., et al. Nat. Biotechnol., 15:7:641-646 (1997)) and recombinant viruses such as adeno and pox (Wendtner et al., Gene Ther., 4:7:726-735 (1997)). These systems are all amenable to the construction and use of expression cassettes for the coexpression of B7 with other molecules of choice such as the antigens or fragment(s) of antigens discussed herein (including polytopes) or cytokines. These delivery systems can be used for induction of the appropriate molecules in vitro and for in vivo vaccination situations. The use of anti-CD28 antibodies to directly stimulate T cells in vitro and in vivo could also be considered. Similarly, the inducible co-stimulatory molecule ICOS which induces T cell responses to foreign antigen could be modulated, for example, by use of anti-ICOS antibodies (Hutloff et al., Nature 397:263-266, 1999).

Lymphocyte function associated antigen-3 (LFA-3) is expressed on APCs and some tumor cells and interacts with CD2 expressed on T cells. This interaction induces T cell IL-2 and IFN-gamma production and can thus complement but not substitute, the B7/CD28 costimulatory interaction (Parra et al., J. Immunol., 158:637-642 (1997), Fenton et al., J. Immunother., 21:2:95-108 (1998)).

Lymphocyte function associated antigen-1 (LFA-1) is expressed on leukocytes and interacts with ICAM-1 expressed on APCs and some tumor cells. This interaction induces T cell IL-2 and IFN-gamma production and can thus complement but not substitute, the B7/CD28 costimulatory interaction (Fenton et al., J. Immunother., 21:2:95-108

(1998)). LFA-1 is thus a further example of a costimulatory molecule that could be provided in a vaccination protocol in the various ways discussed above for B7.

Complete CTL activation and effector function requires Th cell help through the interaction between the Th cell CD40L (CD40 ligand) molecule and the CD40 molecule expressed by DCs (Ridge et al., Nature, 393:474 (1998), Bennett et al., Nature, 393:478 (1998), Schoenberger et al., Nature, 393:480 (1998)). This mechanism of this costimulatory signal is likely to involve upregulation of B7 and associated IL-6/IL-12 production by the DC (APC). The CD40-CD40L interaction thus complements the signal 1 (antigen/MHC-TCR) and signal 2 (B7-CD28) interactions.

The use of anti-CD40 antibodies to stimulate DC cells directly, would be expected to enhance a response to tumor antigens which are normally encountered outside of an inflammatory context or are presented by non-professional APCs (tumor cells). In these situations Th help and B7 costimulation signals are not provided.

The invention contemplates delivery of nucleic acids, polypeptides or fragments thereof for vaccination. Delivery of polypeptides and fragments thereof can be accomplished according to standard vaccination protocols which are well known in the art. In another embodiment, the delivery of nucleic acid is accomplished by ex vivo methods, i.e. by removing a cell from a subject, genetically engineering the cell to include a sarcoma-associated polypeptide, and reintroducing the engineered cell into the subject. One example of such a procedure is outlined in U.S. Pat. No. 5,399,346 and in exhibits submitted in the file history of that patent, all of which are publicly available documents. In general, it involves introduction in vitro of a functional copy of a gene into a cell(s) of a subject, and returning the genetically engineered cell(s) to the subject. The functional copy of the gene is under operable control of regulatory elements which permit expression of the gene in the genetically engineered cell(s). Numerous transfection and transduction techniques as well as appropriate expression vectors are well known to those of ordinary skill in the art, some of which are described in PCT application WO95/00654. In vivo nucleic acid delivery using vectors such as viruses and targeted liposomes also is contemplated according to the invention.

A virus vector for delivering a nucleic acid encoding a sarcoma-associated polypeptide is selected from the group consisting of adenoviruses, adeno-associated viruses, poxviruses including vaccinia viruses and attenuated poxviruses, Semliki Forest virus, Venezuelan equine encephalitis virus, retroviruses, Sindbis virus, and Ty virus-like particle. Examples of viruses and virus-like particles which have been used to deliver exogenous nucleic acids include: replication-defective adenoviruses (e.g., Xiang et al., Virology 219:220-227, 1996; Eloit et al., J. Virol. 7:5375-5381, 1997; Chengalvala et al., Vaccine 15:335-339, 1997), a modified retrovirus (Townsend et al., J. Virol. 71:3365-3374, 1997), a nonreplicating retrovirus (Irwin et al., J. Virol. 68:5036-5044, 1994), a replication defective Semliki Forest virus (Zhao et al., Proc. Natl. Acad. Sci. USA 92:3009-3013, 1995), canarypox virus and highly attenuated vaccinia virus derivative (Paoletti, Proc. Natl. Acad. Sci. USA 93:11349-11353, 1996), non-replicative vaccinia virus (Moss, Proc. Natl. Acad. Sci. USA 93:11341-11348, 1996), replicative vaccinia virus (Moss, Dev. Biol. Stand. 82:55-63, 1994), Venzuelan equine encephalitis virus (Davis et al., J. Virol. 70:3781-3787, 1996), Sindbis virus (Pugachev et al., Virology 212:587-594, 1995), and Ty virus-like particle (Allsopp et al., Eur. J. Immunol 26:1951-1959, 1996). A preferred virus vector is an adenovirus.

Preferably the foregoing nucleic acid delivery vectors: (1) contain exogenous genetic material that can be transcribed and translated in a mammalian cell and that can induce an immune response in a host, and (2) contain on a surface a ligand that selectively binds to a receptor on the surface of a target cell, such as a mammalian cell, and thereby gains entry to the target cell.

Various techniques may be employed for introducing nucleic acids of the invention into cells, depending on whether the nucleic acids are introduced in vitro or in vivo in a host. Such techniques include transfection of nucleic acid-$CaPO_4$ precipitates, transfection of nucleic acids associated with DEAE, transfection or infection with the foregoing viruses including the nucleic acid of interest, liposome mediated transfection, and the like. For certain uses, it is preferred to target the nucleic acid to particular cells. In such instances, a vehicle used for delivering a nucleic acid of the invention into a cell (e.g., a retrovirus, or other virus; a liposome) can have a targeting molecule attached thereto. For example, a molecule such as an antibody specific for a surface membrane protein on the target cell or a ligand for a receptor on the target cell can be bound to or incorporated within the nucleic acid delivery vehicle. Preferred antibodies include antibodies which selectively bind a sarcoma-associated antigen, alone or as a complex with a MHC molecule. Especially preferred are monoclonal antibodies. Where liposomes are employed to deliver the nucleic acids of the invention, proteins which bind to a surface membrane protein associated with endocytosis may be incorporated into the liposome formulation for targeting and/or to facilitate uptake. Such proteins include capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, proteins that target intracellular localization and enhance intracellular half life, and the like. Polymeric delivery systems also have been used successfully to deliver nucleic acids into cells, as is known by those skilled in the art. Such systems even permit oral delivery of nucleic acids.

According to a further aspect of the invention, compositions containing the nucleic acid molecules, proteins, and binding polypeptides of the invention are provided. The compositions contain any of the foregoing therapeutic agents in an optional pharmaceutically acceptable carrier. Thus, in a related aspect, the invention provides a method for forming a medicament that involves placing a therapeutically effective amount of the therapeutic agent in the pharmaceutically acceptable carrier to form one or more doses. The effectiveness of treatment or prevention methods of the invention can be determined using standard diagnostic methods described herein.

When administered, the therapeutic compositions of the present invention are administered in pharmaceutically acceptable preparations. Such preparations may routinely contain pharmaceutically acceptable concentrations of salt, buffering agents, preservatives, compatible carriers, supplementary immune potentiating agents such as adjuvants and cytokines, and optionally other therapeutic agents.

As used herein, the term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredients. The term "physiologically acceptable" refers to a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism. The characteristics of the carrier will depend on the route of administration. Physiologically and pharmaceutically acceptable carriers include diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials which are well known in the art. The term "carrier" denotes an organic or inorganic ingre-

dient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions also are capable of being comingled with the molecules of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficacy.

The therapeutics of the invention can be administered by any conventional route, including injection or by gradual infusion over time. The administration may, for example, be oral, intravenous, intratumoral, intraperitoneal, intramuscular, intracavity, subcutaneous, or transdermal. When antibodies are used therapeutically, a preferred route of administration is by pulmonary aerosol. Techniques for preparing aerosol delivery systems containing antibodies are well known to those of skill in the art. Generally, such systems should utilize components which will not significantly impair the biological properties of the antibodies, such as the paratope binding capacity (see, for example, Sciarra and Cutie, "Aerosols," in Remington's Pharmaceutical Sciences, 18th edition, 1990, pp 1694-1712). Those of skill in the art can readily determine the various parameters and conditions for producing antibody aerosols without undue experimentation. When using antisense preparations of the invention, slow intravenous administration is preferred.

The compositions of the invention are administered in effective amounts. An "effective amount" is that amount of a sarcoma-associated polypeptide composition that alone, or together with further doses, produces the desired response, e.g. increases an immune response to the sarcoma-associated polypeptide. In the case of treating a particular disease or condition characterized by expression of one or more sarcoma-associated polypeptides, such as cancer, the desired response is inhibiting the progression of the disease. This may involve only slowing the progression of the disease temporarily, although more preferably, it involves halting the progression of the disease permanently. This can be monitored by routine methods or can be monitored according to diagnostic methods of the invention discussed herein. The desired response to treatment of the disease or condition also can be delaying the onset or even preventing the onset of the disease or condition.

Such amounts will depend, of course, on the particular condition being treated, the severity of the condition, the individual patient parameters including age, physical condition, size and weight, the duration of the treatment, the nature of concurrent therapy (if any), the specific route of administration and like factors within the knowledge and expertise of the health practitioner. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is generally preferred that a maximum dose of the individual components or combinations thereof be used, that is, the highest safe dose according to sound medical judgment. It will be understood by those of ordinary skill in the art, however, that a patient may insist upon a lower dose or tolerable dose for medical reasons, psychological reasons or for virtually any other reasons.

The pharmaceutical compositions used in the foregoing methods preferably are sterile and contain an effective amount of sarcoma-associated polypeptide or nucleic acid encoding sarcoma-associated polypeptide for producing the desired response in a unit of weight or volume suitable for administration to a patient. The response can, for example, be measured by determining the immune response following administration of the sarcoma-associated polypeptide composition via a reporter system by measuring downstream effects such as gene expression, or by measuring the physiological effects of the sarcoma-associated polypeptide composition, such as regression of a tumor or decrease of disease symptoms. Other assays will be known to one of ordinary skill in the art and can be employed for measuring the level of the response.

The doses of sarcoma-associated polypeptide compositions (e.g., polypeptide, peptide, antibody, cell or nucleic acid) administered to a subject can be chosen in accordance with different parameters, in particular in accordance with the mode of administration used and the state of the subject. Other factors include the desired period of treatment. In the event that a response in a subject is insufficient at the initial doses applied, higher doses (or effectively higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits.

In general, for treatments for eliciting or increasing an immune response, doses of sarcoma-associated antigen are formulated and administered in doses between 1 ng and 1 mg, and preferably between 10 ng and 100 μg, according to any standard procedure in the art. Where nucleic acids encoding sarcoma-associated polypeptides or variants thereof are employed, doses of between 1 ng and 0.1 mg generally will be formulated and administered according to standard procedures. Other protocols for the administration of sarcoma-associated polypeptide compositions will be known to one of ordinary skill in the art, in which the dose amount, schedule of injections, sites of injections, mode of administration (e.g., intra-tumoral) and the like vary from the foregoing. Administration of sarcoma-associated polypeptide compositions to mammals other than humans, e.g. for testing purposes or veterinary therapeutic purposes, is carried out under substantially the same conditions as described above.

Where sarcoma-associated polypeptides are used for vaccination, modes of administration which effectively deliver the sarcoma-associated polypeptide and adjuvant, such that an immune response to the polypeptide is increased, can be used. For administration of a sarcoma-associated polypeptide in adjuvant, preferred methods include intradermal, intravenous, intramuscular and subcutaneous administration. Although these are preferred embodiments, the invention is not limited by the particular modes of administration disclosed herein. Standard references in the art (e.g., Remington's Pharmaceutical Sciences, 18th edition, 1990) provide modes of administration and formulations for delivery of immunogens with adjuvant or in a non-adjuvant carrier.

The pharmaceutical compositions may contain suitable buffering agents, including: acetic acid in a salt; citric acid in a salt; boric acid in a salt; and phosphoric acid in a salt.

The pharmaceutical compositions also may contain, optionally, suitable preservatives, such as: benzalkonium chloride; chlorobutanol; parabens and thimerosal.

The pharmaceutical compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well-known in the art of pharmacy. All methods include the step of bringing the active agent into association with a carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product.

Compositions suitable for oral administration may be presented as discrete units, such as capsules, tablets, lozenges, each containing a predetermined amount of the active compound. Other compositions include suspensions in aqueous liquids or non-aqueous liquids such as a syrup, elixir or an emulsion.

Compositions for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, and lactated Ringer's or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for example, antimicrobials, anti-oxidants, chelating agents, and inert gases, and the like.

The pharmaceutical agents of the invention may be administered alone, in combination with each other, and/or in combination with other anti-cancer drug therapies and/or treatments. These therapies and/or treatments may include, but are not limited to: surgical intervention, chemotherapy, radiotherapy, and adjuvant systemic therapies.

The invention also provides a pharmaceutical kit comprising one or more containers comprising one or more of the pharmaceutical compounds or agents of the invention. Additional materials may be included in any or all kits of the invention, and such materials may include, but are not limited to buffers, water, enzymes, tubes, control molecules, etc. The kit may also include instructions for the use of the one or more pharmaceutical compounds or agents of the invention for the treatment of cancer.

The invention includes kits for assaying the presence of sarcoma-associated antigens and/or antibodies that specifically bind to sarcoma-associated polypeptides. An example of such a kit may include the above-mentioned polypeptides bound to a substrate, for example a dipstick, which is dipped into a blood or body fluid sample of a subject. The surface of the substrate may then be processed using procedures well known to those of skill in the art, to assess whether specific binding occurred between the polypeptides and agents (e.g. antibodies) in the subject's sample. For example, procedures may include, but are not limited to, contact with a secondary antibody, or other method that indicates the presence of specific binding.

Another example of a kit may include an antibody or antigen-binding fragment thereof, that binds specifically to a sarcoma-associated antigen. The antibody or antigen-binding fragment thereof, may be applied to a tissue or cell sample from a patient with cancer and the sample then processed to assess whether specific binding occurs between the antibody and an antigen or other component of the sample. In addition, the antibody or antigen-binding fragment thereof, may be applied to a body fluid sample, such as serum, from a subject, either suspected of having cancer, diagnosed with cancer, or believed to be free of cancer. As will be understood by one of skill in the art, such binding assays may also be performed with a sample or object contacted with an antibody and/or sarcoma-associated antigen that is in solution, for example in a 96-well plate or applied directly to an object surface.

Another example of a kit of the invention is a kit that provides components necessary to determine the level of expression of one or more sarcoma-associated nucleic acid molecules of the invention. Such components may include primers useful for amplification of one or more sarcoma-associated nucleic acid molecules and/or other chemicals for PCR amplification.

Another example of a kit of the invention is a kit that provides components necessary to determine the level of expression of one or more sarcoma-associated nucleic acid molecules of the invention using a method of hybridization.

The foregoing kits can include instructions or other printed material on how to use the various components of the kits for diagnostic purposes.

The invention further includes nucleic acid or protein microarrays (including antibody arrays) for the analysis of expression of sarcoma-associated antigens or nucleic acids encoding such antigens. In this aspect of the invention, standard techniques of microarray technology are utilized to assess expression of the sarcoma-associated antigens and/or identify biological constituents that bind such antigens. The constituents of biological samples include antibodies, lymphocytes (particularly T lymphocytes), and the like. Microarray substrates include but are not limited to glass, silica, aluminosilicates, borosilicates, metal oxides such as alumina and nickel oxide, various clays, nitrocellulose, or nylon. The microarray substrates may be coated with a compound to enhance synthesis of a probe (peptide or nucleic acid) on the substrate. Coupling agents or groups on the substrate can be used to covalently link the first nucleotide or amino acid to the substrate. A variety of coupling agents or groups are known to those of skill in the art. Peptide or nucleic acid probes thus can be synthesized directly on the substrate in a predetermined grid. Alternatively, peptide or nucleic acid probes can be spotted on the substrate, and in such cases the substrate may be coated with a compound to enhance binding of the probe to the substrate. In these embodiments, presynthesized probes are applied to the substrate in a precise, predetermined volume and grid pattern, preferably utilizing a computer-controlled robot to apply probe to the substrate in a contact-printing manner or in a non-contact manner such as ink jet or piezo-electric delivery. Probes may be covalently linked to the substrate. Nucleic acid probes preferably are linked using UV irradiation or heat.

Protein microarray technology, which is also known by other names including protein chip technology and solid-phase protein array technology, is well known to those of ordinary skill in the art and is based on, but not limited to, obtaining an array of identified peptides or proteins on a fixed substrate, binding target molecules or biological constituents to the peptides, and evaluating such binding. See, e.g., G. MacBeath and S. L. Schreiber, "Printing Proteins as Microarrays for High-Throughput Function Determination," *Science* 289(5485):1760-1763, 2000.

Targets are peptides or proteins and may be natural or synthetic. The tissue may be obtained from a subject or may be grown in culture (e.g. from a cell line).

In some embodiments of the invention, one or more control peptide or protein molecules are attached to the substrate. Preferably, control peptide or protein molecules allow determination of factors such as peptide or protein quality and binding characteristics, reagent quality and effectiveness, hybridization success, and analysis thresholds and success.

Nucleic acid arrays, particularly arrays that bind sarcoma-associated antigens, also can be used for diagnostic applications, such as for identifying subjects that have a condition characterized by aberrant sarcoma-associated antigen expression. Nucleic acid microarray technology, which is also known by other names including: DNA chip technology, gene chip technology, and solid-phase nucleic acid array technology, is well known to those of ordinary skill in the art and is based on, but not limited to, obtaining an array of identified nucleic acid probes on a fixed substrate, labeling target molecules with reporter molecules (e.g., radioactive, chemiluminescent, or fluorescent tags such as fluorescein, Cye3-dUTP, or Cye5-dUTP), hybridizing target nucleic acids to the

probes, and evaluating target-probe hybridization. A probe with a nucleic acid sequence that perfectly matches the target sequence will, in general, result in detection of a stronger reporter-molecule signal than will probes with less perfect matches. Many components and techniques utilized in nucleic acid microarray technology are presented in *The Chipping Forecast, Nature Genetics*, Vol. 21, January 1999, the entire contents of which is incorporated by reference herein.

According to the invention, probes are selected from the group of nucleic acids including, but not limited to: DNA, genomic DNA, cDNA, and oligonucleotides; and may be natural or synthetic. Oligonucleotide probes preferably are 20 to 25-mer oligonucleotides and DNA/cDNA probes preferably are 500 to 5000 bases in length, although other lengths may be used. Appropriate probe length may be determined by one of ordinary skill in the art by following art-known procedures. In one embodiment, preferred probes are sets of one or more of the sarcoma-associated nucleic acid molecules as described herein. Probes may be purified to remove contaminants using standard methods known to those of ordinary skill in the art such as gel filtration or precipitation.

In one embodiment, the microarray substrate may be coated with a compound to enhance synthesis of the probe on the substrate. Such compounds include, but are not limited to, oligoethylene glycols. In another embodiment, coupling agents or groups on the substrate can be used to covalently link the first nucleotide or oligonucleotide to the substrate. These agents or groups may include, for example, amino, hydroxy, bromo, and carboxy groups. These reactive groups are preferably attached to the substrate through a hydrocarbyl radical such as an alkylene or phenylene divalent radical, one valence position occupied by the chain bonding and the remaining attached to the reactive groups. These hydrocarbyl groups may contain up to about ten carbon atoms, preferably up to about six carbon atoms. Alkylene radicals are usually preferred containing two to four carbon atoms in the principal chain. These and additional details of the process are disclosed, for example, in U.S. Pat. No. 4,458,066, which is incorporated by reference in its entirety.

In one embodiment, nucleic acid probes are synthesized directly on the substrate in a predetermined grid pattern using methods such as light-directed chemical synthesis, photochemical deprotection, or delivery of nucleotide precursors to the substrate and subsequent probe production.

Targets for microarrays are nucleic acids selected from the group, including but not limited to: DNA, genomic DNA, cDNA, RNA, mRNA and may be natural or synthetic. In all embodiments, nucleic acid target molecules from human tissue are preferred. The tissue may be obtained from a subject or may be grown in culture (e.g. from a cell line).

In embodiments of the invention one or more control nucleic acid molecules are attached to the substrate. Preferably, control nucleic acid molecules allow determination of factors such as nucleic acid quality and binding characteristics, reagent quality and effectiveness, hybridization success, and analysis thresholds and success. Control nucleic acids may include but are not limited to expression products of genes such as housekeeping genes or fragments thereof.

EXAMPLES

Materials and Methods

Cell Lines, Tissues, Sera and RNA

SW1045, SW982, and Fuji synovial sarcoma cell lines were obtained from the cell repository of the Ludwig Institute for Cancer Research (LICR), New York Branch at the Memorial Sloan-Kettering Cancer Center. Tumor tissues and sera were obtained from Memorial Sloan-Kettering Cancer Center, Weill Medical College of Cornell University and Aichi Cancer Center Research Center, Nagoya Japan. Normal tissue RNA preparations were purchased from Clontech laboratories Incorporated (Palo Alto, Calif.) and Ambion Incorporated (Austin, Tex.). Total RNA from tumor tissues was prepared by the guanidinium thiocyanate method.

SEREX Analysis of cDNA Expression Libraries

Poly(A)+ RNA from two sarcoma cell lines, SW1045 and SW982, was prepared using the Fast Track mRNA Purification Kit (Invitrogen, Life Technologies, Carlsbad, Calif.). Poly(A)+ RNA from normal testis was purchased from CLONTECH. Separate cDNA libraries were constructed for each of these in the ZAP Express vector (Stratagene, La Jolla, Calif.) according to the manufacturer's instructions using 5 μg polyA+ mRNA. Libraries containing $1\text{-}2\times10^6$ primary recombinants were obtained and were not amplified before immunoscreening.

To remove serum antibodies reactive with vector-related antigens, sera was absorbed against *E. coli*/bacteriophage lysates prepared in the following manner. Wild-type lambda ZAP Express bacteriophage at a concentration of 5,000 pfu (plaque-forming units) per 15 cm plate were amplified in *E. coli* XL1 Blue MRF' overnight in 100 ml NZY/0.7% agarose. 10 ml of binding buffer (0.1M NaHCO3, pH 8.3) was then added to the plates, and the plates were gently agitated at 4° C. for 15 hours. The resultant supernatants were collected and residual *E. coli* were lysed by sonication. The lysates were then coupled to CNBr-Sepharose 4B (Amersham Pharmacia Biotech, Piscataway, N.J.) according to the manufacturer's instructions. Patient sera (1:10 dilution) were absorbed by batch absorption with an equal volume of Sepharose 4B coupled *E. coli*/phage lysates at 4° C. for 6 hours. This procedure was repeated a total of three times and was followed by a 15 hour incubation with nitrocellulose filters precoated with proteins derived from *E. coli* and *E. coli*/phage lysates. Library screenings were performed as previously described (Scanlan, M. J., et al. Characterization of human colon cancer antigens recognized by autologous antibodies. *Int. J. Cancer* 1998; 76: 652-8. Scanlan, M. J., et al. Antigens recognized by autologous antibody in patients with renal-cell carcinoma. *Int. J. Cancer* 1999; 83: 456-64.) A total of five independent SEREX immunoscreenings of the cDNA libraries were undertaken. Sera from 2 sarcoma patients were used independently, at a dilution of 1:200, to immunoscreen the cDNA libraries. A total of $2.5\text{-}5.0\times10^5$ or 1.75×10^6 recombinants were screened per serum/cDNA library combination. Serum reactive phage clones were converted to plasmid forms and subjected to DNA sequencing (Cornell University DNA Services, Ithaca, N.Y.).

Determination of Serum Antibody Reactivity

Two assays were used to determine serological reactivity, an ELISA-based method and a bacteriophage expression method. With regard to CT antigens, serum antibody reactivity was determined by ELISA as previously described (Stockert E, et al. 1998. A survey of the humoral immune response of cancer patients to a panel of human tumor antigens. J Exp Med 187:1349-54.) Briefly, recombinant proteins (NY-ESO-1, SSX-2, MAGE-A1, MAGE-A3, MAGE-A4, MAGE-A10, CT7 and CT10) were produced in *E. coli* by transfection with pQE30 expression vectors (Qiagen, Chatsworth, Calif.) according to the manufacturer's protocol. 10 ng of recombinant protein (1 μg/ml) was absorbed to TC microwell plates (Nalge Nunc International Corp., Naperville, Ill.) for 15 hours at 4° C. After washing with PBS, plates were then blocked with 2% BSA and incubated with diluted (1:100-1:

25,000) patient sera for 2 hours at room temperature. Following a PBS wash step, 10 μl of a 1:5000 dilution of alkaline phosphatase-conjugated goat anti-human IgG secondary antibody (Southern Biotechnology, Birmingham, Ala.) was added to each well and incubated for 1 hour at room temperature. Following a PBS wash step, plates were incubated with 10 ul/well Attophose substrate (JBL Scientific, San Louis Obispo, Calif.) for 25 min, and the fluorescence was then read by a Cyto-Fluor 2350 (Millipore, Bedford, Mass.).

In the case of SEREX-defined sarcoma antigens, a previously described serum antibody detection array (SADA or spot immunoassay (Scanlan M J, et al. Humoral immunity to human breast cancer: antigen definition and quantitative analysis of mRNA expression. Cancer Immunity 1:4 [epub]; Scanlan M J. et al. 2002. Cancer-Related Serological Recognition of Human Colon Cancer: Identification of Potential Diagnostic and Immunotherapeutic Targets. Cancer Res. 2002 Jul. 15; 16 (14): 4041-7.) was used to determine serological reactivity.

Preabsorbed serum samples from 39 sarcoma patients and 33 healthy blood donors were evaluated for the presence of IgG antibody reactive to a panel of SEREX-defined sarcoma antigens, identified herein, in the following manner. Precut nitrocellulose membranes (80×120 mm) were precoated with a layer (approximately 0.2 mm) of growth media (NZY/0.7% Agarose/2.5 mM isopropyl-β-D-thiogalactopyranoside) and placed on a reservoir layer of NZY/0.7% Agarose in a 86×128 mm Omni Tray (Nalge Nunc). 5.0×10^3 pfu per μl of bacteriophage encoding individual SEREX-defined tumor antigens were mixed with an equal volume of exponentially growing *E. coli* XL-1 Blue MRF' and spotted (0.7 μl aliquots) on the precoated nitrocellulose membranes using a 96 pin replicator (Nalge Nunc). Membranes were incubated for 15 hours at 37° C. and then processed as per the standard SEREX protocol (Scanlan, et al., Int. J. Cancer 1998; 76: 652-8; Scanlan, et al., Int. J. Cancer 1999; 83: 456-64). Briefly, plates were blocked in 0.5% non-fat dried milk; incubated in 10 ml of a 1:200 dilution of sera at room temperature for 15 hours; and then incubated in a 1:3000 dilution of alkaline phosphatase conjugated, Fc fragment specific, goat anti-human IgG (Jackson Immunoresearch laboratories Inc., West Grove Pa.). Serum IgG reactivity was detected with the alkaline phosphatase substrate, 4-nitro blue tetrazolium chloride/5-bromo-4-chloro-3-indolyl-phosphate.

Reverse Transcriptase-PCR (RT-PCR) Analysis

The cDNA preparations used as templates in the RT-PCR reactions were prepared using the Superscript first strand synthesis kit (Invitrogen Life Technologies, Carlsbad, Calif.) according to the manufacturer's instructions using 2.5 μg of total RNA. For evaluation of CT antigens expression in sarcoma cell lines, PCR primers specific for NY-ESO-1, LAGE-1, MAGE-1, MAGE-3, MAGE-4, MAGE-10, SCP-1, BAGE, CT7, SSX-1, SSX-2, and SSX-4 were synthesized commercially (Invitrogen Life Technologies) using published primer sequences (van der Bruggen P, et al. 1991. A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma. Science 254:1643-47, Gaugler, B., et al. Human gene MAGE-3 codes for an antigen recognized on a melanoma by autologous cytolytic T lymphocytes. *J. Exp. Med.* 1994; 179: 921-30, Chen, Y.-T., et al. A testicular antigen aberrantly expressed in human cancers detected by autologous antibody screening. *Proc. Natl. Acad. Sci. USA.* 1997; 94: 1914-18; Boel, P., et al., and van der Bruggen, P. BAGE: a new gene encoding an antigen recognized on human melanomas by cytolytic T lymphocytes. *Immunity* 1995; 2: 167-75. (PMID: 7895173); Sahin U, et al. 1998. Expression of multiple cancer/testis antigens in breast cancer and melanoma: basis for polyvalent CT vaccine strategies. Int J Cancer 78:387-89, Lethe B, et al. 1998. LAGE-1, a new gene with tumor specificity. Int. J. Cancer 76:903-8, Türeci Ö, et al. 1998. Expression of SSX genes in human tumors. Int J Cancer 77:19-23, Gure A O, et al. 1997. SSX: a multigene family with several members transcribed in normal testis and human cancer. Int J Cancer 72:965-971). PCR primers specific for SEREX-defined antigens were also synthesized commercially (Invitrogen Life Technologies) and their sequences are as follows: NY-SAR-12 forward, TggCgCAgAAAggAAAAggAAAAT (SEQ ID NO: 91); NY-SAR-12 reverse, AgAggTAgCTggCAggATgTTAg (SEQ ID NO: 92); NY-SAR-35 forward, CTTggTgCgATCAgCCTTAT (SEQ ID NO: 93); NY-SAR-35 reverse, TTgATgCATgAAAACAgAACTC (SEQ ID NO: 94); NY-SAR-41forward, AgAATTggCAgAggCTCgTCATCA (SEQ ID NO: 95); NY-SAR-41 reverse, TTCCAATTTTgCCTTCTCTAACTg (SEQ ID NO: 96); NY-SAR-73 forward, CCCggAgCACgTCgAggTCTAC (SEQ ID NO: 135); NY-SAR-73 reverse, ggTgAggggCCCAggAAgC (SEQ ID NO: 136); NY-SAR-78 forward, CACAATgTATCCTgTTgAAAg (SEQ ID NO: 137); NY-SAR-78 reverse, gAgATgATACATTCTTCCAg (SEQ ID NO: 138); NY-SAR-92 forward, CTTCCgCCAACTCCTCCTACC (SEQ ID NO: 139); NY-SAR-92 reverse, gATgCCCgTgTCTTgTCCTT (SEQ ID NO: 140); NY-SAR-96 forward, CACTAggCTgCTgAggAAgAT (SEQ ID NO: 141); NY-SAR-96 reverse, gTTTTggTgggCAgCATTgAg (SEQ ID NO: 142); NY-SAR-97 forward, ggACCACCCCAAATAgAA (SEQ ID NO: 143); NY-SAR-97 reverse, CCACCAgCTCAggAAgA (SEQ ID NO: 144); NY-SAR-110 forward, TCTgATggAgCggTgggATgC (SEQ ID NO: 145); NY-SAR-110 reverse, gTgTgCCTCggCTTCTTTCTTC (SEQ ID NO: 146).

RT-PCR was performed in the following manner. Twenty-five μl PCR reaction mixtures, consisting of 2 μl cDNA, 0.2 mM dNTP, 1.5 mM $MgCl_2$, 0.25 μM gene specific forward and reverse primers, and 2.5 U Platinum Taq DNA polymerase (Invitrogen Life Technologies), were heated to 94° C. for 2 min., followed by 35 thermal cycles of 94° C. for 30 seconds, 55° C. for 30 seconds and 72° C. for 1 min., and a final cycle of 94° C. for 30 seconds, 55° C. for 30 seconds and 72° C. for 5 min. Thermal cycling was performed using a GeneAmp PCR System 9700 (Applied Biosystems, Foster City, Calif.). Resultant PCR products were analyzed in 2% Agarose/Tris-Acetate-EDTA gels.

Real-Time Quantitative Reverse Transcription (RT)-PCR

The concentration of NY-SAR-35 mRNA transcripts in normal tissues was measured by real-time RT-PCR using cDNA preparations derived from lung cancer specimens and 16 different normal tissues that had been normalized for 6 housekeeping genes (Clontech). Gene-specific TaqMan probes and PCR primers were designed using Primer Express software (PE Biosystems, Foster City, Calif.). PCR reactions were prepared using 2.5 μl of cDNA diluted in TaqMan PCR Master Mix (PE Biosystems) supplemented with 200 nM 6-carboxy-fluorescein labeled gene-specific TaqMan probe, and a predetermined, optimum concentration of gene specific forward and reverse primers (300-900 nM). Triplicate PCR reactions were prepared for each cDNA sample. PCR consisted of 40 cycles of 95° C. denaturation (15 seconds) and 60° C. annealing/extension (60 seconds). Thermal cycling and fluorescent monitoring were performed using an ABI 7700 sequence analyzer (PE Biosystems). The point at which the PCR product is first detected above a fixed threshold, termed cycle threshold (Ct), was determined for each sample. The abundance of gene-specific transcripts in normal tissues was determined by comparison with a standard curve gener-

ated from the Ct values of known concentrations of plasmid DNA template encoding NY-SAR-35.

TaqMan primers were as follow: NY-SAR-35 forward, TggTgCgATCAgCCTTATCC (SEQ ID NO: 147); NY-SAR-35 reverse, CggTTCgCTCCTCCAgAA (SEQ ID NO: 148). TaqMan probe: NY-SAR-35, TgTCTgCCCATTTATTgCCgCTCTCT (SEQ ID NO: 149).

Northern Blot Analysis.

A Northern blot containing poly A+ RNA (2 μg/lane) from various normal tissues was obtained commercially (Clontech). An NY-SAR-35 cDNA probe (bp 263-1029) was labeled using the Bright Star Psoralen-Biotin Kit (Ambion Inc., Austin, Tex.) and hybridized to the membrane for 15 hours at 68° C. After washing, the hybridization signal was developed using the Bright Star Bio-Detect Kit, according to the manufacturer's instructions (Ambion).

Southern Blot Analysis

Genomic DNA was extracted from normal human testis, and samples (10 μg) were independently digested with EcoRI, HindIII, and BamHI at 37° C. overnight. The DNA was then separated on 0.7% agarose gel and blotted onto a nylon transfer membrane. An NY-SAR-35 cDNA probe (bp 252-1029) was radiolabeled with ^{32}P-dCTP using a random-primer DNA labeling kit (Roche Molecular Biochemicals, Indianapolis, Ind.). The blot was hybridized to a ^{32}P labeled probe at 68° C. After 15 hours of hybridization, the membrane was washed under high stringency conditions (0.1×SSC, 0.5% SDS at 60° C.) and exposed for autoradiography.

Example 1

Results from the First Round of Immunoscreenings by SEREX Analysis

Identification of Human Sarcoma Antigens by SEREX Analysis

Preliminary studies were carried out to determine optimum sources of target antigens and immunoreactive patient sera. Three sarcoma cell lines were typed for expression of NY-ESO-1, LAGE-1, MAGE-1, MAGE-3, MAGE-4, MAGE-10, BAGE, SCP-1, CT7, SSX-1, SSX-2, and SSX-4 transcripts by RT-PCR. As shown in Table 2, all 3 sarcoma cell lines expressed at least one of the transcripts in this panel. Specifically, the SW982 and SW1045 synovial sarcoma cell lines expressed 8 and 10 of the 12 CT antigen transcripts in the panel, respectively, while Fuji synovial sarcoma cells expressed 4/12 CT antigen transcripts.

TABLE 2

Cancer/Testis antigen expression in sarcoma cell lines

	Cell Line		
CT Antigen	SW982 (synovial)	SW1045 (synovial)	Fuji
NY-ESO-1	+	+	+
LAGE-1	Neg	+	+
MAGE-A1	+	+	Neg
MAGE-A3	+	+	Neg
MAGE-A4	+	+	
MAGE-A10	+	+	Neg
BAGE	+	+	Neg
SCP-1	Neg	Neg	Neg
CT7	+	+	Neg
SSX1	Neg	+	Neg
SSX2	Neg	Neg	
SSX4	+	+	Neg
Totals	8/12	10/12	4/12

In order to identify a subset of sarcoma patients that are actively mounting an immune response against tumor antigens, sera from 54 sarcoma patients (various histologies) were tested by ELISA (Stockert E, et al. 1998. A survey of the humoral immune response of cancer patients to a panel of human tumor antigens. J Exp Med 187:1349-54) for the presence of antibodies against a panel of 8 CT antigens consisting of: NY-ESO-1, SSX-2, MAGE-A1, MAGE-A3, MAGE-A4, MAGE-A10, CT7 and CT10. Only 2/54 sarcoma patients, a malignant fibrous histocytoma (MFH) and fibrosarcoma patient (FS), had detectable serum antibodies against a CT antigen, while the remaining 52 patients lacked detectable anti-CT antigen antibodies. Both seropositive patients had antibodies to NY-ESO-1 but lacked antibodies to the other 7 CT antigens tested. Fibrosarcoma tissue from the NY-ESO-1 seropositive patient, FS, was available for CT antigen typing by RT-PCR and was found to express 11/12 different CT antigen transcripts (NY-ESO-1, LAGE-1, MAGE-A1, -A3, -A4, -A10, BAGE, CT7, SSX1, -2 and -4). Tissue from the NY-ESO-1 seropositive patient, MFH, was not available for CT antigen typing by RT-PCR.

Although it was determined that CT antigen expression is frequent in sarcoma tissue, serum antibody responses were not as frequent. This lack of immunogenicity in sarcoma may be an indication of immune escape by sarcoma cells, whereby the immune system fails to recognize CT antigens and eliminate tumor cells expressing these antigens, resulting in the expansion of a homogenous population CT antigen expressing sarcoma cells. Relevant escape mechanisms include defective antigen presentation (Garrido F, Algarra I. MHC antigens and tumor escape from immune surveillance. Adv Cancer Res 2001; 83:117-58) and/or production of immunoinhibitory cytokines, such as TGF-β and IL-10 (Conrad C T, et al. Differential expression of transforming growth factor beta 1 and interleukin 10 in progressing and regressing areas of primary melanoma. J Exp Clin Cancer Res 1999 June; 18(2):225-32). It is also possible that homogeneous NY-ESO-1 and MAGE expression in synovial sarcoma (Jungbluth A A, et al. 2001. Monophasic and biphasic synovial sarcomas abundantly express cancer/testis antigen NY-ESO-1 but not MAGE-A1 or CT7. Int J Cancer 94:252-6; Antonescu C R, et al. MAGE antigen expression in monophasic and biphasic synovial sarcoma. Hum Pathol 2002 February; 33(2):225-9), as opposed to heterogeneous CT antigen expression observed in many other tumor types (Jungbluth A A, et al. 2001. Immunohistochemical analysis of NY-ESO-1 antigen expression in normal and malignant human tissues. Int J Cancer 92:856-60; Jungbluth A A, et al. 2000. Expression of MAGE-antigens in normal tissues and cancer. Int J Cancer 85:460-5), may also be a contributing factor to immune escape.

These 2 patients were chosen as the serum sources for SEREX immunoscreening of cDNA libraries prepared from the SW982 and SW1045 synovial sarcoma cell lines. A total of 4 SEREX immunoscreenings were performed, leading to the identification of 72 distinct sarcoma antigens, designated NY-SAR-1 through NY-SAR-72. As shown in Table 3, immunoscreening with sera from an NY-ESO-1 serum antibody positive MFH patient led to the identification of 28 antigens, including 8 overlapping antigens derived from both the SW982 and SW1045 cDNA libraries, as well as 13 antigens derived solely from the SW982 cDNA library, and 7 antigens derived solely from the SW1045 cDNA library.

Immunoscreening with sera from an NY-ESO-1 serum antibody positive fibrosarcoma patient defined 46 antigens, including 2 overlapping antigens derived from both the SW982 and SW1045 cDNA libraries, as well as 25 antigens

derived solely from the SW982 cDNA library, and 19 antigens derived solely from the SW1045 cDNA library. There was little overlap between the antigens recognized by serum antibodies from the MFH and FS patients. Only three antigens, NY-SAR-1/TMF1, NY-SAR-4/FH and NY-SAR-17/LAGE-1 were identified with both the MFH and FS sera. Because serological reactivity to NY-ESO-1 was the criteria used in selecting sera for cDNA library screening, mutual immunoreactivity to the highly homologous (84% amino acid identity) NY-SAR-17/LAGE-1 antigen was expected, and, although not intending to be bound by a particular theory, is likely to be due to shared epitopes. The 72 antigens (Tables 4-6) represent 58 known proteins and 14 uncharacterized gene products.

TABLE 3

Immunoscreening of synovial sarcoma cDNA expression libraries with allogeneic sarcoma patient sera

Sarcoma Serum	Synovial sarcoma cDNA expression library	Number of recombinants screened	Number of different antigens identified	Total number of distinct antigens
Malignant Fibrous Histocytoma	SW982	5×10^5	21	28
	SW1045	5×10^5	15	
Fibrosarcoma	SW982	2.5×10^5	27	46
	SW1045	2.5×10^5	21	

TABLE 4

SEREX-defined sarcoma antigens: antigens reactive with sera from multiple cancer patients

NY-SAR-Antigen	Identity (Unigene cluster)	Reactivity with Sarcoma Sera	Source of Reactive Sera[1]	SEREX Database ID Number[2] of Equivalent Isolate (Tumor Source[1])
2	STAU (Hs.6113)	2/39	MFH (#3), OS (#2)	614 (PRC), 1273 (BC)
4	FH (Hs.75653)	5/39	MFH (#3), OS (#4, #7), ES (#1), FS (#2)	No Match
12	NESG1 (Hs.158450)	2/39	MFH (#3), LS (#4)	No Match
13	ACTN1 (Hs.119000)	1/39	MFH (#3)	855 (BC)
15	RBM6 (Hs.173993)	1/39	MFH (#3)	76 (LC)
16	FLJ12785 (Hs.192742)	1/39	MFH (#3)	756 (TALL)
17	LAGE-1a (Hs.87225)	2/39	MFH (#3), FS (#2)	1160 (BC)
18	SSSCA1 (Hs.25723)	1/39	MFH (#3)	1799 (CC)
28	MGC: 9727 (Hs.11065)	1/39	MFH (#3)	71 (BC)
30	SNK (Hs.3838)	2/39	FS (#2), RS (#1)	No Match
44	LGALS1 (Hs.227751)	1/39	FS (#2)	704 (RC)
47	MIF (Hs.73798)	1/39	FS (#2)	989 (MEL)
50	PYCR1 (Hs.79217)	3/39	FS (#2), MFH (#2, #4)	No Match
71	None (Hs.314941)	1/39	FS (#2)	1938 (GL)
72	HSPE1 (Hs.1197)	1/39	FS (#2)	882 (HC), 1202 (MEL)

Antigens did not react with sera from normal blood donors (0/33).

[1]Abbreviations: BC, breast cancer; CC, colon cancer; ES, Ewing sarcoma; FS, fibrosarcoma; GC, gastric cancer; GL, glioma; HC, hepatocellular carcinoma; LC, lung cancer; LS, leimyosarcoma; MEL, melanoma; MFH, malignant fibrous histocytoma; OC, ovarian cancer; OS, osteosarcoma; PRC, prostate cancer; RC, renal cancer; RS, rhabdomyosarcoma; TALL, T-cell acute lymphocytic leukemia.

[2]SEREX database ID numbers from the LICR's SEREX database (licr.org/SEREX.html).

TABLE 5

SEREX-defined sarcoma antigens: antigens reactive with sera from both normal donors and sarcoma patients

NY-SAR-Antigen	Identity (Unigene cluster)	SEREX Database ID Number[1] of Equivalent Isolate (Tumor Source[2])	Reactivity with Normal Sera	Reactivity with Sarcoma Sera
1	TMF1 (Hs.267632)	246 (G), 1241 (BC)	2/33	3/39
3	KIAA1536 (Hs.156667)	89 (BR)	2/33	3/39
6	RHAMM (Hs.72550)	1513 (OC)	1/33	3/39
7	PINCH (Hs.112378)	344 (CC), 550 (GC), 1152 (RC), 1281 (BR)	16/21	14/39
10	KIAA0603 (Hs.173802)	No Match	11/33	4/39
11	U2AF1RS2 (Hs.171909)	430 (RC), 786 (HD), 1236 (BC), 1334 (GC)	6/33	17/39
14	SC65 (Hs.207251)	No Match	8/33	4/39
19	HEF1 (Hs.80261)	421 (RC)	3/33	7/39
22	NELIN (Hs.216381)	No Match	4/33	19/39
29	FLJ13441 (Hs.232146)	974 (PC)	6/33	3/39
31	HUMAUANTIG (Hs.75528)	1017 (BC), 1331 (GC), 1475 (OC)	2/33	6/39
32	PDAP1 (Hs.278426)	No Match	4/33	8/39
33	SURF6 (Hs.274430)	No Match	2/33	2/39
41	None (Hs.166670)	No Match	1/33	1/39
45	STIP1 (Hs.75612)	430 (RC)	4/33	2/39

TABLE 5-continued

SEREX-defined sarcoma antigens: antigens reactive with sera from both normal donors and sarcoma patients

NY-SAR-Antigen	Identity (Unigene cluster)	SEREX Database ID Number[1] of Equivalent Isolate (Tumor Source[2])	Reactivity with Normal Sera	Reactivity with Sarcoma Sera
53	FXYD5 (Hs.333418)	No Match	1/33	1/39
54	LMOD1 (Hs.79386)	No Match	7/33	13/39
55	RBM10 (Hs.154583)	No Match	1/33	1/39
58	LIP8 (Hs.348012)	No Match	1/33	3/39
61	ZNF282 (Hs.58167)	No Match	1/33	2/39
64	USP16 (Hs.99819)	No Match	2/33	2/39
65	FDFT1 (Hs.48876)	No Match	2/33	1/39
66	ROCK1 (Hs.109450)	444 (RC)	1/33	1/39
68	P38IP (Hs.333500)	No Match	1/33	3/39

[1]The LICR's SEREX database ID numbers from licr.org/SEREX.html.

[2]Abbreviations: BC, breast cancer; CC, colon cancer; HD, Hodgkins disease; GC, gastric cancer; OC, ovarian cancer; PC, pancreatic cancer; RC, renal cancer.

TABLE 6

SEREX-defined sarcoma antigens: antigens reactive with sera from a single sarcoma patient

NY-SAR-Antigen	Gene Identity (Unigene Cluster)
5	TBC1D1(Hs.278586)
8	BIRC2 (Hs.289107)
9	ATP5B (Hs.25)
20	TCEB3 (Hs.155202)
21	GTF3C3 (Hs.90847)
23	C20orf81 (Hs.29341)
24	None (not clustered)
25	PDE4DIP (Hs.265848)
26	PIASX-BETA (Hs.111323)
27	FLJ10330(Hs.342307)
34	SEC23B (Hs.173497)
35	None (Hs.128580)
36	SSX1(Hs.194759)
37	MP1 (Hs.260116)
38	HMG20B (Hs.32317)
39	PSMD4 (Hs.148495)
40	INPP1 (Hs.32309)
42	BTG3 (Hs.77311)
43	SSX4 (Hs.278632)
46	ARNTL2 (Hs.222024)
48	MGC20533 (Hs.69280)
49	EMK1 (Hs.157199)
51	EDF1 (Hs.174050)
52	Actin (Hs.288061)
56	MLF1Hs.85195)
57	GCN5L2 (Hs.101067)
59	UPF3B (Hs.103832)
60	EGLN1 (Hs.6523)
62	AD034(Hs.281397)
63	USP19(Hs.301373)
67	LUC7L (Hs.16803)
69	ARL1 (Hs.242894)
70	RPL10A (Hs.334895)

[1]Antigens reacted with sera from single sarcoma patient (1/39), but not with sera from normal individuals (0/33). The antigens listed had no matches with existing entries in the SEREX database (licr.org/SEREX.html).

The nucleotide sequences of all uncharacterized gene products (NY-SAR-3, -10, -16, -22, -23, -24, -27, -28, -29, -35, -41, -48, -62, -71) have been deposited in the GenBank database (SEQ ID NOs: 1-14, respectively). The cDNA sequences encoding the 72 sarcoma antigens were also compared to sequences deposited in the SEREX database accessible through a website of the Ludwig Institute for Cancer Research (licr.org/SEREX.html). Examination of this database revealed that 21 of the 72 sarcoma antigens defined in this study (29%) were also identified through SEREX analysis of other tumor types (Tables 4 and 5).

Reactivity Patterns of Sera from Normal Individuals and Cancer Patients with SEREX-Defined Sarcoma Antigens

To determine whether immune recognition of the isolated antigens was cancer-related, allogeneic sera samples obtained from 33 normal blood donors and 39 sarcoma patients (various histologies) were tested for reactivity against the 72 sarcoma antigens defined in the current study using serum antibody detection arrays (SADA). Twenty-four of the 72 antigens (33%) had a serological profile that was not restricted to cancer patients, as evidenced by their reactivity with normal sera. These antigens have been listed in Table 5.

Sera from two normal individuals and three sarcoma patients reacted with NY-SAR-1/TMF1, suggesting the reactivity was unrelated to cancers. With one notable exception (NY-SAR-22/NELIN), the frequency of antibody responses to 23 of the 24 antigens associated with normal sera reactivity was similar in normal blood donors and cancer patients. In the case of NY-SAR-22/NELIN (UniGene cluster Hs.216381), the frequency of antibody responses was considerably higher in cancer patients, in which 19⁄39 (49%) of sarcoma patients and 4⁄33 (12%) of normal individuals had a detectable antibody response. The remaining 48 antigens had a cancer-related serological profile, reacting only with sera from cancer patients.

The 48 antigens having a cancer-related serological profile could be subdivided into 4 categories; a) antigens identified by serum from only a single sarcoma patient; b) antigens that reacted with sera from a single sarcoma patient and, as determined by an analysis of the SEREX database, with sera from patients having other forms of cancer; c) antigens that reacted exclusively with sera from 2 or more sarcoma patients; and d) antigens that reacted with sera from 2 or more sarcoma patients and with sera from patients having other forms of cancer. Of the 48 antigens having a cancer-related serological profile, 33 antigens reacted with sera from a single sarcoma patient (Table 6).

As shown in Table 4, the remaining 15 antigens reacted with sera from 2 or more cancer patients, but not with sera from normal individuals. Nine antigens reacted with sera from a single sarcoma patient, and with sera from patients with other tumor types (NY-SAR-13, -15, -16, -18, -28, -44, -47, -71, -72). Four antigens reacted exclusively with sera from 2 or more sarcoma patients (NY-SAR, -4, -12, -30, -50). The remaining two antigens, NY-SAR-2/STAU and the CT antigen, NY-SAR-17/LAGE-1A, reacted with sera from 2 or more sarcoma patients and with sera from patients with other types of cancer. A cancer-related serological response to

NY-SAR-4/FH occurred most frequently. In this case, serum samples from 5/39 (13%) sarcoma patients were reactive with NY-SAR-4/FH, including 2/10 sera samples from osteosarcoma patients, 1/6 sera samples from malignant fibrous histiocytoma patients, 1/2 patients sera samples from fibrosarcoma patients, and 1/7 sera samples from Ewing sarcoma patients. No serological responses to NY-SAR-4/FH were detected in normal blood donors.

This serological response to NY-SAR-4/FH is of interest as germ-line mutations in the FH gene have been associated with a predisposition to uterine and cutaneous leiomyomata and also renal cell carcinoma (Tomlinson I P, et al. Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. Nat Genet 2002 April; 30(4):406-10) and is a target of somatic mutation in sarcoma (Kiuru, M., et al. (2002) Cancer Res. 62, 4554-4557) suggesting that the immune response is directed against mutated epitopes.

Expression Patterns of mRNA Encoding Serologically Defined Sarcoma Antigens in Normal and Malignant Tissues

A preliminary in silico mRNA expression profile of all gene products identified in this study was carried out based on the tissue distribution of expressed sequence tags (ESTs) in the human EST database. Products with no EST matches, or those having EST matches limited to tumor tissue, fetal tissue, and/or less than 3 normal adult tissues were further examined by RT-PCR. Gene products with restricted EST profiles include the three well-characterized cancer-testis antigens, LAGE-1/NY-SAR-17, NY-SAR-36/SSX1, and NY-SAR-43/SSX4, which are expressed exclusively in normal testis and a range of different tumor types (Lethe B, et al. 1998. LAGE-1, a new gene with tumor specificity. Int. J. Cancer 76:903-8; Türeci Ö, et al. 1998. Expression of SSX genes in human tumors. Int. J. Cancer 77:19-23; Gure A O, et al. 1997. SSX: a multigene family with several members transcribed in normal testis and human cancer. Int. J. Cancer 72:965-971), and 3 putative tissue restricted antigens, including a known gene product, nasopharyngeal specific protein 1(NESG1)/NY-SAR-12 (Li Z, Yao K, Cao Y. Molecular cloning of a novel tissue-specific gene from human nasopharyngeal epithelium. Gene 1999 Sep. 3; 237(1):235-40), and 2 uncharacterized gene products, NY-SAR-35 (UniGene cluster Hs.128580) and NY-SAR-41 (UniGene cluster Hs.166670). With the exception of serum reactivity to NY-SAR-41 occurring in 1/33 normal blood donors, these differentially expressed antigens showed a cancer-related serological profile.

As shown in FIG. **1**A, mRNA expression patterns of NY-SAR-12, -35, and -41 were examined in 17 different human tissues by RT-PCR. NESG1/NY-SAR-12 mRNA was detected in normal placenta, testis, colon, lung, and ovary (9/12 other normal tissues). NY-SAR-35 mRNA was detected only in normal testis (9/15 other normal tissues), while a lower molecular weight transcript was detected in normal ovary. NY-SAR-41 was detected in normal testis, fetal brain, colon, lung, and bladder (9/12 other normal tissues). As shown in FIG. **1**B, the testis restricted expression pattern of NY-SAR-35 was confirmed by real time quantitative RT-PCR at 40 amplification cycles. In these studies, NY-SAR-35 was expressed in normal testis at a level corresponding to 83.2 ag, which was more than 1000 times the level detected in the remaining 15 normal tissues.

The expression of NY-SAR-35 mRNA was also examined in 26 sarcoma specimens of various histologies, and was detected in fibrosarcoma and rhabdomyosarcoma specimens (2/26), as well as the SW1045 synovial sarcoma cell line (Table 7 and FIG. **1**C). With regard to other tumor types, transcripts encoding NY-SAR-35 were detected in 1/16 (6%) melanoma specimens, 5/29 (21%) lung cancer specimens, and 3/13 (23%) breast cancer specimens. NY-SAR-35 mRNA was not detected in small number of colon cancer specimens (0/9) or in small numbers of renal cancer specimens (0/8). Thus, on the basis of its immunogenicity in cancer patients, and its restricted mRNA expression profile, NY-SAR-35 can be considered a novel CT antigen.

TABLE 7

Expression of NY-SAR-35 in sarcoma, sarcoma cell lines and other malignant tissues

Histology	Expression Frequency
Sarcomas	
Synovial sarcoma	0/8
Leimyosarcoma	0/4
Malignant Fibrous Histocytoma	0/4
Ewing Sarcoma	0/2
Osteosarcoma	0/2
Rhabdomyosarcoma	1/1
Fibrosarcoma	1/1
Liposarcoma	0/1
Neurosarcoma	0/1
Chondrosarcoma	0/1
DFSP	0/1
SW1045 synovial sarcoma cell line	positive
SW982 synovial sarcoma cell line	negative
Fuji synovial sarcoma cell line	negative
Other Malignancies	
Melanoma	1/16
Lung Cancer	5/29
Colon Cancer	0/9
Breast Cancer	3/13
Renal Cancer	0/8
Esophageal Cancer	1/12
Ovarian Cancer	1/12
Gastric Cancer	5/6

The NY-SAR-35 Gene, Transcript and Putative Protein and Orthologous Gene

An analysis of the human genome database, mapped the NY-SAR-35 cDNA sequence to Xq28, approximately 5.9 Mbp downstream (3') of the CT10/MAGE-E1 gene and 6.8 Mbp upstream (5') of the NY-ESO-1 gene. The NY-SAR-35 gene is approximately 44 kb in length and spans 6 exons. Analyses of the human genome databases (NCBI GenBank, ncbi.nlm nih gov/genome, and Celera Genomics, Rockville, Md., celera.com) revealed no genomic sequences of high similarity, suggesting that it is a single copy gene with no additional family members. These results were verified by probing Southern blots of human genomic DNA with the NY-SAR-35 cDNA.

The present SEREX immunoscreening provided 4 overlapping NY-SAR-35 cDNA clones, ranging from 677-767 by in length, all contained identical 3' sequences originating from the poly A region. The NY-SAR-35 cDNA sequence was identical to 3 ESTs (GenBank accession nos. AA909915, AA906131, and AW593050) which were all derived from the NFL_T_GBC_S1 mixed tissue (fetal lung, testis, germinal center B cell) cDNA library and found in UniGene cluster Hs.128580 as well as 4 ESTs (GenBank accession nos. BC034320, AK098602, BG771667 and BI465380) derived from a testis cell line and found in Unigene cluster Hs.375082. As shown in FIG. **1**D, Northern blot analysis revealed a single NY-SAR-35 mRNA transcript of 1.1 kB in normal testis, indicating the SEREX-defined clones and EST sequences represent partial transcripts. To obtain a full-length NY-SAR-35 transcript, 5' RACE was performed, yielding 262 by of additional 5' DNA sequence. Thus, the total length of the NY-SAR-35 transcript is 1029 by (SEQ ID NO: 10, GenBank accession no. AY211917), a size that is in agree-

ment with the 1.1 kb hybridization signal seen in Northern blots of testis mRNA probed with NY-SAR-35 cDNA.

The NY-SAR-35 transcript encodes an open reading frame of 255 amino acids (SEQ ID NO: 55, by 68-895) with a predicted molecular mass of 29.2kDa. It is identical to a hypothetical protein, XM098959, predicted from Genefinder analysis of human chromosome X sequences. The putative NY-SAR-35 protein has a signal peptide, a transmembrane domain and a cysteine-rich trefoil/P-domain, found in several secreted proteins of the gastrointestinal tract (Hoffmann W, Hauser F. The P-domain or trefoil motif: a role in renewal and pathology of mucous epithelial Trends Biochem Sci 1993 July; 18(7):239-43). These data suggest that NY-SAR-35 is a-secreted or membrane bound protein.

To identify a murine orthologue of NY-SAR-35, the putative human NY-SAR-35 protein sequence was used to search a translated nonredundant nucleotide database by using the TBLASTN tool of the NCBI (ncbi.nlm nih gov/blast/Blast.cgi). A hypothetical mouse protein, termed XP_150408, generated from a conceptual translation of the mouse X chromosome, was found to have 57% identity (49/85 amino acids) with NY-SAR-35. Using nucleotide primers corresponding to sequences encoding XP_150408, 5' and 3' RACE reactions were undertaken by using mouse testis cDNA. By combining 5' and 3' RACE products, a 1,202 by cDNA was identified (GenBank accession no. AY214130, SEQ ID NO: 133). This cDNA encoded a putative full length mouse protein of 238 amino acids (SEQ ID NO: 134) which is 41% identical to human NY-SAR-35, with conservation of the trefoil and transmembrane domains. This murine NY-SAR-35 (mNY-SAR-35) cDNA sequence was used to search mouse genome sequences (ncbi.nlm nih gov/genome/seq/MmBlast.html) yielding an identical genome sequence, NW 042622, from mouse chromosome X. Analysis of this sequence showed the mNY-SAR-35 gene is composed of approximately 42,600 nucleotides and seven exons.

Example 2

Analysis of the NY-SAR-35 Protein and its Expression

Purification of Recombinant NY-SAR-35 Protein in *E. coli* to Produce Monoclonal Antibodies and to Perform ELISA Assays

There are four ATG codons in exon 1 of the NY-SAR-35 gene. It is expected that the fourth ATG codon in the full length sequence of NY-SAR-35 is the first ATG codon of the translated NY-SAR-35 sequence. It appears then that the predicted protein has two interesting domains. The protein revealed two distinctive hydrophobic domains followed by two hydrophilic turns. One hydrophobic domain is a signal peptide, which are predicted in proteins with cleavage sites between amino acids 25 and 26 with SignalP software tool available at the website cbs.dtu.dk/services/SignalP. The other hydrophobic region is predicted to be a transmembrane domain with the TMHMM2.0 program available at the website cbs.dtu.dk/services/TMHMM/TMHMM2.0b.guide.html. Therefore, the NY-SAR-35 gene encodes a signal peptide and a transmembrane domain (FIG. **2**).

Three kinds of NY-SAR-35 vectors were designed for the purification of the proteins in an *E. coli* expression system (pET System) (Novagen, Madison, Wisc.). The first encoded the largest possible NY-SAR-35 protein from the first ATG codon (SEQ ID NO: 150), the second encoded the NY-SAR-35 protein from the fourth ATG codon (MH7) (SEQ ID NO: 152), and the third encoded the expected extracellular domain from the fourth ATG codon (SEQ ID NO: 154). An illustration of these vectors is provided below. The expected sizes of the resulting proteins are 29 kD (263 amino acids) (SEQ ID NO: 151), 22 kD (201 amino acids) (SEQ ID NO: 153) and 14.6 kD (133 amino acids) (SEQ ID NO: 155), respectively.

I. Whole protein (NY-SAR-35 from the First ATG)

Vector:pET23a(NdeI/XhoI): C-terminal His tag vector

Primer;

SAR35/NdeI:

(SEQ ID NO: 156)

CACACACA**CATATG**TCTTCACATAGGAGGAAAGCGAAG

SAR35/XhoI:

(SEQ ID NO: 157)

CACACA**CTCGAG**CTCGTCACCATGTTCCTCACGTC

(SEQ ID NO: 150)

CATATGTCTTCACATAGGAGGAAAGCGAAGGGGAGGAATAGGAGAAGTCA
CCGTGCCATGCGTGTGGCTCACTTAGAGCTGGCAACTTATGAGTTGGCGG
CAACTGAGTCGAATCCCGAGAGCAGCCATCCTGGATACGAGGCCGCCATG
GCTGACAGGCCTCAGCCAGGATGGCGGGAATCTCTAAAGATGCGGGTCAG
CAAACCCTTTGGGATGCTCATGCTCTCCATTTGGATCCTGCTGTTCGTGT
GCTACTACCTGTCCTACTACCTGTGCTCCGGGTCCTCATATTTTGTGCTT
GCAAATGGACATATCCTGCCCAACAGTGAAAATGCTCATGGCCAATCTCT
GGAAGAAGATTCCGCATTGGAAGCTTTGCTGAATTTTTTCTTTCCAACAA
CTTGCAATCTGAGGGAAAATCAGGTGGCAAAGCCTTGTAATGAGCTGCAA
GATCTTAGTGAGAGTGAATGTTTGAGACACAAATGCTGTTTTTCATCATC
GGGGACCACGAGCTTCAAATGTTTTGCTCCATTTAGAGATGTGCCTAAAC
AGATGATGCAAATGTTTGGGCTTGGTGCGATCAGCCTTATCCTGGTATGT
CTGCCCATTTATTGCCGCTCTCTTTTCTGGAGGAGCGAACCGGCCGATGA
TTTACAAAGGCAGGACAACAGAGTTGTAACGGGTTTGAAGAAACAAAGAA
GGAAGCGAAAGAGGAAGTCTGAAATGTTACAGAAAGCAGCAAGAGGACGT
GAGGAACATGGTGACGAG**CTCGAG**CACCACCACCACCACCACTGA

(SEQ ID NO: 151)

MSSHRRKAKGRNRRSHRAMRVAHLELATYELAATESNPESSHPGYEAAMA
DRPQPGWRESLKMRVSKPFGMLMLSIWILLFVCYYLSYYLCSGSSYFVLA
NGHILPNSENAHGQSLEEDSALEALLNFFFPTTCNLRENQVAKPCNELQD
LSESECLRHKCCFSSSGTTSFKCFAPFRDVPKQMMQMFGLGAISLILVCL
PIYCRSLFWRSEPADDLQRQDNRVVTGLKKQRRKRKRKSEMLQKAARGRE
EHGDELEHHHHHH

II. Partial Protein (MH7 from the Fourth ATG)

Vector; pET23a(NdeI/XhoI)

Primer;

MH7/NdeI:

(SEQ ID NO: 158)

CACACACA**CATATG**CGGGTCAGCAAACCCTTTGGGA

SAR35/XhoI:

(SEQ ID NO: 159)

CACACA**CTCGAG**CTCGTCACCATGTTCCTCACGTC

(SEQ ID NO: 152)

CATATGCGGGTCAGCAAACCCTTTGGGATGCTCATGCTCTCCATTTGGAT
CCTGCTGTTCGTGTGCTACTACCTGTCCTACTACCTGTGCTCCGGGTCCT
CATATTTTGTGCTTGCAAATGGACATATCCTGCCCAACAGTGAAAATGCT
CATGGCCAATCTCTGGAAGAAGATTCCGCATTGGAAGCTTTGCTGAATTT
TTTCTTTCCAACAACTTGCAATCTGAGGGAAAATCAGGTGGCAAAGCCTT
GTAATGAGCTGCAAGATCTTAGTGAGAGTGAATGTTTGAGACACAAATGC
TGTTTTTCATCATCGGGGACCACGAGCTTCAAATGTTTTGCTCCATTTAG
AGATGTGCCTAAACAGATGATGCAAATGTTTGGGCTTGGTGCGATCAGCC
TTATCCTGGTATGTCTGCCCATTTATTGCCGCTCTCTTTTCTGGAGGAGC
GAACCGGCCGATGATTTACAAAGGCAGGACAACAGAGTTGTAACGGGTTT
GAAGAAACAAAGAAGGAAGCGAAAGAGGAAGTCTGAAATGTTACAGAAAG
CAGCAAGAGGACGTGAGGAACATGGTGACGAG**CTCGAG**CACCACCACCAC
CACCACTGA

(SEQ ID NO: 153)

MRVSKPFGMLMLSIWILLFVCYYLSYYLCSGSSYFVLANGHILPNSENAH
GQSLEEDSALEALLNFFFPTTCNLRENQVAKPCNELQDLSESECLRHKCC
FSSSGTTSFKCFAPFRDVPKQMMQMFGLGAISLILVCLPIYCRSLFWRSE
PADDLQRQDNRVVTGLKKQRRKRKRKSEMLQKAARGREEHGDELEHHHHH
H

III. Expected Extracellular Domain of NY-SAR-35 from the Fourth ATG

Vector:pET23a(NdeI/XhoI)

Primer;

MH7/NdeI:

(SEQ ID NO: 160)

CACACACA**CATATG**CGGGTCAGCAAACCCTTTGGGA

MH7/XhoI:

(SEQ ID NO: 161)

CACACA**CTCGAG**CATTTGCATCATCTGTTTAGGC

(SEQ ID NO: 154)

CATATGCGGGTCAGCAAACCCTTTGGGATGCTCATGCTCTCCATTTGGAT
CCTGCTGTTCGTGTGCTACTACCTGTCCTACTACCTGTGCTCCGGGTCCT
CATATTTTGTGCTTGCAAATGGACATATCCTGCCCAACAGTGAAAATGCT
CATGGCCAATCTCTGGAAGAAGATTCCGCATTGGAAGCTTTGCTGAATTT
TTTCTTTCCAACAACTTGCAATCTGAGGGAAAATCAGGTGGCAAAGCCTT
GTAATGAGCTGCAAGATCTTAGTGAGAGTGAATGTTTGAGACACAAATGC
TGTTTTTCATCATCGGGGACCACGAGCTTCAAATGTTTTGCTCCATTTAG
AGATGTGCCTAAACAGATGATGCAAATG**CTCGAG**CACCACCACCACCACC
ACTGA

(SEQ ID NO: 155)

MRVSKPFGMLMLSIWILLFVCYYLSYYLCSGSSYFVLANGHILPNSENAH
GQSLEEDSALEALLNFFFPTTCNLRENQVAKPCNELQDLSESECLRHKCC
FSSSGTTSFKCFAPFRDVPKQMMQMLEHHHHHH

Protein expression was induced in *E. coli*. Three colonies of each domain cloned plasmid were selected and cultured by IPTG induction for 4 hours. When total proteins were separated by SDS-electrophoresis and stained by Simply Blue SafeStain (Invitrogen) the highly expressed protein bands were not detected. However, when total proteins, separated by SDS-polyacrylamide gel, were immunoblotted using an anti-His epitope antibody, the His-tagged NY-SAR-35 proteins were detected. The results are shown in FIG. **3** with the expected sizes of the expressed proteins.

Functional Study of NY-SAR-35

Most cancer-testis antigens ([11/13]) have been found to be expressed in non-malignant human kidney embryonic 293 cell while NY-SAR-35 is not. Human 293 cell and monkey Cos-1 cells were used to stably express the NY-SAR-35 gene for functional and immunolocalization studies.

The expected NY-SAR-35 open reading frame (including the 5' untranslated region) was cloned into pcDNA3.1/V5-HisA vector which had a C-terminal fusion tag (V5 epitope and 6×His epitope). The cloned NY-SAR-35 nucleotide sequence and expected amino acid sequence are as follows:

A. Cloned NY-SAR-35 Nucleotide Sequence

(SEQ ID NO: 162)

GAATTCCTTCTGGGCCACGGACTGCCGGACCGTTGGGCTGTGAGGCAGCG
EcoRI

TCTCAGCGAGGCGGCACCCGGAGCC**ATG**TCTTCACATAGGAGGAAAGCGA

AGGGGAGGAATAGGAGAAGTCACCGTGCC**ATG**CGTGTGGCTCACTTAGAG

CTGGCAACTTATGAGTTGGCGGCAACTGAGTCGAATCCCGAGAGCAGCCA

TCCTGGATACGAGGCCGCC**ATG**GCTGACAGGCCTCAGCCAGGATGGCGGG

AATCTCTAAAG**ATG**CGGGTCAGCAAACCCTTTGGGATGCTCATGCTCTCC

ATTTGGATCCTGCTGTTCGTGTGCTACTACCTGTCCTACTACCTGTGCTC

CGGGTCCTCATATTTTGTGCTTGCAAATGGACATATCCTGCCCAACAGTG

AAAATGCTCATGGCCAATCTCTGGAAGAAGATTCCGCATTGGAAGCTTTG

CTGAATTTTTTCTTTCCAACAACTTGCAATCTGAGGGAAAATCAGGTGGC

-continued

AAAGCCTTGTAATGAGCTGCAAGATCTTAGTGAGAGTGAATGTTTGAGAC

ACAAATGCTGTTTTTCATCATCGGGGACCACGAGCTTCAAATGTTTTGCT

CCATTTAGAGATGTGCCTAAACAGATGATGCAAATGTTTGGGCTTGGTGC

GATCAGCCTTATCCTGGTATGTCTGCCCATTTATTGCCGCTCTCTTTTCT

GGAGGAGCGAACCGGCCGATGATTTACAAAGGCAGGACAACAGAGTTGTA

ACGGGTTTGAAGAAACAAAGAAGGAAGCGAAAGAGGAAGTCTGAAATGTT

ACAGAAAGCAGCAAGAGGACGTGAGGAACATGGTGACGAG**CTCGAG**TCTA
XhoI

GAGGGCCCTTCGAA***GGTAAGCC TAT CCCTAACC CTCTCCTC***
V5 epitope

GGTCTCGATTCTACGCGTACCGGT***CATGATCACCATGACCAT***TGA
His tag

B. Expected Amino Acid Sequence and Expected Size of Expressed Proteins

(SEQ ID NO: 163)

→ 31 Kd

EFLLGHGLPDRWAVRQRLSEAAPGA**M**SSHRRKAKGRNRRSHRA

→ 29 Kd → 26 Kd

MRVAHLELATYELAATESNPESSHPGYEAA**M**ADRPQPGWRESLK

→ 24 Kd

MRVSKPFGMLMLSIWILLFVCYYLSYYLCSGSSYFVLANGHILPNSENAH

GQSLEEDSALEALLNFFFPTTCNLRENQVAKPCNELQDLSESECLRHKCC

FSSSGTTSFKCFAPFRDVPKQMMQMFGLGAISLILVCLPIYCRSLFWRSE

PADDLQRQDNRVVTGLKKQRRKRKRKSEMLQKAARGREEHGDELESRGPF

EGKPIPNPLLGLDSTRTG**HHHHHH**
V5 epitope His tag

Human 293 cells and monkey Cos-1 cell that stably express the NY-SAR-35 gene were tested by RT-PCR and Western blotting. The cells transfected with 0.5 μg pcDNA3.1/V5/HisA/NY-SAR-35 plasmid were selected with 1 mg/ml neomycin for 14 days. Clones were picked and expanded for an additional 1 month and analyzed for NY-SAR-35 mRNA and protein expression. Three sets of NY-SAR-35 5'/3' primers were used and are provided below:

lane 1 (ORF including 5' untranslated region)

(SEQ ID NO: 164)

GGGAATTCATGTCTTCACATAGGAGGAAAGCG/CACACACTCGAGCTCGT
CACCATGTTCCTCACGTC

lane 2 (ORF from the last ATG)

(SEQ ID NO: 165)

CACACACACATATGTCTTCACATAGGAGGAAAGCGAAG/CACACACTCGA
GCTCGTCACCATGTTCCTCACGTC

lane 3 (ORF from the fourth ATG)

(SEQ ID NO: 166)

CACACACACATATGCGGGTCAGCAAACCCTTTGGGA/CACACACACATAT
GTCTTCACATAGGAGGAAAGCGAAG

lane 4 (p53 5'/3')

(SEQ ID NO: 167)

TACTCCCCTGCCCTCAACAAG/CTCAGGCGGCTCATAGGG

Whole cell extracts were made from the same cloned cells. Total proteins were separated by SDS-polyacrylamide gel electrophoresis and immunoblotted to detect NY-SAR-35 proteins by anti-V5 epitope monoclonal antibody(Invitro-

gen). The size of the stably expressed NY-SAR-35 proteins in 293 and Cos-1 cells was found to be 24 kD. This is, therefore, consistent with translation of NY-SAR-35 beginning at the fourth ATG.

Example 3

Results from the Second Round of Immunoscreenings by SEREX Analysis

Identification of Human Sarcoma Antigens by SEREX Analysis

Serum from the two NY-ESO-1 seropositive patients (FS and MFH) were again used to immunoscreen cDNA libraries prepared from the SW982 and SW1045 synovial sarcoma cell lines, both of which were shown to express eight or more known CT antigen transcripts (Table 2). Sera from the FS patient was also used to immunoscreen a cDNA library derived from normal testis. In total, the results from Examples 1 and 3 represent five independent SEREX immunoscreenings performed, which lead to the identification of 113 distinct antigens, designated NY-SAR-1 through NY-SAR-113.

The 113 SEREX-defined antigens represent 91 known proteins and 22 uncharacterized gene products (novel, ESTs, KIAA series, FLJ series, ORFs, DKFZ series). In addition to the uncharacterized gene products described above in Example 1 (NY-SAR-3, -10, -16, -22, -23, -24, -27, -29, -35, -41, -48 and -71) additional immunoscreening identified another 11 uncharacterized gene products (NY-SAR-77, -79, -80, -84, -88, -91, -95, -97, -104, -105 and -113). All of the sequences for these uncharacterized gene products have been deposited in the GenBank database and given the sequential accession numbers AY211909-AY211931. In terms of the serum sources, 27 of the 113 antigens were identified by using sera from a MFH patient and 86 were identified with FS sera. Of the 113 antigens identified, 95 were unique to a particular cDNA library screening and 18 antigens were identified in more than one library. This underlines the beneficial nature of incorporating multiple cDNA libraries into large-scale SEREX analyses of the cancer immunome.

Seroepidemiology of SEREX-Defined Sarcoma Antigens

The cDNA sequences encoding the 113 sarcoma antigens were compared with sequences deposited in the cancer immunome or SEREX database (licr.org/CancerImmunomeDB, formerly licr.org/SEREX.html). These comparisons are in addition to the comparisons presented above in Example 1. In a preliminary analysis, it was found that 39 of the 113 sarcoma antigens defined in this study (34%) were also identified through SEREX analysis of other tumor types (Table 8). Table 9 below provides a complete list of all 113 antigens along with their respective Unigene cluster information, if any. These results represent the information available after all rounds of immunoscreening. Contrary to the results shown, NY-SAR-39, -57, -61, -63 and -64 after the first round of immunoscreenings had not been found in the SEREX database.

TABLE 8

Immunomic analysis of sarcoma/testis antigens: Reactivity with sera from sarcoma patients, patients with other forms of cancer, and normal individuals

NY-SAR-antigen	Gene identity (ugene cluster)	Cancer patient seroreactivity*	Normal seroreactivity
1	TMF1 (Hs.267632)	GC, BC, CC, SRC	2/33
2	STAU (Hs.6113)	PC, BC, SRC	3/30
3	KIAA1536 (Hs.156667)	BC, SRC	2/33
6	RHAMM (Hs.72550)	OC, SRC	1/33
7	PINCH (Hs.112378)	CC, GC, RC, BC HN, ESO, AML, SRC	16/21
11	U2AF1RS2 (Hs.171909)	RC, HD, BC, GC, SRC	6/33
13	ACTN1 (Hs.119000)	BC, SRC	5/30
15	RBM6 (Hs.173993)	LC, SRC	0/33
16	FLJ12785 (Hs.192742)	TALL, SRC	0/33
17	LAGE-1a (Hs.87225)	BC, SRC	0/33
18	SSSCA1(Hs.25723)	CC, SRC	0/33
19	HEF1 (Hs.80261)	RC, SRC	3/33
28	PPIL4 (Hs.11065)	BC, SRC	0/33
29	FLJ13441 (Hs.232146)	PN, SRC	6/33
31	AUANTIG (Hs.75528)	BC, GC, OC, SRC	2/33
39	PSMD4 (Hs.148495)	MEL, SRC	0/33
44	LGALS1 (Hs.227751)	RC, SRC	0/33
45	STIP1 (Hs.75612)	RC, SRC	4/33
47	MIF (Hs.73798)	MEL, SRC	0/33
57	GCN5L2 (Hs.101067)	PC, SRC	0/33
61	ZNF282 (Hs.58167)	RC, SRC	1/33
63	USP19 (Hs.301373)	OC, SRC	0/33
64	USP16 (Hs.99819)	PN, SRC	2/33
66	ROCK1 (Hs.17820)	RC, BC, CC, SRC	1/33
74	RANBP2 (Hs.199179)	BC, GL, BC, SRC	2/33
77	KIAA0992 (Hs.194431)	PC, SRC	4/15
80	FLJ12577 (Hs.87159)	GC, SRC	0/33
81	SDS3 (Hs.20104)	GC, SRC	4/16
82	NYCO45 (Hs.160881)	CC, SRC	0/33
89	SSX2 (Hs.289105)	BC, MEL, SRC	0/33
90	UACA (Hs.49753)	BC, ESO, SRC	4/25
93	NYBR15 (Hs.178175)	BC, SRC	1/12
98	OIP2 (Hs.274170)	BC, SRC	0/33
99	SSX3 (Hs.178749)	BC, MEL, SRC	2/30
101	RANBP2L1 (Hs.179825)	GL, BC, SRC	3/33
102	RBPJK (Hs.356806)	GC, RC, BC, MEL, SRC	1/16
103	Hsp40 (Hs.94)	HN, NCC, SRC	0/33
108	EIF4G (Hs.25732)	GC, SRC	5/27
112	PMSCL1 (Hs.91728)	CC, SRC	0/33

AML, acute myelogenous leukemia; BC, breast cancer; CC, colon cancer; GC, gastric cancer; GL, glioma; HCC, hepatocellular carcinoma; HN, head and neck cancer; LC, lung cancer; MEL, melanoma; OC, ovarian cancer; PC, prostate cancer; PN, pancreatic cancer; RC, renal cancer; SRC, sarcoma; TALL, T cell acute lymphocytic leukemia.
*Determined by sequence comparisons with the SEREX database (licr.org/CancerImmunomeDB/).

TABLE 9

Sarcoma/testes antigens defined by serological analysis of cDNA expression libraries

NY-SAR-antigen	Gene identity (Unigene Cluster)	Sera source	Library source
1	TMF1 (Hs.267632)	MFH, FS	A, T
2	STAU (Hs.6113)	MFH	A
3	KIAA1536 (Hs.156667)	MFH	A
4	FH (Hs.75653)	MFH, FS	A, B
5	TBC1D1(Hs.278586)	MFH	A
6	RHAMM (Hs.72550)	MFH	A, B
7	PINCH (Hs.112378)	MFH	A, B
8	BIRC2 (Hs.289107)	MFH	A, B
9	ATP5B (Hs.25)	MFH	A, B
10	KIAA0603 (Hs.173802)	MFH	A
11	U2AF1RS2 (Hs.171909)	MFH	A, B
12	NESG1 (Hs.158450)	MFH	B

TABLE 9-continued

Sarcoma/testes antigens defined by serological analysis of cDNA expression libraries

NY-SAR-antigen	Gene identity (Unigene Cluster)	Sera source	Library source
13	ACTN1 (Hs.119000)	MFH	A
14	SC65 (Hs.207251)	MFH	A
15	RBM6 (Hs.173993)	MFH	A
16	FLJ12785 (Hs.192742)	MFH	A
17	LAGE-1a (Hs.87225)	MFH, FS	B
18	SSSCA1 (Hs.25723)	MFH	A, B
19	HEF1 (Hs.80261)	MFH	A, B
20	TCEB3 (Hs.155202)	MFH	B
21	GTF3C3 (Hs.90847)	MFH	A
22	NELIN (Hs.216381)	MFH	A
23	C20orf81 (Hs.29341)	MFH	A
24	None (not clustered)	MFH	A
25	PDE4DIP (Hs.265848)	MFH	B
26	PIASX-BETA (Hs.111323)	MFH	B
27	FLJ10330(Hs.342307)	MFH	B
28	PPIL4 (Hs.11065)	FS	B
29	FLJ13441 (Hs.232146)	FS	A
30	SNK (Hs.3838)	FS	A
31	HUMAUANTIG (Hs.75528)	FS	A, B, T
32	PDAP1 (Hs.278426)	FS	A
33	SURF6 (Hs.274430)	FS	B
34	SEC23B (Hs.173497)	FS	B
35	EST (Hs.128580)	FS	B, T
36	SSX1(Hs.194759)	FS	B, T
37	MP1 (Hs.260116)	FS	A, T
38	HMG20B (Hs.32317)	FS	A
39	PSMD4 (Hs.148495)	FS	A
40	INPP1 (Hs.32309)	FS	A
41	EST (Hs.166670)	FS	B
42	BTG3 (Hs.77311)	FS	B, T
43	SSX4 (Hs.278632)	FS	B
44	LGALS1 (Hs.227751)	FS	B
45	STIP1 (Hs.75612)	FS	A
46	ARNTL2 (Hs.222024)	FS	B
47	MIF (Hs.73798)	FS	A
48	MGC20533 (Hs.69280)	FS	A
49	EMK1 (Hs.157199)	FS	A
50	PYCR1 (Hs.79217)	FS	A
51	EDF1 (Hs.174050)	FS	A
52	Actin (Hs.288061)	FS	A
53	FXYD5 (Hs.333418)	FS	A
54	LMOD1 (Hs.79386)	FS	A
55	RBM10 (Hs.154583)	FS	A
56	MLF1(Hs.85195)	FS	A, T
57	GCN5L2 (Hs.101067)	FS	A
58	LIP8 (Hs.348012)	FS	A
59	UPF3B (Hs.103832)	FS	A
60	EGLN1 (Hs.6523)	FS	A
61	ZNF282 (Hs.58167)	FS	A
62	AD034(Hs.281397)	FS	A
63	USP19(Hs.301373)	FS	A
64	USP16 (Hs.99819)	FS	B, T
65	FDFT1 (Hs.48876)	FS	B
66	ROCK1 (Hs.17820)	FS	B, T
67	LUC7L (Hs.16803)	FS	B
68	P38IP (Hs.333500)	FS	B
69	ARL1 (Hs.242894)	FS	B
70	RPL10A (Hs.334895)	FS	B
71	EST (Hs.314941)	FS	B
72	HSPE1 (Hs.1197)	FS	B, T
73	PRM2 (Hs.2324)	FS	T
74	RANBP2 (Hs.199179)	FS	T
75	GKAP42 (Hs.36752)	FS	T
76	TIAL1 (Hs.182741)	FS	T
77	KIAA0992 (Hs.194431)	FS	T
78	TSP-NY (Hs.97643)	FS	T
79	Novel (not clustered)	FS	T
80	FLJ12577 (Hs.87159)	FS	T
81	SDS3 (Hs.20104)	FS	T
82	NYCO45 (Hs.160881)	FS	T
83	SOX6 (Hs.326876)	FS	T
84	DKFZp434 (Hs.131834)	FS	T
85	RAD50 (Hs.41587)	FS	T
86	EPIM (Hs.99865)	FS	T

TABLE 9-continued

Sarcoma/testes antigens defined by serological analysis of cDNA expression libraries

NY-SAR-antigen	Gene identity (Unigene Cluster)	Sera source	Library source
87	SOX5 (Hs.87224)	FS	T
88	DKFZp564 (Hs.93589)	FS	T
89	SSX2 (Hs.289105)	FS	T
90	UACA (Hs.49753)	FS	T
91	FLJ11730 (Hs.17118)	FS	T
92	ESTs (Hs.368781)	FS	T
93	NYBR15 (Hs.178175)	FS	T
94	CG005 (Hs.23518)	FS	T
95	FLJ10637 (Hs.22595)	FS	T
96	MCSP (Hs.111850)	FS	T
97	EST (Hs.128836)	FS	T
98	OIP2 (Hs.274170)	FS	T
99	SSX3 (Hs.178749)	FS	T
100	PGAM2 (Hs.46039)	FS	T
101	RANBP2L1 (Hs.179825)	FS	T
102	RBPJK (Hs.356806)	FS	T
103	Hsp40 (Hs.94)	FS	T
104	DKFZp434 (Hs.131834)	FS	T
105	C11orf14 (Hs.32017)	FS	T
106	CEP11 (Hs.97437)	FS	T
107	UBE1 (Hs.2055)	FS	T
108	EIF4G (Hs.25732)	FS	T
109	SYNJ1 (Hs.127416)	FS	T
110	NYD-SP14 (Hs.98105)	FS	T
111	NDP52 (Hs.154230)	FS	T
112	PMSCL1 (Hs.91728)	FS	T
113	KIAA0442 (Hs.32168)	FS	T

To determine whether immune recognition of these 39 antigens was cancer-related, serum samples from normal individuals (n=33) were tested for reactivity to these antigens. 23 of the 39 antigens (59%) had a serological profile that was not restricted to cancer patients, whereas the remaining 16 antigens had a cancer-related serological profile, reacting only with sera from cancer patients (sarcoma patients and serum source of SEREX database entry), and not with sera from normal individuals. 14 of these 16 antigens reacted only with sera from a single sarcoma patient when tested for reactivity with additional allogeneic sarcoma sera (n=39). The remaining 2 antigens, NY-SAR-17/LAGE-1 and NY-SAR-80/FLJ12577, reacted with 2 of 39 and 3 of 39 sarcoma sera, respectively, and not with sera from normal individuals (n=33).

NY-SAR-80/FLJ12577 is an uncharacterized member of the Mo25 protein family, an evolutionary conserved family of proteins with no known function. Analysis of the tissue distribution and frequency of EST sequences homologous to NY-SAR-80/FLJ12577 indicate widespread mRNA expression, with a preponderance of malignant tissue-derived homologous ESTs suggesting possible overexpression in cancer.

Overall, the relative infrequency of overlapping humoral immune responses among the population of sarcoma patients analyzed is contrary to previous findings for colon (Scanlan M J. et al. 2002. Cancer-Related Serological Recognition of Human Colon Cancer: Identification of Potential Diagnostic and Immunotherapeutic Targets. Cancer Res., 2002; Jul. 15; 62(14), 4041-7.), breast (Scanlan M J, et al. Humoral immunity to human breast cancer: antigen definition and quantitative analysis of mRNA expression. Cancer Immunity 1:4 [epub]) and renal cancers (Scanlan, M. J., et al., and Old, L. J. Antigens recognized by autologous antibody in patients with renal-cell carcinoma. *Int. J. Cancer* 1999; 83: 456-64) in which a subset of antigens were mutually seroreactive in a cancer related manner These results suggest that the immune

response to sarcoma is either highly variable or that distinct sarcoma histiotypes have distinct immunomes.

Expression Patterns of mRNA Encoding Serologically Defined Sarcoma/Testis Antigens in Normal and Malignant Tissues

In addition to the three well-known CT antigens described in Example 1, NY-SAR-89/SSX-2 and NY-SAR-99/SSX-3 were found to have restricted EST profiles, being expressed exclusively in normal testis and a range of different tumor types (Lethe B, et al. 1998. LAGE-1, a new gene with tumor specificity. Int. J. Cancer 76:903-8; Türeci Ö, et al. 1998. Expression of SSX genes in human tumors. Int J Cancer 77:19-23; Gure A O, et al. 1997. SSX: a multigene family with several members transcribed in normal testis and human cancer. Int J Cancer 72:965-971). Six other putative tissue-restricted antigens were identified, including four other known gene products, NY-SAR-73/Protamine 2 (PRM2, Domenjoud, L., Fronia, C., Uhde, F. & Engel, W. (1998) Nucleic Acids Res. 16, 7773), NY-SAR-78/TSP-NY (UniGene cluster Hs.97643), NY-SAR-96/mitochondrial capsule selenoprotein (MCSP, Aho, H., et al. (1996) Geonomics 32, 184-190) and NY-SAR-110/NYD-SP14 (Hs.98105) and two additional uncharacterized gene products, NY-SAR-92 (Hs.368781) and NY-SAR-97 (not clustered).

Two of the six putative tissue restricted antigens, NY-SAR-73/PRM2 and NY-SAR-110/NYD-SP14, were ubiquitously expressed in a panel of 20 normal tissues as determined by RT-PCR (Table 10). The remaining four genes, in addition to NY-SAR-12/nasopharyngeal specific protein 1 (NESG1, Li Z, Yao K, Cao Y. Molecular cloning of a novel tissue-specific gene from human nasopharyngeal epithelium. Gene 1999 Sep. 3; 237(1):235-40), NY-SAR-35 and NY-SAR-41, were found to be expressed with frequencies ranging from 1 to 9 of 20 normal tissues. NY-SAR-35 and NY-SAR-78 were both testis-specific. The mRNA expression profiles of NY-SAR-35 and NY-SAR-78 were then analyzed in various malignant tissues by RT-PCR. Transcripts encoding NY-SAR-78/TSP-NY were not detected in cancer. The tumor specimens examined included, lung cancer (0 of 9), colon cancer (0 of 9), breast cancer (0 of 18), renal cancer (0 of 11), esophageal cancer (0 of 12), ovarian cancer (0 of 14), melanoma (0 of 18) and sarcoma (0 of 8). Thus, although NY-SAR-78/TSP-NY is a "virtual CT antigen" with 100% identity with ESTs derived from prostate cancer and leukemia, its expression in cancer could not be verified in our RT-PCR series.

TABLE 10

Analysis of mRNA expression by RT-PCR of 9 of the 113 sarcoma/testis antigens

	NY-SAR antigen*								
Tissue	12	35	41	73	78	92	96	97	110
Brain	–	–	–	+	–	–	–	–	+
Kidney	–	–	–	+	–	–	–	–	+
Liver	–	–	–	+	–	–	–	–	+
Pancreas	–	–	–	+	–	–	–	–	+
Placenta	+	–	–	+	–	–	–	–	+
Testis	+	+	+	+	+	+	+	+	+
Fetal brain	–	–	+	+	–	–	+	+	+
Small intestine	–	–	–	+	–	–	–	–	+
Heart	–	–	–	+	–	–	–	–	+
Prostate	–	–	–	+	–	–	+	+	+
Adrenal	–	–	–	+	–	–	+	+	+
Spleen	+	–	–	+	–	+	+	+	+
Colon	+	–	+	+	–	–	–	–	+
Stomach	–	–	–	+	–	–	–	–	+
Lung	+	–	+	+	–	–	–	+	+
Bladder	–	–	+	+	–	–	–	+	+
Ovary	+	–	+	+	–	–	–	+	+
Breast	–	–	–	+	–	–	–	+	+
Cervix	–	–	–	+	–	–	–	–	+
Skeletal muscle	–	–	–	+	–	–	–	–	+
Total no. of positive tissues	6/20	1/20	6/20	20/20	1/20	2/20	5/20	9/20	20/20

*Unigene clusters: NY-SAR-12, Hs.158450; NY-SAR-35, Hs.128580; NY-SAR-41, Hs.166670; NY-SAR-73, Hs.2324; NY-SAR-78, Hs.97643; NY-SAR-92, Hs.368781; NY-SAR-96, Hs.111850; NY-SAR-97, Hs.128836; NY-SAR-110, Hs.98105.

The antigens presented herein are of interest for their immunotherapeutic and diagnostic potential. For example, the six known testis-restricted gene antigens (NY-SAR-17/LAGE-1, NY-SAR-36/SSX1, NY-SAR-43/SSX4, NY-SAR-78/TSP-NY, NY-SAR-89/SSX2 and NY-SAR-99/SSX3), four novel gene products that are also differentially expressed antigens (NY-SAR-35, -41, -92 and -91) and two tissue-restricted antigens (NY-SAR-12/NESG1 and NY-SAR-96/MCSP) not previously studied in relation to cancer have are potential vaccine targets and/or targets for therapeutic antibodies as well as for diagnosis of cancer, particularly by screening patient samples for antibodies that recognize the proteins.

NY-SAR-35 mRNA was detected in a variety of tumor specimens, such as melanoma (1 of 16 specimens), sarcoma (2 of 26 specimens), lung cancer (5 of 29 specimens), breast cancer (3 of 13 specimens), bladder cancer (5 of 12 specimens), esophageal cancer (1 of 12 specimens) and ovarian cancer (1 of 12 specimens). As also shown before in Example 1, NY-SAR-35 was not detected in colon cancer (n=9) or renal cancer (n=8). The CT-restricted expression profile of NY-SAR-35 was confirmed by real-time quantitative RT-PCR at 40 amplification cycles (FIG. **4**). In two of the nine non-small lung cancer specimens tested, NY-SAR-35 was expressed at levels that were 0.13 and 0.15 times the level detected in normal testis. In conformity with the proposed nomenclature for CT antigens (Chen Y T, et al. 1998. Identification of multiple cancer/testis antigens by allogeneic anti-

body screening of a melanoma cell line library. Proc. Natl. Acad. Sci. USA. 95:6919-23), NY-SAR-35 is designated CT-20.

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EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

All references disclosed herein are incorporated by reference in their entirety.

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<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1113)..(1113)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1115)..(1115)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1136)..(1137)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1139)..(1139)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1142)..(1144)
<223> OTHER INFORMATION: n = a, c, g or t/u

<400> SEQUENCE: 1

ttnggacagg ggaactgtgt tcagaaccag ctcgatgaga gccagcaaga acggaatgac 60

ctgatgcagc tgaagctaca gctggaggga caggtgacag agctgaggag ccgagtgcag 120

gagctcgaga gggctctggc aactgccagg caggagcaca ctggagctga tggaacagta 180

caaggggatt tcccnggtcc catggggaga tcacagaaga gagggacatc ctgagccggc 240

aacagggaga ccatgtggca cgcatcctgg agctagagga tgacatccag accatcagtg 300

agaaagtgct gacgaaggaa gtggagcctg gacaggctta gagacacagt gaaggccctg 360

actcgggaac aagagaagct ccttgggcaa ctgaaagaag tacaagcaga caaggagcaa 420

agtgaggctg agctccaagt ggcacaacag gagaaccatc acttaaattt ggacctgaag 480

gaggcgaaga gctggcaaga ggagcanagt gctcaggctc agcgactgaa agacaaggtg 540

gcccagatga aggacaccct atgccaggcc cagcagcggg tggcccagct ggagcccttg 600

aaggagcagc ttcnaggggc ccaangagcc ttgncagcct caagccagca naaagccacc 660

ctttcttggg gaggagtttg ccagcngcan cancanccag ggacccntcc atatgccgan 720

ctacaccgga gccgtcctgg aagtggctga agttaacngc aaggtggctg acctcgtttt 780

gnctttgaag ganaaaantc ccatggncca aggaccggnc anggctgntc ncaatgngga 840

ngnncaaaag acaaannctt gaactcnatg caaaatcctn tattgnaaaa gnncttngga 900

ggaaagancc aanccagtgt caaangactg gccggaaaag atnttcctng tcnattnnca 960

annaatcngg nattccaaat ttngnnnncc tgtnngtnca aangaaannc gnncctgggn 1020

naccgaatnt tancnntaaa acnaagcccn nngaagnggc anaancggnt ngtnccncac 1080

agntgngccn tngntnatnc cncttanaca agnanccaaa atagtccctg gctgtnngna 1140

cnnnttttt 1148

<210> SEQ ID NO 2
<211> LENGTH: 914
<212> TYPE: DNA
<213> ORGANISM: homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (10)..(10)

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<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (239)..(239)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (863)..(863)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (900)..(900)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (912)..(912)
<223> OTHER INFORMATION: n = a, c, g or t/u

<400> SEQUENCE: 2

ggagctcgcn cgcctgcagg tcgacactag tggatccaaa gaattcggca cgaggcgcca 60

gcgtccccac cgtcctcagc ttggcaaacg tttcccgaag aggattccga ctccccgcag 120

tttcgaagac gggcacacac gttcagccac ccaccttcaa gcacaaagag aaagctgaat 180

ttgcaggatg ggagggctca gggtgtgcgt tcccctctgc tgaggcagag ctccagtcna 240

acagtgcagt gatggagaag ggagaaaaag gacctcatct acctgcagca atgagtccct 300

aagtgtggga ggaacctctg tcactcctcg ccggatctcc tggcggcagc gcattttcct 360

cagggttgct tctcccatga acaaatctcc ctcagcaatg caacagcaag atggattgga 420

caggaacgag ctgctgccac tgtccccccc ctctccaacc atggaggagg aaccgctggt 480

tgtattcctg tctggggagg atgacccaga aaagattgaa gaaagaaaga aatcaaaaga 540

actgaggagc ttgtggagaa aagctataca ccaacaaatc ttgttacttc gaatggaaaa 600

agaaaaccag aaacttgaag caagcagaga tgaactccag tccagaaaag ttaaattaga 660

ctatgaagaa gttggtgcat gtcagaaaga ggtcttaata acttgggata agaagttgtt 720

aaactgcaga gctaaaatca gatgtgatat ggaagatatt catactcttc ttaagaagga 780

gttcccaaag tcgacgagga gaatttggca gtttctggct tacagtaccg actcaacaca 840

gattgcctaa taacaacagc ctnctgacta ttcttaagga ctttgagcag ctactgctan 900

cagcatgcga tntt 914

<210> SEQ ID NO 3
<211> LENGTH: 891
<212> TYPE: DNA
<213> ORGANISM: homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (677)..(677)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (775)..(775)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (785)..(785)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (807)..(807)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (847)..(847)

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<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (858)..(858)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (879)..(879)
<223> OTHER INFORMATION: n = a, c, g or t/u

<400> SEQUENCE: 3

ggagctcgng cgcctgcagg tcgacactag tggatccaaa gaattcggca cgaggggcac 60

ggggcgcgtc gggcccgcag gtggggaacg ctctgggcag cctggagcca ctgcgctgga 120

tgctgcgctc gcccttcgac cgcaacgtgc cggtcaacct ggagcttcag gagttgctgc 180

tggactacag cttccagcac ctgggtgtct cctcacaggg ctgtgttgat catcccatag 240

ttttgacaga agctgtgtgc aacccactgt attcacggca aatgatgtct gagcttcttt 300

ttgagtgcta cgggattccc aaggttgcct atggaataga cagcctcttc agcttctacc 360

acaataagcc aaagaactcg atgtgcagtg ggctaatcat ttcatctgga taccagtgta 420

cgcatgtttt acccatctta gaagggagat tagatgctaa aaactgcaag cgcatcaatc 480

ttggaggaag ccaagcagct ggttacctcc agcgtctcct ccagctgaag taccctgggc 540

acctggcagc catcaccctc agccgcatgg aggagattct gcatgagcac agctacatcg 600

ctgaggatta tgtggaagaa ttacacaaat ggcggtgtcc tgattattat gagaataatg 660

tccacaagat gcagctncca ttttccagca agctcctggg cagcactctg acctctgagg 720

agaaacaaga aaggcggcag cagcaattgc ggcggctgca ggagctcaat gcccngcggc 780

gggangagaa gctgcagctt ggatcangag cgtctggacc gactgctata tgtgcaggaa 840

cttctanagg atggccanat ggatcagttt acaaagctnt gatgagctga t 891

<210> SEQ ID NO 4
<211> LENGTH: 880
<212> TYPE: DNA
<213> ORGANISM: homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (654)..(654)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (693)..(693)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (698)..(698)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (784)..(784)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (803)..(803)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (813)..(813)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (842)..(842)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (867)..(867)
<223> OTHER INFORMATION: n = a, c, g or t/u

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<400> SEQUENCE: 4

ggcacgaggc ggcggcggcg gcggcggcag cggcagccag aggactccca gcggctggag 60

cagaagtgtt agcggccaga gctcccagac ccctacccac agccaggcgg gacgcgcaca 120

gtccctccac gcggaaagaa gtaccttcgc cggtcaccgg ctcctgcagg gtgcaaatat 180

atacagagct tcataatcag cccaagacca catagagcaa acatgaatga tatttcccaa 240

aaggctgaga ttctgctttc ttcatctaaa cctgtcccaa aaacctatgt accaaaactt 300

ggcaagggtg atgtaaagga taagtttgaa gccatgcaga gagccaggga agaaagaaat 360

caaaggagat ctagagacga aaaacaaaga agaaaagaac aatatattag agagagagaa 420

tggaacagga gaaagcagga gattaaagaa atgcttgctt ctgatgatga ggaagatgta 480

tcttctaaag tagaaaaggc ttatgttcca aaattaacag gaactgtgaa gggtagattt 540

gctgaaatgg agaaacaaag acaagaggaa caaaggaaga gaacggagga ggaacgaaaa 600

cgcagaattg agcaggatat gttagaaaag aggaaaatac agcgtgaatt agcnaaaagg 660

gctgaacagg aaggagatga ttcactactt atnactgngg tacctgtcaa tcatataaac 720

atctggaaaa tgaaaagaat tttgagatct agaaaaagac gtgaagagaa gaaagatcca 780

gtcnaggaga taaagattag atntgagaca cgncctctct caggagcaag ggcttcttag 840

tntggtgtga ataaaaggga gcaaaanatc cttctcccca 880

<210> SEQ ID NO 5
<211> LENGTH: 924
<212> TYPE: DNA
<213> ORGANISM: homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (754)..(754)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (772)..(772)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (783)..(783)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (799)..(799)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (873)..(875)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (898)..(898)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (918)..(918)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (920)..(920)
<223> OTHER INFORMATION: n = a, c, g or t/u

<400> SEQUENCE: 5

ctggagctcg cgcgcctgca ggtcgacact agtggatcca aagaattcgg cacgaggctc 60

actgctcaca gctgcccagc tgaaagccaa gggggagctg agctttgaac aggaccagct 120

ggtggctggg ggccagctgg gcgagctgca caacgggaca cagtatcgtg aggtccgcca 180

gttctgctcg ggctctggcc accaccttgt gcgcttctac ttcctcactc gtgtttactc 240

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cgagtacctt gaggatgttc tggaagagct gacatatgga cctgccccgg acctggtgat 300

catcaactcc tgcctctggg atctctccag atatggtcgc tgctcaatgg agagctaccg 360

ggagaacctg gagcgggtgt ttgtgcgcat ggaccaagta ttgccagact cctgcctgct 420

ggtgtggaac atggcgatgc ccctcgggga acgtatcact gggggtttcc tcctgccaga 480

gctccagccc ctggcaggct ccctgcggcg ggatgtggtt gaagggaact tctacagtgc 540

tacgctggcc ggggaccact gctttgatgt cctagacctc cactttcact tccggcatgc 600

agtacagcac cgtcatcggg atggtgtcca ctgggaccag catgcacacc gccacctctc 660

acacctgctt ctgacccatg tggctgacgc ctggggcgtg gagctgccca agcgtggcta 720

tccccctgac ccgtggattg aggactgggc aganatgaat catccattcc anggaagcca 780

tangcagacc caaacttcng ggagacctgg gccttgctcc accccacttc ttcttgctct 840

ccatgccttt tcctaccggt tctaggcctg cannnttcct tttccaccct gccagganac 900

ccttttccag gcagcctncn ccca 924

<210> SEQ ID NO 6
<211> LENGTH: 929
<212> TYPE: DNA
<213> ORGANISM: homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (640)..(640)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (672)..(672)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (715)..(715)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (724)..(724)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (768)..(768)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (782)..(782)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (795)..(795)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (800)..(800)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (813)..(813)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (818)..(818)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (820)..(820)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (827)..(827)

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<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (829)..(829)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (840)..(840)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (846)..(846)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (849)..(849)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (852)..(852)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (862)..(862)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (873)..(873)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (875)..(875)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (887)..(887)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (889)..(889)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (903)..(903)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (909)..(909)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (913)..(913)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (928)..(928)
<223> OTHER INFORMATION: n = a, c, g or t/u

<400> SEQUENCE: 6

gcggtcacct ngtggatcca agaattcggc acgaggcttg tcttgcattt gaatcaattg 60

gaaggaaata aggaaaagtt tgaaaaacag ttaaagaaga aatctgaaga ggtatattgt 120

ttacagaaag agctaaagat aaaaaatcac agtcttcaag agacttctga gcaaaacgtt 180

attctacagc atactcttca gcaacagcag caaatgttac aacaagagac aattagaaat 240

ggagagctag aagatactca aactaaactt gaaaaacagg tgtcaaaact ggaacaagaa 300

cttcaaaaac aaagggaaag ttcagctgaa aagttgagaa aaatggagga gaaatgtgaa 360

tcagctgcac atgaagcaga tttgaaaagg caaaaagtga ttgagcttac tggcactgcc 420

aggcaagtaa agattgagat ggatcagtac aaagaagagc tgtctaaaat ggaaaaggaa 480

ataatgcacc taaaacgaga tggagaaaat aaagcaatgc acctctctca attagatatg 540

atcttagatc agacaaagac agagctagaa aagaaaacca atgctgtaaa ggagttagaa 600

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aagttacagc acagtactga aactgaacta acagaagccn tgcaaaacgg gaagtacttg 660

agactgacta cnaaatgctc atgggagatt taaaaagtac tttaagacaa ctccnggaat 720

tggngagatg tactacagaa ggctccattt tcattagagg aaaatacnct actataagga 780

tnccccgct ggacntaaan aatgcaagat ggnattgnan acaaaancng gagctcctgn 840

aatggnccng cncttaagag anaattggga ctnangcaaa aacagcncng gtacccttg 900

ganttgctnt tcnggacccg aggaaaang 929

<210> SEQ ID NO 7
<211> LENGTH: 935
<212> TYPE: DNA
<213> ORGANISM: homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (792)..(792)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (799)..(799)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (820)..(820)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (856)..(856)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (872)..(872)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (875)..(875)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (886)..(886)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (899)..(899)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (904)..(904)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (906)..(906)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (922)..(922)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (926)..(927)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (935)..(935)
<223> OTHER INFORMATION: n = a, c, g or t/u

<400> SEQUENCE: 7

ngctggagct cgcgcgcctg caggtcgaca ctagtggatc caaagaattc ggcacgaggg 60

aaacataaag aagacaaaga tgataggcgg cacagagatg acaaaagaga ttccaagaaa 120

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gagaaaaaac acagtagaag cagaagcaga gaaaggaaac acagaagtag gagtcgaagt 180

agaaatgcag ggaaacgaag tagaagtaga agcaaagaga aatcaagtaa acataaaaat 240

gaaagtaaag aaaaatcaaa taaacgaagt cgaagtggca gtcaaggaag aactgacagt 300

gttgaaaaat caaaaaaacg ggaacatagt cccagcaaag aaaaatctag aaagcgtagt 360

agaagcaaag aacgttccca caaacgagat cacagtgata gtaaggacca gtcagacaaa 420

catgatcgtc gaaggagcca aagtatagaa caagagagcc aagaaaaaca gcataaaaac 480

aaagatgaga ctgtgtgaaa atattttgta aaagtggatc acattgaatc ctataaatga 540

ttaaatctgc ttttttcccc cacgttgaga ttgtgcagta gttcgcactc ctcaagctct 600

ccctgtaggc tgcattttca tttcctcttt cgtgtaggga agtgcctttg taattccatt 660

tattgcattg gtgttttcac ccaattgtta agtttgatac atgatgcaca gattggtctt 720

gcatttttat tgtttggttt tgaatgtaca gtctgtacta tgtcctgaaa tggtttattc 780

ctttggcatg gntgcctgnt ggttaatttg tataggcatn aactgcccta tctaaaaaaa 840

aaaaaaaaaa ctcgangtct ttaaagcggc gnggncctcg atttcnccgg gggggaccng 900

taangnccca tccccttag gngcgnntaa atccn 935

<210> SEQ ID NO 8
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<212> TYPE: DNA
<213> ORGANISM: homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (741)..(741)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (796)..(796)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (823)..(823)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (842)..(842)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (857)..(857)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
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<222> LOCATION: (869)..(869)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (873)..(873)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (898)..(898)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (911)..(911)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (915)..(916)
<223> OTHER INFORMATION: n = a, c, g or t/u

<400> SEQUENCE: 8

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aaangctgga gctcgcgcgc ctgcaggtcg acactagtgg atccaaagaa ttcggcacga 60

ggcaagagtg atttcaagga gtatgaaaaa gaacaggata aaccacctaa tttggttctg 120

aaagataaag taaagcccaa acaggataca aaatacgatc ttatattaga tgagcaggcc 180

gaagactcaa aatcaagtca ctcacacaca agtaaaaaac acaagaagaa aacccatcac 240

tgttctgaag agaaagaaga tgaggactac atgccaatca aaaatactaa tcaggatatc 300

tatagagaaa tggggtttgg tcactatgaa gaagaagaaa gctgttggga gaaacaaaag 360

agtgaaaaga gagaccgaac tcagaaccga agtcgtagcc gatctcgaga gagggatggc 420

cattatagta atagtcataa atcaaaatac caaacagatc tttatgaaag agaaaggagt 480

aaaaagagag accgaagcag aagtccaaag aagtccaaag ataaagaaaa atctaagtat 540

agatgaaaga tgaagaggca gaattgagag gctaacatat ttactcttgt ctaacttaag 600

agtgccagga aagcagatgc ttagattttg tgtcaaagct tgttatttt ttcatactag 660

gattatggtc tttagattaa tactgattat atagagcacg gaaagataaa gaattgacat 720

tttctttgta tacttttac nctaatttt atggtataca taatggtagt cttcattttt 780

gaagtcttca ttttcnctct ttttttatgg agtatttcta ctncaaaatc cttaacgttt 840

tntaagggta ataatgnaat atctggtcnc tcncacttag atacgtgtgc gacttttnag 900

tccctaggcc ncccnnccaa aatatttgga tttgggtggc ttg 943

<210> SEQ ID NO 9
<211> LENGTH: 910
<212> TYPE: DNA
<213> ORGANISM: homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (584)..(584)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (626)..(626)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (723)..(723)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (751)..(751)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (756)..(756)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (775)..(775)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (784)..(784)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (796)..(796)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (833)..(833)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (844)..(844)

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<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (870)..(870)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (884)..(884)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (894)..(894)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (903)..(903)
<223> OTHER INFORMATION: n = a, c, g or t/u

<400> SEQUENCE: 9

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gggcgagctc ggcaacctcg gcgcagcgag cgcgggcggc cagccagggc caggggcgg 120

tggcggccaa ggtccgaccg ggtgccagct gttcccagcc cccgcctcgg gcccgccgcc 180

ggcgccgcca tgggcaagaa gcacaagaag cacaaggccg agtggcgctc gtcctacgag 240

gattatgccg acaagcccct ggagaagcct ctaaagctag tcctgaaggt cggaggaagt 300

gaagtgactg aactctcagg atccggccac gactccagtt actatgatga caggtcagac 360

catgagcgag agaggcacaa agaaaagaaa aagaagaaga agaagaagtc cgagaaggag 420

aagcatctgg acgatgagga aagaaggaag cgaaaggaag agaagaagcg gaagcgagag 480

agggagcact gtgacacgga gggagaggct gacgactttg atcctgggaa gaaggtggag 540

gtggagccgc ccccagatcg gccagtccga gcgtgccgga cacngccagc cgaaaatgag 600

agcacaccta ttcagcaact cctggnaaca cttcctccgc cagcttcaga gaaaagatcc 660

ccatggattt tttgcttttc ctgtcacgga tgcaattgct cctgggatat tccatgataa 720

tanaacctcc catggatttt ggcaccatga nagacnaaat tgtagctaat gaatncaagt 780

cagntacgga atttanggca attccacgct gatgtgtgat atgcatggac ttncataggc 840

cagntccgtg tactacagtt ggcaagagan cttcccgcag cttnaagatg atgngcaacc 900

gcngctcttt 910

<210> SEQ ID NO 10
<211> LENGTH: 1029
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

tctgggccac ggactgccgg accgttgggc tgtgaggcag cgtctcagcg aggcggcacc 60

cggagccatg tcttcacata ggaggaaagc gaaggggagg aataggagaa gtcaccgtgc 120

catgcgtgtg gctcacttag agctggcaac ttatgagttg gcggcaactg agtcgaatcc 180

cgagagcagc catcctggat acgaggccgc catggctgac aggcctcagc caggatggcg 240

ggaatctcta aagatgcggg tcagcaaacc ctttgggatg ctcatgctct ccatttggat 300

cctgctgttc gtgtgctact acctgtccta ctacctgtgc tccgggtcct catattttgt 360

gcttgcaaat ggacatatcc tgcccaacag tgaaaatgct catggccaat ctctggaaga 420

agattccgca ttggaagctt tgctgaattt tttctttcca acaacttgca atctgaggga 480

aaatcaggtg gcaaagcctt gtaatgagct gcaagatctt agtgagagtg aatgtttgag 540

acacaaatgc tgtttttcat catcggggac cacgagcttc aaatgttttg ctccatttag 600

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agatgtgcct aaacagatga tgcaaatgtt tgggcttggt gcgatcagcc ttatcctggt 660

atgtctgccc atttattgcc gctctctttt ctggaggagc gaaccggccg atgatttaca 720

aaggcaggac aacagagttg taacgggttt gaagaaacaa agaaggaagc gaaagaggaa 780

gtctgaaatg ttacagaaag cagcaagagg acgtgaggaa catggtgacg agtagcaaga 840

gaccaaagca ttattttccc ctcaagacaa cagaaaccat tcagagcaga ggggactgtc 900

tcagccatgc aaacctcatg gagcattttg gaaagttaaa attgattctt atttttgtca 960

tgtttacttt caaacatgaa ataaaattga gttctgtttt catgcatcaa aaaaaaaaaa 1020

aaaaaaaaa 1029

<210> SEQ ID NO 11
<211> LENGTH: 924
<212> TYPE: DNA
<213> ORGANISM: homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (204)..(204)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (752)..(752)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (754)..(754)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (756)..(759)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (761)..(761)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (765)..(765)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (770)..(770)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (773)..(775)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (777)..(779)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (781)..(781)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (802)..(802)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (812)..(812)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (829)..(829)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (833)..(833)

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<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (849)..(849)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (866)..(866)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (873)..(873)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (879)..(880)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (886)..(886)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (901)..(901)
<223> OTHER INFORMATION: n = a, c, g or t/u

<400> SEQUENCE: 11

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gggagaaaaa gagtttataa tgctacaaaa tgaacaggag ataagtcaac tgaaaaaaga 120

aattgaaaga acacaacaaa ggatgaaaga aatggagagt gttatgaaag agcaagaaca 180

gtacattgcc actcagtaca aggnggccat agatttgggg caagaattga ggctgacccg 240

ggagcaggtg cagaactctc atacagaatt ggcagaggct cgtcatcagc aagtccaagc 300

acagagagaa atagaaaggc tctctagtga actggaggat atgaagcaac tctctaaaga 360

gaaagatgct catggaaacc atttagctga agaactgggg gcttctaaag tacgtgaagc 420

tcatttagaa gcaagaatgc aagcagaaat caagaaattg tcagcagaag tagaatctct 480

caaagaagct tatcatatgg agatgatttc acatcaagag aaccatgcaa agtggaagat 540

ttctgctgac tctcaaaagt cttctgttca gcaactaaac gaacagttag agaaggcaaa 600

attggaatta gaagaagctc aggatactgt aagcaatttg catcaacaag tccaagatag 660

gaatgaagta attgaagctg caaatgaagc attacttact aaagtaagta aacatataaa 720

agtattaaag catatctatg aaaacaaaac cncncnnnnc ngccntcccn ccnnnannnc 780

ntctcgagag tacttctaaa gnggccgcgg gnccctccga tttcccccng ggnggggtac 840

caggtaagng tacccaattc cccctntagg agncgtatnn aattcnctgg ccgccgttta 900

ncacctcgtg ctgggaaaac ctgg 924

<210> SEQ ID NO 12
<211> LENGTH: 917
<212> TYPE: DNA
<213> ORGANISM: homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (745)..(745)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (784)..(784)
<223> OTHER INFORMATION: n = a, c, g or t/u

<400> SEQUENCE: 12

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ggggaaaatg gcggattcct cggggcgagg cgctgggaag cctgcaaccg gccccacaaa    120

ttctagcagt gccaagaaga aggataaaag agttcaaggt ggaagagtga ttgagtcccg    180

gtatctgcag tatgaaaaga agacaaccca aaaggctcct gcaggagatg ggtcacagac    240

ccgagggaag atgtctgaag gtggaaggaa atccagcctg ctccagaaaa gcaaagcaga    300

tagcagtggg gtcggaaagg gtgacctgca gtccacgttg ctggaagggc atggcacagc    360

tccacctgac ctggatctct ctgctattaa tgacaaaagc atcgtcaaaa agacgccaca    420

gttagcaaaa acaatatcaa agaaacctga gtcaacatca ttttctgccc ctcggaaaaa    480

gagcccggat ttatctgaag caatggaaat gatggagtct cagacactac tgctgacgct    540

actatccgta aagatggaga acaatcttgc tgagtttgaa agaagggcag aaaagaattt    600

attaataatg tgtaaggaga aggagaagct acagaaaaag gcccacgagc tgaagcgcag    660

gcttctcctc tctcagagga agcgggagct ggcagatgtc ctggatgccc agatcgagat    720

gctcagcccc cttcgaggca gtggncacac gcttcaagga gcaatacagg acattcgcca    780

cggnccttgg acactaccag gcacgagctg cccgtgaggt ccatccacct ggagggagat    840

gggcagcagc tcttagacgc cctgcagcat gactggtgac cctcagcgcc tcctgggaaa    900

cttgatgttg gtgatcg                                                   917
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<210> SEQ ID NO 13
<211> LENGTH: 921
<212> TYPE: DNA
<213> ORGANISM: homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (742)..(742)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (808)..(808)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (822)..(822)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (842)..(842)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (858)..(858)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (895)..(895)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (912)..(912)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (918)..(918)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (920)..(920)
<223> OTHER INFORMATION: n = a, c, g or t/u

<400> SEQUENCE: 13
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ggtgaggggc ttccggttgg ggtggcaggg tggtggatct gttggtcccg ttttcccgtc 120

gcacgtggtg gccactgttg gcttctgaat ggtttgcaag gcggatatcc acgccaaggc 180

ctttggatcg gccgtgggta catccgtctg agccgttcct ttccatcgca gagcggcggc 240

ctccggcggc gctctccagt catggactac cggcggcttc tcatgagccg ggtggtcccc 300

gggcaattcg acgacgcgga ctcctctgac agtgaaaaca gagacttgaa gacagtcaaa 360

gagaaggatg acattctgtt tgaagacctt caagacaatg tgaatgagaa tggtgaaggt 420

gaaatagaag atgaggagga ggagggttat gacgatgatg atgatgactg ggactgggat 480

gaaggagttg gaaaactcgc caagggttat gtctggaatg gaggaagcaa cccacaggca 540

aatcgacaga cctccgacag cagttcagcc aaaatgtcta ctccagcaga caaggtctta 600

cggaaaattt gagaataaaa ttaatttaga taagctaaat gttactgatt ccgtcataaa 660

taaagtcacc gaaaagtcta gacaaaagga agcagatatg tatcgcatca aagataaggc 720

agacagagca actgtagaac angtgttgga tcccagacca agaatgattt tattcaagat 780

gttgactaga ggaatcataa cagagatnaa tggctgcatt anccaggaaa aaagctaatg 840

tnaccatgct acccagcnaa tggagagagc agaccatcaa atttataaac ttctntttgg 900

ggttcaagat cnggatantn t 921

<210> SEQ ID NO 14
<211> LENGTH: 901
<212> TYPE: DNA
<213> ORGANISM: homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (836)..(836)
<223> OTHER INFORMATION: n = a, c, g or t/u
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (892)..(892)
<223> OTHER INFORMATION: n = a, c, g or t/u

<400> SEQUENCE: 14

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gacgctactt cccctatcat agaagagctt atcacctttc atgatcacgc cctcataatc 120

attttcctta tctgcttcct agtcctgtat gccctttttcc taacactcac aacaaaacta 180

actaatacta acatctcaga cgctcaggaa atagaaaccg tctgaactat cctgcccgcc 240

atcatcctag tcctcatcgc cctcccatcc ctacgcatcc tttacataac agacgaggtc 300

aacgatccct cccttaccat caaatcaatt ggccaccaat ggtactgaac ctacgagtac 360

accgactacg gcggactaat cttcaactcc tacatacttc ccccattatt cctagaacca 420

ggcgacctgc gactccttga cgttgacaat cgagtagtac tcccgattga agcccccatt 480

cgtataataa ttacatcaca agacgtcttg cactcatgag ctgtccccac attaggctta 540

aaaacagatg caattcccgg acgtctaaac caaaccactt tcaccgctac acgaccgggg 600

gtatactacg gtcaatgctc tgaaatctgt ggagcaaacc acagtttcat gcccatcgtc 660

ctagaattaa ttcccctaaa aatctttgaa ataggacccg tatttaccct atagcacccc 720

ctctaccccc tctagagcca aaaaaaaaaa aaaaaaactc gagactagtt ctctccggac 780

attcagactg agcgtgccta ccaaaagcag ccgaccatct ttcaaaacaa gaaganggtc 840

ctgctgggag aactggcaag gagaagctcc gcggtactac aagaacatcg gnctgggctt 900

c 901

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<210> SEQ ID NO 15
<211> LENGTH: 1850
<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 15

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agcacagctg gcatcctgag ctcctcttct gccgcttcca acaggtcaag gaataaggct 120

cgctatcgga ccaaagccgt gagctctgag gtggatgaga gcctctttgg agatatcaag 180

tccccagccc agggccagag cgacagcccc attgtgctgc tccgagataa gcataccctt 240

caaaaaactc tcactgcttt gggcttggat cgcaagccag agaccatcca gctcatcacc 300

cgggacatgg tccgagaact cattgttccc acagaggatc cctccgggga gtccctaatc 360

atcagccctg aggagtttga gcgaatcaaa tgggcatccc atgtcctgac cagagaagaa 420

cttgaggcca gggaccaggc cttcaagaag gagaaggaag ccaccatgga tgcagtgatg 480

acacgaaaga agatcatgaa acagaaggag atggtgtgga acaacaacaa gaagctcagt 540

gacctggagg aggtggccaa ggaacgggcc cagaacctcc tgcagagagc caacaagctg 600

cggatggagc aggaggagga gctcaaggac atgagcaaga ttatcctcaa tgctaagtgc 660

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gaagagaagc ggttggatca gatgatggaa gtggagcggc agaaatccat tcaaaggcag 780

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<211> LENGTH: 1791
<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 16

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<211> LENGTH: 3258
<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 17

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gacgacatta accaatcagg agcaggcgac tatttttgaa gaggttcaga aattgagacc 780

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aaatgcaact tatgtttt 3258

<210> SEQ ID NO 18
<211> LENGTH: 3496
<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 18

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aaattgatta atgtttacaa catgactgat aattatagct gaatagtcct taaatgatga 240

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atagagttta cagtttttga actttaagcc aaattcattt gacatcaagc actatagcag 480

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<210> SEQ ID NO 19
<211> LENGTH: 1807
<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 19

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ggaattc 1807

<210> SEQ ID NO 20
<211> LENGTH: 2676
<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 20

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<212> TYPE: DNA
<213> ORGANISM: homo sapiens

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aaaaaaacag ttcactatta cgcagagctt ggccaatgct cagttttccc agcaacagat 1980

gctcctgagc aatttattag tcaagtgacg gtgctgaaat acttttctca ttacatggag 2040

gagaacctca tggatggtgg agatctgcct agtgttactg atattcgaag acctcggctc 2100

tacctccttc agtggctaaa atctgataag gccctaatga tgctctttaa tgatggcacc 2160

tttcaggtga atttctacca tgatcataca aaaatcatca tctgtagcca aaatgaagaa 2220

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ctgatgtctg gctgttcatc agaattaaaa aatcgaatgg aatatgccct gaacatgctc 2340

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ggtggtacga aaacaattcc cctgtggcct gctggactgg gtggaaccca gaaccaggct 2520

aaggcataca gttcttgact ttggacaatc ccaagagtga accagaatgc agttttcctt 2580

gagatacctg ttttaaaagg tttttcagac aattttgcag aaaggtgcat tgattcttaa 2640

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aggggaggga gaagggagga agctcccatg ttgtttaaag gctgtaattg gagcagcttt 2760

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gcagtattta ttatcaaaat gtctttttttt ttatgttgac cattttaaac cgttggcaat 2940

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<210> SEQ ID NO 25
<211> LENGTH: 2805
<212> TYPE: DNA

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<213> ORGANISM: homo sapiens

<400> SEQUENCE: 25

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gttcatccag cagaatgaag aacgggatgg tgtgcgtttt agttggaacg tgtggccttc 180

cagccggctg gaggctacaa gaatggttgt acccctggct tgtctcctta ctcctttgaa 240

agaacgtcca gacctacctc ctgtacaata tgaacctgtg ctttgcagca ggccaacttg 300

taaagctgtt ctcaacccac tttgtcaggt tgattatcga gcaaaacttt gggcctgtaa 360

tttctgtttt caaagaaatc agtttcctcc agcttatgga ggcatatctg aggtgaatca 420

acctgccgaa ttgatgcccc agttttctac aattgagtac gtgatacagc gaggtgctca 480

gtcccctctg atctttctct atgtggttga cacatgcctg gaggaagatg accttcaagc 540

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ctgttaagct gaggatacaa ccaggaaatg caacggtgtc agattgtgtt caaaatgtct 2460

agaaaggctt gataacattc ctgttacttt tctagcagat tttaacaaat aatcaaggac 2520

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aatattgcta atacaaatgt gatttcctga aaaaaaaaaa aaaaa 2805

<210> SEQ ID NO 26
<211> LENGTH: 766
<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 26

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acccagggat gatgctaaag catcagagaa gagaagcaag gcctttgatg atattgccac 180

atacttctct aagaaagagt ggaaaaagat gaaatactcg gagaaaatca gctatgtgta 240

tatgaagaga aactataagg ccatgactaa actaggtttc aaagtcaccc tcccaccttt 300

catgtgtaat aaacaggcca cagacttcca ggggaatgat tttgataatg accataaccg 360

caggattcag gttgaacatc ctcagatgac tttcggcagg ctccacagaa tcatcccgaa 420

gatcatgccc aagaagccag cagaggacga aaatgattcg aagggagtgt cagaagcatc 480

tggcccacaa aacgatggga aacaactgca ccccccagga aaagcaaata tttctgagaa 540

gattaataag agatctggac ccaaaagggg gaaacatgcc tggacccaca gactgcgtga 600

gagaaagcag ctggtgattt atgaagagat cagtgaccct gaggaagatg acgagtaact 660

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catgggcatg gctgcggctc cctcgtcatc aggtgcatag caagtg 766

<210> SEQ ID NO 27
<211> LENGTH: 3432
<212> TYPE: DNA
<213> ORGANISM: homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2741)..(2741)
<223> OTHER INFORMATION: n = a, c, g or t/u

<400> SEQUENCE: 27

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tgttcccgag ctgttcctga ctgcagtgaa gctcacccat gatgacacag gagccaggta 240

tttacacctg gccagagaag acacgaataa tctgttcagc gtgcagttcc gtaccactcc 300

catggacagt actggtgttc ctcacattct tgagcatacc gtcctttgtg ggtctcaaaa 360

atatccgtgc agaaaccctt tcttcaaaat gttgaaccgg tccctctcca cgttcatgaa 420

cgccttcaca gctagtgatt atactctgta tccattttcc acacaaaatc ccaaggactt 480

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gggtgaccca ctgtgcatcc cggagcttac atgggagcag cttaagcagt ttcatgccac 780

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gcccaattct ccctttaca aagccttgat tgaatctggc cttggcacag aattttctcc 1140

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cgccaaagcc cttgactggc gagtcaaaaa ctcagatcta tcttaagagt gaccaggaag 3300

aggttcattg aaataatcat gcatgaagcg ccaaagatgc accatgtaga attttcactt 3360

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aactctgact ta 3432

<210> SEQ ID NO 28
<211> LENGTH: 1232
<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 28

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taccagcagt ctgaagccta taagatgtgc acggagaaga tccaggagaa gaagatcaag 180

aaagaagact cgagctctgg gctcatgaac actctcctga atggacacaa gggtggggac 240

tgcgatggct tctccacctt cgatgttccc atcttcactg aagagttctt ggaccaaaac 300

aaagcgcgtg aggcggagct tcggcgcttg cggaagatga atgtggcctt cgaggagcag 360

aacgcggtac tgcagaggca aaacgcagag catgagcagc gcgcgcgagc gtctggagca 420

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gctgggcact ctggacttct acatggcccg gcttcacgga gccatcgagc gcgaccccgc 600

ccagcacgag aagctcatcg tccgcatcaa ggaaatcctg gcccaggtcg ccagcgagca 660

cctgtgagga gtgggcgggc ccacgatgca gaggagaagc tgtgggcgcg gccctgccac 720

accccacccc gtggacgaga ggctgggggt ccacccttg gggcctggtc ccatcctgca 780

cctttggggg ctccagcccc cctaaaatta aatttctgca gcatcccttt agctttcaat 840

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acagccgagg gtgcccctcc tcggaggaca gccacgcgct acactggctc tccgggccac 960

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<210> SEQ ID NO 29
<211> LENGTH: 1313
<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 29

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acttcttacc caccaggctg caggcccagc aggatgctgt caacatagtt tgtcattcaa 180

agacccgcag caaccctgag aacaacgtgg gccttatcac actggctaat gactgtgaag 240

tgctgaccac actcacccca gacactggcc gtatcctgtc caagctacat actgtccaac 300

ccaagggcaa gatcaccttc tgcacgggca tccgcgtggc ccatctggct ctgaagcacc 360

gacaaggcaa gaatcacaag atgcgcatca ttgcctttgt gggaagccca gtggaggaca 420

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ccaaggagga ggatgattac gacgtgatgc aggaccccga gttccttcag agtgtcctag 1080

agaacctccc aggtgtggat cccaacaatg aagccattcg aaatgctatg ggctccctgg 1140

cctcccaggc caccaaggac ggcaagaagg acaagaagga ggaagacaag aagtgagact 1200

ggagggaaag ggtagctgag tctgcttagg ggactgcatg ggaagcacgg aatatagggt 1260

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<210> SEQ ID NO 30
<211> LENGTH: 1682
<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 30

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cccagcgccc ctcgcctaac ctcccgccgg gccgcgcctc ctcctcctcc tgctccccgc 180

cgcttccgtt tctcgaggga aaggctgctg cctcctgctc tgtcctcatc cccggcttag 240

ctgacggccc agaggtgggt gccaattcca ccagcagctg caactgaaaa gcaaggttca 300

gaaatgtcag atatcctccg ggagctgctc tgtgtctctg agaaggctgc taacattgcc 360

cgggcgtgca gacagcagga agccctcttc cagctgctga tcgaagaaaa gaaagaggga 420

gaaaagaaca agaagtttgc agttgacttc aagactctgg ctgatgtact ggtacaggaa 480

gttataaaac agaatatgga gaacaagttt ccaggcttgg aaaaaaatat ttttggagaa 540

gaatccaatg agtttactaa tgactggggg gaaaagatta ccttgaggtt gtgttcaaca 600

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gagatcaatg ttccacagga cattttggga atttgggtgg accccataga ttcaacttat 780

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gc 1682

<210> SEQ ID NO 31
<211> LENGTH: 1511
<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 31

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gccgaagagc ggcggcggca gcggcgggaa aaaaatgaag aatgaaattg ctgccgttgt 180

cttctttttc acaaggctag ttcgaaaaca tgataagttg aaaaaagagg cagttgagag 240

gtttgctgag aaattgaccc taatacttca agaaaaatat aaaaatcact ggtatccaga 300

aaaaccatcg aaaggacagg cctacagatg tattcgtgtc aataaatttc agagagttga 360

tcctgatgtc ctgaaagcct gtgaaaacag ctgcatcttg tatagtgacc tgggcttgcc 420

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tggagagaaa aacaatgcat tcattgttgc cagctttgaa aataaagatg agaacaagga 660

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<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 34

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<213> ORGANISM: homo sapiens

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cctgacctcc ctgggagggt gctatcagtt ctgtcctggc cctttcagtt ttataagttg 1620

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<211> LENGTH: 639
<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 36

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cattctatta ccaagaacac ggccaagctg gaccgggaga cagaggagct gcaccatgac 240

agggtgaccc tggaggtggg caaggtgatc cagcaaggtc ggcagagcaa ggggcttacg 300

cagaaggacc tggccacgaa aatcaatgag aagccacagg tgatcgcgga ctatgagagc 360

ggacgggcca tacccaataa ccaggtgctt ggcaaaatcg agcgggccat tggcctcaag 420

ctccggggaa aggacattgg aaagcccatc gagaaggggc ctagggcgaa atgaacacaa 480

agcctcgaaa tcagtgcgct ccagctgatc tcgttccgcc ggttcccctt ggccgccagt 540

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<210> SEQ ID NO 37
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<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 37

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<210> SEQ ID NO 38
<211> LENGTH: 1116
<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 38

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ctgaacagca gttttgagga tgaccccttc ttctctgagt ccattcttgc acaccgagaa 180

aatatgcgac agatgataag aagtttttct gaacccttg gaagagactt gctcagtatc 240

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atcaatatga atgaaagcga tgctcatgct tttgatgagg agtggcaaag tgaggttttg 720

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<210> SEQ ID NO 39
<211> LENGTH: 3074
<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 39

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<210> SEQ ID NO 40
<211> LENGTH: 2381
<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 40

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ccctgttaac ccccgccggg gccacaggca gcggtggtgg gacctcgggg gacagctcca 180

agggggaaga taagcaggat cgcaacaagg agaagaaaga agcgctgagc aaggtggtaa 240

ttcgaagatt acctcccact ttgaccaagg agcagcttca ggaacatctt caacctatgc 300

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gagaagaaag gaggaggaga gaaatagaaa gaaaaagaca aagagaagaa gagaggagga 780

aatggaaaga agaagagaaa cgaaaaagga aagatataga aaagctaaag aagatagaca 840

gaattccaga aagggacaaa ttaaaggatg aaccaaagat taaggtacac aggtttctgt 900

tacaagctgt gaatcagaaa aatctgctca agaagccaga aaaaggagat gaaaaagaat 960

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<210> SEQ ID NO 41
<211> LENGTH: 5163
<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 41

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tacccacttc atagcattgt atgatgatta aattggttaa tatttttaaa atgcttagaa 240

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aaggacatcc gaggcgataa gatcacctgg atcgagggca aggagcccgg ctgcgaaacc 3960

attgggctgc tcatgagcag catggacgac ctgatacgcc actgtaacgg gaagctgggc 4020

agctacaaaa tcaatggccg gacgaaagcc atggttgctt gttatccggg caatggaacg 4080

ggttatgtac gtcatgttga taatccaaat ggagatggaa gatgtgtgac atgtatatat 4140

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tatcttaata aagactggga tgccaaggta agtggaggta tacttcgaat ttttccagaa 4200

ggcaaagccc agtttgctga cattgaaccc aaatttgata gactgctgtt tttctggtct 4260

gaccgtcgca accctcatga agtacaacca gcatatgcta caaggtacgc aataactgtt 4320

tggtattttg atgcagatga gagagcacga gctaaagtaa aatatctaac aggtgaaaaa 4380

ggtgtgaggg ttgaactcaa taaaccttca gattcggtcg gtaaagacgt cttctagagc 4440

ctttgatcca gcaatacccc acttcaccta caatattgtt aactatttgt taacttgtga 4500

atacgaataa atgggataaa gaaaaatага caaccagttc gcattttaat aaggaaacag 4560

aaacaacttt ttgtgttgca tcaaacagaa gattttgact gctgtgactt tgtactgcat 4620

gatcaacttc aaatctgtga ttgcttacag gaggaagata agctactaat tgaaaatggt 4680

ttttacatct ggatatgaaa taagtgccct gtgtagaatt tttttcattc ttatattttg 4740

ccagatctgt tatctagctg agttcatttc atctctccct tttttatatc aagtttgaat 4800

ttgggataat ttttctatat taggtacaat ttatctaaac tgaattgaga aaaaattaca 4860

gtattattcc tcaaaataac atcaatctat ttttgtaaac ctgttcatac tattaaattt 4920

tgccctaaaa gacctcttaa taatgattgt tgccagtgac tgatgattaa ttttatttta 4980

cttaaaataa gaaaaggagc actttaatta caactgaaaa atcagattgt tttgcagtcc 5040

ttccttacac taatttgaac tcttaaagat tgctgctttt tttttgacat tgtcaataac 5100

gaaacctaat tgtaaaacag tcaccattta ctaccaataa cttttagtta atgttttaca 5160

agg 5163

<210> SEQ ID NO 42
<211> LENGTH: 4506
<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 42

ggcggtggcg gcggcgccgg gacgggggag gggcgcgccg gaaccggaac cgacctgcgc 60

cggaaccgga acggagagcg ggttgccagg gcccgaagag ggctggctgc ggcggtctcg 120

ctcggctgtc cgttccttgc tggagaattt ggccacaaag agttgccaag atagctgggc 180

caggaagaaa gcgccgcagc cctgacccag acgctgttgc cgaccccggg gcactctggc 240

tgtcgaccaa gcggctcaag atgtctggcg gggccagtgc cacaggccca aggagagggc 300

ccccaggact ggaggacacc actagtaaga agaagcagaa ggatcgagca aaccaggaga 360

gcaaggatgg agatcctagg aaagagacag ggtctcgata tgttgcccag gctggtcttg 420

aacctctggc ctcaggtgat ccttctgcct cagcctccca tgcagctggg atcacaggct 480

cacgccaccg tacccggctg ttctttcctt catcgtcagg gtcagcatcc actcctcaag 540

aggagcagac caaagaggga gcttgtgaag accctcatga tctcttggct actcccactc 600

cagagttgtt gctcgattgg aggcagagtg cagaagaggt gattgtcaag cttcgtgtgg 660

gagtaggtcc cctgcagctg gaggatgtag atgctgcttt cacagataca gactgtgtgg 720

tgcggtttgc aggtggtcag cagtggggtg gtgtcttcta tgctgagata aaaagctctt 780

gtgctaaagt gcaaacccgc aagggcagtc tcctgcacct gacactgccc aaaaaggtgc 840

ctatgctcac gtggccctcc ctcctggttg aggctgatga acagctttgc ataccaccgc 900

tgaactccca aacctgtctc ctgggctcag aggagaattt agccccttg gcaggagaga 960

aagcagtgcc tcccgggaat gacccagtct ctccagccat ggtccggagc agaaaccctg 1020

ggaaagatga ctgtgccaag gaggagatgg cagtggcagc agatgctgca accttggtgg 1080

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atgagcccga gtcgatggtg aacctggcgt ttgtcaagaa tgactcgtat gagaagggcc 1140

cggattcagt ggtggtgcac gtgtacgtga aggagatctg cagggacacc tcaagagtac 1200

ttttccgtga gcaggacttc acgctcatct tccagaccag ggatggaaac ttcctgaggc 1260

tgcacccggg ctgtgggccc cacaccacct tccgttggca ggtgaagctc aggaatctga 1320

ttgagccaga gcagtgcacc ttctgtttca cggcttctcg catcgacatc tgccttcgta 1380

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ccccaaagcc agagacacac ctggcctcgc ccaagcctac atgcatggtg cctcccatgc 1680

cccacagccc agttagtgga gacagcgtgg aggaggagga agaggaagag aagaaggtgt 1740

gtctgccagg cttcactggc cttgtcaatt taggcaacac ctgcttcatg aacagcgtca 1800

ttcagtctct gtccaacact cgggaactcc gggacttctt ccatgaccgc tcctttgagg 1860

ctgagatcaa ctacaacaac ccactaggga ctggtgggcg tctggccatt ggctttgccg 1920

tgctgcttcg ggcgctgtgg aagggcaccc accatgcctt ccagccttcc aagttgaagg 1980

ccattgtggc gagtaaggcc agccagttca caggctatgc acagcatgat gcccaggagt 2040

tcatggcttt cctgctggat gggctgcacg aggacctgaa tcgcattcag aacaagccct 2100

acacagagac cgtggattca gatgggcggc ccgatgaggt ggtagctgag gaagcatggc 2160

agcggcacaa gatgaggaat gactctttca tcgtggacct atttcagggg cagtacaagt 2220

cgaagctggt gtgccctgtg tgtgccaagg tctccatcac ttttgacccg tttctttatc 2280

tgccggtgcc cttgccacaa aagcaaaagg ttctccctgt cttttatttt gcccgagagc 2340

cccacagcaa gcccatcaag ttcctggtga gcgtcagcaa ggagaactcc actgcgagcg 2400

aagtattgga ctccctctct cagagtgttc atgtgaagcc tgagaacctg cgtttggcag 2460

aggtaattaa gaatcgtttt catcgtgtgt tcctaccctc ccactcactg gacactgtgt 2520

ccccatctga tacgctcctc tgctttgagc tgctatcctc agagttggct aaggagcggg 2580

tagtggtgct agaggtgcaa cagcgccccc aggtgcccag cgtccccatc tccaagtgtg 2640

cagcctgcca gcggaagcaa cagtcggagg atgaaaagct gaagcgctgt acccggtgct 2700

accgtgtggg ctactgcaac cagctctgcc agaaaaccca ctggcctgac cacaagggcc 2760

tctgccgacc tgagaacatt ggctaccccc tcctggtcag tgtacctgcc tcacgcctca 2820

cttatgcccg cctcgctcag ttgctagagg gctatgcccg gtactctgtg agtgtattcc 2880

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tgctctccac aggttccctg gaggctgggg acagcgagag agaccccatt cagccacctg 3000

agctccagct ggtgacccct atggctgagg gggacacagg gcttccccgg gtgtgggcag 3060

cccctgaccg gggtcctgtg cccagcacca gtggaatttc ttctgagatg ctggccagtg 3120

ggcccattga ggttggctcc ttgccagctg gcgagagggt gtcccgaccc gaagctgctg 3180

tgcctgggta ccagcatcca agtgaagcta tgaatgccca cacaccccag ttcttcatct 3240

ataaaattga ttcatccaac cgagagcagc ggctagagga caaaggagac accccactgg 3300

agctgggtga cgactgtagc ctggctctcg tctggcggaa caatgagcgc ttgcaggagt 3360

ttgtgttggt agcctccaag gagctggaat gtgctgagga tccaggctct gccggtgagg 3420

ctgcccgggc cggccacttc accctggacc agtgcctcaa cctcttcaca cggcctgagg 3480

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ttcgtagttt tatctggcgt gacaagatca atgacttggt ggagttccct gttaggaacc 3660

tggacctgag caagttctgc attggtcaga aagaggagca gctgcccagc tacgatctat 3720

atgctgtcat caaccactat ggaggcatga ttggtggcca ctacactgcc tgtgcacgcc 3780

tgcccaatga tcgtagcagt cagcgcagtg acgtgggctg gcgcttgttt gatgacagca 3840

cagtgacaac ggtagacgag agccaggttg tgacgcgtta tgcctatgta ctcttctacc 3900

gccggcggaa ctctcctgtg gagaggcccc ccagggcagg tcactctgag caccacccag 3960

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gcctgcccca ggccatgcct gcctttgttg tggggaacac ctctgggctt tgggcctcag 4320

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agggtgtgta tccatctggc tgtctgtcca ttcatcctgc tgctctgacc cttggcctca 4440

ggcttggccc tgcccaagct acttcctgta cttaaaagtg ttaataaaac cagactattc 4500

aggccc 4506

<210> SEQ ID NO 43
<211> LENGTH: 1542
<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 43

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gccgaccccg tcgcctccgc cggctaccat gtccgcccag gcgcagatgc gggccctgct 120

ggaccagctc atgggcacgg ctcgggacgg agacgaaacc agacagaggg tcaagtttac 180

agatgaccgt gtctgcaaga gtcaccttct ggactgctgc ccccatgaca tcctggctgg 240

gacgcgcatg gatttaggag aatgtaccaa aatccacgac ttggccctcc gagcagatta 300

tgagattgca agtaaagaaa gagacctgtt ttttgaatta gatgcaatgg atcacttgga 360

gtcctttatt gctgaatgtg atcggagaac tgagctcgcc aagaagcggc tggcagaaac 420

acaggaggaa atcagtgcgg aagtttctgc aaaggcagaa aaagtacatg agttaaatga 480

agaaatagga aaactccttg ctaaagccga acagctaggg gctgaaggta atgtggatga 540

atcccagaag attcttatgg aagtggaaaa agttcgtgcg aagaaaaaag aagctgagga 600

agaatacaga aattccatgc ctgcatccag ttttcagcag caaaagctgc gtgtctgcga 660

ggtctgttca gcctaccttg gtctccatga caatgaccgt cgcctggcag accacttcgg 720

tggcaagtta cacttggggt tcattcagat ccgagagaag cttgatcagt tgaggaaaac 780

tgtcgctgaa aagcaggaga agagaaatca ggatcgcttg aggaggagag aggagaggga 840

acgggaggag cgtctgagca ggaggtcggg atcaagaacc agagatcgca ggaggtcacg 900

ctcccgggat cggcgtcgga ggcggtcaag atctacctcc cgagagcgac ggaaattgtc 960

ccggtcccgg tcccgagata gacatcggcg ccaccgcagc cgttcccgga gccacagccg 1020

gggacatcgt cgggcttccc gggaccgaag tgcgaaatac aagtaactac tctgactcct 1080

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tcggtagctg caaccaggag tgagcccttc tctgtgttcc cagggtctgc tgagggccgt 1140

gtctggtggg gatggggctg ggctcaccct caggagtagg gctggggagt cgtgaacggg 1200

actcaggtgt gggaagaggc gagagggctg tggaggagct cgcacggcgc caggtgatgg 1260

gctgcacagg cactgtcccc tgcctgcgtc ctggggcctg tgcactgttg cgtccatgct 1320

cagagtggct gagacttgtg tcctgaccag gccctgctta cctctgtttt ggtttttgtt 1380

tttgatattt ttttttccat tgtgttttta cgtagtgtca tgttctgtgc atatagtgtt 1440

gtattctcct ttgcactgtt tatgttacag tgaaggctct ccttattaaa aatcttcgca 1500

aaggtcaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aa 1542

<210> SEQ ID NO 44
<211> LENGTH: 968
<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 44

gggggaagtt gctggctgac tgggcttgcg aggaaaccgc ctcggagctg cagcgaaggc 60

caaggaatca ctgaagatcg gcgagggagg acagggggtt catcatgggt ggctttttct 120

caagtatatt ttccagtctg tttggaactc gggaaatgag aattttaatt ttgggattag 180

atggagcagg aaaaaccaca attttgtaca gattacaagt gggagaagtt gttactacta 240

tacctaccat tggatttaat gtagagacgg tgacgtacaa aaaccttaaa ttccaagtct 300

gggatttagg aggacagaca agtatcaggc catactggag atgttactat tcaaacacag 360

atgcagtcat ttatgtagta gacagttgtg accgagaccg aattggcatt tccaaatcag 420

agttagttgc catgttggag gaagaagagc tgagaaaagc cattttagtg gtgtttgcaa 480

ataaacagga catggaacag gccatgactt cctcagagat ggcaaattca cttgggttac 540

ctgccttgaa ggaccgaaaa tggcagatat tcaaaacgtc agcaaccaaa ggcaccggcc 600

ttgatgaggc aatggaatgg ttagttgaaa cattaaaaag cagacagtaa ttcagtccat 660

tcttctcccc tgaaatgaag actacatcac ctctctccct ttggaaacag tcaagtgtac 720

ttcacactac tagatgttaa aactatatga ttattggcat atactgactg actgcaatat 780

ttgtagtaaa tagggaaaat aagtatttag ttggagggat aatttgatcg aatcacctga 840

atgttctatg taatgtaaaa tattcttttc ttgctttctt gtgttaaggt atatattcta 900

tttgtatgga attcttattc aaatacagtt gtattaaaga gtatactcct attggatgaa 960

aaaaacct 968

<210> SEQ ID NO 45
<211> LENGTH: 700
<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 45

gcggcgtgag aagccatgag cagcaaagtc tctcgcgaca ccctgtacga ggcggtgcgg 60

gaagtcctgc acgggaacca gcgcaagcgc cgcaagttcc tggagacggt ggagttgcag 120

atcagcttga agaactatga tccccagaag gacaagcgct tctcgggcac cgtcaggctt 180

aagtccactc cccgccctaa gttctctgtg tgtgtcctgg gggaccagca gcactgtgac 240

gaggctaagg ccgtggatat cccccacatg gacatcgagg cgctgaaaaa actcaacaag 300

aataaaaaac tggtcaagaa gctggccaag aagtatgatg cgtttttggc ctcagagtct 360

ctgatcaagc agattccacg aatcctcggc ccaggtttaa ataaggcagg aaagttccct 420

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tccctgctca cacacaacga aaacatggtg gccaaagtgg atgaggtgaa gtccacaatc 480

aagttccaaa tgaagaaggt gttatgtctg gctgtagctg ttggtcacgt gaagatgaca 540

gacgatgagc ttgtgtataa cattcacctg gctgtcaact tcttggtgtc attgctcaag 600

aaaaactggc agaatgtccg ggccttatat atcaagagca ccatgggcaa gccccagcgc 660

ctatattaag gcacatttga ataaattcta ttaccagttc 700

<210> SEQ ID NO 46
<211> LENGTH: 145
<212> TYPE: PRT
<213> ORGANISM: homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (65)..(65)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (101)..(101)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (105)..(105)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (108)..(108)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (113)..(113)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (125)..(128)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (132)..(132)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (136)..(136)
<223> OTHER INFORMATION: Xaa = any amino acid

<400> SEQUENCE: 46

Arg Arg Lys Trp Ser Leu Asp Arg Leu Arg Asp Thr Val Lys Ala Leu
1 5 10 15

Thr Arg Glu Gln Glu Lys Leu Leu Gly Gln Leu Lys Glu Val Gln Ala
20 25 30

Asp Lys Glu Gln Ser Glu Ala Glu Leu Gln Val Ala Gln Gln Glu Asn
35 40 45

His His Leu Asn Leu Asp Leu Lys Glu Ala Lys Ser Trp Gln Glu Glu
50 55 60

Xaa Ser Ala Gln Ala Gln Arg Leu Lys Asp Lys Val Ala Gln Met Lys
65 70 75 80

Asp Thr Leu Cys Gln Ala Gln Gln Arg Val Ala Gln Leu Glu Pro Leu
85 90 95

Lys Glu Gln Leu Xaa Gly Ala Gln Xaa Ala Leu Xaa Ala Ser Ser Gln
100 105 110

Xaa Lys Ala Thr Leu Ser Trp Gly Gly Val Cys Gln Xaa Xaa Xaa Xaa
115 120 125

Pro Gly Thr Xaa Pro Tyr Ala Xaa Leu His Arg Ser Arg Pro Gly Ser
130 135 140

Gly
145

<210> SEQ ID NO 47
<211> LENGTH: 208
<212> TYPE: PRT
<213> ORGANISM: homosapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa = any amino acid

<400> SEQUENCE: 47

Gly Arg Ala Pro Val Xaa Gln Cys Ser Asp Gly Glu Gly Arg Lys Arg
1 5 10 15

Thr Ser Ser Thr Cys Ser Asn Glu Ser Leu Ser Val Gly Gly Thr Ser
20 25 30

Val Thr Pro Arg Arg Ile Ser Trp Arg Gln Arg Ile Phe Leu Arg Val
35 40 45

Ala Ser Pro Met Asn Lys Ser Pro Ser Ala Met Gln Gln Gln Asp Gly
50 55 60

Leu Asp Arg Asn Glu Leu Leu Pro Leu Ser Pro Leu Ser Pro Thr Met
65 70 75 80

Glu Glu Glu Pro Leu Val Val Phe Leu Ser Gly Glu Asp Asp Pro Glu
85 90 95

Lys Ile Glu Glu Arg Lys Lys Ser Lys Glu Leu Arg Ser Leu Trp Arg
100 105 110

Lys Ala Ile His Gln Gln Ile Leu Leu Leu Arg Met Glu Lys Glu Asn
115 120 125

Gln Lys Leu Glu Ala Ser Arg Asp Glu Leu Gln Ser Arg Lys Val Lys
130 135 140

Leu Asp Tyr Glu Glu Val Gly Ala Cys Gln Lys Glu Val Leu Ile Thr
145 150 155 160

Trp Asp Lys Lys Leu Leu Asn Cys Arg Ala Lys Ile Arg Cys Asp Met
165 170 175

Glu Asp Ile His Thr Leu Leu Lys Lys Glu Phe Pro Lys Ser Thr Arg
180 185 190

Arg Ile Trp Gln Phe Leu Ala Tyr Ser Thr Asp Ser Thr Gln Ile Ala
195 200 205

<210> SEQ ID NO 48
<211> LENGTH: 256
<212> TYPE: PRT
<213> ORGANISM: homosapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (186)..(186)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (219)..(219)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (222)..(222)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (230)..(230)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (243)..(243)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (247)..(247)
<223> OTHER INFORMATION: Xaa = any amino acid

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<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (254)..(254)
<223> OTHER INFORMATION: Xaa = any amino acid

<400> SEQUENCE: 48

Met Leu Arg Ser Pro Phe Asp Arg Asn Val Pro Val Asn Leu Glu Leu
1 5 10 15

Gln Glu Leu Leu Leu Asp Tyr Ser Phe Gln His Leu Gly Val Ser Ser
20 25 30

Gln Gly Cys Val Asp His Pro Ile Val Leu Thr Glu Ala Val Cys Asn
35 40 45

Pro Leu Tyr Ser Arg Gln Met Met Ser Glu Leu Leu Phe Glu Cys Tyr
50 55 60

Gly Ile Pro Lys Val Ala Tyr Gly Ile Asp Ser Leu Phe Ser Phe Tyr
65 70 75 80

His Asn Lys Pro Lys Asn Ser Met Cys Ser Gly Leu Ile Ile Ser Ser
85 90 95

Gly Tyr Gln Cys Thr His Val Leu Pro Ile Leu Glu Gly Arg Leu Asp
100 105 110

Ala Lys Asn Cys Lys Arg Ile Asn Leu Gly Gly Ser Gln Ala Ala Gly
115 120 125

Tyr Leu Gln Arg Leu Leu Gln Leu Lys Tyr Pro Gly His Leu Ala Ala
130 135 140

Ile Thr Leu Ser Arg Met Glu Glu Ile Leu His Glu His Ser Tyr Ile
145 150 155 160

Ala Glu Asp Tyr Val Glu Glu Leu His Lys Trp Arg Cys Pro Asp Tyr
165 170 175

Tyr Glu Asn Asn Val His Lys Met Gln Xaa Pro Phe Ser Ser Lys Leu
180 185 190

Leu Gly Ser Thr Leu Thr Ser Glu Glu Lys Gln Glu Arg Arg Gln Gln
195 200 205

Gln Leu Arg Arg Leu Gln Glu Leu Asn Ala Xaa Arg Arg Xaa Glu Lys
210 215 220

Leu Gln Leu Gly Ser Xaa Ala Ser Gly Pro Thr Ala Ile Cys Ala Gly
225 230 235 240

Thr Ser Xaa Gly Trp Pro Xaa Gly Ser Val Tyr Lys Ala Xaa Met Ser
245 250 255

<210> SEQ ID NO 49
<211> LENGTH: 205
<212> TYPE: PRT
<213> ORGANISM: homosapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (144)..(144)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (157)..(157)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (159)..(159)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (188)..(188)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (194)..(194)
<223> OTHER INFORMATION: Xaa = any amino acid

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<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (197)..(197)
<223> OTHER INFORMATION: Xaa = any amino acid

<400> SEQUENCE: 49

Met Asn Asp Ile Ser Gln Lys Ala Glu Ile Leu Leu Ser Ser Ser Lys
1 5 10 15

Pro Val Pro Lys Thr Tyr Val Pro Lys Leu Gly Lys Gly Asp Val Lys
20 25 30

Asp Lys Phe Glu Ala Met Gln Arg Ala Arg Glu Glu Arg Asn Gln Arg
35 40 45

Arg Ser Arg Asp Glu Lys Gln Arg Arg Lys Glu Gln Tyr Ile Arg Glu
50 55 60

Arg Glu Trp Asn Arg Arg Lys Gln Glu Ile Lys Glu Met Leu Ala Ser
65 70 75 80

Asp Asp Glu Glu Asp Val Ser Ser Lys Val Glu Lys Ala Tyr Val Pro
85 90 95

Lys Leu Thr Gly Thr Val Lys Gly Arg Phe Ala Glu Met Glu Lys Gln
100 105 110

Arg Gln Glu Glu Gln Arg Lys Arg Thr Glu Glu Glu Arg Lys Arg Arg
115 120 125

Ile Glu Gln Asp Met Leu Glu Lys Arg Lys Ile Gln Arg Glu Leu Xaa
130 135 140

Lys Arg Ala Glu Gln Glu Gly Asp Asp Ser Leu Leu Xaa Thr Xaa Val
145 150 155 160

Pro Val Asn His Ile Asn Ile Trp Lys Met Lys Arg Ile Leu Arg Ser
165 170 175

Arg Lys Arg Arg Glu Glu Lys Lys Asp Pro Val Xaa Glu Ile Lys Ile
180 185 190

Arg Xaa Glu Thr Xaa Pro Leu Ser Gly Ala Arg Ala Ser
195 200 205

<210> SEQ ID NO 50
<211> LENGTH: 172
<212> TYPE: PRT
<213> ORGANISM: homosapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (136)..(136)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (142)..(142)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (146)..(146)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (151)..(151)
<223> OTHER INFORMATION: Xaa = any amino acid

<400> SEQUENCE: 50

Met Glu Ser Tyr Arg Glu Asn Leu Glu Arg Val Phe Val Arg Met Asp
1 5 10 15

Gln Val Leu Pro Asp Ser Cys Leu Leu Val Trp Asn Met Ala Met Pro
20 25 30

Leu Gly Glu Arg Ile Thr Gly Gly Phe Leu Leu Pro Glu Leu Gln Pro
35 40 45

Leu Ala Gly Ser Leu Arg Arg Asp Val Val Glu Gly Asn Phe Tyr Ser

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    50                  55                  60

Ala Thr Leu Ala Gly Asp His Cys Phe Asp Val Leu Asp Leu His Phe
65                  70                  75                  80

His Phe Arg His Ala Val Gln His Arg His Arg Asp Gly Val His Trp
                85                  90                  95

Asp Gln His Ala His Arg His Leu Ser His Leu Leu Leu Thr His Val
            100                 105                 110

Ala Asp Ala Trp Gly Val Glu Leu Pro Lys Arg Gly Tyr Pro Pro Asp
        115                 120                 125

Pro Trp Ile Glu Asp Trp Ala Xaa Met Asn His Pro Phe Xaa Gly Ser
    130                 135                 140

His Xaa Gln Thr Gln Thr Xaa Gly Arg Pro Gly Pro Cys Ser Thr Pro
145                 150                 155                 160

Leu Leu Leu Ala Leu His Ala Phe Ser Tyr Arg Phe
                165                 170


<210> SEQ ID NO 51
<211> LENGTH: 159
<212> TYPE: PRT
<213> ORGANISM: homosapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (143)..(143)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (153)..(153)
<223> OTHER INFORMATION: Xaa = any amino acid

<400> SEQUENCE: 51

Met Leu Gln Gln Glu Thr Ile Arg Asn Gly Glu Leu Glu Asp Thr Gln
1               5                   10                  15

Thr Lys Leu Glu Lys Gln Val Ser Lys Leu Glu Gln Glu Leu Gln Lys
            20                  25                  30

Gln Arg Glu Ser Ser Ala Glu Lys Leu Arg Lys Met Glu Glu Lys Cys
        35                  40                  45

Glu Ser Ala Ala His Glu Ala Asp Leu Lys Arg Gln Lys Val Ile Glu
    50                  55                  60

Leu Thr Gly Thr Ala Arg Gln Val Lys Ile Glu Met Asp Gln Tyr Lys
65                  70                  75                  80

Glu Glu Leu Ser Lys Met Glu Lys Glu Ile Met His Leu Lys Arg Asp
                85                  90                  95

Gly Glu Asn Lys Ala Met His Leu Ser Gln Leu Asp Met Ile Leu Asp
            100                 105                 110

Gln Thr Lys Thr Glu Leu Glu Lys Lys Thr Asn Ala Val Lys Glu Leu
        115                 120                 125

Glu Lys Leu Gln His Ser Thr Glu Thr Glu Leu Thr Glu Ala Xaa Gln
    130                 135                 140

Asn Gly Lys Tyr Leu Arg Leu Thr Xaa Lys Cys Ser Trp Glu Ile
145                 150                 155


<210> SEQ ID NO 52
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: homosapiens

<400> SEQUENCE: 52

Met Ile Gly Gly Thr Glu Met Thr Lys Glu Ile Pro Arg Lys Arg Lys
1               5                   10                  15
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Asn Thr Val Glu Ala Glu Ala Glu Lys Gly Asn Thr Glu Val Gly Val
            20                  25                  30

Glu Val Glu Met Gln Gly Asn Glu Val Glu Val Glu Ala Lys Arg Asn
        35                  40                  45

Gln Val Asn Ile Lys Met Lys Val Lys Lys Asn Gln Ile Asn Glu Val
    50                  55                  60

Glu Val Ala Val Lys Glu Glu Leu Thr Val Leu Lys Asn Gln Lys Asn
65                  70                  75                  80

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

Lys Asn Val Pro Thr Asn Glu Ile Thr Val Ile Val Arg Thr Ser Gln
            100                 105                 110

Thr Asn Met Ile Val Glu Gly Ala Lys Val
        115                 120


<210> SEQ ID NO 53
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: homosapiens

<400> SEQUENCE: 53

Met Ser Arg Pro Lys Thr Gln Asn Gln Val Thr His Thr Gln Val Lys
1               5                   10                  15

Asn Thr Arg Arg Lys Pro Ile Thr Val Leu Lys Arg Lys Lys Met Arg
            20                  25                  30

Thr Thr Cys Gln Ser Lys Ile Leu Ile Arg Ile Ser Ile Glu Lys Trp
        35                  40                  45

Gly Leu Val Thr Met Lys Lys Lys Lys Ala Val Gly Arg Asn Lys Arg
    50                  55                  60

Val Lys Arg Glu Thr Glu Leu Arg Thr Glu Val Val Ala Asp Leu Glu
65                  70                  75                  80

Arg Gly Met Ala Ile Ile Val Ile Val Ile Asn Gln Asn Thr Lys Gln
                85                  90                  95

Ile Phe Met Lys Glu Lys Gly Val Lys Arg Glu Thr Glu Ala Glu Val
            100                 105                 110

Gln Arg Ser Pro Lys Ile Lys Lys Asn Leu Ser Ile Asp Glu Arg
        115                 120                 125


<210> SEQ ID NO 54
<211> LENGTH: 175
<212> TYPE: PRT
<213> ORGANISM: homosapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (132)..(132)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (146)..(146)
<223> OTHER INFORMATION: Xaa = any amino acid

<400> SEQUENCE: 54

Met Gly Lys Lys His Lys Lys His Lys Ala Glu Trp Arg Ser Ser Tyr
1               5                   10                  15

Glu Asp Tyr Ala Asp Lys Pro Leu Glu Lys Pro Leu Lys Leu Val Leu
            20                  25                  30

Lys Val Gly Gly Ser Glu Val Thr Glu Leu Ser Gly Ser Gly His Asp
        35                  40                  45

Ser Ser Tyr Tyr Asp Asp Arg Ser Asp His Glu Arg Glu Arg His Lys
    50                  55                  60
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Glu Lys Lys Lys Lys Lys Lys Lys Ser Glu Lys Glu Lys His Leu
65                  70                  75                  80

Asp Asp Glu Glu Arg Arg Lys Arg Lys Glu Glu Lys Lys Arg Lys Arg
                85                  90                  95

Glu Arg Glu His Cys Asp Thr Glu Gly Glu Ala Asp Asp Phe Asp Pro
            100                 105                 110

Gly Lys Lys Val Glu Val Glu Pro Pro Pro Asp Arg Pro Val Arg Ala
        115                 120                 125

Cys Arg Thr Xaa Pro Ala Glu Asn Glu Ser Thr Pro Ile Gln Gln Leu
    130                 135                 140

Leu Xaa Thr Leu Pro Pro Pro Ala Ser Glu Lys Arg Ser Pro Trp Ile
145                 150                 155                 160

Phe Cys Phe Ser Cys His Gly Cys Asn Cys Ser Trp Asp Ile Pro
                165                 170                 175


<210> SEQ ID NO 55
<211> LENGTH: 255
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

Met Ser Ser His Arg Arg Lys Ala Lys Gly Arg Asn Arg Arg Ser His
1               5                   10                  15

Arg Ala Met Arg Val Ala His Leu Glu Leu Ala Thr Tyr Glu Leu Ala
            20                  25                  30

Ala Thr Glu Ser Asn Pro Glu Ser Ser His Pro Gly Tyr Glu Ala Ala
        35                  40                  45

Met Ala Asp Arg Pro Gln Pro Gly Trp Arg Glu Ser Leu Lys Met Arg
    50                  55                  60

Val Ser Lys Pro Phe Gly Met Leu Met Leu Ser Ile Trp Ile Leu Leu
65                  70                  75                  80

Phe Val Cys Tyr Tyr Leu Ser Tyr Tyr Leu Cys Ser Gly Ser Ser Tyr
                85                  90                  95

Phe Val Leu Ala Asn Gly His Ile Leu Pro Asn Ser Glu Asn Ala His
            100                 105                 110

Gly Gln Ser Leu Glu Glu Asp Ser Ala Leu Glu Ala Leu Leu Asn Phe
        115                 120                 125

Phe Phe Pro Thr Thr Cys Asn Leu Arg Glu Asn Gln Val Ala Lys Pro
    130                 135                 140

Cys Asn Glu Leu Gln Asp Leu Ser Glu Ser Glu Cys Leu Arg His Lys
145                 150                 155                 160

Cys Cys Phe Ser Ser Ser Gly Thr Thr Ser Phe Lys Cys Phe Ala Pro
                165                 170                 175

Phe Arg Asp Val Pro Lys Gln Met Met Gln Met Phe Gly Leu Gly Ala
            180                 185                 190

Ile Ser Leu Ile Leu Val Cys Leu Pro Ile Tyr Cys Arg Ser Leu Phe
        195                 200                 205

Trp Arg Ser Glu Pro Ala Asp Asp Leu Gln Arg Gln Asp Asn Arg Val
    210                 215                 220

Val Thr Gly Leu Lys Lys Gln Arg Arg Lys Arg Lys Arg Lys Ser Glu
225                 230                 235                 240

Met Leu Gln Lys Ala Ala Arg Gly Arg Glu Glu His Gly Asp Glu
                245                 250                 255


<210> SEQ ID NO 56
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<211> LENGTH: 239
<212> TYPE: PRT
<213> ORGANISM: homosapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (42)..(42)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (225)..(229)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (231)..(234)
<223> OTHER INFORMATION: Xaa = any amino acid

<400> SEQUENCE: 56

Met Leu Gln Asn Glu Gln Glu Ile Ser Gln Leu Lys Lys Glu Ile Glu
1 5 10 15

Arg Thr Gln Gln Arg Met Lys Glu Met Glu Ser Val Met Lys Glu Gln
20 25 30

Glu Gln Tyr Ile Ala Thr Gln Tyr Lys Xaa Ala Ile Asp Leu Gly Gln
35 40 45

Glu Leu Arg Leu Thr Arg Glu Gln Val Gln Asn Ser His Thr Glu Leu
50 55 60

Ala Glu Ala Arg His Gln Gln Val Gln Ala Gln Arg Glu Ile Glu Arg
65 70 75 80

Leu Ser Ser Glu Leu Glu Asp Met Lys Gln Leu Ser Lys Glu Lys Asp
85 90 95

Ala His Gly Asn His Leu Ala Glu Glu Leu Gly Ala Ser Lys Val Arg
100 105 110

Glu Ala His Leu Glu Ala Arg Met Gln Ala Glu Ile Lys Lys Leu Ser
115 120 125

Ala Glu Val Glu Ser Leu Lys Glu Ala Tyr His Met Glu Met Ile Ser
130 135 140

His Gln Glu Asn His Ala Lys Trp Lys Ile Ser Ala Asp Ser Gln Lys
145 150 155 160

Ser Ser Val Gln Gln Leu Asn Glu Gln Leu Glu Lys Ala Lys Leu Glu
165 170 175

Leu Glu Glu Ala Gln Asp Thr Val Ser Asn Leu His Gln Gln Val Gln
180 185 190

Asp Arg Asn Glu Val Ile Glu Ala Ala Asn Glu Ala Leu Leu Thr Lys
195 200 205

Val Ser Lys His Ile Lys Val Leu Lys His Ile Tyr Glu Asn Lys Thr
210 215 220

Xaa Xaa Xaa Xaa Xaa Pro Xaa Xaa Xaa Xaa Ser Arg Glu Tyr Phe
225 230 235

<210> SEQ ID NO 57
<211> LENGTH: 249
<212> TYPE: PRT
<213> ORGANISM: homosapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (226)..(226)
<223> OTHER INFORMATION: Xaa = any amino acid
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (239)..(239)
<223> OTHER INFORMATION: Xaa = any amino acid

<400> SEQUENCE: 57

Met Ala Asp Ser Ser Gly Arg Gly Ala Gly Lys Pro Ala Thr Gly Pro

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1               5                   10                  15

Thr Asn Ser Ser Ser Ala Lys Lys Lys Asp Lys Arg Val Gln Gly Gly
            20                  25                  30

Arg Val Ile Glu Ser Arg Tyr Leu Gln Tyr Glu Lys Lys Thr Thr Gln
        35                  40                  45

Lys Ala Pro Ala Gly Asp Gly Ser Gln Thr Arg Gly Lys Met Ser Glu
    50                  55                  60

Gly Gly Arg Lys Ser Ser Leu Leu Gln Lys Ser Lys Ala Asp Ser Ser
65                  70                  75                  80

Gly Val Gly Lys Gly Asp Leu Gln Ser Thr Leu Leu Glu Gly His Gly
                85                  90                  95

Thr Ala Pro Pro Asp Leu Asp Leu Ser Ala Ile Asn Asp Lys Ser Ile
            100                 105                 110

Val Lys Lys Thr Pro Gln Leu Ala Lys Thr Ile Ser Lys Lys Pro Glu
        115                 120                 125

Ser Thr Ser Phe Ser Ala Pro Arg Lys Lys Ser Pro Asp Leu Ser Glu
    130                 135                 140

Ala Met Glu Met Met Glu Ser Gln Thr Leu Leu Leu Thr Leu Leu Ser
145                 150                 155                 160

Val Lys Met Glu Asn Asn Leu Ala Glu Phe Glu Arg Arg Ala Glu Lys
                165                 170                 175

Asn Leu Leu Ile Met Cys Lys Glu Lys Glu Lys Leu Gln Lys Lys Ala
            180                 185                 190

His Glu Leu Lys Arg Arg Leu Leu Leu Ser Gln Arg Lys Arg Glu Leu
        195                 200                 205

Ala Asp Val Leu Asp Ala Gln Ile Glu Met Leu Ser Pro Leu Arg Gly
    210                 215                 220

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

Trp Thr Leu Pro Gly Thr Ser Cys Pro
                245


<210> SEQ ID NO 58
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: homosapiens

<400> SEQUENCE: 58

Met Asp Tyr Arg Arg Leu Leu Met Ser Arg Val Val Pro Gly Gln Phe
1               5                   10                  15

Asp Asp Ala Asp Ser Ser Asp Ser Glu Asn Arg Asp Leu Lys Thr Val
            20                  25                  30

Lys Glu Lys Asp Asp Ile Leu Phe Glu Asp Leu Gln Asp Asn Val Asn
        35                  40                  45

Glu Asn Gly Glu Gly Glu Ile Glu Asp Glu Glu Glu Glu Gly Tyr Asp
    50                  55                  60

Asp Asp Asp Asp Asp Trp Asp Trp Asp Glu Gly Val Gly Lys Leu Ala
65                  70                  75                  80

Lys Gly Tyr Val Trp Asn Gly Gly Ser Asn Pro Gln Ala Asn Arg Gln
                85                  90                  95

Thr Ser Asp Ser Ser Ser Ala Lys Met Ser Thr Pro Ala Asp Lys Val
            100                 105                 110

Leu Arg Lys Ile
        115
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<210> SEQ ID NO 59
<211> LENGTH: 225
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 59

Met Ala His Ala Ala Gln Val Gly Leu Gln Asp Ala Thr Ser Pro Ile
1 5 10 15

Met Glu Glu Leu Ile Thr Phe His Asp His Ala Leu Met Ile Ile Phe
20 25 30

Leu Ile Cys Phe Leu Val Leu Tyr Ala Leu Phe Leu Thr Leu Thr Thr
35 40 45

Lys Leu Thr Asn Thr Asn Ile Ser Asp Ala Gln Glu Met Val Trp Thr
50 55 60

Ile Leu Pro Ala Ile Ile Leu Val Leu Ile Ala Leu Pro Ser Leu Arg
65 70 75 80

Ile Leu Tyr Met Thr Asp Glu Val Asn Asp Pro Ser Leu Thr Ile Lys
85 90 95

Ser Ile Gly His Gln Trp Tyr Trp Thr Tyr Glu Tyr Thr Asp Tyr Gly
100 105 110

Gly Leu Ile Phe Asn Ser Tyr Met Leu Pro Pro Leu Phe Leu Glu Pro
115 120 125

Gly Asp Leu Arg Leu Leu Asp Val Asp Asn Arg Val Val Leu Pro Ile
130 135 140

Glu Ala Pro Ile Arg Met Met Ile Thr Ser Gln Asp Val Leu His Ser
145 150 155 160

Trp Ala Val Pro Thr Leu Gly Leu Lys Thr Asp Ala Ile Pro Gly Arg
165 170 175

Leu Asn Gln Thr Thr Phe Thr Ala Thr Arg Pro Gly Val Tyr Tyr Gly
180 185 190

Gln Cys Ser Glu Ile Cys Gly Ala Asn His Ser Phe Met Pro Ile Val
195 200 205

Leu Glu Leu Ile Pro Leu Lys Ile Phe Glu Met Gly Pro Val Phe Thr
210 215 220

Leu
225

<210> SEQ ID NO 60
<211> LENGTH: 384
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 60

Met Asp Ala Val Met Thr Arg Lys Lys Ile Met Lys Gln Lys Glu Met
1 5 10 15

Val Trp Asn Asn Asn Lys Lys Leu Ser Asp Leu Glu Glu Val Ala Lys
20 25 30

Glu Arg Ala Gln Asn Leu Leu Gln Arg Ala Asn Lys Leu Arg Met Glu
35 40 45

Gln Glu Glu Glu Leu Lys Asp Met Ser Lys Ile Ile Leu Asn Ala Lys
50 55 60

Cys His Ala Ile Arg Asp Ala Gln Ile Leu Glu Lys Gln Gln Ile Gln
65 70 75 80

Lys Glu Leu Asp Thr Glu Glu Lys Arg Leu Asp Gln Met Met Glu Val
85 90 95

Glu Arg Gln Lys Ser Ile Gln Arg Gln Glu Glu Leu Glu Arg Lys Arg
100 105 110

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Arg Glu Glu Arg Ile Arg Gly Arg Arg Gln Ile Val Glu Gln Met Glu
        115                 120                 125

Lys Asn Gln Glu Glu Arg Ser Leu Leu Ala Glu Gln Arg Glu Gln Glu
    130                 135                 140

Lys Glu Gln Met Leu Glu Tyr Met Glu Gln Leu Gln Glu Glu Asp Leu
145                 150                 155                 160

Lys Asp Met Glu Arg Arg Gln Gln Gln Lys Leu Lys Met Gln Ala Glu
                165                 170                 175

Ile Lys Arg Ile Asn Asp Glu Asn Gln Lys Gln Lys Ala Glu Leu Leu
            180                 185                 190

Ala Gln Glu Lys Leu Ala Asp Gln Met Val Met Glu Phe Thr Lys Lys
        195                 200                 205

Lys Met Ala Arg Glu Ala Glu Phe Glu Ala Glu Gln Glu Arg Ile Arg
    210                 215                 220

Arg Glu Lys Glu Lys Glu Ile Ala Arg Leu Arg Ala Met Gln Glu Lys
225                 230                 235                 240

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

Gln Glu Val Ala Asp Arg Glu Trp Arg Arg Lys Glu Lys Glu Asn Ala
            260                 265                 270

Arg Lys Lys Met Glu Ala Glu Leu Arg Lys Ser Arg Leu Glu Gln Val
        275                 280                 285

Ala Phe Lys Glu His Ala Leu Ala Val Gln Val His Gly Thr Gly Met
    290                 295                 300

Ser Ser Arg Gly Phe Phe Gly Leu Arg Glu Asn Arg Leu Arg Arg Ser
305                 310                 315                 320

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

Ser Ser Gly Ala Arg Cys Ala Arg Thr Ser Arg Arg Lys Cys Arg Thr
            340                 345                 350

Gly Leu Pro Pro Leu Arg Gly Ala Gly Ala Ser Lys Arg Arg Pro Arg
        355                 360                 365

Asn Ala Val Ser Ala Ser Met Arg Ser Arg Gly Lys Ser Leu Lys Ser
    370                 375                 380


<210> SEQ ID NO 61
<211> LENGTH: 510
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 61

Met Tyr Arg Ala Leu Arg Leu Leu Ala Arg Ser Arg Pro Leu Val Arg
1               5                   10                  15

Ala Pro Ala Ala Ala Leu Ala Ser Ala Pro Gly Leu Gly Gly Ala Ala
            20                  25                  30

Val Pro Ser Phe Trp Pro Pro Asn Ala Ala Arg Met Ala Ser Gln Asn
        35                  40                  45

Ser Phe Arg Ile Glu Tyr Asp Thr Phe Gly Glu Leu Lys Val Pro Asn
    50                  55                  60

Asp Lys Tyr Tyr Gly Ala Gln Thr Val Arg Ser Thr Met Asn Phe Lys
65                  70                  75                  80

Ile Gly Gly Val Thr Glu Arg Met Pro Thr Pro Val Ile Lys Ala Phe
                85                  90                  95

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

Glu Gly Lys Leu Asn Asp His Phe Pro Leu Val Val Trp Gln Thr Gly
    130                 135                 140

Ser Gly Thr Gln Thr Asn Met Asn Val Asn Glu Val Ile Ser Asn Arg
145                 150                 155                 160

Ala Ile Glu Met Leu Gly Gly Glu Leu Gly Ser Lys Ile Pro Val His
                165                 170                 175

Pro Asn Asp His Val Asn Lys Ser Gln Ser Ser Asn Asp Thr Phe Pro
            180                 185                 190

Thr Ala Met His Ile Ala Ala Ala Ile Glu Val His Glu Val Leu Leu
        195                 200                 205

Pro Gly Leu Gln Lys Leu His Asp Ala Leu Asp Ala Lys Ser Lys Glu
    210                 215                 220

Phe Ala Gln Ile Ile Lys Ile Gly Arg Thr His Thr Gln Asp Ala Val
225                 230                 235                 240

Pro Leu Thr Leu Gly Gln Glu Phe Ser Gly Tyr Val Gln Gln Val Lys
                245                 250                 255

Tyr Ala Met Thr Arg Ile Lys Ala Ala Met Pro Arg Ile Tyr Glu Leu
            260                 265                 270

Ala Ala Gly Gly Thr Ala Val Gly Thr Gly Leu Asn Thr Arg Ile Gly
        275                 280                 285

Phe Ala Glu Lys Val Ala Ala Lys Val Ala Ala Leu Thr Gly Leu Pro
    290                 295                 300

Phe Val Thr Ala Pro Asn Lys Phe Glu Ala Leu Ala Ala His Asp Ala
305                 310                 315                 320

Leu Val Glu Leu Ser Gly Ala Met Asn Thr Thr Ala Cys Ser Leu Met
                325                 330                 335

Lys Ile Ala Asn Asp Ile Arg Phe Leu Gly Ser Gly Pro Arg Ser Gly
            340                 345                 350

Leu Gly Glu Leu Ile Leu Pro Glu Asn Glu Pro Gly Ser Ser Ile Met
        355                 360                 365

Pro Gly Lys Val Asn Pro Thr Gln Cys Glu Ala Met Thr Met Val Ala
    370                 375                 380

Ala Gln Val Met Gly Asn His Val Ala Val Thr Val Gly Gly Ser Asn
385                 390                 395                 400

Gly His Phe Glu Leu Asn Val Phe Lys Pro Met Met Ile Lys Asn Val
                405                 410                 415

Leu His Ser Ala Arg Leu Leu Gly Asp Ala Ser Val Ser Phe Thr Glu
            420                 425                 430

Asn Cys Val Val Gly Ile Gln Ala Asn Thr Glu Arg Ile Asn Lys Leu
        435                 440                 445

Met Asn Glu Ser Leu Met Leu Val Thr Ala Leu Asn Pro His Ile Gly
    450                 455                 460

Tyr Asp Lys Ala Ala Lys Ile Ala Lys Thr Ala His Lys Asn Gly Ser
465                 470                 475                 480

Thr Leu Lys Glu Thr Ala Ile Glu Leu Gly Tyr Leu Thr Ala Glu Gln
                485                 490                 495

Phe Asp Glu Trp Val Lys Pro Lys Asp Met Leu Gly Pro Lys
            500                 505                 510


<210> SEQ ID NO 62
<211> LENGTH: 937
<212> TYPE: PRT
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-continued

<213> ORGANISM: homo sapiens

<400> SEQUENCE: 62

Met Arg Lys Ser Phe Ser Gln Pro Gly Leu Arg Ser Leu Ala Phe Arg
1 5 10 15

Lys Glu Leu Gln Asp Gly Gly Leu Arg Ser Ser Gly Phe Phe Ser Ser
20 25 30

Phe Glu Glu Ser Asp Ile Glu Asn His Leu Ile Ser Gly His Asn Ile
35 40 45

Val Gln Pro Thr Asp Ile Glu Glu Asn Arg Thr Met Leu Phe Thr Ile
50 55 60

Gly Gln Ser Glu Val Tyr Leu Ile Ser Pro Asp Thr Lys Lys Ile Ala
65 70 75 80

Leu Glu Lys Asn Phe Lys Glu Ile Ser Phe Cys Ser Gln Gly Ile Arg
85 90 95

His Val Asp His Phe Gly Phe Ile Cys Arg Glu Ser Ser Gly Gly Gly
100 105 110

Gly Phe His Phe Val Cys Tyr Val Phe Gln Cys Thr Asn Glu Ala Leu
115 120 125

Val Asp Glu Ile Met Met Thr Leu Lys Gln Ala Phe Thr Val Ala Ala
130 135 140

Val Gln Gln Thr Ala Lys Ala Pro Ala Gln Leu Cys Glu Gly Cys Pro
145 150 155 160

Leu Gln Ser Leu His Lys Leu Cys Glu Arg Ile Glu Gly Met Asn Ser
165 170 175

Ser Lys Thr Lys Leu Glu Leu Gln Lys His Leu Thr Thr Leu Thr Asn
180 185 190

Gln Glu Gln Ala Thr Ile Phe Glu Glu Val Gln Lys Leu Arg Pro Arg
195 200 205

Asn Glu Gln Arg Glu Asn Glu Leu Ile Ile Ser Phe Leu Arg Cys Leu
210 215 220

Tyr Glu Glu Lys Gln Lys Glu His Ile His Ile Gly Glu Met Lys Gln
225 230 235 240

Thr Ser Gln Met Ala Ala Glu Asn Ile Gly Ser Glu Leu Pro Pro Ser
245 250 255

Ala Thr Arg Phe Arg Leu Asp Met Leu Lys Asn Lys Ala Lys Arg Ser
260 265 270

Leu Thr Glu Ser Leu Glu Ser Ile Leu Ser Arg Gly Asn Lys Ala Arg
275 280 285

Gly Leu Gln Glu His Ser Ile Ser Val Asp Leu Asp Ser Ser Leu Ser
290 295 300

Ser Thr Leu Ser Asn Thr Ser Lys Glu Pro Ser Val Cys Glu Lys Glu
305 310 315 320

Ala Leu Pro Ile Ser Glu Ser Ser Phe Lys Leu Leu Gly Ser Ser Glu
325 330 335

Asp Leu Ser Ser Asp Ser Glu Ser His Leu Pro Glu Glu Pro Ala Pro
340 345 350

Leu Ser Pro Gln Gln Ala Phe Arg Arg Arg Ala Asn Thr Leu Ser His
355 360 365

Phe Pro Ile Glu Cys Gln Glu Pro Pro Gln Pro Ala Arg Gly Ser Pro
370 375 380

Gly Val Ser Gln Arg Lys Leu Met Arg Tyr His Ser Val Ser Thr Glu
385 390 395 400

Thr Pro His Glu Arg Lys Asp Phe Glu Ser Lys Ala Asn His Leu Gly

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               405                 410                 415

Asp Ser Gly Gly Thr Pro Val Lys Thr Arg Arg His Ser Trp Arg Gln
            420                 425                 430

Gln Ile Phe Leu Arg Val Ala Thr Pro Gln Lys Ala Cys Asp Ser Ser
        435                 440                 445

Ser Arg Tyr Glu Asp Tyr Ser Glu Leu Gly Glu Leu Pro Pro Arg Ser
    450                 455                 460

Pro Leu Glu Pro Val Cys Glu Asp Gly Pro Phe Gly Pro Pro Pro Glu
465                 470                 475                 480

Glu Lys Lys Arg Thr Ser Arg Glu Leu Arg Glu Leu Trp Gln Lys Ala
                485                 490                 495

Ile Leu Gln Gln Ile Leu Leu Leu Arg Met Glu Lys Glu Asn Gln Lys
            500                 505                 510

Leu Gln Ala Ser Glu Asn Asp Leu Leu Asn Lys Arg Leu Lys Leu Asp
        515                 520                 525

Tyr Glu Glu Ile Thr Pro Cys Leu Lys Glu Val Thr Thr Val Trp Glu
    530                 535                 540

Lys Met Leu Ser Thr Pro Gly Arg Ser Lys Ile Lys Phe Asp Met Glu
545                 550                 555                 560

Lys Met His Ser Ala Val Gly Gln Gly Val Pro Arg His His Arg Gly
                565                 570                 575

Glu Ile Trp Lys Phe Leu Ala Glu Gln Phe His Leu Lys His Gln Phe
            580                 585                 590

Pro Ser Lys Gln Gln Pro Lys Asp Val Pro Tyr Lys Glu Leu Leu Lys
        595                 600                 605

Gln Leu Thr Ser Gln Gln His Ala Ile Leu Ile Asp Leu Gly Arg Thr
    610                 615                 620

Phe Pro Thr His Pro Tyr Phe Ser Ala Gln Leu Gly Ala Gly Gln Leu
625                 630                 635                 640

Ser Leu Tyr Asn Ile Leu Lys Ala Tyr Ser Leu Leu Asp Gln Glu Val
                645                 650                 655

Gly Tyr Cys Gln Gly Leu Ser Phe Val Ala Gly Ile Leu Leu Leu His
            660                 665                 670

Met Ser Glu Glu Glu Ala Phe Lys Met Leu Lys Phe Leu Met Phe Asp
        675                 680                 685

Met Gly Leu Arg Lys Gln Tyr Arg Pro Asp Met Ile Ile Leu Gln Ile
    690                 695                 700

Gln Met Tyr Gln Leu Ser Arg Leu Leu His Asp Tyr His Arg Asp Leu
705                 710                 715                 720

Tyr Asn His Leu Glu Glu His Glu Ile Gly Pro Ser Leu Tyr Ala Ala
                725                 730                 735

Pro Trp Phe Leu Thr Met Phe Ala Ser Gln Phe Pro Leu Gly Phe Val
            740                 745                 750

Ala Arg Val Phe Asp Met Ile Phe Leu Gln Gly Thr Glu Val Ile Phe
        755                 760                 765

Lys Val Ala Leu Ser Leu Leu Gly Ser His Lys Pro Leu Ile Leu Gln
    770                 775                 780

His Glu Asn Leu Glu Thr Ile Val Asp Phe Ile Lys Ser Thr Leu Pro
785                 790                 795                 800

Asn Leu Gly Leu Val Gln Met Glu Lys Thr Ile Asn Gln Val Phe Glu
                805                 810                 815

Met Asp Ile Ala Lys Gln Leu Gln Ala Tyr Glu Val Glu Tyr His Val
            820                 825                 830
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Leu Gln Glu Glu Leu Ile Asp Ser Ser Pro Leu Ser Asp Asn Gln Arg
        835                 840                 845

Met Asp Lys Leu Glu Lys Thr Asn Ser Ser Leu Arg Lys Gln Asn Leu
    850                 855                 860

Asp Leu Leu Glu Gln Leu Gln Val Ala Asn Gly Arg Ile Gln Ser Leu
865                 870                 875                 880

Glu Ala Thr Ile Glu Lys Leu Leu Ser Ser Glu Ser Lys Leu Lys Gln
                885                 890                 895

Ala Met Leu Thr Leu Glu Leu Glu Arg Ser Ala Leu Leu Gln Thr Val
            900                 905                 910

Glu Glu Leu Arg Arg Arg Ser Ala Glu Pro Ser Asp Arg Glu Pro Glu
        915                 920                 925

Cys Thr Gln Pro Glu Pro Thr Gly Asp
    930                 935


<210> SEQ ID NO 63
<211> LENGTH: 618
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 63

Met His Lys Thr Ala Ser Gln Arg Leu Phe Pro Gly Pro Ser Tyr Gln
1               5                   10                  15

Asn Ile Lys Ser Ile Met Glu Asp Ser Thr Ile Leu Ser Asp Trp Thr
            20                  25                  30

Asn Ser Asn Lys Gln Lys Met Lys Tyr Asp Phe Ser Cys Glu Leu Tyr
        35                  40                  45

Arg Met Ser Thr Tyr Ser Thr Phe Pro Ala Gly Val Pro Val Ser Glu
    50                  55                  60

Arg Ser Leu Ala Arg Ala Gly Phe Tyr Tyr Thr Gly Val Asn Asp Lys
65                  70                  75                  80

Val Lys Cys Phe Cys Cys Gly Leu Met Leu Asp Asn Trp Lys Leu Gly
                85                  90                  95

Asp Ser Pro Ile Gln Lys His Lys Gln Leu Tyr Pro Ser Cys Ser Phe
            100                 105                 110

Ile Gln Asn Leu Val Ser Ala Ser Leu Gly Ser Thr Ser Lys Asn Thr
        115                 120                 125

Ser Pro Met Arg Asn Ser Phe Ala His Ser Leu Ser Pro Thr Leu Glu
    130                 135                 140

His Ser Ser Leu Phe Ser Gly Ser Tyr Ser Ser Leu Ser Pro Asn Pro
145                 150                 155                 160

Leu Asn Ser Arg Ala Val Glu Asp Ile Ser Ser Ser Arg Thr Asn Pro
                165                 170                 175

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

Met Trp Pro Leu Thr Phe Leu Ser Pro Ser Glu Leu Ala Arg Ala Gly
        195                 200                 205

Phe Tyr Tyr Ile Gly Pro Gly Asp Arg Val Ala Cys Phe Ala Cys Gly
    210                 215                 220

Gly Lys Leu Ser Asn Trp Glu Pro Lys Asp Asp Ala Met Ser Glu His
225                 230                 235                 240

Arg Arg His Phe Pro Asn Cys Pro Phe Leu Glu Asn Ser Leu Glu Thr
                245                 250                 255

Leu Arg Phe Ser Ile Ser Asn Leu Ser Met Gln Thr His Ala Ala Arg
            260                 265                 270
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```
Met Arg Thr Phe Met Tyr Trp Pro Ser Ser Val Pro Val Gln Pro Glu
        275                 280                 285

Gln Leu Ala Ser Ala Gly Phe Tyr Tyr Val Gly Arg Asn Asp Asp Val
    290                 295                 300

Lys Cys Phe Cys Cys Asp Gly Gly Leu Arg Cys Trp Glu Ser Gly Asp
305                 310                 315                 320

Asp Pro Trp Val Glu His Ala Lys Trp Phe Pro Arg Cys Glu Phe Leu
                325                 330                 335

Ile Arg Met Lys Gly Gln Glu Phe Val Asp Glu Ile Gln Gly Arg Tyr
            340                 345                 350

Pro His Leu Leu Glu Gln Leu Leu Ser Thr Ser Asp Thr Thr Gly Glu
        355                 360                 365

Glu Asn Ala Asp Pro Pro Ile Ile His Phe Gly Pro Gly Glu Ser Ser
    370                 375                 380

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

Glu Met Gly Phe Asn Arg Asp Leu Val Lys Gln Thr Val Gln Ser Lys
                405                 410                 415

Ile Leu Thr Thr Gly Glu Asn Tyr Lys Thr Val Asn Asp Ile Val Ser
            420                 425                 430

Ala Leu Leu Asn Ala Glu Asp Glu Lys Arg Glu Glu Glu Lys Glu Lys
        435                 440                 445

Gln Ala Glu Glu Met Ala Ser Asp Asp Leu Ser Leu Ile Arg Lys Asn
    450                 455                 460

Arg Met Ala Leu Phe Gln Gln Leu Thr Cys Val Leu Pro Ile Leu Asp
465                 470                 475                 480

Asn Leu Leu Lys Ala Asn Val Ile Asn Lys Gln Glu His Asp Ile Ile
                485                 490                 495

Lys Gln Lys Thr Gln Ile Pro Leu Gln Ala Arg Glu Leu Ile Asp Thr
            500                 505                 510

Ile Leu Val Lys Gly Asn Ala Ala Ala Asn Ile Phe Lys Asn Cys Leu
        515                 520                 525

Lys Glu Ile Asp Ser Thr Leu Tyr Lys Asn Leu Phe Val Asp Lys Asn
    530                 535                 540

Met Lys Tyr Ile Pro Thr Glu Asp Val Ser Gly Leu Ser Leu Glu Glu
545                 550                 555                 560

Gln Leu Arg Arg Leu Gln Glu Glu Arg Thr Cys Lys Val Cys Met Asp
                565                 570                 575

Lys Glu Val Ser Val Val Phe Ile Pro Cys Gly His Leu Val Val Cys
            580                 585                 590

Gln Glu Cys Ala Pro Ser Leu Arg Lys Cys Pro Ile Cys Arg Gly Ile
        595                 600                 605

Ile Lys Gly Thr Val Arg Thr Phe Leu Ser
    610                 615


<210> SEQ ID NO 64
<211> LENGTH: 539
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 64

Met Thr Ser Leu Trp Gly Lys Gly Thr Gly Cys Lys Leu Phe Lys Phe
1               5                   10                  15

Arg Val Ala Ala Ala Pro Ala Ser Gly Ala Leu Arg Arg Leu Thr Pro
            20                  25                  30
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```
Ser Ala Ser Leu Pro Pro Ala Gln Leu Leu Leu Arg Ala Val Arg Arg
        35                  40                  45

Arg Ser His Pro Val Arg Asp Tyr Ala Ala Gln Thr Ser Pro Ser Pro
    50                  55                  60

Lys Ala Gly Ala Ala Thr Gly Arg Ile Val Ala Val Ile Gly Ala Val
65                  70                  75                  80

Val Asp Val Gln Phe Asp Glu Gly Leu Pro Pro Ile Leu Asn Ala Leu
                85                  90                  95

Glu Val Gln Gly Arg Glu Thr Arg Leu Val Leu Glu Val Ala Gln His
            100                 105                 110

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

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

Pro Val Gly Pro Glu Thr Leu Gly Arg Ile Met Asn Val Ile Gly Glu
145                 150                 155                 160

Pro Ile Asp Glu Arg Gly Pro Ile Lys Thr Lys Gln Phe Ala Pro Ile
                165                 170                 175

His Ala Glu Ala Pro Glu Phe Met Glu Met Ser Val Glu Gln Glu Ile
            180                 185                 190

Leu Val Thr Gly Ile Lys Val Val Asp Leu Leu Ala Pro Tyr Ala Lys
        195                 200                 205

Gly Gly Lys Ile Gly Leu Phe Gly Gly Ala Gly Val Gly Lys Thr Val
    210                 215                 220

Leu Ile Met Glu Leu Ile Asn Asn Val Ala Lys Ala His Gly Gly Tyr
225                 230                 235                 240

Ser Val Phe Ala Gly Val Gly Glu Arg Thr Arg Glu Gly Asn Asp Leu
                245                 250                 255

Tyr His Glu Met Ile Glu Ser Gly Val Ile Asn Leu Lys Asp Ala Thr
            260                 265                 270

Ser Lys Val Ala Leu Val Tyr Gly Gln Met Asn Gln Pro Pro Gly Ala
        275                 280                 285

Arg Ala Arg Val Ala Leu Thr Gly Leu Thr Val Ala Glu Tyr Phe Arg
    290                 295                 300

Asp Gln Glu Gly Gln Asp Val Leu Leu Phe Ile Asp Asn Ile Phe Arg
305                 310                 315                 320

Phe Thr Gln Ala Gly Ser Glu Val Ser Ala Leu Leu Gly Arg Ile Pro
                325                 330                 335

Ser Ala Val Gly Tyr Gln Pro Thr Leu Ala Thr Asp Met Gly Thr Met
            340                 345                 350

Gln Glu Arg Ile Thr Thr Thr Lys Lys Gly Ser Ile Thr Ser Val Gln
        355                 360                 365

Ala Ile Tyr Val Pro Ala Asp Asp Leu Thr Asp Pro Ala Pro Ala Thr
    370                 375                 380

Thr Phe Ala His Leu Asp Ala Thr Thr Val Leu Ser Arg Ala Ile Ala
385                 390                 395                 400

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

Ile Met Asp Pro Asn Ile Val Gly Ser Glu His Tyr Asp Val Ala Arg
            420                 425                 430

Gly Val Gln Lys Ile Leu Gln Asp Tyr Lys Ser Leu Gln Asp Ile Ile
        435                 440                 445

Ala Ile Leu Gly Met Asp Glu Leu Ser Glu Glu Asp Lys Leu Thr Val
    450                 455                 460
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Ser Arg Ala Arg Lys Ile Gln Arg Phe Leu Ser Gln Pro Phe Gln Val
465                 470                 475                 480

Ala Glu Val Phe Thr Gly His Met Gly Lys Leu Val Pro Leu Lys Glu
                485                 490                 495

Thr Ile Lys Gly Phe Gln Gln Ile Leu Ala Gly Glu Tyr Asp His Leu
            500                 505                 510

Pro Glu Gln Ala Phe Tyr Met Val Gly Pro Ile Glu Glu Ala Val Ala
        515                 520                 525

Lys Ala Asp Lys Leu Ala Glu Glu His Ser Ser
    530                 535


<210> SEQ ID NO 65
<211> LENGTH: 772
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 65

Met Ala Ala Glu Ser Ala Leu Gln Val Val Glu Lys Leu Gln Ala Arg
1               5                   10                  15

Leu Ala Ala Asn Pro Asp Pro Lys Lys Leu Leu Lys Tyr Leu Lys Lys
            20                  25                  30

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

Gly Lys Thr Val Asn Ser Leu Arg Lys His Glu His Val Gly Ser Phe
    50                  55                  60

Ala Arg Asp Leu Val Ala Gln Trp Lys Lys Leu Val Pro Val Glu Arg
65                  70                  75                  80

Asn Ala Glu Pro Asp Glu Gln Asp Phe Glu Lys Ser Asn Ser Arg Lys
                85                  90                  95

Arg Pro Arg Asp Ala Leu Gln Lys Glu Glu Glu Met Glu Gly Asp Tyr
            100                 105                 110

Gln Glu Thr Trp Lys Ala Thr Gly Ser Arg Ser Tyr Ser Pro Asp His
        115                 120                 125

Arg Gln Lys Lys His Arg Lys Leu Ser Glu Leu Glu Arg Pro His Lys
    130                 135                 140

Val Ser His Gly His Glu Arg Arg Asp Glu Arg Lys Arg Cys His Arg
145                 150                 155                 160

Met Ser Pro Thr Tyr Ser Ser Asp Pro Glu Ser Ser Asp Tyr Gly His
                165                 170                 175

Val Gln Ser Pro Pro Ser Cys Thr Ser Pro His Gln Met Tyr Val Asp
            180                 185                 190

His Tyr Arg Ser Leu Glu Glu Asp Gln Glu Pro Ile Val Ser His Gln
        195                 200                 205

Lys Pro Gly Lys Gly His Ser Asn Ala Phe Gln Asp Arg Leu Gly Ala
    210                 215                 220

Ser Gln Glu Arg His Leu Gly Glu Pro His Gly Lys Gly Val Val Ser
225                 230                 235                 240

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

Ala Lys Ser Asp Glu Lys Ala Ser Val Val Ser Arg Glu Lys Ser His
            260                 265                 270

Lys Ala Leu Ser Lys Glu Glu Asn Arg Arg Pro Pro Ser Gly Asp Asn
        275                 280                 285

Ala Arg Glu Lys Pro Pro Ser Ser Gly Val Lys Lys Glu Lys Asp Arg
    290                 295                 300
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Glu Gly Ser Ser Leu Lys Lys Lys Cys Leu Pro Pro Ser Glu Ala Ala
305                 310                 315                 320

Ser Asp Asn His Leu Lys Lys Pro Lys His Arg Asp Pro Glu Lys Ala
                325                 330                 335

Lys Leu Asp Lys Ser Lys Gln Gly Leu Asp Ser Phe Asp Thr Gly Lys
            340                 345                 350

Gly Ala Gly Asp Leu Leu Pro Lys Val Lys Glu Lys Gly Ser Asn Asn
        355                 360                 365

Leu Lys Thr Pro Glu Gly Lys Val Lys Thr Asn Leu Asp Arg Lys Ser
    370                 375                 380

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

Glu Gln Pro Thr Met Ser Phe Glu Ser Tyr Leu Ser Tyr Asp Gln Pro
                405                 410                 415

Arg Lys Lys Lys Lys Lys Ile Val Lys Thr Ser Ala Thr Ala Leu Gly
            420                 425                 430

Asp Lys Gly Leu Lys Lys Asn Asp Ser Lys Ser Thr Gly Lys Asn Leu
        435                 440                 445

Asp Ser Val Gln Lys Leu Pro Lys Val Asn Lys Thr Lys Ser Glu Lys
    450                 455                 460

Pro Ala Gly Ala Asp Leu Ala Lys Leu Arg Lys Val Pro Asp Val Leu
465                 470                 475                 480

Pro Val Leu Pro Asp Leu Pro Leu Pro Ala Ile Gln Ala Asn Tyr Arg
                485                 490                 495

Pro Leu Pro Ser Leu Glu Leu Ile Ser Ser Phe Gln Pro Lys Arg Lys
            500                 505                 510

Ala Phe Ser Ser Pro Gln Glu Glu Glu Glu Ala Gly Phe Thr Gly Arg
        515                 520                 525

Arg Met Asn Ser Lys Met Gln Val Tyr Ser Gly Ser Lys Cys Ala Tyr
    530                 535                 540

Leu Pro Lys Met Met Thr Leu His Gln Gln Cys Ile Arg Val Leu Lys
545                 550                 555                 560

Asn Asn Ile Asp Ser Ile Phe Glu Val Gly Gly Val Pro Tyr Ser Val
                565                 570                 575

Leu Glu Pro Val Leu Glu Arg Cys Thr Pro Asp Gln Leu Tyr Arg Ile
            580                 585                 590

Glu Glu Tyr Asn His Val Leu Ile Glu Glu Thr Asp Gln Leu Trp Lys
        595                 600                 605

Val His Cys His Arg Asp Phe Lys Glu Glu Arg Pro Glu Glu Tyr Glu
    610                 615                 620

Ser Trp Arg Glu Met Tyr Leu Arg Leu Gln Asp Ala Arg Glu Gln Arg
625                 630                 635                 640

Leu Arg Val Leu Thr Lys Asn Ile Gln Phe Ala His Ala Asn Lys Pro
                645                 650                 655

Lys Gly Arg Gln Ala Lys Met Ala Phe Val Asn Ser Val Ala Lys Pro
            660                 665                 670

Pro Arg Asp Val Arg Arg Arg Gln Glu Lys Phe Gly Thr Gly Gly Ala
        675                 680                 685

Ala Val Pro Glu Lys Ile Lys Ile Lys Pro Ala Pro Tyr Pro Met Gly
    690                 695                 700

Ser Ser His Ala Ser Ala Ser Ser Ile Ser Phe Asn Pro Ser Pro Glu
705                 710                 715                 720

Glu Pro Ala Tyr Asp Gly Pro Ser Thr Ser Ser Ala His Leu Ala Pro
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                725                 730                 735

Val Val Ser Ser Thr Val Ser Tyr Asp Pro Arg Lys Pro Thr Val Lys
            740                 745                 750

Lys Ile Ala Pro Met Met Ala Lys Thr Ile Lys Ala Phe Lys Asn Arg
        755                 760                 765

Phe Ser Arg Arg
    770


<210> SEQ ID NO 66
<211> LENGTH: 886
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 66

Met Ser Gly Phe Ser Pro Glu Leu Ile Asp Tyr Leu Glu Gly Lys Ile
1               5                   10                  15

Ser Phe Glu Glu Phe Glu Arg Arg Arg Glu Glu Arg Lys Thr Arg Glu
            20                  25                  30

Lys Lys Ser Leu Gln Glu Lys Gly Lys Leu Ser Ala Glu Glu Asn Pro
        35                  40                  45

Asp Asp Ser Glu Val Pro Ser Ser Ser Gly Ile Asn Ser Thr Lys Ser
    50                  55                  60

Gln Asp Lys Asp Val Asn Glu Gly Glu Thr Ser Asp Gly Val Arg Lys
65                  70                  75                  80

Ser Val His Lys Val Phe Ala Ser Met Leu Gly Glu Asn Glu Asp Asp
                85                  90                  95

Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Thr
            100                 105                 110

Pro Glu Gln Pro Thr Ala Gly Asp Val Phe Val Leu Glu Met Val Leu
        115                 120                 125

Asn Arg Glu Thr Lys Lys Met Met Lys Glu Lys Arg Pro Arg Ser Lys
    130                 135                 140

Leu Pro Arg Ala Leu Arg Gly Leu Met Gly Glu Ala Asn Ile Arg Phe
145                 150                 155                 160

Ala Arg Gly Glu Arg Glu Glu Ala Ile Leu Met Cys Met Glu Ile Ile
                165                 170                 175

Arg Gln Ala Pro Leu Ala Tyr Glu Pro Phe Ser Thr Leu Ala Met Ile
            180                 185                 190

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

Ala Ala His Leu Asn Pro Ser Asp Thr Glu Glu Trp Val Arg Leu Ala
    210                 215                 220

Glu Met Ser Leu Glu Gln Asp Asn Ile Lys Gln Ala Ile Phe Cys Tyr
225                 230                 235                 240

Thr Lys Ala Leu Lys Tyr Glu Pro Thr Asn Val Arg Tyr Leu Trp Glu
                245                 250                 255

Arg Ser Ser Leu Tyr Glu Gln Met Gly Asp His Lys Met Ala Met Asp
            260                 265                 270

Gly Tyr Arg Arg Ile Leu Asn Leu Leu Ser Pro Ser Asp Gly Glu Arg
        275                 280                 285

Phe Met Gln Leu Ala Arg Asp Met Ala Lys Ser Tyr Tyr Glu Ala Asn
    290                 295                 300

Asp Val Thr Ser Ala Ile Asn Ile Ile Asp Glu Ala Phe Ser Lys His
305                 310                 315                 320

Gln Gly Leu Val Ser Met Glu Asp Val Asn Ile Ala Ala Glu Leu Tyr
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                325                 330                 335

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

Ser Gly Ile Val Leu Glu Lys Lys Thr Ser Glu Glu Gly Thr Ser Glu
        355                 360                 365

Glu Asn Lys Ala Pro Glu Asn Val Thr Cys Thr Ile Pro Asp Gly Val
    370                 375                 380

Pro Ile Asp Ile Thr Val Lys Leu Met Val Cys Leu Val His Leu Asn
385                 390                 395                 400

Ile Leu Glu Pro Leu Asn Pro Leu Leu Thr Thr Leu Val Glu Gln Asn
                405                 410                 415

Pro Glu Asp Met Gly Asp Leu Tyr Leu Asp Val Ala Glu Ala Phe Leu
            420                 425                 430

Asp Val Gly Glu Tyr Asn Ser Ala Leu Pro Leu Leu Ser Ala Leu Val
        435                 440                 445

Cys Ser Glu Arg Tyr Asn Leu Ala Val Val Trp Leu Arg His Ala Glu
    450                 455                 460

Cys Leu Lys Ala Leu Gly Tyr Met Glu Arg Ala Ala Glu Ser Tyr Gly
465                 470                 475                 480

Lys Val Val Asp Leu Ala Pro Leu His Leu Asp Ala Arg Ile Ser Leu
                485                 490                 495

Ser Thr Leu Gln Gln Gln Leu Gly Gln Pro Glu Lys Ala Leu Glu Ala
            500                 505                 510

Leu Glu Pro Met Tyr Asp Pro Asp Thr Leu Ala Gln Asp Ala Asn Ala
        515                 520                 525

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

Ser Gln Gly Lys Met Tyr Gly Tyr Val Asp Thr Leu Leu Thr Met Leu
545                 550                 555                 560

Ala Met Leu Leu Lys Val Ala Met Asn Arg Ala Gln Val Cys Leu Ile
                565                 570                 575

Ser Ser Ser Lys Ser Gly Glu Arg His Leu Tyr Leu Ile Lys Val Ser
            580                 585                 590

Arg Asp Lys Ile Ser Asp Ser Asn Asp Gln Glu Ser Ala Asn Cys Asp
        595                 600                 605

Ala Lys Ala Ile Phe Ala Val Leu Thr Ser Val Leu Thr Lys Asp Asp
    610                 615                 620

Trp Trp Asn Leu Leu Leu Lys Ala Ile Tyr Ser Leu Cys Asp Leu Ser
625                 630                 635                 640

Arg Phe Gln Glu Ala Glu Leu Leu Val Asp Ser Ser Leu Glu Tyr Tyr
                645                 650                 655

Ser Phe Tyr Asp Asp Arg Gln Lys Arg Lys Glu Leu Glu Tyr Phe Gly
            660                 665                 670

Leu Ser Ala Ala Ile Leu Asp Lys Asn Phe Arg Lys Ala Tyr Asn Tyr
        675                 680                 685

Ile Arg Ile Met Val Met Glu Asn Val Asn Lys Pro Gln Leu Trp Asn
    690                 695                 700

Ile Phe Asn Gln Val Thr Met His Ser Gln Asp Val Arg His His Arg
705                 710                 715                 720

Phe Cys Leu Arg Leu Met Leu Lys Asn Pro Glu Asn His Ala Leu Cys
                725                 730                 735

Val Leu Asn Gly His Asn Ala Phe Val Ser Gly Ser Phe Lys His Ala
            740                 745                 750
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```
Leu Gly Gln Tyr Val Gln Ala Phe Arg Thr His Pro Asp Glu Pro Leu
        755                 760                 765

Tyr Ser Phe Cys Ile Gly Leu Thr Phe Ile His Met Ala Ser Gln Lys
    770                 775                 780

Tyr Val Leu Arg Arg His Ala Leu Ile Val Gln Gly Phe Ser Phe Leu
785                 790                 795                 800

Asn Arg Tyr Leu Ser Leu Arg Gly Pro Cys Gln Glu Ser Phe Tyr Asn
                805                 810                 815

Leu Gly Arg Gly Leu His Gln Leu Gly Leu Ile His Leu Ala Ile His
            820                 825                 830

Tyr Tyr Gln Lys Ala Leu Glu Leu Pro Pro Leu Val Val Glu Gly Ile
        835                 840                 845

Glu Leu Asp Gln Leu Asp Leu Arg Arg Asp Ile Ala Tyr Asn Leu Ser
    850                 855                 860

Leu Ile Tyr Gln Ser Ser Gly Asn Thr Gly Met Ala Gln Thr Leu Leu
865                 870                 875                 880

Tyr Thr Tyr Cys Ser Ile
                885


<210> SEQ ID NO 67
<211> LENGTH: 1130
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 67

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

Arg Arg Trp Ile Phe His Thr Ala Ser Lys Leu Asn Leu Gln Val Leu
            20                  25                  30

Leu Ser His Val Leu Gly Lys Asp Val Pro Arg Asp Gly Lys Ala Glu
        35                  40                  45

Phe Ala Cys Ser Lys Cys Ala Phe Met Leu Asp Arg Ile Tyr Arg Phe
    50                  55                  60

Asp Thr Val Ile Ala Arg Ile Glu Ala Leu Ser Ile Glu Arg Leu Gln
65                  70                  75                  80

Lys Leu Leu Leu Glu Lys Asp Arg Leu Lys Phe Cys Ile Ala Ser Met
                85                  90                  95

Tyr Arg Lys Asn Asn Asp Asp Ser Gly Ala Glu Ile Lys Ala Gly Asn
            100                 105                 110

Gly Thr Val Asp Met Ser Val Leu Pro Asp Ala Arg Tyr Ser Ala Leu
        115                 120                 125

Leu Gln Glu Asp Phe Ala Tyr Ser Gly Phe Glu Cys Trp Val Glu Asn
    130                 135                 140

Glu Asp Gln Ile Gln Glu Pro His Ser Cys His Gly Ser Glu Gly Pro
145                 150                 155                 160

Gly Asn Arg Pro Arg Arg Cys Arg Gly Cys Ala Ala Leu Arg Val Ala
                165                 170                 175

Asp Ser Asp Tyr Glu Ala Ile Cys Lys Val Pro Arg Lys Val Ala Arg
            180                 185                 190

Ser Ile Ser Cys Gly Pro Ser Ser Arg Trp Ser Thr Ser Ile Cys Thr
        195                 200                 205

Glu Glu Pro Ala Leu Ser Glu Val Gly Pro Pro Asp Leu Ala Ser Thr
    210                 215                 220

Lys Val Pro Pro Asp Gly Glu Ser Met Glu Glu Glu Thr Pro Gly Ser
225                 230                 235                 240
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```
Ser Val Glu Ser Leu Asp Ala Ser Val Gln Ala Ser Pro Pro Gln Gln
                245                 250                 255

Lys Asp Glu Glu Thr Glu Arg Ser Ala Lys Glu Leu Gly Lys Cys Asp
            260                 265                 270

Cys Cys Ser Asp Asp Gln Ala Pro Gln His Gly Cys Asn His Lys Leu
        275                 280                 285

Glu Leu Ala Leu Ser Met Ile Lys Gly Leu Asp Tyr Lys Pro Ile Gln
    290                 295                 300

Ser Pro Arg Gly Ser Arg Leu Pro Ile Pro Val Lys Ser Ser Leu Pro
305                 310                 315                 320

Gly Ala Lys Pro Gly Pro Ser Met Thr Asp Gly Val Ser Ser Gly Phe
                325                 330                 335

Leu Asn Arg Ser Leu Lys Pro Leu Tyr Lys Thr Pro Val Ser Tyr Pro
            340                 345                 350

Leu Glu Leu Ser Asp Leu Gln Glu Leu Trp Asp Asp Leu Cys Glu Asp
        355                 360                 365

Tyr Leu Pro Leu Arg Val Gln Pro Met Thr Glu Glu Leu Leu Lys Gln
    370                 375                 380

Gln Lys Leu Asn Ser His Glu Thr Thr Ile Thr Gln Gln Ser Val Ser
385                 390                 395                 400

Asp Ser His Leu Ala Glu Leu Gln Glu Lys Ile Gln Gln Thr Glu Ala
                405                 410                 415

Thr Asn Lys Ile Leu Gln Glu Lys Leu Asn Glu Met Ser Tyr Glu Leu
            420                 425                 430

Lys Cys Ala Gln Glu Ser Ser Gln Lys Gln Asp Gly Thr Ile Gln Asn
        435                 440                 445

Leu Lys Glu Thr Leu Lys Ser Arg Glu Arg Glu Thr Glu Glu Leu Tyr
    450                 455                 460

Gln Val Ile Glu Gly Gln Asn Asp Thr Met Ala Lys Leu Arg Glu Met
465                 470                 475                 480

Leu His Gln Ser Gln Leu Gly Gln Leu His Ser Ser Glu Gly Thr Ser
                485                 490                 495

Pro Ala Gln Gln Gln Val Ala Leu Leu Asp Leu Gln Ser Ala Leu Phe
            500                 505                 510

Cys Ser Gln Leu Glu Ile Gln Lys Leu Gln Arg Val Val Arg Gln Lys
        515                 520                 525

Glu Arg Gln Leu Ala Asp Ala Lys Gln Cys Val Gln Phe Val Glu Ala
    530                 535                 540

Ala Ala His Glu Ser Glu Gln Gln Lys Glu Ala Ser Trp Lys His Asn
545                 550                 555                 560

Gln Glu Leu Arg Lys Ala Leu Gln Gln Leu Gln Glu Glu Leu Gln Asn
                565                 570                 575

Lys Ser Gln Gln Leu Arg Ala Trp Glu Ala Glu Lys Tyr Asn Glu Ile
            580                 585                 590

Arg Thr Gln Glu Gln Asn Ile Gln His Leu Asn His Ser Leu Ser His
        595                 600                 605

Lys Glu Gln Leu Leu Gln Glu Phe Arg Glu Leu Leu Gln Tyr Arg Asp
    610                 615                 620

Asn Ser Asp Lys Thr Leu Glu Ala Asn Glu Met Leu Leu Glu Lys Leu
625                 630                 635                 640

Arg Gln Arg Ile His Asp Lys Ala Val Ala Leu Glu Arg Ala Ile Asp
                645                 650                 655

Glu Lys Phe Ser Ala Leu Glu Glu Lys Glu Lys Glu Leu Arg Gln Leu
            660                 665                 670
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-continued

```
Arg Leu Ala Val Arg Glu Arg Asp His Asp Leu Glu Arg Leu Arg Asp
        675                 680                 685

Val Leu Ser Ser Asn Glu Ala Thr Met Gln Ser Met Glu Ser Leu Leu
    690                 695                 700

Arg Ala Lys Gly Leu Glu Val Glu Gln Leu Ser Thr Thr Cys Gln Asn
705                 710                 715                 720

Leu Gln Trp Leu Lys Glu Glu Met Lys Phe Ser Arg Trp Gln Lys Glu
                725                 730                 735

Gln Glu Ser Ile Ile Gln Gln Leu Gln Thr Ser Leu His Asp Arg Asn
            740                 745                 750

Lys Glu Val Glu Asp Leu Ser Ala Thr Leu Leu Cys Lys Leu Gly Pro
        755                 760                 765

Gly Gln Ser Glu Ile Ala Glu Glu Leu Cys Gln Arg Leu Gln Arg Lys
    770                 775                 780

Glu Arg Met Leu Gln Asp Leu Leu Ser Asp Arg Asn Lys Gln Val Leu
785                 790                 795                 800

Glu His Glu Met Glu Ile Gln Gly Leu Leu Gln Ser Val Ser Thr Arg
                805                 810                 815

Glu Gln Glu Ser Gln Ala Ala Ala Glu Lys Leu Val Gln Ala Leu Met
            820                 825                 830

Glu Arg Asn Ser Glu Leu Gln Ala Leu Arg Gln Tyr Leu Gly Gly Arg
        835                 840                 845

Asp Ser Leu Met Ser Gln Ala Pro Ile Ser Asn Gln Gln Ala Glu Val
    850                 855                 860

Thr Pro Thr Gly Arg Leu Gly Lys Gln Thr Asp Gln Gly Ser Met Gln
865                 870                 875                 880

Ile Pro Ser Arg Asp Asp Ser Thr Ser Leu Thr Ala Lys Glu Asp Val
                885                 890                 895

Ser Ile Pro Arg Ser Thr Leu Gly Asp Leu Asp Thr Val Ala Gly Leu
            900                 905                 910

Glu Lys Glu Leu Ser Asn Ala Lys Glu Glu Leu Glu Leu Met Ala Lys
        915                 920                 925

Lys Glu Arg Glu Ser Gln Met Glu Leu Ser Ala Leu Gln Ser Met Met
    930                 935                 940

Ala Val Gln Glu Glu Glu Leu Gln Val Gln Ala Ala Asp Met Glu Ser
945                 950                 955                 960

Leu Thr Arg Asn Ile Gln Ile Lys Glu Asp Leu Ile Lys Asp Leu Gln
                965                 970                 975

Met Gln Leu Val Asp Pro Glu Asp Ile Pro Ala Met Glu Arg Leu Thr
            980                 985                 990

Gln Glu Val Leu Leu Leu Arg Glu  Lys Val Ala Ser Val  Glu Ser Gln
        995                 1000                1005

Gly Gln  Glu Ile Ser Gly Asn  Arg Arg Gln Gln Leu  Leu Leu Met
    1010                1015                1020

Leu Glu  Gly Leu Val Asp Glu  Arg Ser Arg Leu Asn  Glu Ala Leu
    1025                1030                1035

Gln Ala  Glu Arg Gln Leu Tyr  Ser Ser Leu Val Lys  Phe His Ala
    1040                1045                1050

His Pro  Glu Ser Ser Glu Arg  Asp Arg Thr Leu Gln  Val Glu Leu
    1055                1060                1065

Glu Gly  Ala Gln Val Leu Arg  Ser Arg Leu Glu Glu  Val Leu Gly
    1070                1075                1080

Arg Ser  Leu Glu Arg Leu Asn  Arg Leu Glu Thr Leu  Ala Ala Ile
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    1085                1090                1095

Gly Gly  Ala Ala Ala Gly Asp  Asp Thr Glu Asp Thr  Ser Thr Glu
    1100                1105                1110

Phe Thr  Asp Ser Ile Glu Glu  Glu Ala Ala His His  Ser His Gln
    1115                1120                1125

Gln Leu
    1130


<210> SEQ ID NO 68
<211> LENGTH: 621
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 68

Met Ala Asp Phe Glu Glu Leu Arg Asn Met Val Ser Ser Phe Arg Val
1               5                   10                  15

Ser Glu Leu Gln Val Leu Leu Gly Phe Ala Gly Arg Asn Lys Ser Gly
            20                  25                  30

Arg Lys His Asp Leu Leu Met Arg Ala Leu His Leu Leu Lys Ser Gly
        35                  40                  45

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

Tyr Pro Arg Thr Leu Glu Gly Leu Ser Asp Leu Ser Thr Ile Lys Ser
65                  70                  75                  80

Ser Val Phe Ser Leu Asp Gly Gly Ser Ser Pro Val Glu Pro Asp Leu
                85                  90                  95

Ala Val Ala Gly Ile His Ser Leu Pro Ser Thr Ser Val Thr Pro His
            100                 105                 110

Ser Pro Ser Ser Pro Val Gly Ser Val Leu Leu Gln Asp Thr Lys Pro
        115                 120                 125

Thr Phe Glu Met Gln Gln Pro Ser Pro Pro Ile Pro Pro Val His Pro
    130                 135                 140

Asp Val Gln Leu Lys Asn Leu Pro Phe Tyr Asp Val Leu Asp Val Leu
145                 150                 155                 160

Ile Lys Pro Thr Ser Leu Val Gln Ser Ser Ile Gln Arg Phe Gln Glu
                165                 170                 175

Lys Phe Phe Ile Phe Ala Leu Thr Pro Gln Gln Val Arg Glu Ile Cys
            180                 185                 190

Ile Ser Arg Asp Phe Leu Pro Gly Gly Arg Arg Asp Tyr Thr Val Gln
        195                 200                 205

Val Gln Leu Arg Leu Cys Leu Ala Glu Thr Ser Cys Pro Gln Glu Asp
    210                 215                 220

Asn Tyr Pro Asn Ser Leu Cys Ile Lys Val Asn Gly Lys Leu Phe Pro
225                 230                 235                 240

Leu Pro Gly Tyr Ala Pro Pro Pro Lys Asn Gly Ile Glu Gln Lys Arg
                245                 250                 255

Pro Gly Arg Pro Leu Asn Ile Thr Ser Leu Val Arg Leu Ser Ser Ala
            260                 265                 270

Val Pro Asn Gln Ile Ser Ile Ser Trp Ala Ser Glu Ile Gly Lys Asn
        275                 280                 285

Tyr Ser Met Ser Val Tyr Leu Val Arg Gln Leu Thr Ser Ala Met Leu
    290                 295                 300

Leu Gln Arg Leu Lys Met Lys Gly Ile Arg Asn Pro Asp His Ser Arg
305                 310                 315                 320

Ala Leu Ile Lys Glu Lys Leu Thr Ala Asp Pro Asp Ser Glu Ile Ala
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               325                 330                 335

Thr Thr Ser Leu Arg Val Ser Leu Met Cys Pro Leu Gly Lys Met Arg
            340                 345                 350

Leu Thr Ile Pro Cys Arg Ala Val Thr Cys Thr His Leu Gln Cys Phe
        355                 360                 365

Asp Ala Ala Leu Tyr Leu Gln Met Asn Glu Lys Lys Pro Thr Trp Ile
    370                 375                 380

Cys Pro Val Cys Asp Lys Lys Ala Ala Tyr Glu Ser Leu Ile Leu Asp
385                 390                 395                 400

Gly Leu Phe Met Glu Ile Leu Asn Asp Cys Ser Asp Val Asp Glu Ile
                405                 410                 415

Lys Phe Gln Glu Asp Gly Ser Trp Cys Pro Met Arg Pro Lys Lys Glu
            420                 425                 430

Ala Met Lys Val Ser Ser Gln Pro Cys Thr Lys Ile Glu Ser Ser Ser
        435                 440                 445

Val Leu Ser Lys Pro Cys Ser Val Thr Val Ala Ser Glu Ala Ser Lys
    450                 455                 460

Lys Lys Val Asp Val Ile Asp Leu Thr Ile Glu Ser Ser Ser Asp Glu
465                 470                 475                 480

Glu Glu Asp Pro Pro Ala Lys Arg Lys Cys Ile Phe Met Ser Glu Thr
                485                 490                 495

Gln Ser Ser Pro Thr Lys Gly Val Leu Met Tyr Gln Pro Ser Ser Val
            500                 505                 510

Arg Val Pro Ser Val Thr Ser Val Asp Pro Ala Ala Ile Pro Pro Ser
        515                 520                 525

Leu Thr Asp Tyr Ser Val Pro Phe His His Thr Pro Ile Ser Ser Met
    530                 535                 540

Ser Ser Asp Leu Pro Gly Leu Asp Phe Leu Ser Leu Ile Pro Val Asp
545                 550                 555                 560

Pro Gln Tyr Cys Pro Pro Met Phe Leu Asp Ser Leu Thr Ser Pro Leu
                565                 570                 575

Thr Ala Ser Ser Thr Ser Val Thr Thr Thr Ser Ser His Glu Ser Ser
            580                 585                 590

Thr His Val Ser Ser Ser Ser Ser Arg Ser Glu Thr Gly Val Ile Thr
        595                 600                 605

Ser Ser Gly Ser Asn Ile Pro Glu Ile Ile Ser Leu Asp
    610                 615                 620


<210> SEQ ID NO 69
<211> LENGTH: 685
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 69

Met Glu Leu Leu Arg Thr Ile Thr Tyr Gln Pro Ala Ala Ser Thr Lys
1               5                   10                  15

Met Cys Glu Gln Ala Leu Gly Lys Gly Cys Gly Gly Asp Ser Lys Lys
            20                  25                  30

Lys Arg Pro Pro Gln Pro Pro Glu Glu Ser Gln Pro Pro Gln Ser Gln
        35                  40                  45

Ala Gln Val Pro Pro Ala Ala Pro His His His His His His Ser His
    50                  55                  60

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

Arg Tyr Cys Arg Gly Lys Val Leu Gly Lys Gly Gly Phe Ala Lys Cys
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                85                  90                  95

Tyr Glu Met Thr Asp Leu Thr Asn Asn Lys Val Tyr Ala Ala Lys Ile
            100                 105                 110

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

Lys Glu Ile Glu Leu His Arg Ile Leu His His Lys His Val Val Gln
    130                 135                 140

Phe Tyr His Tyr Phe Glu Asp Lys Glu Asn Ile Tyr Ile Leu Leu Glu
145                 150                 155                 160

Tyr Cys Ser Arg Arg Ser Met Ala His Ile Leu Lys Ala Arg Lys Val
                165                 170                 175

Leu Thr Glu Pro Glu Val Arg Tyr Tyr Leu Arg Gln Ile Val Ser Gly
            180                 185                 190

Leu Lys Tyr Leu His Glu Gln Glu Ile Leu His Arg Asp Leu Lys Leu
        195                 200                 205

Gly Asn Phe Phe Ile Asn Glu Ala Met Glu Leu Lys Val Gly Asp Phe
    210                 215                 220

Gly Leu Ala Ala Arg Leu Glu Pro Leu Glu His Arg Arg Arg Thr Ile
225                 230                 235                 240

Cys Gly Thr Pro Asn Tyr Leu Ser Pro Glu Val Leu Asn Lys Gln Gly
                245                 250                 255

His Gly Cys Glu Ser Asp Ile Trp Ala Leu Gly Cys Val Met Tyr Thr
            260                 265                 270

Met Leu Leu Gly Arg Pro Pro Phe Glu Thr Thr Asn Leu Lys Glu Thr
        275                 280                 285

Tyr Arg Cys Ile Arg Glu Ala Arg Tyr Thr Met Pro Ser Ser Leu Leu
    290                 295                 300

Ala Pro Ala Lys His Leu Ile Ala Ser Met Leu Ser Lys Asn Pro Glu
305                 310                 315                 320

Asp Arg Pro Ser Leu Asp Asp Ile Ile Arg His Asp Phe Phe Leu Gln
                325                 330                 335

Gly Phe Thr Pro Asp Arg Leu Ser Ser Ser Cys Cys His Thr Val Pro
            340                 345                 350

Asp Phe His Leu Ser Ser Pro Ala Lys Asn Phe Phe Lys Lys Ala Ala
        355                 360                 365

Ala Ala Leu Phe Gly Gly Lys Lys Asp Lys Ala Arg Tyr Ile Asp Thr
    370                 375                 380

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

Asp Leu Lys Lys Thr Ser Ile Thr Gln Gln Pro Ser Lys His Arg Thr
                405                 410                 415

Asp Glu Glu Leu Gln Pro Pro Thr Thr Thr Val Ala Arg Ser Gly Thr
            420                 425                 430

Pro Ala Val Glu Asn Lys Gln Gln Ile Gly Asp Ala Ile Arg Met Ile
        435                 440                 445

Val Arg Gly Thr Leu Gly Ser Cys Ser Ser Ser Ser Glu Cys Leu Glu
    450                 455                 460

Asp Ser Thr Met Gly Ser Val Ala Asp Thr Val Ala Arg Val Leu Arg
465                 470                 475                 480

Gly Cys Leu Glu Asn Met Pro Glu Ala Asp Cys Ile Pro Lys Glu Gln
                485                 490                 495

Leu Ser Thr Ser Phe Gln Trp Val Thr Lys Trp Val Asp Tyr Ser Asn
            500                 505                 510
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Lys Tyr Gly Phe Gly Tyr Gln Leu Ser Asp His Thr Val Gly Val Leu
        515                 520                 525

Phe Asn Asn Gly Ala His Met Ser Leu Leu Pro Asp Lys Lys Thr Val
    530                 535                 540

His Tyr Tyr Ala Glu Leu Gly Gln Cys Ser Val Phe Pro Ala Thr Asp
545                 550                 555                 560

Ala Pro Glu Gln Phe Ile Ser Gln Val Thr Val Leu Lys Tyr Phe Ser
                565                 570                 575

His Tyr Met Glu Glu Asn Leu Met Asp Gly Gly Asp Leu Pro Ser Val
            580                 585                 590

Thr Asp Ile Arg Arg Pro Arg Leu Tyr Leu Leu Gln Trp Leu Lys Ser
        595                 600                 605

Asp Lys Ala Leu Met Met Leu Phe Asn Asp Gly Thr Phe Gln Val Asn
    610                 615                 620

Phe Tyr His Asp His Thr Lys Ile Ile Ile Cys Ser Gln Asn Glu Glu
625                 630                 635                 640

Tyr Leu Leu Thr Tyr Ile Asn Glu Asp Arg Ile Ser Thr Thr Phe Arg
                645                 650                 655

Leu Thr Thr Leu Leu Met Ser Gly Cys Ser Ser Glu Leu Lys Asn Arg
            660                 665                 670

Met Glu Tyr Ala Leu Asn Met Leu Leu Gln Arg Cys Asn
        675                 680                 685


<210> SEQ ID NO 70
<211> LENGTH: 767
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 70

Met Ala Thr Tyr Leu Glu Phe Ile Gln Gln Asn Glu Glu Arg Asp Gly
1               5                   10                  15

Val Arg Phe Ser Trp Asn Val Trp Pro Ser Ser Arg Leu Glu Ala Thr
            20                  25                  30

Arg Met Val Val Pro Leu Ala Cys Leu Leu Thr Pro Leu Lys Glu Arg
        35                  40                  45

Pro Asp Leu Pro Pro Val Gln Tyr Glu Pro Val Leu Cys Ser Arg Pro
    50                  55                  60

Thr Cys Lys Ala Val Leu Asn Pro Leu Cys Gln Val Asp Tyr Arg Ala
65                  70                  75                  80

Lys Leu Trp Ala Cys Asn Phe Cys Phe Gln Arg Asn Gln Phe Pro Pro
                85                  90                  95

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

Gln Phe Ser Thr Ile Glu Tyr Val Ile Gln Arg Gly Ala Gln Ser Pro
        115                 120                 125

Leu Ile Phe Leu Tyr Val Val Asp Thr Cys Leu Glu Glu Asp Asp Leu
    130                 135                 140

Gln Ala Leu Lys Glu Ser Leu Gln Met Ser Leu Ser Leu Leu Pro Pro
145                 150                 155                 160

Asp Ala Leu Val Gly Leu Ile Thr Phe Gly Arg Met Val Gln Val His
                165                 170                 175

Glu Leu Ser Cys Glu Gly Ile Ser Lys Ser Tyr Val Phe Arg Gly Thr
            180                 185                 190

Lys Asp Leu Thr Ala Lys Gln Ile Gln Asp Met Leu Gly Leu Thr Lys
        195                 200                 205
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Pro Ala Met Pro Met Gln Gln Ala Arg Pro Ala Gln Pro Gln Glu His
    210                 215                 220

Pro Phe Ala Ser Ser Arg Phe Leu Gln Pro Val His Lys Ile Asp Met
225                 230                 235                 240

Asn Leu Thr Asp Leu Leu Gly Glu Leu Gln Arg Asp Pro Trp Pro Val
                245                 250                 255

Thr Gln Gly Lys Arg Pro Leu Arg Ser Thr Gly Val Ala Leu Ser Ile
            260                 265                 270

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

Met Leu Phe Thr Gly Gly Pro Pro Thr Gln Gly Pro Gly Met Val Val
    290                 295                 300

Gly Asp Glu Leu Lys Ile Pro Ile Arg Ser Trp His Asp Ile Glu Lys
305                 310                 315                 320

Asp Asn Ala Arg Phe Met Lys Lys Ala Thr Lys His Tyr Glu Met Leu
                325                 330                 335

Ala Asn Arg Thr Ala Ala Asn Gly His Cys Ile Asp Ile Tyr Ala Cys
            340                 345                 350

Ala Leu Asp Gln Thr Gly Leu Leu Glu Met Lys Cys Cys Ala Asn Leu
        355                 360                 365

Thr Gly Gly Tyr Met Val Met Gly Asp Ser Phe Asn Thr Ser Leu Phe
    370                 375                 380

Lys Gln Thr Phe Gln Arg Ile Phe Thr Lys Asp Phe Asn Gly Asp Phe
385                 390                 395                 400

Arg Met Ala Phe Gly Ala Thr Leu Asp Val Lys Thr Ser Arg Glu Leu
                405                 410                 415

Lys Ile Ala Gly Ala Ile Gly Pro Cys Val Ser Leu Asn Val Lys Gly
            420                 425                 430

Pro Cys Val Ser Glu Asn Glu Leu Gly Val Gly Gly Thr Ser Gln Trp
        435                 440                 445

Lys Ile Cys Gly Leu Asp Pro Thr Ser Thr Leu Gly Ile Tyr Phe Glu
    450                 455                 460

Val Val Asn Gln His Asn Thr Pro Ile Pro Gln Gly Gly Arg Gly Ala
465                 470                 475                 480

Ile Gln Phe Val Thr His Tyr Gln His Ser Ser Thr Gln Arg Arg Ile
                485                 490                 495

Arg Val Thr Thr Ile Ala Arg Asn Trp Ala Asp Val Gln Ser Gln Leu
            500                 505                 510

Arg His Ile Glu Ala Ala Phe Asp Gln Glu Ala Ala Ala Val Leu Met
        515                 520                 525

Ala Arg Leu Gly Val Phe Arg Ala Glu Ser Glu Glu Gly Pro Asp Val
    530                 535                 540

Leu Arg Trp Leu Asp Arg Gln Leu Ile Arg Leu Cys Gln Lys Phe Gly
545                 550                 555                 560

Gln Tyr Asn Lys Glu Asp Pro Thr Ser Phe Arg Leu Ser Asp Ser Phe
                565                 570                 575

Ser Leu Tyr Pro Gln Phe Met Phe His Leu Arg Arg Ser Pro Phe Leu
            580                 585                 590

Gln Val Phe Asn Asn Ser Pro Asp Glu Ser Ser Tyr Tyr Arg His His
        595                 600                 605

Phe Ala Arg Gln Asp Leu Thr Gln Ser Leu Ile Met Ile Gln Pro Ile
    610                 615                 620

Leu Tyr Ser Tyr Ser Phe His Gly Pro Pro Glu Pro Val Leu Leu Asp
625                 630                 635                 640
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```
Ser Ser Ser Ile Leu Ala Asp Arg Ile Leu Leu Met Asp Thr Phe Phe
                645                 650                 655

Gln Ile Val Ile Tyr Leu Gly Glu Thr Ile Ala Gln Trp Arg Lys Ala
            660                 665                 670

Gly Tyr Gln Asp Met Pro Glu Tyr Glu Asn Phe Lys His Leu Leu Gln
        675                 680                 685

Ala Pro Leu Asp Asp Ala Gln Glu Ile Leu Gln Ala Arg Phe Pro Met
    690                 695                 700

Pro Arg Tyr Ile Asn Thr Glu His Gly Gly Ser Gln Ala Arg Phe Leu
705                 710                 715                 720

Leu Ser Lys Val Asn Pro Ser Gln Thr His Asn Asn Leu Tyr Ala Trp
                725                 730                 735

Gly Gln Glu Thr Gly Ala Pro Ile Leu Thr Asp Asp Val Ser Leu Gln
            740                 745                 750

Val Phe Met Asp His Leu Lys Lys Leu Ala Val Ser Ser Ala Cys
        755                 760                 765


<210> SEQ ID NO 71
<211> LENGTH: 188
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 71

Met Asn Gly Asp Asp Thr Phe Ala Lys Arg Pro Arg Asp Asp Ala Lys
1               5                   10                  15

Ala Ser Glu Lys Arg Ser Lys Ala Phe Asp Asp Ile Ala Thr Tyr Phe
            20                  25                  30

Ser Lys Lys Glu Trp Lys Lys Met Lys Tyr Ser Glu Lys Ile Ser Tyr
        35                  40                  45

Val Tyr Met Lys Arg Asn Tyr Lys Ala Met Thr Lys Leu Gly Phe Lys
    50                  55                  60

Val Thr Leu Pro Pro Phe Met Cys Asn Lys Gln Ala Thr Asp Phe Gln
65                  70                  75                  80

Gly Asn Asp Phe Asp Asn Asp His Asn Arg Arg Ile Gln Val Glu His
                85                  90                  95

Pro Gln Met Thr Phe Gly Arg Leu His Arg Ile Ile Pro Lys Ile Met
            100                 105                 110

Pro Lys Lys Pro Ala Glu Asp Glu Asn Asp Ser Lys Gly Val Ser Glu
        115                 120                 125

Ala Ser Gly Pro Gln Asn Asp Gly Lys Gln Leu His Pro Pro Gly Lys
    130                 135                 140

Ala Asn Ile Ser Glu Lys Ile Asn Lys Arg Ser Gly Pro Lys Arg Gly
145                 150                 155                 160

Lys His Ala Trp Thr His Arg Leu Arg Glu Arg Lys Gln Leu Val Ile
                165                 170                 175

Tyr Glu Glu Ile Ser Asp Pro Glu Glu Asp Asp Glu
            180                 185


<210> SEQ ID NO 72
<211> LENGTH: 1038
<212> TYPE: PRT
<213> ORGANISM: homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (910)..(910)
<223> OTHER INFORMATION: Xaa = any amino acid

<400> SEQUENCE: 72
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Met Trp Arg Cys Gly Gly Arg Gln Gly Leu Cys Val Leu Arg Arg Leu
1               5                  10                  15

Ser Gly Gly His Ala His His Arg Ala Trp Arg Trp Asn Ser Asn Arg
            20                  25                  30

Ala Cys Glu Arg Ala Leu Gln Tyr Lys Leu Gly Asp Lys Ile His Gly
        35                  40                  45

Phe Thr Val Asn Gln Val Thr Ser Val Pro Glu Leu Phe Leu Thr Ala
    50                  55                  60

Val Lys Leu Thr His Asp Asp Thr Gly Ala Arg Tyr Leu His Leu Ala
65                  70                  75                  80

Arg Glu Asp Thr Asn Asn Leu Phe Ser Val Gln Phe Arg Thr Thr Pro
                85                  90                  95

Met Asp Ser Thr Gly Val Pro His Ile Leu Glu His Thr Val Leu Cys
            100                 105                 110

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

Arg Ser Leu Ser Thr Phe Met Asn Ala Phe Thr Ala Ser Asp Tyr Thr
    130                 135                 140

Leu Tyr Pro Phe Ser Thr Gln Asn Pro Lys Asp Phe Gln Asn Leu Leu
145                 150                 155                 160

Ser Val Tyr Leu Asp Ala Thr Phe Ser Pro Cys Leu Arg Glu Leu Asp
                165                 170                 175

Phe Trp Gln Glu Gly Trp Arg Leu Glu His Glu Asn Pro Ser Asp Pro
            180                 185                 190

Gln Thr Pro Leu Val Phe Lys Gly Val Val Phe Asn Glu Met Lys Gly
        195                 200                 205

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

Leu Leu Pro Asp His Thr Tyr Ser Val Val Ser Gly Gly Asp Pro Leu
225                 230                 235                 240

Cys Ile Pro Glu Leu Thr Trp Glu Gln Leu Lys Gln Phe His Ala Thr
                245                 250                 255

His Tyr His Pro Ser Asn Ala Arg Phe Phe Thr Tyr Gly Asn Phe Pro
            260                 265                 270

Leu Glu Gln His Leu Lys Gln Ile His Glu Glu Ala Leu Ser Lys Phe
        275                 280                 285

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

Lys Pro Arg Glu Phe Gln Ile Thr Cys Gly Pro Asp Ser Phe Ala Thr
305                 310                 315                 320

Asp Pro Ser Lys Gln Thr Thr Val Ser Val Ser Phe Leu Leu Pro Asp
                325                 330                 335

Ile Thr Asp Thr Phe Glu Ala Phe Thr Leu Ser Leu Leu Ser Ser Leu
            340                 345                 350

Leu Thr Ser Gly Pro Asn Ser Pro Phe Tyr Lys Ala Leu Ile Glu Ser
        355                 360                 365

Gly Leu Gly Thr Glu Phe Ser Pro Asp Val Gly Tyr Asn Gly Tyr Thr
    370                 375                 380

Arg Glu Ala Tyr Phe Ser Val Gly Leu Gln Gly Ile Val Glu Lys Asp
385                 390                 395                 400

Ile Glu Thr Val Arg Ser Leu Ile Asp Arg Thr Ile Asp Glu Val Val
                405                 410                 415

Glu Thr Arg Ile Glu Asp Asp Arg Ile Glu Ala Leu Leu His Lys Ile
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            420                 425                 430

Glu Ile Gln Met Lys His Gln Ser Thr Ser Phe Gly Leu Met Leu Thr
        435                 440                 445

Ser Tyr Ile Ala Ser Cys Trp Asn His Asp Gly Asp Pro Val Glu Leu
    450                 455                 460

Leu Lys Leu Gly Asn Gln Leu Ala Lys Phe Arg Gln Cys Leu Gln Glu
465                 470                 475                 480

Asn Pro Lys Phe Leu Gln Glu Lys Val Lys Gln Tyr Phe Lys Asn Asn
                485                 490                 495

Gln His Lys Leu Thr Leu Ser Met Arg Pro Asp Asp Lys Tyr His Glu
            500                 505                 510

Lys Gln Ala Gln Val Glu Ala Thr Lys Leu Lys Gln Lys Val Glu Ala
        515                 520                 525

Leu Ser Pro Gly Asp Arg Gln Gln Ile Tyr Glu Lys Gly Leu Glu Leu
    530                 535                 540

Arg Ser Gln Gln Ser Lys Pro Gln Asp Ala Ser Cys Leu Pro Ala Leu
545                 550                 555                 560

Lys Val Ser Asp Ile Glu Pro Thr Ile Pro Val Thr Glu Leu Asp Val
                565                 570                 575

Val Leu Thr Ala Gly Asp Ile Pro Val Gln Tyr Cys Ala Gln Pro Thr
            580                 585                 590

Asn Gly Met Val Tyr Phe Arg Ala Phe Ser Ser Leu Asn Thr Leu Pro
        595                 600                 605

Glu Glu Leu Arg Pro Tyr Val Pro Leu Phe Cys Ser Ile Leu Thr Lys
    610                 615                 620

Leu Gly Cys Gly Leu Leu Asp Tyr Arg Glu Gln Ala Gln Gln Ile Glu
625                 630                 635                 640

Leu Lys Thr Gly Gly Met Ser Ala Ser Pro His Val Leu Pro Asp Asp
                645                 650                 655

Ser His Met Asp Thr Tyr Glu Gln Val Gly Val Leu Phe Ser Ser Leu
            660                 665                 670

Cys Leu Asp Arg Asn Leu Pro Asp Met Met Gln Leu Trp Ser Glu Ile
        675                 680                 685

Phe Asn Asn Pro Cys Phe Glu Glu Glu Glu His Phe Lys Val Leu Val
    690                 695                 700

Lys Met Thr Ala Gln Glu Leu Ala Asn Gly Ile Pro Asp Ser Gly His
705                 710                 715                 720

Leu Tyr Ala Ser Ile Arg Ala Gly Arg Thr Leu Thr Pro Ala Gly Asp
                725                 730                 735

Leu Gln Glu Thr Phe Ser Gly Met Asp Gln Val Arg Leu Met Lys Arg
            740                 745                 750

Ile Ala Glu Met Thr Asp Ile Lys Pro Ile Leu Arg Lys Leu Pro Arg
        755                 760                 765

Ile Lys Lys His Leu Leu Asn Gly Asp Asn Met Arg Cys Ser Val Asn
    770                 775                 780

Ala Thr Pro Gln Gln Met Pro Gln Thr Glu Lys Ala Val Glu Asp Phe
785                 790                 795                 800

Leu Arg Ser Ile Gly Arg Ser Lys Lys Glu Arg Arg Pro Val Arg Pro
                805                 810                 815

His Thr Val Glu Lys Pro Val Pro Ser Ser Ser Gly Gly Asp Ala His
            820                 825                 830

Val Pro His Gly Ser Gln Val Ile Arg Lys Leu Val Met Glu Pro Thr
        835                 840                 845
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Phe Lys Pro Trp Gln Met Lys Thr His Phe Leu Met Pro Phe Pro Val
    850                 855                 860

Asn Tyr Val Gly Glu Cys Ile Arg Thr Val Pro Tyr Thr Asp Pro Asp
865                 870                 875                 880

His Ala Ser Leu Lys Ile Leu Ala Arg Leu Met Thr Ala Lys Phe Leu
                885                 890                 895

His Thr Glu Ile Arg Glu Lys Gly Gly Ala Tyr Gly Gly Xaa Ala Lys
            900                 905                 910

Leu Ser His Asn Gly Ile Phe Thr Leu Tyr Ser Tyr Arg Asp Pro Asn
        915                 920                 925

Thr Ile Glu Thr Leu Gln Ser Phe Gly Lys Ala Val Asp Trp Ala Lys
    930                 935                 940

Ser Gly Lys Phe Thr Gln Gln Asp Ile Asp Glu Ala Lys Leu Ser Val
945                 950                 955                 960

Phe Ser Thr Val Asp Ala Pro Val Ala Pro Ser Asp Lys Gly Met Asp
                965                 970                 975

His Phe Leu Tyr Gly Leu Ser Asp Glu Met Lys Gln Ala His Arg Glu
            980                 985                 990

Gln Leu Phe Ala Val Ser His Asp  Lys Leu Leu Ala Val  Ser Asp Arg
        995                 1000                1005

Tyr Leu  Gly Thr Gly Lys Ser  Thr His Gly Leu Ala  Ile Leu Gly
    1010                1015                1020

Pro Glu  Asn Pro Lys Ile Ala  Lys Asp Pro Ser Trp  Ile Ile Arg
    1025                1030                1035


<210> SEQ ID NO 73
<211> LENGTH: 341
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 73

Met Leu Gly Ala Glu Trp Ser Lys Leu Gln Pro Thr Glu Lys Gln Arg
1               5                   10                  15

Tyr Leu Asp Glu Ala Glu Arg Glu Lys Gln Gln Tyr Met Lys Glu Leu
            20                  25                  30

Arg Ala Tyr Gln Gln Ser Glu Ala Tyr Lys Met Cys Thr Glu Lys Ile
        35                  40                  45

Gln Glu Lys Lys Ile Lys Lys Glu Asp Ser Ser Ser Gly Leu Met Asn
    50                  55                  60

Thr Leu Leu Asn Gly His Lys Gly Gly Asp Cys Asp Gly Phe Ser Thr
65                  70                  75                  80

Phe Asp Val Pro Ile Phe Thr Glu Glu Phe Leu Asp Gln Asn Lys Ala
                85                  90                  95

Arg Glu Ala Glu Leu Arg Arg Leu Arg Lys Met Asn Val Ala Phe Glu
            100                 105                 110

Glu Gln Asn Ala Val Leu Gln Arg Gln Asn Ala Glu His Glu Gln Arg
        115                 120                 125

Ala Arg Ala Ser Gly Ala Gly Ala Gly Ala Gly Gly Ala Glu Asp Ala
    130                 135                 140

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

Leu Arg Leu Thr Ala Gly Ala Gly His Gly Arg Asn Ala His Ala Gly
                165                 170                 175

His Ser Gly Leu Leu His Gly Pro Ala Ser Arg Ser His Arg Ala Arg
            180                 185                 190
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```
Pro Arg Pro Ala Arg Glu Ala His Arg Pro His Gln Gly Asn Pro Gly
        195                 200                 205

Pro Gly Arg Gln Arg Ala Pro Val Arg Ser Gly Arg Ala His Asp Ala
    210                 215                 220

Glu Glu Lys Leu Trp Ala Arg Pro Cys His Thr Pro Pro Arg Gly Arg
225                 230                 235                 240

Glu Ala Gly Gly Pro Pro Phe Gly Ala Trp Ser His Pro Ala Pro Leu
                245                 250                 255

Gly Ala Pro Ala Pro Leu Lys Leu Asn Phe Cys Ser Ile Pro Leu Ala
            260                 265                 270

Phe Asn Leu Pro Ser Pro Leu Asn Pro Glu Lys Ala Leu Ala Ala Arg
        275                 280                 285

Tyr Thr Gln Lys Asn Leu Thr Ala Glu Gly Ala Pro Pro Arg Arg Thr
    290                 295                 300

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

Thr Lys Pro Thr Pro Ser Thr Arg Gln Asp Pro Pro Asn Tyr Ser Leu
                325                 330                 335

Arg Gly Ala Val Pro
            340


<210> SEQ ID NO 74
<211> LENGTH: 377
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 74

Met Val Leu Glu Ser Thr Met Val Cys Val Asp Asn Ser Glu Tyr Met
1               5                   10                  15

Arg Asn Gly Asp Phe Leu Pro Thr Arg Leu Gln Ala Gln Gln Asp Ala
            20                  25                  30

Val Asn Ile Val Cys His Ser Lys Thr Arg Ser Asn Pro Glu Asn Asn
        35                  40                  45

Val Gly Leu Ile Thr Leu Ala Asn Asp Cys Glu Val Leu Thr Thr Leu
    50                  55                  60

Thr Pro Asp Thr Gly Arg Ile Leu Ser Lys Leu His Thr Val Gln Pro
65                  70                  75                  80

Lys Gly Lys Ile Thr Phe Cys Thr Gly Ile Arg Val Ala His Leu Ala
                85                  90                  95

Leu Lys His Arg Gln Gly Lys Asn His Lys Met Arg Ile Ile Ala Phe
            100                 105                 110

Val Gly Ser Pro Val Glu Asp Asn Glu Lys Asp Leu Val Lys Leu Ala
        115                 120                 125

Lys Arg Leu Lys Lys Glu Lys Val Asn Val Asp Ile Ile Asn Phe Gly
    130                 135                 140

Glu Glu Glu Val Asn Thr Glu Lys Leu Thr Ala Phe Val Asn Thr Leu
145                 150                 155                 160

Asn Gly Lys Asp Gly Thr Gly Ser His Leu Val Thr Val Pro Pro Gly
                165                 170                 175

Pro Ser Leu Ala Asp Ala Leu Ile Ser Ser Pro Ile Leu Ala Gly Glu
            180                 185                 190

Gly Gly Ala Met Leu Gly Leu Gly Ala Ser Asp Phe Glu Phe Gly Val
        195                 200                 205

Asp Pro Ser Ala Asp Pro Glu Leu Ala Leu Ala Leu Arg Val Ser Met
    210                 215                 220
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Glu Glu Gln Arg Gln Arg Gln Glu Glu Glu Ala Arg Arg Ala Ala Ala
225                 230                 235                 240

Ala Ser Ala Ala Glu Ala Gly Ile Ala Thr Thr Gly Thr Glu Asp Ser
                245                 250                 255

Asp Asp Ala Leu Leu Lys Met Thr Ile Ser Gln Gln Glu Phe Gly Arg
            260                 265                 270

Thr Gly Leu Pro Asp Leu Ser Ser Met Thr Glu Glu Glu Gln Ile Ala
        275                 280                 285

Tyr Ala Met Gln Met Ser Leu Gln Gly Ala Glu Phe Gly Gln Ala Glu
    290                 295                 300

Ser Ala Asp Ile Asp Ala Ser Ser Ala Met Asp Thr Ser Glu Pro Ala
305                 310                 315                 320

Lys Glu Glu Asp Asp Tyr Asp Val Met Gln Asp Pro Glu Phe Leu Gln
                325                 330                 335

Ser Val Leu Glu Asn Leu Pro Gly Val Asp Pro Asn Asn Glu Ala Ile
            340                 345                 350

Arg Asn Ala Met Gly Ser Leu Ala Ser Gln Ala Thr Lys Asp Gly Lys
        355                 360                 365

Lys Asp Lys Lys Glu Glu Asp Lys Lys
    370                 375


<210> SEQ ID NO 75
<211> LENGTH: 399
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 75

Met Ser Asp Ile Leu Arg Glu Leu Leu Cys Val Ser Glu Lys Ala Ala
1               5                   10                  15

Asn Ile Ala Arg Ala Cys Arg Gln Gln Glu Ala Leu Phe Gln Leu Leu
            20                  25                  30

Ile Glu Glu Lys Lys Glu Gly Glu Lys Asn Lys Lys Phe Ala Val Asp
        35                  40                  45

Phe Lys Thr Leu Ala Asp Val Leu Val Gln Glu Val Ile Lys Gln Asn
    50                  55                  60

Met Glu Asn Lys Phe Pro Gly Leu Glu Lys Asn Ile Phe Gly Glu Glu
65                  70                  75                  80

Ser Asn Glu Phe Thr Asn Asp Trp Gly Glu Lys Ile Thr Leu Arg Leu
                85                  90                  95

Cys Ser Thr Glu Glu Glu Thr Ala Glu Leu Leu Ser Lys Val Leu Asn
            100                 105                 110

Gly Asn Lys Val Ala Ser Glu Ala Leu Ala Arg Val Val His Gln Asp
        115                 120                 125

Val Ala Phe Thr Asp Pro Thr Leu Asp Ser Thr Glu Ile Asn Val Pro
    130                 135                 140

Gln Asp Ile Leu Gly Ile Trp Val Asp Pro Ile Asp Ser Thr Tyr Gln
145                 150                 155                 160

Tyr Ile Lys Gly Ser Ala Asp Ile Lys Ser Asn Gln Gly Ile Phe Pro
                165                 170                 175

Cys Gly Leu Gln Cys Val Thr Ile Leu Ile Gly Val Tyr Asp Ile Gln
            180                 185                 190

Thr Gly Val Pro Leu Met Gly Val Ile Asn Gln Pro Phe Val Ser Arg
        195                 200                 205

Asp Pro Asn Thr Leu Arg Trp Lys Gly Gln Cys Tyr Trp Gly Leu Ser
    210                 215                 220
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Tyr Met Gly Thr Asn Met His Ser Leu Gln Leu Thr Ile Ser Arg Arg
225                 230                 235                 240

Asn Gly Ser Glu Thr His Thr Gly Asn Thr Gly Ser Glu Ala Ala Phe
                245                 250                 255

Ser Pro Ser Phe Ser Ala Val Ile Ser Thr Ser Glu Lys Glu Thr Ile
            260                 265                 270

Lys Ala Ala Leu Ser Arg Val Cys Gly Asp Arg Ile Phe Gly Ala Ala
        275                 280                 285

Gly Ala Gly Tyr Lys Ser Leu Cys Val Val Gln Gly Leu Val Asp Ile
    290                 295                 300

Tyr Ile Phe Ser Glu Asp Thr Thr Phe Lys Trp Asp Ser Cys Ala Ala
305                 310                 315                 320

His Ala Ile Leu Arg Ala Met Gly Gly Gly Ile Val Asp Leu Lys Glu
                325                 330                 335

Cys Leu Glu Arg Asn Pro Glu Thr Gly Leu Asp Leu Pro Gln Leu Val
            340                 345                 350

Tyr His Val Glu Asn Glu Gly Ala Ala Gly Val Asp Arg Trp Ala Asn
        355                 360                 365

Lys Gly Gly Leu Ile Ala Tyr Arg Ser Arg Lys Arg Leu Glu Thr Phe
    370                 375                 380

Leu Ser Leu Leu Val Gln Asn Leu Ala Pro Ala Glu Thr His Thr
385                 390                 395


<210> SEQ ID NO 76
<211> LENGTH: 296
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 76

Met Lys Asn Glu Ile Ala Ala Val Val Phe Phe Phe Thr Arg Leu Val
1               5                   10                  15

Arg Lys His Asp Lys Leu Lys Lys Glu Ala Val Glu Arg Phe Ala Glu
            20                  25                  30

Lys Leu Thr Leu Ile Leu Gln Glu Lys Tyr Lys Asn His Trp Tyr Pro
        35                  40                  45

Glu Lys Pro Ser Lys Gly Gln Ala Tyr Arg Cys Ile Arg Val Asn Lys
    50                  55                  60

Phe Gln Arg Val Asp Pro Asp Val Leu Lys Ala Cys Glu Asn Ser Cys
65                  70                  75                  80

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

Asp Pro Cys Glu Val Cys Cys Arg Arg Asp Gly Val Ser Pro Cys Trp
            100                 105                 110

Pro Asp Cys Ser Gln Thr Pro Asp Leu Val Ile Arg Pro Pro Trp Pro
        115                 120                 125

Pro Lys Ala Leu Asp Tyr Arg Arg Glu Pro Leu Arg Pro Ala Ser Ser
    130                 135                 140

Phe Leu Ile Met Tyr Gly Glu Lys Asn Asn Ala Phe Ile Val Ala Ser
145                 150                 155                 160

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

Arg Ala Leu Asp Lys Val Thr Ser Asp Tyr His Ser Gly Ser Ser Ser
            180                 185                 190

Ser Asp Glu Glu Thr Ser Lys Glu Met Glu Val Lys Pro Ser Ser Val
        195                 200                 205
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Thr Ala Ala Ala Ser Pro Val Tyr Gln Ile Ser Glu Leu Ile Phe Pro
    210                 215                 220

Pro Leu Pro Met Trp His Pro Leu Pro Arg Lys Lys Pro Gly Met Tyr
225                 230                 235                 240

Arg Gly Asn Gly His Gln Asn His Tyr Pro Pro Pro Val Pro Phe Gly
                245                 250                 255

Tyr Pro Asn Gln Gly Arg Lys Asn Lys Pro Tyr Arg Pro Ile Pro Val
            260                 265                 270

Thr Trp Val Pro Pro Pro Gly Met His Cys Asp Arg Asn His Trp Ile
        275                 280                 285

Asn Pro His Met Leu Ala Pro His
    290                 295


<210> SEQ ID NO 77
<211> LENGTH: 188
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 77

Met Asn Gly Asp Asp Ala Phe Ala Arg Arg Pro Arg Asp Asp Ala Gln
1               5                   10                  15

Ile Ser Glu Lys Leu Arg Lys Ala Phe Asp Asp Ile Ala Lys Tyr Phe
            20                  25                  30

Ser Lys Lys Glu Trp Glu Lys Met Lys Ser Ser Glu Lys Ile Val Tyr
        35                  40                  45

Val Tyr Met Lys Leu Asn Tyr Glu Val Met Thr Lys Leu Gly Phe Lys
    50                  55                  60

Val Thr Leu Pro Pro Phe Met Arg Ser Lys Arg Ala Ala Asp Phe His
65                  70                  75                  80

Gly Asn Asp Phe Gly Asn Asp Arg Asn His Arg Asn Gln Val Glu Arg
                85                  90                  95

Pro Gln Met Thr Phe Gly Ser Leu Gln Arg Ile Phe Pro Lys Ile Met
            100                 105                 110

Pro Lys Lys Pro Ala Glu Glu Glu Asn Gly Leu Lys Glu Val Pro Glu
        115                 120                 125

Ala Ser Gly Pro Gln Asn Asp Gly Lys Gln Leu Cys Pro Pro Gly Asn
    130                 135                 140

Pro Ser Thr Leu Glu Lys Ile Asn Lys Thr Ser Gly Pro Lys Arg Gly
145                 150                 155                 160

Lys His Ala Trp Thr His Arg Leu Arg Glu Arg Lys Gln Leu Val Val
                165                 170                 175

Tyr Glu Glu Ile Ser Asp Pro Glu Glu Asp Asp Glu
            180                 185


<210> SEQ ID NO 78
<211> LENGTH: 602
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 78

Met Ala Ala Glu Glu Glu Ala Ala Ala Gly Gly Lys Val Leu Arg Glu
1               5                   10                  15

Glu Asn Gln Cys Ile Ala Pro Val Val Ser Ser Arg Val Ser Pro Gly
            20                  25                  30

Thr Arg Pro Thr Ala Met Gly Ser Phe Ser Ser His Met Thr Glu Phe
        35                  40                  45

Pro Arg Lys Arg Lys Gly Ser Asp Ser Asp Pro Ser Gln Val Glu Asp
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    50                  55                  60

Gly Glu His Gln Val Lys Met Lys Ala Phe Arg Glu Ala His Ser Gln
65                  70                  75                  80

Thr Glu Lys Arg Arg Arg Asp Lys Met Asn Asn Leu Ile Glu Glu Leu
                85                  90                  95

Ser Ala Met Ile Pro Gln Cys Asn Pro Met Ala Arg Lys Leu Asp Lys
            100                 105                 110

Leu Thr Val Leu Arg Met Ala Val Gln His Leu Arg Ser Leu Lys Gly
        115                 120                 125

Leu Thr Asn Ser Tyr Val Gly Ser Asn Tyr Arg Pro Ser Phe Leu Gln
    130                 135                 140

Asp Asn Glu Leu Arg His Leu Ile Leu Lys Thr Ala Glu Gly Phe Leu
145                 150                 155                 160

Phe Val Val Gly Cys Glu Arg Gly Lys Ile Leu Phe Val Ser Lys Ser
                165                 170                 175

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

Leu Phe Asp Phe Leu His Pro Lys Asp Val Ala Lys Val Lys Glu Gln
        195                 200                 205

Leu Ser Ser Phe Asp Ile Ser Pro Arg Glu Lys Leu Ile Asp Ala Lys
    210                 215                 220

Thr Gly Leu Gln Val His Ser Asn Leu His Ala Gly Arg Thr Arg Val
225                 230                 235                 240

Tyr Ser Gly Ser Arg Arg Ser Phe Phe Cys Arg Ile Lys Ser Cys Lys
                245                 250                 255

Ile Ser Val Lys Glu Glu His Gly Cys Leu Pro Asn Ser Lys Lys Lys
            260                 265                 270

Glu His Arg Lys Phe Tyr Thr Ile His Cys Thr Gly Tyr Leu Arg Ser
        275                 280                 285

Trp Pro Pro Asn Ile Val Gly Met Glu Glu Glu Arg Asn Ser Lys Lys
    290                 295                 300

Asp Asn Ser Asn Phe Thr Cys Leu Val Ala Ile Gly Arg Leu Gln Pro
305                 310                 315                 320

Tyr Ile Val Pro Gln Asn Ser Gly Glu Ile Asn Val Lys Pro Thr Glu
                325                 330                 335

Phe Ile Thr Arg Phe Ala Val Asn Gly Lys Phe Val Tyr Val Asp Gln
            340                 345                 350

Arg Ala Thr Ala Ile Leu Gly Tyr Leu Pro Gln Glu Leu Leu Gly Thr
        355                 360                 365

Ser Cys Tyr Glu Tyr Phe His Gln Asp Asp His Asn Asn Leu Thr Asp
    370                 375                 380

Lys His Lys Ala Val Leu Gln Ser Lys Glu Lys Ile Leu Thr Asp Ser
385                 390                 395                 400

Tyr Lys Phe Arg Ala Lys Asp Gly Ser Phe Val Thr Leu Lys Ser Gln
                405                 410                 415

Trp Phe Ser Phe Thr Asn Pro Trp Thr Lys Glu Leu Glu Tyr Ile Val
            420                 425                 430

Ser Val Asn Thr Leu Val Leu Gly His Ser Glu Pro Gly Glu Ala Ser
        435                 440                 445

Phe Leu Pro Cys Ser Ser Gln Ser Ser Glu Glu Ser Ser Arg Gln Ser
    450                 455                 460

Cys Met Ser Val Pro Gly Met Ser Thr Gly Thr Val Leu Gly Ala Gly
465                 470                 475                 480
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Ser Ile Gly Thr Asp Ile Ala Asn Glu Ile Leu Asp Leu Gln Arg Leu
                485                 490                 495

Gln Ser Ser Ser Tyr Leu Asp Asp Ser Ser Pro Thr Gly Leu Met Lys
            500                 505                 510

Asp Thr His Thr Val Asn Cys Arg Ser Met Ser Asn Lys Glu Leu Phe
        515                 520                 525

Pro Pro Ser Pro Ser Glu Met Gly Glu Leu Glu Ala Thr Arg Gln Asn
    530                 535                 540

Gln Ser Thr Val Ala Val His Ser His Glu Pro Leu Leu Ser Asp Gly
545                 550                 555                 560

Ala Gln Leu Asp Phe Asp Ala Leu Cys Asp Asn Asp Asp Thr Ala Met
                565                 570                 575

Ala Ala Phe Met Asn Tyr Leu Glu Ala Glu Gly Gly Leu Gly Asp Pro
            580                 585                 590

Gly Asp Phe Ser Asp Ile Gln Trp Thr Leu
        595                 600


<210> SEQ ID NO 79
<211> LENGTH: 745
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 79

Met Ile Arg Gly Arg Asn Ser Ala Thr Ser Ala Asp Glu Gln Pro His
1               5                   10                  15

Ile Gly Asn Tyr Arg Leu Leu Lys Thr Ile Gly Lys Gly Asn Phe Ala
            20                  25                  30

Lys Val Lys Leu Ala Arg His Ile Leu Thr Gly Lys Glu Val Ala Val
        35                  40                  45

Lys Ile Ile Asp Lys Thr Gln Leu Asn Ser Ser Ser Leu Gln Lys Leu
    50                  55                  60

Phe Arg Glu Val Arg Ile Met Lys Val Leu Asn His Pro Asn Ile Val
65                  70                  75                  80

Lys Leu Phe Glu Val Ile Glu Thr Glu Lys Thr Leu Tyr Leu Val Met
                85                  90                  95

Glu Tyr Ala Ser Gly Gly Glu Val Phe Asp Tyr Leu Val Ala His Gly
            100                 105                 110

Arg Met Lys Glu Lys Glu Ala Arg Ala Lys Phe Arg Gln Ile Val Ser
        115                 120                 125

Ala Val Gln Tyr Cys His Gln Lys Phe Ile Val His Arg Asp Leu Lys
    130                 135                 140

Ala Glu Asn Leu Leu Leu Asp Ala Asp Met Asn Ile Lys Ile Ala Asp
145                 150                 155                 160

Phe Gly Phe Ser Asn Glu Phe Thr Phe Gly Asn Lys Leu Asp Thr Phe
                165                 170                 175

Cys Gly Ser Pro Pro Tyr Ala Ala Pro Glu Leu Phe Gln Gly Lys Lys
            180                 185                 190

Tyr Asp Gly Pro Glu Val Asp Val Trp Ser Leu Gly Val Ile Leu Tyr
        195                 200                 205

Thr Leu Val Ser Gly Ser Leu Pro Phe Asp Gly Gln Asn Leu Lys Glu
    210                 215                 220

Leu Arg Glu Arg Val Leu Arg Gly Lys Tyr Arg Ile Pro Phe Tyr Met
225                 230                 235                 240

Ser Thr Asp Cys Glu Asn Leu Leu Lys Lys Phe Leu Ile Leu Asn Pro
                245                 250                 255
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Ser Lys Arg Gly Thr Leu Glu Gln Ile Met Lys Asp Arg Trp Met Asn
            260                 265                 270

Val Gly His Glu Asp Asp Glu Leu Lys Pro Tyr Val Glu Pro Leu Pro
        275                 280                 285

Asp Tyr Lys Asp Pro Arg Arg Thr Glu Leu Met Val Ser Met Gly Tyr
    290                 295                 300

Thr Arg Glu Glu Ile Gln Asp Ser Leu Val Gly Gln Arg Tyr Asn Glu
305                 310                 315                 320

Val Met Ala Thr Tyr Leu Leu Leu Gly Tyr Lys Ser Ser Glu Leu Glu
                325                 330                 335

Gly Asp Thr Ile Thr Leu Lys Pro Arg Pro Ser Ala Asp Leu Thr Asn
            340                 345                 350

Ser Ser Ala Gln Phe Pro Ser His Lys Val Gln Arg Ser Val Ser Ala
        355                 360                 365

Asn Pro Lys Gln Arg Arg Phe Ser Asp Gln Ala Gly Pro Ala Ile Pro
    370                 375                 380

Thr Ser Asn Ser Tyr Ser Lys Lys Thr Gln Ser Asn Asn Ala Glu Asn
385                 390                 395                 400

Lys Arg Pro Glu Glu Asp Arg Glu Ser Gly Arg Lys Ala Ser Ser Thr
                405                 410                 415

Ala Lys Val Pro Ala Ser Pro Leu Pro Gly Leu Glu Arg Lys Lys Thr
            420                 425                 430

Thr Pro Thr Pro Ser Thr Asn Ser Val Leu Ser Thr Ser Thr Asn Arg
        435                 440                 445

Ser Arg Asn Ser Pro Leu Leu Glu Arg Ala Ser Leu Gly Gln Ala Ser
    450                 455                 460

Ile Gln Asn Gly Lys Asp Ser Leu Thr Met Pro Gly Ser Arg Ala Ser
465                 470                 475                 480

Thr Ala Ser Ala Ser Ala Ala Val Ser Ala Ala Arg Pro Arg Gln His
                485                 490                 495

Gln Lys Ser Met Ser Ala Ser Val His Pro Asn Lys Ala Ser Gly Leu
            500                 505                 510

Pro Pro Thr Glu Ser Asn Cys Glu Val Pro Arg Pro Ser Thr Ala Pro
        515                 520                 525

Gln Arg Val Pro Val Ala Ser Pro Ser Ala His Asn Ile Ser Ser Ser
    530                 535                 540

Gly Gly Ala Pro Asp Arg Thr Asn Phe Pro Arg Gly Val Ser Ser Arg
545                 550                 555                 560

Ser Thr Phe His Ala Gly Gln Leu Arg Gln Val Arg Asp Gln Gln Asn
                565                 570                 575

Leu Pro Tyr Gly Val Thr Pro Ala Ser Pro Ser Gly His Ser Gln Gly
            580                 585                 590

Arg Arg Gly Ala Ser Gly Ser Ile Phe Ser Lys Phe Thr Ser Lys Phe
        595                 600                 605

Val Arg Arg Asn Leu Asn Glu Pro Glu Ser Lys Asp Arg Val Glu Thr
    610                 615                 620

Leu Arg Pro His Val Val Gly Ser Gly Gly Asn Asp Lys Glu Lys Glu
625                 630                 635                 640

Glu Phe Arg Glu Ala Lys Pro Arg Ser Leu Arg Phe Thr Trp Ser Met
                645                 650                 655

Lys Thr Thr Ser Ser Met Glu Pro Asn Glu Met Met Arg Glu Ile Arg
            660                 665                 670

Lys Val Leu Asp Ala Asn Ser Cys Gln Ser Glu Leu His Glu Lys Tyr
        675                 680                 685
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Met Leu Leu Cys Met His Gly Thr Pro Gly His Glu Asp Phe Val Gln
    690                 695                 700

Trp Glu Met Glu Val Cys Lys Leu Pro Arg Leu Ser Leu Asn Gly Val
705                 710                 715                 720

Arg Phe Lys Arg Ile Ser Gly Thr Ser Met Ala Phe Lys Asn Ile Ala
                725                 730                 735

Ser Lys Ile Ala Asn Glu Leu Lys Leu
            740                 745


<210> SEQ ID NO 80
<211> LENGTH: 319
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 80

Met Ser Val Gly Phe Ile Gly Ala Gly Gln Leu Ala Phe Ala Leu Ala
1               5                   10                  15

Lys Gly Phe Thr Ala Ala Gly Val Leu Ala Ala His Lys Ile Met Ala
            20                  25                  30

Ser Ser Pro Asp Met Asp Leu Ala Thr Val Ser Ala Leu Arg Lys Met
        35                  40                  45

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

Val Leu Phe Leu Ala Val Lys Pro His Ile Ile Pro Phe Ile Leu Asp
65                  70                  75                  80

Glu Ile Gly Ala Asp Ile Glu Asp Arg His Ile Val Val Ser Cys Ala
                85                  90                  95

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

Pro Ala Pro Arg Val Ile Arg Cys Met Thr Asn Thr Pro Val Val Val
        115                 120                 125

Arg Glu Gly Ala Thr Val Tyr Ala Thr Gly Thr His Ala Gln Val Glu
    130                 135                 140

Asp Gly Arg Leu Met Glu Gln Leu Leu Ser Thr Val Gly Phe Cys Thr
145                 150                 155                 160

Glu Val Glu Glu Asp Leu Ile Asp Ala Val Thr Gly Leu Ser Gly Ser
                165                 170                 175

Gly Pro Ala Tyr Ala Phe Thr Ala Leu Asp Ala Leu Ala Asp Gly Gly
            180                 185                 190

Val Lys Met Gly Leu Pro Arg Arg Leu Ala Val Arg Leu Gly Ala Gln
        195                 200                 205

Ala Leu Leu Gly Ala Ala Lys Met Leu Leu His Ser Glu Gln His Pro
    210                 215                 220

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

Ala Leu His Val Leu Glu Ser Gly Gly Phe Arg Ser Leu Leu Ile Asn
                245                 250                 255

Ala Val Glu Ala Ser Cys Ile Arg Thr Arg Glu Leu Gln Ser Met Ala
            260                 265                 270

Asp Gln Glu Gln Val Ser Pro Ala Ala Ile Lys Lys Thr Ile Leu Asp
        275                 280                 285

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

His Thr Lys Leu Leu Pro Arg Ser Leu Ala Pro Ala Gly Lys Asp
305                 310                 315
```

<210> SEQ ID NO 81
<211> LENGTH: 148
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 81

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

Pro Thr Ala Ala Gln Ala Lys Ser Lys Gln Ala Ile Leu Ala Ala Gln
20 25 30

Arg Arg Gly Glu Asp Val Glu Thr Ser Lys Lys Trp Ala Ala Gly Gln
35 40 45

Asn Lys Gln His Ser Ile Thr Lys Asn Thr Ala Lys Leu Asp Arg Glu
50 55 60

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

Ile Gln Gln Gly Arg Gln Ser Lys Gly Leu Thr Gln Lys Asp Leu Ala
85 90 95

Thr Lys Ile Asn Glu Lys Pro Gln Val Ile Ala Asp Tyr Glu Ser Gly
100 105 110

Arg Ala Ile Pro Asn Asn Gln Val Leu Gly Lys Ile Glu Arg Ala Ile
115 120 125

Gly Leu Lys Leu Arg Gly Lys Asp Ile Gly Lys Pro Ile Glu Lys Gly
130 135 140

Pro Arg Ala Lys
145

<210> SEQ ID NO 82
<211> LENGTH: 375
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 82

Met Asp Asp Asp Ile Ala Ala Leu Val Val Asp Asn Gly Ser Gly Met
1 5 10 15

Cys Lys Ala Gly Phe Ala Gly Asp Asp Ala Pro Arg Ala Val Phe Pro
20 25 30

Ser Ile Val Gly Arg Pro Arg His Gln Gly Val Met Val Gly Met Gly
35 40 45

Gln Lys Asp Ser Tyr Val Gly Asp Glu Ala Gln Ser Lys Arg Gly Ile
50 55 60

Leu Thr Leu Lys Tyr Pro Ile Glu His Gly Ile Val Thr Asn Trp Asp
65 70 75 80

Asp Met Glu Lys Ile Trp His His Thr Phe Tyr Asn Glu Leu Arg Val
85 90 95

Ala Pro Glu Glu His Pro Val Leu Leu Thr Glu Ala Pro Leu Asn Pro
100 105 110

Lys Ala Asn Arg Glu Lys Met Thr Gln Ile Met Phe Glu Thr Phe Asn
115 120 125

Thr Pro Ala Met Tyr Val Ala Ile Gln Ala Val Leu Ser Leu Tyr Ala
130 135 140

Ser Gly Arg Thr Thr Gly Ile Val Met Asp Ser Gly Asp Gly Val Thr
145 150 155 160

His Thr Val Pro Ile Tyr Glu Gly Tyr Ala Leu Pro His Ala Ile Leu
165 170 175

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Arg Leu Asp Leu Ala Gly Arg Asp Leu Thr Asp Tyr Leu Met Lys Ile
            180                 185                 190

Leu Thr Glu Arg Gly Tyr Ser Phe Thr Thr Thr Ala Glu Arg Glu Ile
        195                 200                 205

Val Arg Asp Ile Lys Glu Lys Leu Cys Tyr Val Ala Leu Asp Phe Glu
    210                 215                 220

Gln Glu Met Ala Thr Ala Ala Ser Ser Ser Ser Leu Glu Lys Ser Tyr
225                 230                 235                 240

Glu Leu Pro Asp Gly Gln Val Ile Thr Ile Gly Asn Glu Arg Phe Arg
                245                 250                 255

Cys Pro Glu Ala Leu Phe Gln Pro Ser Phe Leu Gly Met Glu Ser Cys
            260                 265                 270

Gly Ile His Glu Thr Thr Phe Asn Ser Ile Met Lys Cys Asp Val Asp
        275                 280                 285

Ile Arg Lys Asp Leu Tyr Ala Asn Thr Val Leu Ser Gly Gly Thr Thr
    290                 295                 300

Met Tyr Pro Gly Ile Ala Asp Arg Met Gln Lys Glu Ile Thr Ala Leu
305                 310                 315                 320

Ala Pro Ser Thr Met Lys Ile Lys Ile Ile Ala Pro Pro Glu Arg Lys
                325                 330                 335

Tyr Ser Val Trp Ile Gly Gly Ser Ile Leu Ala Ser Leu Ser Thr Phe
            340                 345                 350

Gln Gln Met Trp Ile Ser Lys Gln Glu Tyr Asp Glu Ser Gly Pro Ser
        355                 360                 365

Ile Val His Arg Lys Cys Phe
    370                 375


<210> SEQ ID NO 83
<211> LENGTH: 268
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 83

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

Glu Ser Ile Leu Ala His Arg Glu Asn Met Arg Gln Met Ile Arg Ser
            20                  25                  30

Phe Ser Glu Pro Phe Gly Arg Asp Leu Leu Ser Ile Ser Asp Gly Arg
        35                  40                  45

Gly Arg Ala His Asn Arg Arg Gly His Asn Asp Gly Glu Asp Ser Leu
    50                  55                  60

Thr His Thr Asp Val Ser Ser Phe Gln Thr Met Asp Gln Met Val Ser
65                  70                  75                  80

Asn Met Arg Asn Tyr Met Gln Lys Leu Glu Arg Asn Phe Gly Gln Leu
                85                  90                  95

Ser Val Asp Pro Asn Gly His Ser Phe Cys Ser Ser Ser Val Met Thr
            100                 105                 110

Tyr Ser Lys Ile Gly Asp Glu Pro Pro Lys Val Phe Gln Ala Ser Thr
        115                 120                 125

Gln Thr Arg Arg Ala Pro Gly Gly Ile Lys Glu Thr Arg Lys Ala Met
    130                 135                 140

Arg Asp Ser Asp Ser Gly Leu Glu Lys Met Ala Ile Gly His His Ile
145                 150                 155                 160

His Asp Arg Ala His Val Ile Lys Lys Ser Lys Asn Lys Lys Thr Gly
                165                 170                 175
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```
Asp Glu Glu Val Asn Gln Glu Phe Ile Asn Met Asn Glu Ser Asp Ala
            180                 185                 190

His Ala Phe Asp Glu Glu Trp Gln Ser Glu Val Leu Lys Tyr Lys Pro
        195                 200                 205

Gly Arg His Asn Leu Gly Asn Thr Arg Met Arg Ser Val Gly His Glu
    210                 215                 220

Asn Pro Gly Ser Arg Glu Leu Lys Arg Arg Glu Lys Pro Gln Gln Ser
225                 230                 235                 240

Pro Ala Ile Glu His Gly Arg Arg Ser Asn Val Leu Gly Asp Lys Leu
                245                 250                 255

His Ile Lys Gly Ser Ser Val Lys Ser Asn Lys Lys
            260                 265


<210> SEQ ID NO 84
<211> LENGTH: 837
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 84

Met Ala Glu Pro Ser Gln Ala Pro Thr Pro Ala Pro Ala Ala Gln Pro
1               5                   10                  15

Arg Pro Leu Gln Ser Pro Ala Pro Ala Pro Thr Pro Thr Pro Ala Pro
            20                  25                  30

Ser Pro Ala Ser Ala Pro Ile Pro Thr Pro Thr Pro Ala Pro Ala Pro
        35                  40                  45

Ala Pro Ala Ala Ala Pro Ala Gly Ser Thr Gly Thr Gly Gly Pro Gly
    50                  55                  60

Val Gly Ser Gly Gly Ala Gly Ser Gly Gly Asp Pro Ala Arg Pro Gly
65                  70                  75                  80

Leu Ser Gln Gln Gln Arg Ala Ser Gln Arg Lys Ala Gln Val Arg Gly
                85                  90                  95

Leu Pro Arg Ala Lys Lys Leu Glu Lys Leu Gly Val Phe Ser Ala Cys
            100                 105                 110

Lys Ala Asn Gly Thr Cys Lys Cys Asn Gly Trp Lys Asn Pro Lys Pro
        115                 120                 125

Pro Thr Ala Pro Arg Ile Asp Leu Gln Gln Pro Ala Ala Asn Leu Ser
    130                 135                 140

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

Leu Glu Asn Val Ser Glu Asp Glu Ile Asn Arg Leu Leu Gly Met Val
                165                 170                 175

Val Asp Val Glu Asn Leu Phe Met Ser Val His Lys Glu Glu Asp Thr
            180                 185                 190

Asp Thr Lys Gln Val Tyr Phe Tyr Leu Phe Lys Leu Leu Arg Lys Cys
        195                 200                 205

Ile Leu Gln Met Thr Arg Pro Val Val Glu Gly Ser Leu Gly Ser Pro
    210                 215                 220

Pro Phe Glu Lys Pro Asn Ile Glu Gln Gly Val Leu Asn Phe Val Gln
225                 230                 235                 240

Tyr Lys Phe Ser His Leu Ala Pro Arg Glu Arg Gln Thr Met Phe Glu
                245                 250                 255

Leu Ser Lys Met Phe Leu Leu Cys Leu Asn Tyr Trp Glu Leu Glu Thr
            260                 265                 270

Pro Ala Gln Phe Arg Gln Arg Ser Gln Ala Glu Asp Val Ala Thr Tyr
        275                 280                 285
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```
Lys Val Asn Tyr Thr Arg Trp Leu Cys Tyr Cys His Val Pro Gln Ser
    290                 295                 300

Cys Asp Ser Leu Pro Arg Tyr Glu Thr Thr His Val Phe Gly Arg Ser
305                 310                 315                 320

Leu Leu Arg Ser Ile Phe Thr Val Thr Arg Arg Gln Leu Leu Glu Lys
                325                 330                 335

Phe Arg Val Glu Lys Asp Lys Leu Val Pro Glu Lys Arg Thr Leu Ile
            340                 345                 350

Leu Thr His Phe Pro Lys Phe Leu Ser Met Leu Glu Glu Glu Ile Tyr
        355                 360                 365

Gly Ala Asn Ser Pro Ile Trp Glu Ser Gly Phe Thr Met Pro Pro Ser
    370                 375                 380

Glu Gly Thr Gln Leu Val Pro Arg Pro Ala Ser Val Ser Ala Ala Val
385                 390                 395                 400

Val Pro Ser Thr Pro Ile Phe Ser Pro Ser Met Gly Gly Gly Ser Asn
                405                 410                 415

Ser Ser Leu Ser Leu Asp Ser Ala Gly Ala Glu Pro Met Pro Gly Glu
            420                 425                 430

Lys Arg Thr Leu Pro Glu Asn Leu Thr Leu Glu Asp Ala Lys Arg Leu
        435                 440                 445

Arg Val Met Gly Asp Ile Pro Met Glu Leu Val Asn Glu Val Met Leu
    450                 455                 460

Thr Ile Thr Asp Pro Ala Ala Met Leu Gly Pro Glu Thr Ser Leu Leu
465                 470                 475                 480

Ser Ala Asn Ala Ala Arg Asp Glu Thr Ala Arg Leu Glu Glu Arg Arg
                485                 490                 495

Gly Ile Ile Glu Phe His Val Ile Gly Asn Ser Leu Thr Pro Lys Ala
            500                 505                 510

Asn Arg Arg Val Leu Leu Trp Leu Val Gly Leu Gln Asn Val Phe Ser
        515                 520                 525

His Gln Leu Pro Arg Met Pro Lys Glu Tyr Ile Ala Arg Leu Val Phe
    530                 535                 540

Asp Pro Lys His Lys Thr Leu Ala Leu Ile Lys Asp Gly Arg Val Ile
545                 550                 555                 560

Gly Gly Ile Cys Phe Arg Met Phe Pro Thr Gln Gly Phe Thr Glu Ile
                565                 570                 575

Val Phe Cys Ala Val Thr Ser Asn Glu Gln Val Lys Gly Tyr Gly Thr
            580                 585                 590

His Leu Met Asn His Leu Lys Glu Tyr His Ile Lys His Asn Ile Leu
        595                 600                 605

Tyr Phe Leu Thr Tyr Ala Asp Glu Tyr Ala Ile Gly Tyr Phe Lys Lys
    610                 615                 620

Gln Gly Phe Ser Lys Asp Ile Lys Val Pro Lys Ser Arg Tyr Leu Gly
625                 630                 635                 640

Tyr Ile Lys Asp Tyr Glu Gly Ala Thr Leu Met Glu Cys Glu Leu Asn
                645                 650                 655

Pro Arg Ile Pro Tyr Thr Glu Leu Ser His Ile Ile Lys Lys Gln Lys
            660                 665                 670

Glu Ile Ile Lys Lys Leu Ile Glu Arg Lys Gln Ala Gln Ile Arg Lys
        675                 680                 685

Val Tyr Pro Gly Leu Ser Cys Phe Lys Glu Gly Val Arg Gln Ile Pro
    690                 695                 700

Val Glu Ser Val Pro Gly Ile Arg Glu Thr Gly Trp Lys Pro Leu Gly
705                 710                 715                 720
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```
Lys Glu Lys Gly Lys Glu Leu Lys Asp Pro Asp Gln Leu Tyr Thr Thr
                725                 730                 735

Leu Lys Asn Leu Leu Ala Gln Ile Lys Ser His Pro Ser Ala Trp Pro
            740                 745                 750

Phe Met Glu Pro Val Lys Lys Ser Glu Ala Pro Asp Tyr Tyr Glu Val
        755                 760                 765

Ile Arg Phe Pro Ile Asp Leu Lys Thr Met Thr Glu Arg Leu Arg Ser
    770                 775                 780

Arg Tyr Tyr Val Thr Arg Lys Leu Phe Val Ala Asp Leu Gln Arg Val
785                 790                 795                 800

Ile Ala Asn Cys Arg Glu Tyr Asn Pro Pro Asp Ser Glu Tyr Cys Arg
                805                 810                 815

Cys Ala Ser Ala Leu Glu Lys Phe Phe Tyr Phe Lys Leu Lys Glu Gly
            820                 825                 830

Gly Leu Ile Asp Lys
        835


<210> SEQ ID NO 85
<211> LENGTH: 483
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 85

Met Lys Glu Glu Lys Glu His Arg Pro Lys Glu Lys Arg Val Thr Leu
1               5                   10                  15

Leu Thr Pro Ala Gly Ala Thr Gly Ser Gly Gly Gly Thr Ser Gly Asp
            20                  25                  30

Ser Ser Lys Gly Glu Asp Lys Gln Asp Arg Asn Lys Glu Lys Lys Glu
        35                  40                  45

Ala Leu Ser Lys Val Val Ile Arg Arg Leu Pro Pro Thr Leu Thr Lys
    50                  55                  60

Glu Gln Leu Gln Glu His Leu Gln Pro Met Pro Glu His Asp Tyr Phe
65                  70                  75                  80

Glu Phe Phe Ser Asn Asp Thr Ser Leu Tyr Pro His Met Tyr Ala Arg
                85                  90                  95

Ala Tyr Ile Asn Phe Lys Asn Gln Glu Asp Ile Ile Leu Phe Arg Asp
            100                 105                 110

Arg Phe Asp Gly Tyr Val Phe Leu Asp Asn Lys Gly Gln Glu Tyr Pro
        115                 120                 125

Ala Ile Val Glu Phe Ala Pro Phe Gln Lys Ala Ala Lys Lys Lys Thr
    130                 135                 140

Lys Lys Arg Asp Thr Lys Val Gly Thr Ile Asp Asp Asp Pro Glu Tyr
145                 150                 155                 160

Arg Lys Phe Leu Glu Ser Tyr Ala Thr Asp Asn Glu Lys Met Thr Ser
                165                 170                 175

Thr Pro Glu Thr Leu Leu Glu Glu Ile Glu Ala Lys Asn Arg Glu Leu
            180                 185                 190

Ile Ala Lys Lys Thr Thr Pro Leu Leu Ser Phe Leu Lys Asn Lys Gln
        195                 200                 205

Arg Met Arg Glu Glu Lys Arg Glu Glu Arg Arg Arg Arg Glu Ile Glu
    210                 215                 220

Arg Lys Arg Gln Arg Glu Glu Glu Arg Arg Lys Trp Lys Glu Glu Glu
225                 230                 235                 240

Lys Arg Lys Arg Lys Asp Ile Glu Lys Leu Lys Lys Ile Asp Arg Ile
                245                 250                 255
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```
Pro Glu Arg Asp Lys Leu Lys Asp Glu Pro Lys Ile Lys Val His Arg
            260                 265                 270

Phe Leu Leu Gln Ala Val Asn Gln Lys Asn Leu Leu Lys Lys Pro Glu
        275                 280                 285

Lys Gly Asp Glu Lys Glu Leu Asp Lys Arg Glu Lys Ala Lys Lys Leu
    290                 295                 300

Asp Lys Glu Asn Leu Ser Asp Glu Arg Ala Ser Gly Gln Ser Cys Thr
305                 310                 315                 320

Leu Pro Lys Arg Ser Asp Ser Glu Leu Lys Asp Glu Lys Pro Lys Arg
                325                 330                 335

Pro Glu Asp Glu Ser Gly Arg Asp Tyr Arg Glu Arg Glu Arg Glu Tyr
            340                 345                 350

Glu Arg Asp Gln Glu Arg Ile Leu Arg Glu Arg Glu Arg Leu Lys Arg
        355                 360                 365

Gln Glu Glu Glu Arg Arg Arg Gln Lys Glu Arg Tyr Glu Lys Glu Lys
    370                 375                 380

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

Arg Asp Lys Gly Lys Lys Ala Glu Ser Thr Glu Ser Ile Gly Ser Ser
                405                 410                 415

Glu Lys Thr Glu Lys Lys Glu Glu Val Val Lys Arg Asp Arg Ile Arg
            420                 425                 430

Asn Lys Asp Arg Pro Ala Met Gln Leu Tyr Gln Pro Gly Ala Arg Ser
        435                 440                 445

Arg Asn Arg Leu Cys Pro Pro Asp Asp Ser Thr Lys Ser Gly Asp Ser
    450                 455                 460

Ala Ala Glu Arg Lys Gln Glu Ser Gly Ile Ser His Arg Lys Glu Gly
465                 470                 475                 480

Gly Glu Glu
```

<210> SEQ ID NO 86
<211> LENGTH: 426
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 86

```
Met Ala Asn Asp Ser Gly Gly Pro Gly Gly Pro Ser Pro Ser Glu Arg
1               5                   10                  15

Asp Arg Gln Tyr Cys Glu Leu Cys Gly Lys Met Glu Asn Leu Leu Arg
            20                  25                  30

Cys Ser Arg Cys Arg Ser Ser Phe Tyr Cys Cys Lys Glu His Gln Arg
        35                  40                  45

Gln Asp Trp Lys Lys His Lys Leu Val Cys Gln Gly Ser Glu Gly Ala
    50                  55                  60

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

Ala Ala Val Pro Pro Pro Arg Ala Gly Ala Arg Glu Pro Arg Lys Ala
                85                  90                  95

Ala Ala Arg Arg Asp Asn Ala Ser Gly Asp Ala Ala Lys Gly Lys Val
            100                 105                 110

Lys Ala Lys Pro Pro Ala Asp Pro Ala Ala Ala Ala Ser Pro Cys Arg
        115                 120                 125

Ala Ala Ala Gly Gly Gln Gly Ser Ala Val Ala Ala Glu Ala Glu Pro
    130                 135                 140
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Gly Lys Glu Glu Pro Pro Ala Arg Ser Ser Leu Phe Gln Glu Lys Ala
145                 150                 155                 160

Asn Leu Tyr Pro Pro Ser Asn Thr Pro Gly Asp Ala Leu Ser Pro Gly
                165                 170                 175

Gly Gly Leu Arg Pro Asn Gly Gln Thr Lys Pro Leu Pro Ala Leu Lys
            180                 185                 190

Leu Ala Leu Glu Tyr Ile Val Pro Cys Met Asn Lys His Gly Ile Cys
        195                 200                 205

Val Val Asp Asp Phe Leu Gly Lys Glu Thr Gly Gln Gln Ile Gly Asp
    210                 215                 220

Glu Val Arg Ala Leu His Asp Thr Gly Lys Phe Thr Asp Gly Gln Leu
225                 230                 235                 240

Val Ser Gln Lys Ser Asp Ser Ser Lys Asp Ile Arg Gly Asp Lys Ile
                245                 250                 255

Thr Trp Ile Glu Gly Lys Glu Pro Gly Cys Glu Thr Ile Gly Leu Leu
            260                 265                 270

Met Ser Ser Met Asp Asp Leu Ile Arg His Cys Asn Gly Lys Leu Gly
        275                 280                 285

Ser Tyr Lys Ile Asn Gly Arg Thr Lys Ala Met Val Ala Cys Tyr Pro
    290                 295                 300

Gly Asn Gly Thr Gly Tyr Val Arg His Val Asp Asn Pro Asn Gly Asp
305                 310                 315                 320

Gly Arg Cys Val Thr Cys Ile Tyr Tyr Leu Asn Lys Asp Trp Asp Ala
                325                 330                 335

Lys Val Ser Gly Gly Ile Leu Arg Ile Phe Pro Glu Gly Lys Ala Gln
            340                 345                 350

Phe Ala Asp Ile Glu Pro Lys Phe Asp Arg Leu Leu Phe Phe Trp Ser
        355                 360                 365

Asp Arg Arg Asn Pro His Glu Val Gln Pro Ala Tyr Ala Thr Arg Tyr
    370                 375                 380

Ala Ile Thr Val Trp Tyr Phe Asp Ala Asp Glu Arg Ala Arg Ala Lys
385                 390                 395                 400

Val Lys Tyr Leu Thr Gly Glu Lys Gly Val Arg Val Glu Leu Asn Lys
                405                 410                 415

Pro Ser Asp Ser Val Gly Lys Asp Val Phe
            420                 425


<210> SEQ ID NO 87
<211> LENGTH: 1320
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 87

Met Ser Gly Gly Ala Ser Ala Thr Gly Pro Arg Arg Gly Pro Pro Gly
1               5                   10                  15

Leu Glu Asp Thr Thr Ser Lys Lys Lys Gln Lys Asp Arg Ala Asn Gln
            20                  25                  30

Glu Ser Lys Asp Gly Asp Pro Arg Lys Glu Thr Gly Ser Arg Tyr Val
        35                  40                  45

Ala Gln Ala Gly Leu Glu Pro Leu Ala Ser Gly Asp Pro Ser Ala Ser
    50                  55                  60

Ala Ser His Ala Ala Gly Ile Thr Gly Ser Arg His Arg Thr Arg Leu
65                  70                  75                  80

Phe Phe Pro Ser Ser Ser Gly Ser Ala Ser Thr Pro Gln Glu Glu Gln
                85                  90                  95
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```
Thr Lys Glu Gly Ala Cys Glu Asp Pro His Asp Leu Leu Ala Thr Pro
            100                 105                 110

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

Val Lys Leu Arg Val Gly Val Gly Pro Leu Gln Leu Glu Asp Val Asp
    130                 135                 140

Ala Ala Phe Thr Asp Thr Asp Cys Val Val Arg Phe Ala Gly Gly Gln
145                 150                 155                 160

Gln Trp Gly Gly Val Phe Tyr Ala Glu Ile Lys Ser Ser Cys Ala Lys
                165                 170                 175

Val Gln Thr Arg Lys Gly Ser Leu Leu His Leu Thr Leu Pro Lys Lys
            180                 185                 190

Val Pro Met Leu Thr Trp Pro Ser Leu Leu Val Glu Ala Asp Glu Gln
        195                 200                 205

Leu Cys Ile Pro Pro Leu Asn Ser Gln Thr Cys Leu Leu Gly Ser Glu
    210                 215                 220

Glu Asn Leu Ala Pro Leu Ala Gly Glu Lys Ala Val Pro Pro Gly Asn
225                 230                 235                 240

Asp Pro Val Ser Pro Ala Met Val Arg Ser Arg Asn Pro Gly Lys Asp
                245                 250                 255

Asp Cys Ala Lys Glu Glu Met Ala Val Ala Ala Asp Ala Ala Thr Leu
            260                 265                 270

Val Asp Glu Pro Glu Ser Met Val Asn Leu Ala Phe Val Lys Asn Asp
        275                 280                 285

Ser Tyr Glu Lys Gly Pro Asp Ser Val Val Val His Val Tyr Val Lys
    290                 295                 300

Glu Ile Cys Arg Asp Thr Ser Arg Val Leu Phe Arg Glu Gln Asp Phe
305                 310                 315                 320

Thr Leu Ile Phe Gln Thr Arg Asp Gly Asn Phe Leu Arg Leu His Pro
                325                 330                 335

Gly Cys Gly Pro His Thr Thr Phe Arg Trp Gln Val Lys Leu Arg Asn
            340                 345                 350

Leu Ile Glu Pro Glu Gln Cys Thr Phe Cys Phe Thr Ala Ser Arg Ile
        355                 360                 365

Asp Ile Cys Leu Arg Lys Arg Gln Ser Gln Arg Trp Gly Gly Leu Glu
    370                 375                 380

Ala Pro Ala Ala Arg Gly Ala Val Gly Gly Ala Lys Val Ala Val Pro
385                 390                 395                 400

Thr Gly Pro Thr Pro Leu Asp Ser Thr Pro Pro Gly Gly Ala Pro His
                405                 410                 415

Pro Leu Thr Gly Gln Glu Glu Ala Arg Ala Val Glu Lys Asp Lys Ser
            420                 425                 430

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

Pro Met Glu His Val Thr Pro Lys Pro Glu Thr His Leu Ala Ser Pro
    450                 455                 460

Lys Pro Thr Cys Met Val Pro Pro Met Pro His Ser Pro Val Ser Gly
465                 470                 475                 480

Asp Ser Val Glu Glu Glu Glu Glu Glu Glu Lys Lys Val Cys Leu Pro
                485                 490                 495

Gly Phe Thr Gly Leu Val Asn Leu Gly Asn Thr Cys Phe Met Asn Ser
            500                 505                 510

Val Ile Gln Ser Leu Ser Asn Thr Arg Glu Leu Arg Asp Phe Phe His
        515                 520                 525
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Asp Arg Ser Phe Glu Ala Glu Ile Asn Tyr Asn Asn Pro Leu Gly Thr
    530                 535                 540

Gly Gly Arg Leu Ala Ile Gly Phe Ala Val Leu Leu Arg Ala Leu Trp
545                 550                 555                 560

Lys Gly Thr His His Ala Phe Gln Pro Ser Lys Leu Lys Ala Ile Val
                565                 570                 575

Ala Ser Lys Ala Ser Gln Phe Thr Gly Tyr Ala Gln His Asp Ala Gln
            580                 585                 590

Glu Phe Met Ala Phe Leu Leu Asp Gly Leu His Glu Asp Leu Asn Arg
        595                 600                 605

Ile Gln Asn Lys Pro Tyr Thr Glu Thr Val Asp Ser Asp Gly Arg Pro
    610                 615                 620

Asp Glu Val Val Ala Glu Glu Ala Trp Gln Arg His Lys Met Arg Asn
625                 630                 635                 640

Asp Ser Phe Ile Val Asp Leu Phe Gln Gly Gln Tyr Lys Ser Lys Leu
                645                 650                 655

Val Cys Pro Val Cys Ala Lys Val Ser Ile Thr Phe Asp Pro Phe Leu
            660                 665                 670

Tyr Leu Pro Val Pro Leu Pro Gln Lys Gln Lys Val Leu Pro Val Phe
        675                 680                 685

Tyr Phe Ala Arg Glu Pro His Ser Lys Pro Ile Lys Phe Leu Val Ser
    690                 695                 700

Val Ser Lys Glu Asn Ser Thr Ala Ser Glu Val Leu Asp Ser Leu Ser
705                 710                 715                 720

Gln Ser Val His Val Lys Pro Glu Asn Leu Arg Leu Ala Glu Val Ile
                725                 730                 735

Lys Asn Arg Phe His Arg Val Phe Leu Pro Ser His Ser Leu Asp Thr
            740                 745                 750

Val Ser Pro Ser Asp Thr Leu Leu Cys Phe Glu Leu Leu Ser Ser Glu
        755                 760                 765

Leu Ala Lys Glu Arg Val Val Val Leu Glu Val Gln Gln Arg Pro Gln
    770                 775                 780

Val Pro Ser Val Pro Ile Ser Lys Cys Ala Ala Cys Gln Arg Lys Gln
785                 790                 795                 800

Gln Ser Glu Asp Glu Lys Leu Lys Arg Cys Thr Arg Cys Tyr Arg Val
                805                 810                 815

Gly Tyr Cys Asn Gln Leu Cys Gln Lys Thr His Trp Pro Asp His Lys
            820                 825                 830

Gly Leu Cys Arg Pro Glu Asn Ile Gly Tyr Pro Phe Leu Val Ser Val
        835                 840                 845

Pro Ala Ser Arg Leu Thr Tyr Ala Arg Leu Ala Gln Leu Leu Glu Gly
    850                 855                 860

Tyr Ala Arg Tyr Ser Val Ser Val Phe Gln Pro Pro Phe Gln Pro Gly
865                 870                 875                 880

Arg Met Ala Leu Glu Ser Gln Ser Pro Gly Cys Thr Thr Leu Leu Ser
                885                 890                 895

Thr Gly Ser Leu Glu Ala Gly Asp Ser Glu Arg Asp Pro Ile Gln Pro
            900                 905                 910

Pro Glu Leu Gln Leu Val Thr Pro Met Ala Glu Gly Asp Thr Gly Leu
        915                 920                 925

Pro Arg Val Trp Ala Ala Pro Asp Arg Gly Pro Val Pro Ser Thr Ser
    930                 935                 940

Gly Ile Ser Ser Glu Met Leu Ala Ser Gly Pro Ile Glu Val Gly Ser
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945                 950                 955                 960

Leu Pro Ala Gly Glu Arg Val Ser Arg Pro Glu Ala Ala Val Pro Gly
                965                 970                 975

Tyr Gln His Pro Ser Glu Ala Met Asn Ala His Thr Pro Gln Phe Phe
            980                 985                 990

Ile Tyr Lys Ile Asp Ser Ser Asn  Arg Glu Gln Arg Leu  Glu Asp Lys
        995                 1000                1005

Gly Asp  Thr Pro Leu Glu Leu  Gly Asp Asp Cys Ser  Leu Ala Leu
    1010                1015                1020

Val Trp  Arg Asn Asn Glu Arg  Leu Gln Glu Phe Val  Leu Val Ala
    1025                1030                1035

Ser Lys  Glu Leu Glu Cys Ala  Glu Asp Pro Gly Ser  Ala Gly Glu
    1040                1045                1050

Ala Ala  Arg Ala Gly His Phe  Thr Leu Asp Gln Cys  Leu Asn Leu
    1055                1060                1065

Phe Thr  Arg Pro Glu Val Leu  Ala Pro Glu Glu Ala  Trp Tyr Cys
    1070                1075                1080

Pro Gln  Cys Lys Gln His Arg  Glu Ala Ser Lys Gln  Leu Leu Leu
    1085                1090                1095

Trp Arg  Leu Pro Asn Val Leu  Ile Val Gln Leu Lys  Arg Phe Ser
    1100                1105                1110

Phe Arg  Ser Phe Ile Trp Arg  Asp Lys Ile Asn Asp  Leu Val Glu
    1115                1120                1125

Phe Pro  Val Arg Asn Leu Asp  Leu Ser Lys Phe Cys  Ile Gly Gln
    1130                1135                1140

Lys Glu  Glu Gln Leu Pro Ser  Tyr Asp Leu Tyr Ala  Val Ile Asn
    1145                1150                1155

His Tyr  Gly Gly Met Ile Gly  Gly His Tyr Thr Ala  Cys Ala Arg
    1160                1165                1170

Leu Pro  Asn Asp Arg Ser Ser  Gln Arg Ser Asp Val  Gly Trp Arg
    1175                1180                1185

Leu Phe  Asp Asp Ser Thr Val  Thr Thr Val Asp Glu  Ser Gln Val
    1190                1195                1200

Val Thr  Arg Tyr Ala Tyr Val  Leu Phe Tyr Arg Arg  Arg Asn Ser
    1205                1210                1215

Pro Val  Glu Arg Pro Pro Arg  Ala Gly His Ser Glu  His His Pro
    1220                1225                1230

Asp Leu  Gly Pro Ala Ala Glu  Ala Ala Ala Ser Gln  Ala Ser Arg
    1235                1240                1245

Ile Trp  Gln Glu Leu Glu Ala  Glu Glu Glu Pro Val  Pro Glu Gly
    1250                1255                1260

Ser Gly  Pro Leu Gly Pro Trp  Gly Pro Gln Asp Trp  Val Gly Pro
    1265                1270                1275

Leu Pro  Arg Gly Pro Thr Thr  Pro Asp Glu Gly Cys  Leu Arg Tyr
    1280                1285                1290

Phe Val  Leu Gly Thr Val Ala  Ala Leu Val Ala Leu  Val Leu Asn
    1295                1300                1305

Val Phe  Tyr Pro Leu Val Ser  Gln Ser Arg Trp Arg
    1310                1315                1320


<210> SEQ ID NO 88
<211> LENGTH: 325
<212> TYPE: PRT
<213> ORGANISM: homo sapiens
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<400> SEQUENCE: 88

Met Ser Ala Gln Ala Gln Met Arg Ala Leu Leu Asp Gln Leu Met Gly
1 5 10 15

Thr Ala Arg Asp Gly Asp Glu Thr Arg Gln Arg Val Lys Phe Thr Asp
20 25 30

Asp Arg Val Cys Lys Ser His Leu Leu Asp Cys Cys Pro His Asp Ile
35 40 45

Leu Ala Gly Thr Arg Met Asp Leu Gly Glu Cys Thr Lys Ile His Asp
50 55 60

Leu Ala Leu Arg Ala Asp Tyr Glu Ile Ala Ser Lys Glu Arg Asp Leu
65 70 75 80

Phe Phe Glu Leu Asp Ala Met Asp His Leu Glu Ser Phe Ile Ala Glu
85 90 95

Cys Asp Arg Arg Thr Glu Leu Ala Lys Lys Arg Leu Ala Glu Thr Gln
100 105 110

Glu Glu Ile Ser Ala Glu Val Ser Ala Lys Ala Glu Lys Val His Glu
115 120 125

Leu Asn Glu Glu Ile Gly Lys Leu Leu Ala Lys Ala Glu Gln Leu Gly
130 135 140

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

Lys Val Arg Ala Lys Lys Lys Glu Ala Glu Glu Glu Tyr Arg Asn Ser
165 170 175

Met Pro Ala Ser Ser Phe Gln Gln Gln Lys Leu Arg Val Cys Glu Val
180 185 190

Cys Ser Ala Tyr Leu Gly Leu His Asp Asn Asp Arg Arg Leu Ala Asp
195 200 205

His Phe Gly Gly Lys Leu His Leu Gly Phe Ile Gln Ile Arg Glu Lys
210 215 220

Leu Asp Gln Leu Arg Lys Thr Val Ala Glu Lys Gln Glu Lys Arg Asn
225 230 235 240

Gln Asp Arg Leu Arg Arg Arg Glu Glu Arg Glu Arg Glu Glu Arg Leu
245 250 255

Ser Arg Arg Ser Gly Ser Arg Thr Arg Asp Arg Arg Arg Ser Arg Ser
260 265 270

Arg Asp Arg Arg Arg Arg Arg Ser Arg Ser Thr Ser Arg Glu Arg Arg
275 280 285

Lys Leu Ser Arg Ser Arg Ser Arg Asp Arg His Arg Arg His Arg Ser
290 295 300

Arg Ser Arg Ser His Ser Arg Gly His Arg Arg Ala Ser Arg Asp Arg
305 310 315 320

Ser Ala Lys Tyr Lys
325

<210> SEQ ID NO 89
<211> LENGTH: 181
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 89

Met Gly Gly Phe Phe Ser Ser Ile Phe Ser Ser Leu Phe Gly Thr Arg
1 5 10 15

Glu Met Arg Ile Leu Ile Leu Gly Leu Asp Gly Ala Gly Lys Thr Thr
20 25 30

Ile Leu Tyr Arg Leu Gln Val Gly Glu Val Val Thr Thr Ile Pro Thr

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        35                  40                  45

Ile Gly Phe Asn Val Glu Thr Val Thr Tyr Lys Asn Leu Lys Phe Gln
    50                  55                  60

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

Tyr Tyr Ser Asn Thr Asp Ala Val Ile Tyr Val Val Asp Ser Cys Asp
                85                  90                  95

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

Glu Glu Glu Leu Arg Lys Ala Ile Leu Val Val Phe Ala Asn Lys Gln
        115                 120                 125

Asp Met Glu Gln Ala Met Thr Ser Ser Glu Met Ala Asn Ser Leu Gly
    130                 135                 140

Leu Pro Ala Leu Lys Asp Arg Lys Trp Gln Ile Phe Lys Thr Ser Ala
145                 150                 155                 160

Thr Lys Gly Thr Gly Leu Asp Glu Ala Met Glu Trp Leu Val Glu Thr
                165                 170                 175

Leu Lys Ser Arg Gln
            180


<210> SEQ ID NO 90
<211> LENGTH: 217
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 90

Met Ser Ser Lys Val Ser Arg Asp Thr Leu Tyr Glu Ala Val Arg Glu
1               5                   10                  15

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

Glu Leu Gln Ile Ser Leu Lys Asn Tyr Asp Pro Gln Lys Asp Lys Arg
        35                  40                  45

Phe Ser Gly Thr Val Arg Leu Lys Ser Thr Pro Arg Pro Lys Phe Ser
    50                  55                  60

Val Cys Val Leu Gly Asp Gln Gln His Cys Asp Glu Ala Lys Ala Val
65                  70                  75                  80

Asp Ile Pro His Met Asp Ile Glu Ala Leu Lys Lys Leu Asn Lys Asn
                85                  90                  95

Lys Lys Leu Val Lys Lys Leu Ala Lys Lys Tyr Asp Ala Phe Leu Ala
            100                 105                 110

Ser Glu Ser Leu Ile Lys Gln Ile Pro Arg Ile Leu Gly Pro Gly Leu
        115                 120                 125

Asn Lys Ala Gly Lys Phe Pro Ser Leu Leu Thr His Asn Glu Asn Met
    130                 135                 140

Val Ala Lys Val Asp Glu Val Lys Ser Thr Ile Lys Phe Gln Met Lys
145                 150                 155                 160

Lys Val Leu Cys Leu Ala Val Ala Val Gly His Val Lys Met Thr Asp
                165                 170                 175

Asp Glu Leu Val Tyr Asn Ile His Leu Ala Val Asn Phe Leu Val Ser
            180                 185                 190

Leu Leu Lys Lys Asn Trp Gln Asn Val Arg Ala Leu Tyr Ile Lys Ser
        195                 200                 205

Thr Met Gly Lys Pro Gln Arg Leu Tyr
    210                 215
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<210> SEQ ID NO 91
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 91

tggcgcagaa aggaaaagga aaat 24

<210> SEQ ID NO 92
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 92

agaggtagct ggcaggatgt tag 23

<210> SEQ ID NO 93
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 93

cttggtgcga tcagccttat 20

<210> SEQ ID NO 94
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 94

ttgatgcatg aaaacagaac tc 22

<210> SEQ ID NO 95
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 95

agaattggca gaggctcgtc atca 24

<210> SEQ ID NO 96
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 96

ttccaatttt gccttctcta actg 24

<210> SEQ ID NO 97
<211> LENGTH: 884
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (727)..(727)
<223> OTHER INFORMATION: n is a, c, g, or t

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (729)..(729)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (868)..(868)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 97

cacgaggcaa gggtgtcacc cccgcaggat ttccaaagaa ggccagtaga actgctagaa 60

tagcctccga tgaggaaatt caaggcacaa aggatgctgt tattcaagac ctggaacgaa 120

aacttcgctt caaggaggac ctcctgaaca atggccagcc gaggttaaca tacgaagaaa 180

gaatggctcg tcgactgcta ggtgctgaca gtgcaactgt ctttaatatt caggagccag 240

aagaggaaac agctaatcag gaatacaaag tctccagctg tgaacagaga ctcatcagtg 300

aaatagagta caggctagaa aggtctcctg tggatgaatc aggtgatgaa gttcagtatg 360

gagatgtgcc tgtggaaaat ggaatggcac cattctttga gatgaagctg aaacattaca 420

agatctttga gggaatgcca gtaactttca catgtagagt ggctggaaat ccaaagccaa 480

agatctattg gtttaaagat gggaagcaga tctctccaaa gagtgatcac tacaccattc 540

aaagagatct cgatgggacc tgctccctcc ataccacagc ctccacccta gatgatgatg 600

ggaattatac aattatggct gcaaaccctc agggccgcat cagttgtact ggacggctaa 660

tggtacaggc tgtcaaccaa agaggtcgaa gtccccggtc tccctcaggc catcctcatg 720

tcagaangnc tcgttctaga tcaagggaca gtggagacga aaatgaccca attcaggagc 780

gattcttcag acctcacttc ttgcaggctc ctggagatct gactggtcaa gaaggaaact 840

ctgcagatgg actgcaaagt cagtgggnta ccaccccaga tcta 884

<210> SEQ ID NO 98
<211> LENGTH: 886
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (695)..(695)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (731)..(731)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (740)..(740)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (798)..(798)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (807)..(807)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (809)..(809)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (844)..(844)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (852)..(852)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature

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<222> LOCATION: (857)..(857)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (876)..(876)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (878)..(878)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 98

cgaggggaaa ttacaaatag tgaccaaacc aaagcagatt tggactcgtc tctagatata 60

aaaaaaaatc ctgttccatg tcagaaatat agtttacgga attcaagtaa tgttatgtta 120

gatgataaac aatgtaaaat aaaacaaata caactgttaa ctaaaaaaag tgagtgcagc 180

atattacttt ctaaacaaac ttcagatttt ctgcaagtct gtaatgatac tttagagaaa 240

tctgaactaa ctgttccctg tgatatagta atcgaccacc atgtttcata tgctgctttt 300

agtgctaatt caaaactact tctgaagaac tcagataaaa atgtccatag tatgtctatg 360

ttggtgaaac ctaactcaag ccctggggga aaaactatgt gtaaaaatat gagtgatatg 420

caaaacagtc aatttaataa ctgtttggga tacttagaaa acactaatgt gaacatttcc 480

catcttcatc ttaacaatga gaatagtcat gcttcacaag ccaaagatgt gaaaactgct 540

gttcacatga aaacttgcac agaaacagag ttttccaata aaaagaatca gattgatgag 600

aatcaggtaa ctgaagccac aaaaaatgac ctcttccttt ttgtgagcat taatgaaaga 660

cagcatacat tgtttaaata atacagagga aaacnggaat cattaaatga cattgtttcc 720

aggaaaaatg ntcagtgaan gacagctgga ggaatcacat tcatttcaca tagagcctct 780

ggagatttag taacagancg ggaaggncna cctttgatct ttcacttcag ataaaaaact 840

gagnaaactc cngtatnatg atttttcaga cccggncntg ggcaag 886

<210> SEQ ID NO 99
<211> LENGTH: 851
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 99

cacgagggtc gagaggccgg catcactgga gtggtggcgc agctgtttcc tccggatatc 60

catcaaatat tgagaagaaa gaatatcagg agcaaagtgt tctaagttgc tgctcagaac 120

gtaaagatgc gaaccccaaa tcagtggttt gttcattctt catgcaagag caatgcacta 180

aaggagagaa gcaagctgtg gtgatcagtg actttggtga aagctaagaa ggttcaaaca 240

aatttgcaaa tgatatacaa cttctaagca ttccatattg gaagaagaga tttctacaca 300

tgaaaaaaat gcctttgttt agtaaatcac acaaaaatcc agcagaaatt gtgaaaatcc 360

tgaaagacaa tttggccatt ttggaaaagc aagacaaaaa gacagacaag gcttcagaag 420

aagtgtctaa atcactgcaa gcaatgaaag aaattctgtg tggtacaaac gagaaagaac 480

ccccaacaga agcagtggct cagctagcac aagaactcta cagcagtggc ctgctagtga 540

cactgatagc tgacctgcag ctgatagact ttgagggaaa aaaagatgtg acccagatat 600

ttaacaacat cttgagaaga cagataggca ctcggagtcc tactgtggag tatattagtg 660

ctcatcctca tatcctgttt atgctcctca aaggatatga agccccacag attgccttac 720

gttgtgggga ttatgctgag agaatgtatt cgacatgaac cccttgccaa aatcatcctc 780

ttttctaatc aattcagaga tttctttagg tacgtggagt tgtccacatt tgatattgct 840

tcaaatgcct t 851

-continued

<210> SEQ ID NO 100
<211> LENGTH: 639
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 100

cgaggggatg acagtgtttt cattgcagtt aaagaaattg gtcgtgatct gtacaggggc 60

ttgcctacag aggaaaggat ccagaaacta gagttcatgt tggataagct acagaatgaa 120

attgatcagg agttggaaca caataattcc cttgttagag aagaaaaaga gacaactgat 180

acaaggaaaa aatcacttct ttctgctgcc ttagctaaat caggtgaaag gctacaagct 240

ctaacacttc ttatgattca ctacagagca ggcattgaag atatagaaac tttagaaagt 300

ctgtctttag accagcactc caaaaaaata agcaagtaca cagatgatac agaagaagac 360

cttgataatg aaataagcca actaatagac tctcagccat tcagcagcat atcagatgac 420

ttatttggcc catccgagtc tgtgtagcag acaggtctat ttaaactttc aaatgaacag 480

ggtaaagttg catctaaagt accacagata caaccatgtt taaatcctcg tatgcactct 540

ggcctgcttc tccagttact tgcttgtgta agaacaaaaa tgagaaaggt tgttttccag 600

taaaaacatg accagcttac taaaaaaaaa aaaaaaaaa 639

<210> SEQ ID NO 101
<211> LENGTH: 907
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (797)..(797)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 101

cgagggtcat gtgccaaact gctcagcaag gaagaggaag caggtgttaa ggaattagca 60

aagcaggtga agagtttgcc agtggtaaat tacaacctcc tcaagtatat ttgcagattc 120

ttggatgaag tacagtccta ctcgggagtt aacaaaatga gtgtgcagaa cttggcaacg 180

gtctttggtc ctaatatcct gcgccccaaa gtggaagatc ctttgactat catggagggc 240

actgtggtgg tccagcagtt gatgtcagtg atgattagca aacatgattg cctctttccc 300

aaagatgcag aactacaaag caagccccaa gatggagtga gcaacaacaa tgaaattcag 360

aagaaagcca ccatggggca gttacagaac aaggagaaca ataacaccaa ggacagccct 420

agtaggcagt gctcctggga caagtctgag tcaccccaga gaagcagcat gaacaatgga 480

tcccccacag ctctatcagg cagcaaaacc aacagcccaa agaacagtgt tcacaagcta 540

gatgtgtcta gaagcccccc tctcatggtc aaaaagaacc cagcctttaa taagggtagt 600

gggatagtta ccaatgggtc cttcagcagc agtaatgcag aaggtcttga gaaaacccaa 660

accaccccca atgggagcct acaggccaga aggagctctt cactgaaggt atctggtacc 720

aaaatgggca cgcacagtgt acagaatgga acggtgcgca tgggcatttt gaacagcgac 780

acactcggga acccacnaat gttcgaacat gagctggctg ccaatggcta tgtgacctga 840

gggatacaag cagaagacag ctggagagta ggcacacaca gatgtcccct tgatatgtca 900

tcacagt 907

<210> SEQ ID NO 102
<211> LENGTH: 931
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (881)..(881)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 102

cgagggcaca acaaggcggc gccgccgcag atcccggaca cccggcggga gctggcggag 60

ctcgtgaagc ggaagcagga gctggcggaa acattggcaa atttggagcg acagatctat 120

gcttttgagg gaagctacct ggaagacact cagatgtatg gcaatattat tcgtggctgg 180

gatcggtatc tgaccaacca aaaaaactcc aatagcaaaa atgatcgaag gaaccggaag 240

tttaaggaag ctgagcggct cttcagtaaa tcctcggtta cctcagcagc tgcagtaagt 300

gcattggcag gagttcagga ccagctcatt gaaaagaggg agccaggaag tgggacggaa 360

agtgacactt ctccagactt ccacaatcag gaaaatgagc ccagccagga ggaccctgag 420

gatctggatg gatctgtgca gggagtgaaa cctcagaagg ctgcttcttc tacttcctca 480

gggagtcacc acagcagcca taaaaagcga aagaataaaa accggcacag gattgatctg 540

aagttaaaca aaaaaccacg agctgactat tagaagacac attagtgcag aagcttccag 600

gctgtagagc cctgcttccc ttctctgacc tcacaaagat aaacatcctt cacctgagtt 660

cgtggccatc cacctctgct ctcccagacc cagtgcctgt gactttgagt agtttgttct 720

aaatgtggtg acaaacaagt catttctgta agacattggg tcttacttta tgtcattttt 780

agtaacagaa ctgcaggaag atcaagacat gttgtaatcc cggcaagttg ctactgtgcg 840

ttctcccttc ttagatgatt gtctccccaa actggctggc ncagcttctc tgtgatacct 900

tcagaatgtt ctctggtttg tttatgctga a 931

<210> SEQ ID NO 103
<211> LENGTH: 737
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (636)..(636)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (646)..(646)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (689)..(689)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 103

ggaagaacag catgctaaca catctgccaa ttatgatgtg gagctacttc atcacaaaga 60

tgcacatgta gatttcctga aaagtggtga ttcgcatcta ggtggcggca gtcgagaagg 120

ctcgtttaaa gaaacaataa cattaaagtg gtgtacacca aggacaaata acattgaatt 180

acactattgt actggagctt atcggatttc acctgtagat gtaaatagta gaccttcctc 240

ctgccttact aattttcttc taaatggtcg ttctgtttta ttggaacaac cacgaaagtc 300

aggttctaaa gtcattagtc atatgcttag tagccatgga ggagagattt ttttgcacgt 360

ccttagcagt tctcgatcca ttctagaaga tccaccttca attagtgaag gatgtggagg 420

aagagttaca gactaccggg attacagatt ttggtgaatt tatgagggaa aacagattaa 480

ctccttttct agaccccaga tataaaatcg atggaagtct tgaggtccct ttgggaacga 540

gcaaaagatc agttagaaaa acatacccgt tactggccta tgatcatttc acaaaccacc 600

atttttaaca tgcaagcggt agttccatta gccagngtta ttgtgnaaaa aatctctgac 660

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agaagagaat gtgttaaact gtcaaaaanc atatacaact tagttgatat ggaaagaaaa 720

atgatcctct acctatt 737

<210> SEQ ID NO 104
<211> LENGTH: 770
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (141)..(141)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (640)..(641)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 104

cgaggactac ttgtacctac aagacctgct actcgccaag ggctgattgg gagaataatg 60

gaatctgaaa atatggattc tgaaaatatg aagacagaaa atatggaatc tcaaaatgta 120

gactttgaga gtgtttcttc ngttacagct ctggaagccc tctctaagct acttaatcct 180

gaagaagagg atgattctga ctatggacag acaaatggtt tatctactat tggagccatg 240

ggtcctggga atattggacc accccaaata gaagagctca aagtcatccc tgaaaccagc 300

gaggaaaata atgaggacat ctggaattca gaagagattc cagaaggagc agaatatgat 360

gatatgtggg atgttagaga aatcccagag tatgagatta tattcagaca gcaggtggga 420

actgaagata tatttttagg gttgtcaaaa aaggactcct caacaggttg ttgcagtgaa 480

ctagtggcta aaattaaatt gccaaataca aacccttctg atattcaaat tgatatccag 540

ggaaacaatc cttgaccttc gtactcctca gaagaagctg ttgataactc ttcctgagct 600

ggtggaatgt accagtgcca aagcattcta tatcccagan nactgaaact cttgaaatca 660

ctatgactat gaaaagagag ttagatattg ctaatttctt ctgaaactgc atgaaaaaga 720

taaaaagtag taaaatggca ttggtaacaa ttaaaaaact ttgaaaaaag 770

<210> SEQ ID NO 105
<211> LENGTH: 920
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (687)..(687)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (750)..(750)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (807)..(807)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (810)..(810)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (826)..(827)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (849)..(849)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (870)..(870)
<223> OTHER INFORMATION: n is a, c, g, or t

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (874)..(874)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (882)..(882)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (889)..(889)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (909)..(909)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 105

gaggctttac gcgcgtgccc ttcacccact ggttcttctc cttcgtggaa gacccgctga 60

tcgacttcga ggtgcgctcc cagtttgaag ggcggcccat gccccagctc acctccatca 120

tcgtcaacca gctcaagaag atcatcaagc gcaagcacac cctaccgaat tacaagatca 180

ggtttaagcc gttttttcca taccagacct tgcaaggatt tgaagaagat gaagagcata 240

tccatataca acaatgggca cttactgaag gccgtcttaa agttacgttg ttagaatgta 300

gcaggttact cattttgga tcctatgaca gagaggcaaa tgttcattgc acacttgagt 360

taagcagtag tgtttgggaa gaaaaacaga ggagttctat taagacggtt gaattaataa 420

aaggaaattt acaaagtgtt ggacttacac ttcgtcttgt ccagtcaact gatgggtatg 480

ctgggcacgt catcattgaa actgtggctc caaactcgcc tgctgcaatt gcagatcttc 540

agcggggaga tcgacttatc gccattggga ggtgtgaaaa tcacatcaac actgcaagtg 600

ttgaagctta tcaagcaggc tggtgaccga gtcctggtgt actatgaaag gcctgttggc 660

cagagtaatc aaggtgcagt gctgcangat aactttggcc agttggaaga aaacttttg 720

tcaagctcat gccaatcggg ttatgaagan gaaactgccg ggttgacagt aaatactgaa 780

aagtaaagag ctgggattct gaatttngan aacttggcaa gtgganntcc agagcccaaa 840

atgagttcna agatgaggca caatcattan gtcntagtcc cnaacgggnt ccaacaacac 900

ttttctatna aacccccttgg 920

<210> SEQ ID NO 106
<211> LENGTH: 938
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (678)..(678)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (728)..(728)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (860)..(860)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (865)..(865)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (867)..(867)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (874)..(874)
<223> OTHER INFORMATION: n is a, c, g, or t

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (876)..(876)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (882)..(882)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (908)..(908)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 106

ctgcagaggc gcctcatgga aaccaacctg tctaagctcc gaagcggtcc ccgtgtccct 60

tgggcctcta agacgaacaa actcaatcag gctaagtctg aggggctaaa gaagtctgag 120

gaggatgaca tgattttggt ttcttgccag tgtgctggaa aggatgtgaa agccttggtt 180

gacacaggct gcctatataa tctcatctct ttggcctgtg tggacagatt gggactcaag 240

gagcatgtca aatcccacaa gcatgaagga gaaaagcttt ctctaccccg gcatctcaaa 300

gtagtgggcc agattgagca cctagtgatc acactgggct ccctccgcct ggactgccca 360

gcagctgtgg ttgatgacaa tgagaaaaac ttgtcccttg gtctacagac tctccgatct 420

ctgaagtgca tcataaactt ggataagcac cggctgatca tggggaagac agacaaggaa 480

gaaatccctt ttgtggagac agtctctttg aatgaagaca acacttcaga agcataacta 540

cagcctgcag catgtctgca cgtgtgcatg catacacacc gggttgacag attgagaaaa 600

ctgggtttga accaaatgcc gtagtgactt gctgtggacc aagtccttcc atctaataga 660

agctccaggg gctccttncc attcagacct ctctagacta tagtctatgc ttagagatct 720

tgtctggnta tggccattgt tttttactac tttgatcact taacttatag acctttttg 780

acactgccag tctcactggg ggctatttct ctgctccttc cagaatttgc ttttattagt 840

caagtatagg gctgccaggn tctgngnccc atananatat gngcttcttt cctaagctaa 900

tggataanaa caggacctga cttttaaaaa aaaaaaaa 938

<210> SEQ ID NO 107
<211> LENGTH: 949
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (705)..(705)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (765)..(765)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (818)..(818)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (831)..(831)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (844)..(844)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (865)..(865)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (875)..(875)
<223> OTHER INFORMATION: n is a, c, g, or t

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (893)..(893)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (906)..(906)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (908)..(908)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (910)..(910)
<223> OTHER INFORMATION: n is a, c, g, or t
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (918)..(918)
<223> OTHER INFORMATION: n is a, c, g, or t

<400> SEQUENCE: 107

cacgagggtg gtgtctgtca gacacacaca ggccgccagt gacttcacac acacctcatg 60

tgagaaccat gccttttta gtgtgtccta tttcatacct gtacacactt cctcgttttg 120

taatgagatt tacttacacc caaacagatc ctgaaagaaa gcttcaagtt ttctcagatg 180

atggatatgt tttcactgta ttcaataact gacggatgta aggtgcacgt ttcctgatgt 240

gacgcactgt attccagctg gtgatcaagt ctgggaacag ccgtaacagg tcaaccttgt 300

ggagccatcg cgagttagag ggtgaaagat ggcagaaaaa aaagtcttgt gtgtgagtgt 360

gttttttgag tttgcatcaa tcttaatgtc tcttcataat acttttataa tacattaagc 420

ctcttgtcta catatttgga gagaatatga ctttactagc agagaaatac aatatatctt 480

gtctactgga ctgtaaaata tatgtatgaa ataaaattag ttccatttgg tcttctagta 540

tattaaagtg ctatctgacg ttgttatcct gtttttgcaa aaaaaaaaaa aaaaaagtta 600

actacagacc attgtttcta ataagcagag agatctattt tagtagtaaa ctgaaggttt 660

agttgtgagc ttcagatttt gtgaactcca gatgttgtgc ggggnttttt ttttttttt 720

aagaccacca ctaaaaaatg ccaggaatat gtacctggga actgnagggg agctttcagt 780

attggaaaaa gattgttcta tacggacctt tttgctgntt atccgggatg naaaaagcct 840

tccnaaacct atgggaaaaa aaagngagca ctgantctcc cctgttcctt cgnggaccct 900

tttggnangn aaactggnct gtttttaaaa tgggactaaa aaaaaaaaa 949

<210> SEQ ID NO 108
<211> LENGTH: 784
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 108

agaaggcttt ggcttctgat agtcatggac tcactaggct gctgaggaag atcaataata 60

cctactggaa tcagtcatga gaagtcaagc atggaaattg tgaattgtgt gtgtggccag 120

accagtacct ccaagtgttc agaagatgtg tgaccagaca aaacacagta aatgctgccc 180

agcaaaaggc aatcaatgct gcccaccaca gcagaaccag tgctgccagt caaaaggcaa 240

tcaatgctgc ccaccaaaac agaaccagtg ctgccagcca aaaggcagtc aatgctgccc 300

accaaaacac aatcactgct gccagccaaa acccccatgc tgcattcagg ccaggtgctg 360

tggtttggag accaagcctg aagtctcacc ccttaacatg gagtctgagc ccaactcacc 420

gcaaactcag gacaagggct gtcaaaccca gcagcagccc catagcccac aaaatgagtc 480

caggccaagc aaatgagagc agaagaagtc aaacaaagaa gaagtccctg gggccatgcc 540

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tttcactttg tagggtgggg gattactgag agtcaggcta gacctgtgtt tagagaagca 600

gttttcacag tgactaccat ttccacccaa tgagaggctc ctatttccca tcatagctcc 660

ctaccctagg gaggcctcca tctggaaatg ggaggatgaa gaggctagaa tcatctttcc 720

tagtgatcct gacatttaga cagcacagaa ataaagagca ataaaaagaa aaaaaaaaaa 780

aaaa 784

<210> SEQ ID NO 109
<211> LENGTH: 294
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (242)..(243)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (289)..(289)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 109

Arg Gly Lys Gly Val Thr Pro Ala Gly Phe Pro Lys Lys Ala Ser Arg
1 5 10 15

Thr Ala Arg Ile Ala Ser Asp Glu Glu Ile Gln Gly Thr Lys Asp Ala
20 25 30

Val Ile Gln Asp Leu Glu Arg Lys Leu Arg Phe Lys Glu Asp Leu Leu
35 40 45

Asn Asn Gly Gln Pro Arg Leu Thr Tyr Glu Glu Arg Met Ala Arg Arg
50 55 60

Leu Leu Gly Ala Asp Ser Ala Thr Val Phe Asn Ile Gln Glu Pro Glu
65 70 75 80

Glu Glu Thr Ala Asn Gln Glu Tyr Lys Val Ser Ser Cys Glu Gln Arg
85 90 95

Leu Ile Ser Glu Ile Glu Tyr Arg Leu Glu Arg Ser Pro Val Asp Glu
100 105 110

Ser Gly Asp Glu Val Gln Tyr Gly Asp Val Pro Val Glu Asn Gly Met
115 120 125

Ala Pro Phe Phe Glu Met Lys Leu Lys His Tyr Lys Ile Phe Glu Gly
130 135 140

Met Pro Val Thr Phe Thr Cys Arg Val Ala Gly Asn Pro Lys Pro Lys
145 150 155 160

Ile Tyr Trp Phe Lys Asp Gly Lys Gln Ile Ser Pro Lys Ser Asp His
165 170 175

Tyr Thr Ile Gln Arg Asp Leu Asp Gly Thr Cys Ser Leu His Thr Thr
180 185 190

Ala Ser Thr Leu Asp Asp Asp Gly Asn Tyr Thr Ile Met Ala Ala Asn
195 200 205

Pro Gln Gly Arg Ile Ser Cys Thr Gly Arg Leu Met Val Gln Ala Val
210 215 220

Asn Gln Arg Gly Arg Ser Pro Arg Ser Pro Ser Gly His Pro His Val
225 230 235 240

Arg Xaa Xaa Arg Ser Arg Ser Arg Asp Ser Gly Asp Glu Asn Asp Pro
245 250 255

Ile Gln Glu Arg Phe Phe Arg Pro His Phe Leu Gln Ala Pro Gly Asp
260 265 270

Leu Thr Gly Gln Glu Gly Asn Ser Ala Asp Gly Leu Gln Ser Gln Trp
275 280 285

Xaa Thr Thr Pro Asp Leu
290

<210> SEQ ID NO 110
<211> LENGTH: 226
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 110

Arg Gly Glu Ile Thr Asn Ser Asp Gln Thr Lys Ala Asp Leu Asp Ser
1 5 10 15

Ser Leu Asp Ile Lys Lys Asn Pro Val Pro Cys Gln Lys Tyr Ser Leu
20 25 30

Arg Asn Ser Ser Asn Val Met Leu Asp Asp Lys Gln Cys Lys Ile Lys
35 40 45

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

Lys Gln Thr Ser Asp Phe Leu Gln Val Cys Asn Asp Thr Leu Glu Lys
65 70 75 80

Ser Glu Leu Thr Val Pro Cys Asp Ile Val Ile Asp His His Val Ser
85 90 95

Tyr Ala Ala Phe Ser Ala Asn Ser Lys Leu Leu Leu Lys Asn Ser Asp
100 105 110

Lys Asn Val His Ser Met Ser Met Leu Val Lys Pro Asn Ser Ser Pro
115 120 125

Gly Gly Lys Thr Met Cys Lys Asn Met Ser Asp Met Gln Asn Ser Gln
130 135 140

Phe Asn Asn Cys Leu Gly Tyr Leu Glu Asn Thr Asn Val Asn Ile Ser
145 150 155 160

His Leu His Leu Asn Asn Glu Asn Ser His Ala Ser Gln Ala Lys Asp
165 170 175

Val Lys Thr Ala Val His Met Lys Thr Cys Thr Glu Thr Glu Phe Ser
180 185 190

Asn Lys Lys Asn Gln Ile Asp Glu Asn Gln Val Thr Glu Ala Thr Lys
195 200 205

Asn Asp Leu Phe Leu Phe Val Ser Ile Asn Glu Arg Gln His Thr Leu
210 215 220

Phe Lys
225

<210> SEQ ID NO 111
<211> LENGTH: 74
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 111

Arg Gly Ser Arg Gly Arg His His Trp Ser Gly Gly Ala Ala Val Ser
1 5 10 15

Ser Gly Tyr Pro Ser Asn Ile Glu Lys Lys Glu Tyr Gln Glu Gln Ser
20 25 30

Val Leu Ser Cys Cys Ser Glu Arg Lys Asp Ala Asn Pro Lys Ser Val
35 40 45

Val Cys Ser Phe Phe Met Gln Glu Gln Cys Thr Lys Gly Glu Lys Gln
50 55 60

Ala Val Val Ile Ser Asp Phe Gly Glu Ser
65 70

<210> SEQ ID NO 112
<211> LENGTH: 148
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 112

Arg Gly Asp Asp Ser Val Phe Ile Ala Val Lys Glu Ile Gly Arg Asp
1 5 10 15

Leu Tyr Arg Gly Leu Pro Thr Glu Glu Arg Ile Gln Lys Leu Glu Phe
20 25 30

Met Leu Asp Lys Leu Gln Asn Glu Ile Asp Gln Glu Leu Glu His Asn
35 40 45

Asn Ser Leu Val Arg Glu Glu Lys Glu Thr Thr Asp Thr Arg Lys Lys
50 55 60

Ser Leu Leu Ser Ala Ala Leu Ala Lys Ser Gly Glu Arg Leu Gln Ala
65 70 75 80

Leu Thr Leu Leu Met Ile His Tyr Arg Ala Gly Ile Glu Asp Ile Glu
85 90 95

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

Tyr Thr Asp Asp Thr Glu Glu Asp Leu Asp Asn Glu Ile Ser Gln Leu
115 120 125

Ile Asp Ser Gln Pro Phe Ser Ser Ile Ser Asp Asp Leu Phe Gly Pro
130 135 140

Ser Glu Ser Val
145

<210> SEQ ID NO 113
<211> LENGTH: 279
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (266)..(266)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 113

Arg Gly Ser Cys Ala Lys Leu Leu Ser Lys Glu Glu Glu Ala Gly Val
1 5 10 15

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

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

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

Asn Ile Leu Arg Pro Lys Val Glu Asp Pro Leu Thr Ile Met Glu Gly
65 70 75 80

Thr Val Val Val Gln Gln Leu Met Ser Val Met Ile Ser Lys His Asp
85 90 95

Cys Leu Phe Pro Lys Asp Ala Glu Leu Gln Ser Lys Pro Gln Asp Gly
100 105 110

Val Ser Asn Asn Asn Glu Ile Gln Lys Lys Ala Thr Met Gly Gln Leu
115 120 125

Gln Asn Lys Glu Asn Asn Asn Thr Lys Asp Ser Pro Ser Arg Gln Cys
130 135 140

Ser Trp Asp Lys Ser Glu Ser Pro Gln Arg Ser Ser Met Asn Asn Gly
145 150 155 160

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Ser Pro Thr Ala Leu Ser Gly Ser Lys Thr Asn Ser Pro Lys Asn Ser
                165                 170                 175

Val His Lys Leu Asp Val Ser Arg Ser Pro Pro Leu Met Val Lys Lys
            180                 185                 190

Asn Pro Ala Phe Asn Lys Gly Ser Gly Ile Val Thr Asn Gly Ser Phe
        195                 200                 205

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

Gly Ser Leu Gln Ala Arg Arg Ser Ser Ser Leu Lys Val Ser Gly Thr
225                 230                 235                 240

Lys Met Gly Thr His Ser Val Gln Asn Gly Thr Val Arg Met Gly Ile
                245                 250                 255

Leu Asn Ser Asp Thr Leu Gly Asn Pro Xaa Met Phe Glu His Glu Leu
            260                 265                 270

Ala Ala Asn Gly Tyr Val Thr
        275


<210> SEQ ID NO 114
<211> LENGTH: 190
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 114

Arg Gly His Asn Lys Ala Ala Pro Pro Gln Ile Pro Asp Thr Arg Arg
1               5                   10                  15

Glu Leu Ala Glu Leu Val Lys Arg Lys Gln Glu Leu Ala Glu Thr Leu
            20                  25                  30

Ala Asn Leu Glu Arg Gln Ile Tyr Ala Phe Glu Gly Ser Tyr Leu Glu
        35                  40                  45

Asp Thr Gln Met Tyr Gly Asn Ile Ile Arg Gly Trp Asp Arg Tyr Leu
    50                  55                  60

Thr Asn Gln Lys Asn Ser Asn Ser Lys Asn Asp Arg Arg Asn Arg Lys
65                  70                  75                  80

Phe Lys Glu Ala Glu Arg Leu Phe Ser Lys Ser Ser Val Thr Ser Ala
                85                  90                  95

Ala Ala Val Ser Ala Leu Ala Gly Val Gln Asp Gln Leu Ile Glu Lys
            100                 105                 110

Arg Glu Pro Gly Ser Gly Thr Glu Ser Asp Thr Ser Pro Asp Phe His
        115                 120                 125

Asn Gln Glu Asn Glu Pro Ser Gln Glu Asp Pro Glu Asp Leu Asp Gly
    130                 135                 140

Ser Val Gln Gly Val Lys Pro Gln Lys Ala Ala Ser Ser Thr Ser Ser
145                 150                 155                 160

Gly Ser His His Ser Ser His Lys Lys Arg Lys Asn Lys Asn Arg His
                165                 170                 175

Arg Ile Asp Leu Lys Leu Asn Lys Lys Pro Arg Ala Asp Tyr
            180                 185                 190


<210> SEQ ID NO 115
<211> LENGTH: 151
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 115

Glu Glu Gln His Ala Asn Thr Ser Ala Asn Tyr Asp Val Glu Leu Leu
1               5                   10                  15

His His Lys Asp Ala His Val Asp Phe Leu Lys Ser Gly Asp Ser His
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            20                  25                  30

Leu Gly Gly Gly Ser Arg Glu Gly Ser Phe Lys Glu Thr Ile Thr Leu
        35                  40                  45

Lys Trp Cys Thr Pro Arg Thr Asn Asn Ile Glu Leu His Tyr Cys Thr
    50                  55                  60

Gly Ala Tyr Arg Ile Ser Pro Val Asp Val Asn Ser Arg Pro Ser Ser
65                  70                  75                  80

Cys Leu Thr Asn Phe Leu Leu Asn Gly Arg Ser Val Leu Leu Glu Gln
                85                  90                  95

Pro Arg Lys Ser Gly Ser Lys Val Ile Ser His Met Leu Ser Ser His
            100                 105                 110

Gly Gly Glu Ile Phe Leu His Val Leu Ser Ser Ser Arg Ser Ile Leu
        115                 120                 125

Glu Asp Pro Pro Ser Ile Ser Glu Gly Cys Gly Gly Arg Val Thr Asp
    130                 135                 140

Tyr Arg Asp Tyr Arg Phe Trp
145                 150


<210> SEQ ID NO 116
<211> LENGTH: 184
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 116

Arg Gly Leu Leu Val Pro Thr Arg Pro Ala Thr Arg Gln Gly Leu Ile
1               5                   10                  15

Gly Arg Ile Met Glu Ser Glu Asn Met Asp Ser Glu Asn Met Lys Thr
            20                  25                  30

Glu Asn Met Glu Ser Gln Asn Val Asp Phe Glu Ser Val Ser Ser Val
        35                  40                  45

Thr Ala Leu Glu Ala Leu Ser Lys Leu Leu Asn Pro Glu Glu Glu Asp
    50                  55                  60

Asp Ser Asp Tyr Gly Gln Thr Asn Gly Leu Ser Thr Ile Gly Ala Met
65                  70                  75                  80

Gly Pro Gly Asn Ile Gly Pro Pro Gln Ile Glu Glu Leu Lys Val Ile
                85                  90                  95

Pro Glu Thr Ser Glu Glu Asn Asn Glu Asp Ile Trp Asn Ser Glu Glu
            100                 105                 110

Ile Pro Glu Gly Ala Glu Tyr Asp Asp Met Trp Asp Val Arg Glu Ile
        115                 120                 125

Pro Glu Tyr Glu Ile Ile Phe Arg Gln Gln Val Gly Thr Glu Asp Ile
    130                 135                 140

Phe Leu Gly Leu Ser Lys Lys Asp Ser Ser Thr Gly Cys Cys Ser Glu
145                 150                 155                 160

Leu Val Ala Lys Ile Lys Leu Pro Asn Thr Asn Pro Ser Asp Ile Gln
                165                 170                 175

Ile Asp Ile Gln Gly Asn Asn Pro
            180


<210> SEQ ID NO 117
<211> LENGTH: 207
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 117

Gly Phe Thr Arg Val Pro Phe Thr His Trp Phe Phe Ser Phe Val Glu
1               5                   10                  15
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Asp Pro Leu Ile Asp Phe Glu Val Arg Ser Gln Phe Glu Gly Arg Pro
            20                  25                  30

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

Lys Arg Lys His Thr Leu Pro Asn Tyr Lys Ile Arg Phe Lys Pro Phe
    50                  55                  60

Phe Pro Tyr Gln Thr Leu Gln Gly Phe Glu Glu Asp Glu Glu His Ile
65                  70                  75                  80

His Ile Gln Gln Trp Ala Leu Thr Glu Gly Arg Leu Lys Val Thr Leu
                85                  90                  95

Leu Glu Cys Ser Arg Leu Leu Ile Phe Gly Ser Tyr Asp Arg Glu Ala
            100                 105                 110

Asn Val His Cys Thr Leu Glu Leu Ser Ser Ser Val Trp Glu Glu Lys
        115                 120                 125

Gln Arg Ser Ser Ile Lys Thr Val Glu Leu Ile Lys Gly Asn Leu Gln
    130                 135                 140

Ser Val Gly Leu Thr Leu Arg Leu Val Gln Ser Thr Asp Gly Tyr Ala
145                 150                 155                 160

Gly His Val Ile Ile Glu Thr Val Ala Pro Asn Ser Pro Ala Ala Ile
                165                 170                 175

Ala Asp Leu Gln Arg Gly Asp Arg Leu Ile Ala Ile Gly Arg Cys Glu
            180                 185                 190

Asn His Ile Asn Thr Ala Ser Val Glu Ala Tyr Gln Ala Gly Trp
        195                 200                 205


<210> SEQ ID NO 118
<211> LENGTH: 178
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 118

Leu Gln Arg Arg Leu Met Glu Thr Asn Leu Ser Lys Leu Arg Ser Gly
1               5                   10                  15

Pro Arg Val Pro Trp Ala Ser Lys Thr Asn Lys Leu Asn Gln Ala Lys
            20                  25                  30

Ser Glu Gly Leu Lys Lys Ser Glu Glu Asp Asp Met Ile Leu Val Ser
        35                  40                  45

Cys Gln Cys Ala Gly Lys Asp Val Lys Ala Leu Val Asp Thr Gly Cys
    50                  55                  60

Leu Tyr Asn Leu Ile Ser Leu Ala Cys Val Asp Arg Leu Gly Leu Lys
65                  70                  75                  80

Glu His Val Lys Ser His Lys His Glu Gly Glu Lys Leu Ser Leu Pro
                85                  90                  95

Arg His Leu Lys Val Val Gly Gln Ile Glu His Leu Val Ile Thr Leu
            100                 105                 110

Gly Ser Leu Arg Leu Asp Cys Pro Ala Ala Val Val Asp Asp Asn Glu
        115                 120                 125

Lys Asn Leu Ser Leu Gly Leu Gln Thr Leu Arg Ser Leu Lys Cys Ile
    130                 135                 140

Ile Asn Leu Asp Lys His Arg Leu Ile Met Gly Lys Thr Asp Lys Glu
145                 150                 155                 160

Glu Ile Pro Phe Val Glu Thr Val Ser Leu Asn Glu Asp Asn Thr Ser
                165                 170                 175

Glu Ala
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<210> SEQ ID NO 119
<211> LENGTH: 69
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 119

Arg Gly Trp Cys Leu Ser Asp Thr His Arg Pro Pro Val Thr Ser His
1 5 10 15

Thr Pro His Val Arg Thr Met Pro Phe Leu Val Cys Pro Ile Ser Tyr
20 25 30

Leu Tyr Thr Leu Pro Arg Phe Val Met Arg Phe Thr Tyr Thr Gln Thr
35 40 45

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

Thr Val Phe Asn Asn
65

<210> SEQ ID NO 120
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 120

Met Cys Asp Gln Thr Lys His Ser Lys Cys Cys Pro Ala Lys Gly Asn
1 5 10 15

Gln Cys Cys Pro Pro Gln Gln Asn Gln Cys Cys Gln Ser Lys Gly Asn
20 25 30

Gln Cys Cys Pro Pro Lys Gln Asn Gln Cys Cys Gln Pro Lys Gly Ser
35 40 45

Gln Cys Cys Pro Pro Lys His Asn His Cys Cys Gln Pro Lys Pro Pro
50 55 60

Cys Cys Ile Gln Ala Arg Cys Cys Gly Leu Glu Thr Lys Pro Glu Val
65 70 75 80

Ser Pro Leu Asn Met Glu Ser Glu Pro Asn Ser Pro Gln Thr Gln Asp
85 90 95

Lys Gly Cys Gln Thr Gln Gln Gln Pro His Ser Pro Gln Asn Glu Ser
100 105 110

Arg Pro Ser Lys
115

<210> SEQ ID NO 121
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 121

atgcgggtca gcaaaccctt tgggatgctc atgctctcca tttggatcct gctgttcgtg 60

tgctactacc tgtcctacta cctgtgctcc gggtcctcat attttgtgct tgcaaatgga 120

catatcctgc ccaacagtga aaatgctcat ggccaatctc tggaagaaga ttccgcattg 180

gaagctttgc tgaatttttt ctttccaaca acttgcaatc tgagggaaaa tcaggtggca 240

aagccttgta atgagctgca agatcttagt gagagtgaat gtttgagaca caaatgctgt 300

ttttcatcat cggggaccac gagcttcaaa tgttttgctc catttagaga tgtgcctaaa 360

cagatgatgc aa 372

<210> SEQ ID NO 122
<211> LENGTH: 124

-continued

<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 122

Met Arg Val Ser Lys Pro Phe Gly Met Leu Met Leu Ser Ile Trp Ile
1 5 10 15

Leu Leu Phe Val Cys Tyr Tyr Leu Ser Tyr Tyr Leu Cys Ser Gly Ser
20 25 30

Ser Tyr Phe Val Leu Ala Asn Gly His Ile Leu Pro Asn Ser Glu Asn
35 40 45

Ala His Gly Gln Ser Leu Glu Glu Asp Ser Ala Leu Glu Ala Leu Leu
50 55 60

Asn Phe Phe Phe Pro Thr Thr Cys Asn Leu Arg Glu Asn Gln Val Ala
65 70 75 80

Lys Pro Cys Asn Glu Leu Gln Asp Leu Ser Glu Ser Glu Cys Leu Arg
85 90 95

His Lys Cys Cys Phe Ser Ser Ser Gly Thr Thr Ser Phe Lys Cys Phe
100 105 110

Ala Pro Phe Arg Asp Val Pro Lys Gln Met Met Gln
115 120

<210> SEQ ID NO 123
<211> LENGTH: 129
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 123

acttgcaatc tgagggaaaa tcaggtggca aagccttgta atgagctgca agatcttagt 60

gagagtgaat gtttgagaca caaatgctgt ttttcatcat cggggaccac gagcttcaaa 120

tgttttgct 129

<210> SEQ ID NO 124
<211> LENGTH: 43
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 124

Thr Cys Asn Leu Arg Glu Asn Gln Val Ala Lys Pro Cys Asn Glu Leu
1 5 10 15

Gln Asp Leu Ser Glu Ser Glu Cys Leu Arg His Lys Cys Cys Phe Ser
20 25 30

Ser Ser Gly Thr Thr Ser Phe Lys Cys Phe Ala
35 40

<210> SEQ ID NO 125
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 125

aagaaacaaa gaaggaagcg aaagaggaag 30

<210> SEQ ID NO 126
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 126

Lys Lys Gln Arg Arg Lys Arg Lys Arg Lys
1 5 10

<210> SEQ ID NO 127
<211> LENGTH: 75
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 127

atgcgggtca gcaaaccctt tgggatgctc atgctctcca tttggatcct gctgttcgtg 60

tgctactacc tgtcc 75

<210> SEQ ID NO 128
<211> LENGTH: 25
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 128

Met Arg Val Ser Lys Pro Phe Gly Met Leu Met Leu Ser Ile Trp Ile
1 5 10 15

Leu Leu Phe Val Cys Tyr Tyr Leu Ser
20 25

<210> SEQ ID NO 129
<211> LENGTH: 69
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 129

atgtttgggc ttggtgcgat cagccttatc ctggtatgtc tgcccattta ttgccgctct 60

cttttctgg 69

<210> SEQ ID NO 130
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 130

Met Phe Gly Leu Gly Ala Ile Ser Leu Ile Leu Val Cys Leu Pro Ile
1 5 10 15

Tyr Cys Arg Ser Leu Phe Trp
20

<210> SEQ ID NO 131
<211> LENGTH: 582
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 131

atgcgggtca gcaaaccctt tgggatgctc atgctctcca tttggatcct gctgttcgtg 60

tgctactacc tgtcctacta cctgtgctcc gggtcctcat attttgtgct tgcaaatgga 120

catatcctgc ccaacagtga aaatgctcat ggccaatctc tggaagaaga ttccgcattg 180

gaagctttgc tgaatttttt ctttccaaca acttgcaatc tgagggaaaa tcaggtggca 240

aagccttgta atgagctgca agatcttagt gagagtgaat gtttgagaca caaatgctgt 300

ttttcatcat cggggaccac gagcttcaaa tgttttgctc catttagaga tgtgcctaaa 360

cagatgatgc aaatgtttgg gcttggtgcg atcagcctta tcctggtatg tctgcccatt 420

tattgccgct ctcttttctg gaggagcgaa ccggccgatg atttacaaag gcaggacaac 480

agagttgtaa cgggtttgaa gaaacaaaga aggaagcgaa agaggaagtc tgaaatgtta 540

cagaaagcag caagaggacg tgaggaacat ggtgacgagc tc 582

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<210> SEQ ID NO 132
<211> LENGTH: 193
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 132

Met Arg Val Ser Lys Pro Phe Gly Met Leu Met Leu Ser Ile Trp Ile
1 5 10 15

Leu Leu Phe Val Cys Tyr Tyr Leu Ser Tyr Tyr Leu Cys Ser Gly Ser
20 25 30

Ser Tyr Phe Val Leu Ala Asn Gly His Ile Leu Pro Asn Ser Glu Asn
35 40 45

Ala His Gly Gln Ser Leu Glu Glu Asp Ser Ala Leu Glu Ala Leu Leu
50 55 60

Asn Phe Phe Phe Pro Thr Thr Cys Asn Leu Arg Glu Asn Gln Val Ala
65 70 75 80

Lys Pro Cys Asn Glu Leu Gln Asp Leu Ser Glu Ser Glu Cys Leu Arg
85 90 95

His Lys Cys Cys Phe Ser Ser Ser Gly Thr Thr Ser Phe Lys Cys Phe
100 105 110

Ala Pro Phe Arg Asp Val Pro Lys Gln Met Met Gln Met Phe Gly Leu
115 120 125

Gly Ala Ile Ser Leu Ile Leu Val Cys Leu Pro Ile Tyr Cys Arg Ser
130 135 140

Leu Phe Trp Arg Ser Glu Pro Ala Asp Asp Leu Gln Arg Gln Asp Asn
145 150 155 160

Arg Val Val Thr Gly Leu Lys Lys Gln Arg Arg Lys Arg Lys Arg Lys
165 170 175

Ser Glu Met Leu Gln Lys Ala Ala Arg Gly Arg Glu Glu His Gly Asp
180 185 190

Glu

<210> SEQ ID NO 133
<211> LENGTH: 717
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 133

atgccttcgg atcgaaggcc aagtcagaga aggaatagat ctaagagccg tgattatcgt 60

ggtgcacggt caaaggtaac aagagctgat acgaggaaca gagacgatac tcttgccctc 120

agtatgtatc aggggcctcc gagtgccgac caggggaaca acatggcgga tgcccctcgg 180

tttggcttct ggacttcagt aagccaatgt ctgcaatact tgtgggccag gaggcacttg 240

ggcctgcttc tacttttatt ctggacgctg gtgatcctgt tccgtcctgt gaacactgcg 300

aaattgccca ttcttgctga agctgcagaa cttgaacccc ctttgggaaa tatgttggac 360

tttttctttc caacagcctg catcataagg gacaaccagg tggtggtggc atgtaataac 420

cagccgtatc ttagcgagag tgaatgttta aaatccaagt gctgttcttc aacatctggg 480

actataatca aatgctatgc cccagtaagg gacaagccta cacaggtgct acgggtgttt 540

ggccttgctg cgatcagcat tctagtcctg ggatttctgc ctatgtgctg ctgctccatg 600

tgctggagga ggaagaggat gaacaggatg ttgaaggttt tgaagaaaca gaaatcaaaa 660

gggaagaagc ctaaaggaag gaaggcgtca gaagagagag ctttactgtc ccattga 717

<210> SEQ ID NO 134
<211> LENGTH: 238
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 134

Met Pro Ser Asp Arg Arg Pro Ser Gln Arg Arg Asn Arg Ser Lys Ser
1 5 10 15

Arg Asp Tyr Arg Gly Ala Arg Ser Lys Val Thr Arg Ala Asp Thr Arg
20 25 30

Asn Arg Asp Asp Thr Leu Ala Leu Ser Met Tyr Gln Gly Pro Pro Ser
35 40 45

Ala Asp Gln Gly Asn Asn Met Ala Asp Ala Pro Arg Phe Gly Phe Trp
50 55 60

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

Gly Leu Leu Leu Leu Leu Phe Trp Thr Leu Val Ile Leu Phe Arg Pro
85 90 95

Val Asn Thr Ala Lys Leu Pro Ile Leu Ala Glu Ala Ala Glu Leu Glu
100 105 110

Pro Pro Leu Gly Asn Met Leu Asp Phe Phe Phe Pro Thr Ala Cys Ile
115 120 125

Ile Arg Asp Asn Gln Val Val Val Ala Cys Asn Asn Gln Pro Tyr Leu
130 135 140

Ser Glu Ser Glu Cys Leu Lys Ser Lys Cys Cys Ser Ser Thr Ser Gly
145 150 155 160

Thr Ile Ile Lys Cys Tyr Ala Pro Val Arg Asp Lys Pro Thr Gln Val
165 170 175

Leu Arg Val Phe Gly Leu Ala Ala Ile Ser Ile Leu Val Leu Gly Phe
180 185 190

Leu Pro Met Cys Cys Cys Ser Met Cys Trp Arg Arg Lys Arg Met Asn
195 200 205

Arg Met Leu Lys Val Leu Lys Lys Gln Lys Ser Lys Gly Lys Lys Pro
210 215 220

Lys Gly Arg Lys Ala Ser Glu Glu Arg Ala Leu Leu Ser His
225 230 235

<210> SEQ ID NO 135
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 135

cccggagcac gtcgaggtct ac 22

<210> SEQ ID NO 136
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 136

ggtgaggggc ccaggaagc 19

<210> SEQ ID NO 137
<211> LENGTH: 21
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 137

cacaatgtat cctgttgaaa g 21

<210> SEQ ID NO 138
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 138

gagatgatac attcttccag 20

<210> SEQ ID NO 139
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 139

cttccgccaa ctcctcctac c 21

<210> SEQ ID NO 140
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 140

gatgcccgtg tcttgtcctt 20

<210> SEQ ID NO 141
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 141

cactaggctg ctgaggaaga t 21

<210> SEQ ID NO 142
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 142

gttttggtgg gcagcattga g 21

<210> SEQ ID NO 143
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 143

ggaccacccc aaatagaa 18

-continued

<210> SEQ ID NO 144
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 144

ccaccagctc aggaaga 17

<210> SEQ ID NO 145
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 145

tctgatggag cggtgggatg c 21

<210> SEQ ID NO 146
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 146

gtgtgcctcg gcttctttct tc 22

<210> SEQ ID NO 147
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 147

tggtgcgatc agccttatcc 20

<210> SEQ ID NO 148
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 148

cggttcgctc ctccagaa 18

<210> SEQ ID NO 149
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 149

tgtctgccca tttattgccg ctctct 26

<210> SEQ ID NO 150
<211> LENGTH: 795
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

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<400> SEQUENCE: 150

catatgtctt cacataggag gaaagcgaag gggaggaata ggagaagtca ccgtgccatg 60

cgtgtggctc acttagagct ggcaacttat gagttggcgg caactgagtc gaatcccgag 120

agcagccatc ctggatacga ggccgccatg gctgacaggc ctcagccagg atggcgggaa 180

tctctaaaga tgcgggtcag caaacccttt gggatgctca tgctctccat ttggatcctg 240

ctgttcgtgt gctactacct gtcctactac ctgtgctccg ggtcctcata ttttgtgctt 300

gcaaatggac atatcctgcc caacagtgaa aatgctcatg gccaatctct ggaagaagat 360

tccgcattgg aagctttgct gaatttttc tttccaacaa cttgcaatct gagggaaaat 420

caggtggcaa agccttgtaa tgagctgcaa gatcttagtg agagtgaatg tttgagacac 480

aaatgctgtt tttcatcatc ggggaccacg agcttcaaat gttttgctcc atttagagat 540

gtgcctaaac agatgatgca aatgtttggg cttggtgcga tcagccttat cctggtatgt 600

ctgcccattt attgccgctc tcttttctgg aggagcgaac cggccgatga tttacaaagg 660

caggacaaca gagttgtaac gggtttgaag aaacaaagaa ggaagcgaaa gaggaagtct 720

gaaatgttac agaaagcagc aagaggacgt gaggaacatg gtgacgagct cgagcaccac 780

caccaccacc actga 795

<210> SEQ ID NO 151
<211> LENGTH: 263
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 151

Met Ser Ser His Arg Arg Lys Ala Lys Gly Arg Asn Arg Arg Ser His
1 5 10 15

Arg Ala Met Arg Val Ala His Leu Glu Leu Ala Thr Tyr Glu Leu Ala
20 25 30

Ala Thr Glu Ser Asn Pro Glu Ser Ser His Pro Gly Tyr Glu Ala Ala
35 40 45

Met Ala Asp Arg Pro Gln Pro Gly Trp Arg Glu Ser Leu Lys Met Arg
50 55 60

Val Ser Lys Pro Phe Gly Met Leu Met Leu Ser Ile Trp Ile Leu Leu
65 70 75 80

Phe Val Cys Tyr Tyr Leu Ser Tyr Tyr Leu Cys Ser Gly Ser Ser Tyr
85 90 95

Phe Val Leu Ala Asn Gly His Ile Leu Pro Asn Ser Glu Asn Ala His
100 105 110

Gly Gln Ser Leu Glu Glu Asp Ser Ala Leu Glu Ala Leu Leu Asn Phe
115 120 125

Phe Phe Pro Thr Thr Cys Asn Leu Arg Glu Asn Gln Val Ala Lys Pro
130 135 140

Cys Asn Glu Leu Gln Asp Leu Ser Glu Ser Glu Cys Leu Arg His Lys
145 150 155 160

Cys Cys Phe Ser Ser Ser Gly Thr Thr Ser Phe Lys Cys Phe Ala Pro
165 170 175

Phe Arg Asp Val Pro Lys Gln Met Met Gln Met Phe Gly Leu Gly Ala
180 185 190

Ile Ser Leu Ile Leu Val Cys Leu Pro Ile Tyr Cys Arg Ser Leu Phe
195 200 205

Trp Arg Ser Glu Pro Ala Asp Asp Leu Gln Arg Gln Asp Asn Arg Val

-continued

```
    210                 215                 220

Val Thr Gly Leu Lys Lys Gln Arg Arg Lys Arg Lys Arg Lys Ser Glu
225                 230                 235                 240

Met Leu Gln Lys Ala Ala Arg Gly Arg Glu Glu His Gly Asp Glu Leu
                245                 250                 255

Glu His His His His His His
            260
```

<210> SEQ ID NO 152
<211> LENGTH: 609
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 152

```
catatgcggg tcagcaaacc ctttgggatg ctcatgctct ccatttggat cctgctgttc     60

gtgtgctact acctgtccta ctacctgtgc tccgggtcct catattttgt gcttgcaaat    120

ggacatatcc tgcccaacag tgaaaatgct catggccaat ctctggaaga agattccgca    180

ttggaagctt tgctgaattt tttctttcca acaacttgca atctgaggga aaatcaggtg    240

gcaaagcctt gtaatgagct gcaagatctt agtgagagtg aatgtttgag acacaaatgc    300

tgtttttcat catcggggac cacgagcttc aaatgttttg ctccatttag agatgtgcct    360

aaacagatga tgcaaatgtt tgggcttggt gcgatcagcc ttatcctggt atgtctgccc    420

atttattgcc gctctctttt ctggaggagc gaaccggccg atgatttaca aaggcaggac    480

aacagagttg taacgggttt gaagaaacaa agaaggaagc gaaagaggaa gtctgaaatg    540

ttacagaaag cagcaagagg acgtgaggaa catggtgacg agctcgagca ccaccaccac    600

caccactga                                                            609
```

<210> SEQ ID NO 153
<211> LENGTH: 201
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 153

```
Met Arg Val Ser Lys Pro Phe Gly Met Leu Met Leu Ser Ile Trp Ile
1               5                   10                  15

Leu Leu Phe Val Cys Tyr Tyr Leu Ser Tyr Tyr Leu Cys Ser Gly Ser
            20                  25                  30

Ser Tyr Phe Val Leu Ala Asn Gly His Ile Leu Pro Asn Ser Glu Asn
        35                  40                  45

Ala His Gly Gln Ser Leu Glu Glu Asp Ser Ala Leu Glu Ala Leu Leu
    50                  55                  60

Asn Phe Phe Phe Pro Thr Thr Cys Asn Leu Arg Glu Asn Gln Val Ala
65                  70                  75                  80

Lys Pro Cys Asn Glu Leu Gln Asp Leu Ser Glu Ser Glu Cys Leu Arg
                85                  90                  95

His Lys Cys Cys Phe Ser Ser Ser Gly Thr Thr Ser Phe Lys Cys Phe
            100                 105                 110

Ala Pro Phe Arg Asp Val Pro Lys Gln Met Met Gln Met Phe Gly Leu
        115                 120                 125

Gly Ala Ile Ser Leu Ile Leu Val Cys Leu Pro Ile Tyr Cys Arg Ser
    130                 135                 140
```

-continued

```
Leu Phe Trp Arg Ser Glu Pro Ala Asp Asp Leu Gln Arg Gln Asp Asn
145                 150                 155                 160

Arg Val Val Thr Gly Leu Lys Lys Gln Arg Arg Lys Arg Lys Arg Lys
                165                 170                 175

Ser Glu Met Leu Gln Lys Ala Ala Arg Gly Arg Glu Glu His Gly Asp
            180                 185                 190

Glu Leu Glu His His His His His His
        195                 200
```

<210> SEQ ID NO 154
<211> LENGTH: 405
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 154

```
catatgcggg tcagcaaacc ctttgggatg ctcatgctct ccatttggat cctgctgttc     60

gtgtgctact acctgtccta ctacctgtgc tccgggtcct catattttgt gcttgcaaat    120

ggacatatcc tgcccaacag tgaaaatgct catggccaat ctctggaaga agattccgca    180

ttggaagctt tgctgaattt tttctttcca acaacttgca atctgaggga aaatcaggtg    240

gcaaagcctt gtaatgagct gcaagatctt agtgagagtg aatgtttgag acacaaatgc    300

tgtttttcat catcggggac cacgagcttc aaatgttttg ctccatttag agatgtgcct    360

aaacagatga tgcaaatgct cgagcaccac caccaccacc actga                    405
```

<210> SEQ ID NO 155
<211> LENGTH: 133
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 155

```
Met Arg Val Ser Lys Pro Phe Gly Met Leu Met Leu Ser Ile Trp Ile
1               5                   10                  15

Leu Leu Phe Val Cys Tyr Tyr Leu Ser Tyr Tyr Leu Cys Ser Gly Ser
            20                  25                  30

Ser Tyr Phe Val Leu Ala Asn Gly His Ile Leu Pro Asn Ser Glu Asn
        35                  40                  45

Ala His Gly Gln Ser Leu Glu Glu Asp Ser Ala Leu Glu Ala Leu Leu
    50                  55                  60

Asn Phe Phe Phe Pro Thr Thr Cys Asn Leu Arg Glu Asn Gln Val Ala
65                  70                  75                  80

Lys Pro Cys Asn Glu Leu Gln Asp Leu Ser Glu Ser Glu Cys Leu Arg
                85                  90                  95

His Lys Cys Cys Phe Ser Ser Ser Gly Thr Thr Ser Phe Lys Cys Phe
            100                 105                 110

Ala Pro Phe Arg Asp Val Pro Lys Gln Met Met Gln Met Leu Glu His
        115                 120                 125

His His His His His
    130
```

<210> SEQ ID NO 156
<211> LENGTH: 38
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 156

cacacacaca tatgtcttca cataggagga aagcgaag 38

<210> SEQ ID NO 157
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 157

cacacactcg agctcgtcac catgttcctc acgtc 35

<210> SEQ ID NO 158
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 158

cacacacaca tatgcgggtc agcaaaccct ttggga 36

<210> SEQ ID NO 159
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 159

cacacactcg agctcgtcac catgttcctc acgtc 35

<210> SEQ ID NO 160
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 160

cacacacaca tatgcgggtc agcaaaccct ttggga 36

<210> SEQ ID NO 161
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 161

cacacactcg agcatttgca tcatctgttt aggc 34

<210> SEQ ID NO 162
<211> LENGTH: 936
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 162

gaattccttc tgggccacgg actgccggac cgttgggctg tgaggcagcg tctcagcgag 60

gcggcacccg gagccatgtc ttcacatagg aggaaagcga aggggaggaa taggagaagt 120

caccgtgcca tgcgtgtggc tcacttagag ctggcaactt atgagttggc ggcaactgag 180

-continued

tcgaatcccg agagcagcca tcctggatac gaggccgcca tggctgacag gcctcagcca 240

ggatggcggg aatctctaaa gatgcgggtc agcaaaccct ttgggatgct catgctctcc 300

atttggatcc tgctgttcgt gtgctactac ctgtcctact acctgtgctc cgggtcctca 360

tattttgtgc ttgcaaatgg acatatcctg cccaacagtg aaaatgctca tggccaatct 420

ctggaagaag attccgcatt ggaagctttg ctgaattttt tctttccaac aacttgcaat 480

ctgagggaaa atcaggtggc aaagccttgt aatgagctgc aagatcttag tgagagtgaa 540

tgtttgagac acaaatgctg tttttcatca tcggggacca cgagcttcaa atgttttgct 600

ccatttagag atgtgcctaa acagatgatg caaatgtttg ggcttggtgc gatcagcctt 660

atcctggtat gtctgcccat ttattgccgc tctcttttct ggaggagcga accggccgat 720

gatttacaaa ggcaggacaa cagagttgta acgggtttga agaaacaaag aaggaagcga 780

aagaggaagt ctgaaatgtt acagaaagca gcaagaggac gtgaggaaca tggtgacgag 840

ctcgagtcta gagggccctt cgaaggtaag cctatcccta accctctcct cggtctcgat 900

tctacgcgta ccggtcatca tcaccatcac cattga 936

<210> SEQ ID NO 163
<211> LENGTH: 311
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 163

Glu Phe Leu Leu Gly His Gly Leu Pro Asp Arg Trp Ala Val Arg Gln
1 5 10 15

Arg Leu Ser Glu Ala Ala Pro Gly Ala Met Ser Ser His Arg Arg Lys
20 25 30

Ala Lys Gly Arg Asn Arg Arg Ser His Arg Ala Met Arg Val Ala His
35 40 45

Leu Glu Leu Ala Thr Tyr Glu Leu Ala Ala Thr Glu Ser Asn Pro Glu
50 55 60

Ser Ser His Pro Gly Tyr Glu Ala Ala Met Ala Asp Arg Pro Gln Pro
65 70 75 80

Gly Trp Arg Glu Ser Leu Lys Met Arg Val Ser Lys Pro Phe Gly Met
85 90 95

Leu Met Leu Ser Ile Trp Ile Leu Leu Phe Val Cys Tyr Tyr Leu Ser
100 105 110

Tyr Tyr Leu Cys Ser Gly Ser Ser Tyr Phe Val Leu Ala Asn Gly His
115 120 125

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

Ser Ala Leu Glu Ala Leu Leu Asn Phe Phe Phe Pro Thr Thr Cys Asn
145 150 155 160

Leu Arg Glu Asn Gln Val Ala Lys Pro Cys Asn Glu Leu Gln Asp Leu
165 170 175

Ser Glu Ser Glu Cys Leu Arg His Lys Cys Cys Phe Ser Ser Ser Gly
180 185 190

Thr Thr Ser Phe Lys Cys Phe Ala Pro Phe Arg Asp Val Pro Lys Gln
195 200 205

Met Met Gln Met Phe Gly Leu Gly Ala Ile Ser Leu Ile Leu Val Cys
210 215 220

Leu Pro Ile Tyr Cys Arg Ser Leu Phe Trp Arg Ser Glu Pro Ala Asp

-continued

```
225                 230                 235                 240

Asp Leu Gln Arg Gln Asp Asn Arg Val Val Thr Gly Leu Lys Lys Gln
                245                 250                 255

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

Gly Arg Glu Glu His Gly Asp Glu Leu Glu Ser Arg Gly Pro Phe Glu
        275                 280                 285

Gly Lys Pro Ile Pro Asn Pro Leu Leu Gly Leu Asp Ser Thr Arg Thr
    290                 295                 300

Gly His His His His His His
305                 310


<210> SEQ ID NO 164
<211> LENGTH: 67
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 164

gggaattcat gtcttcacat aggaggaaag cgcacacact cgagctcgtc accatgttcc     60

tcacgtc                                                               67


<210> SEQ ID NO 165
<211> LENGTH: 73
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 165

cacacacaca tatgtcttca cataggagga aagcgaagca cacactcgag ctcgtcacca     60

tgttcctcac gtc                                                        73


<210> SEQ ID NO 166
<211> LENGTH: 74
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 166

cacacacaca tatgcgggtc agcaaaccct ttgggacaca cacacatatg tcttcacata     60

ggaggaaagc gaag                                                       74


<210> SEQ ID NO 167
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Oligonucleotide

<400> SEQUENCE: 167

tactcccctg ccctcaacaa gctcaggcgg ctcataggg                            39
```

What is claimed is:

1. An isolated antibody or antigen-binding antibody fragment that selectively binds to an extracellular domain of NY-SAR-35 as set forth as SEQ ID NO: 155 or a fragment thereof that is at least 8 amino acids in length.

2. The isolated antibody or antigen-binding antibody fragment of claim **1**, wherein the fragment of the NY-SAR-35 extracellular domain is at least 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 75 or 100 amino acids in length.

3. A method for diagnosing cancer in a subject comprising:
obtaining a biological sample from a subject, and
determining the expression of a sarcoma-associated antigen in the biological sample by contacting the sample with an isolated antibody or antigen-binding antibody fragment of claim 1,
wherein the expression of the sarcoma-associated antigen in the sample is diagnostic for cancer in the subject.

4. The method of claim 3, wherein the antibody is a monoclonal, chimeric, human, humanized or single chain antibody; or wherein the antigen-binding antibody fragment is a $F(ab')_2$, Fab, Fd, or Fv fragment.

5. The isolated antibody or antigen-binding antibody fragment of claim 1, wherein the antibody is a monoclonal, chimeric, human, humanized or single chain antibody; or wherein the antigen-binding fragment is a $F(ab')_2$, Fab, Fd, or Fv fragment.

6. The isolated antibody or antigen-binding antibody fragment of claim 1, wherein the antibody or antigen-binding fragment is labeled with a detectable label.

7. The isolated antibody or antigen-binding antibody fragment of claim 6, wherein the detectable label is a fluorescent or radioactive label.

8. The method of claim 3, wherein the sample is selected from the group consisting of tissue, cells, and blood.

9. The method of claim 3, wherein the cancer is a sarcoma.

10. A kit for the diagnosis of cancer in a subject, comprising:
one or more isolated antibodies or antigen-binding antibody fragments of claim 1 and instructions for the use of the one or more isolated binding polypeptides in the diagnosis of cancer.

11. The kit of claim 10, wherein the one or more isolated antibodies or antigen-binding antibody fragments are antibodies or antigen-binding fragments thereof.

12. The kit of claim 10, wherein the one or more isolated antibodies or antigen-binding antibody fragments are bound to a substrate.

13. A kit for the diagnosis of cancer in a subject, comprising:
one or more isolated antibodies or antigen-binding antibody fragments, that selectively binds to a polypeptide consisting of a sequence as set forth as SEQ ID NO: 55, or a fragment thereof that is at least 8 amino acids in length;
instructions for the use of the one or more isolated antibodies or antigen-binding antibody fragments in the diagnosis of cancer; and
one or more agents that bind specifically to a cancer-associated antigen other than a polypeptide consisting of a sequence as set forth as SEQ ID NO: 55 or a fragment thereof that is at least 8 amino acids in length.

14. A kit for the diagnosis of cancer in a subject, comprising:
one or more isolated antibodies or antigen-binding antibody fragments that selectively binds to a polypeptide consisting of a sequence as set forth as SEQ ID NO: 155, or a fragment thereof that is at least 8 amino acids in length; and
instructions for the use of the one or more isolated antibodies or antigen-binding antibody fragments in the diagnosis of cancer,
wherein the cancer is a sarcoma.

15. A composition, comprising:
an isolated antibody or antigen-binding antibody fragment of claim 1.

16. The composition of claim 15, wherein the antibody is a monoclonal, chimeric, human, humanized or single chain antibody; or wherein the antigen-binding antibody fragment is a $F(ab')_2$, Fab, Fd, or Fv fragment.

17. A composition, comprising
an isolated binding polypeptide that selectively binds to a polypeptide consisting of a sequence as set forth as SEQ ID NO: 55, or a fragment thereof that is at least 8 amino acids in length, wherein the isolated binding polypeptide is an antibody or antigen-binding fragment thereof, and wherein the antibody or antigen-binding fragment is conjugated to a cytotoxic or chemotherapeutic agent.

18. A composition, comprising
an isolated binding polypeptide that selectively binds to a polypeptide consisting of a sequence as set forth as SEQ ID NO: 55, or a fragment thereof that is at least 8 amino acids in length, wherein the isolated binding polypeptide is an antibody or antigen-binding fragment thereof, and
a cytotoxic or chemotherapeutic agent.

19. The composition of claim 15, further comprising a pharmaceutically acceptable carrier.

20. The isolated antibody or antigen-binding antibody fragment of claim 1, wherein the extracellular domain of NY-SAR-35 comprises SEQ ID NO:155.

21. The isolated antibody or antigen-binding antibody fragment of claim 20, wherein the fragment of the NY-SAR-35 extracellular domain is at least 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 75 or 100 amino acids of SEQ ID NO:155.

22. The isolated antibody or antigen-binding antibody fragment of claim 20, wherein the antibody is a monoclonal, chimeric, human, humanized or single chain antibody; or wherein the antigen-binding fragment is a $F(ab')_2$, Fab, Fd, or Fv fragment.

23. The isolated antibody or antigen-binding antibody fragment of claim 20, wherein the antibody or antigen-binding fragment is labeled with a detectable label.

24. The isolated antibody or antigen-binding antibody fragment of claim 23, wherein the detectable label is a fluorescent or radioactive label.

* * * * *

专利名称(译)	人肉瘤相关抗原		
公开(公告)号	US8252903	公开(公告)日	2012-08-28
申请号	US12/683374	申请日	2010-01-06
[标]申请(专利权)人(译)	路德维格癌症研究所		
申请(专利权)人(译)	路德维希癌症研究所有限公司.		
当前申请(专利权)人(译)	路德维希癌症研究所		
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IPC分类号	C07K16/00 G01N33/53		
CPC分类号	G01N33/57488 C07K14/4748 A61K38/00 Y10T436/143333 A61P35/00		
优先权	10/529655 2010-02-16 US PCT/US2003/030870 2003-09-30 WO 10/260708 2009-07-14 US		
其他公开文献	US20100172910A1		
外部链接	Espacenet USPTO		

摘要(译)

本发明涉及肉瘤相关抗原和编码它们的核酸分子。本发明进一步涉及与肉瘤相关的核酸分子，多肽及其片段在用于诊断和治疗诸如癌症的疾病的方法和组合物中的用途。更具体地，本发明涉及新型癌症/睾丸（CT）抗原NY-SAR-35的发现。

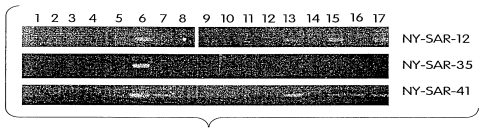

Fig. 1A

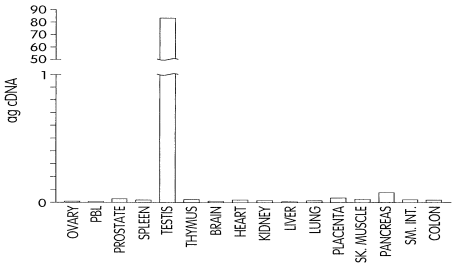

Fig. 1B