

(19) World Intellectual Property
Organization
International Bureau



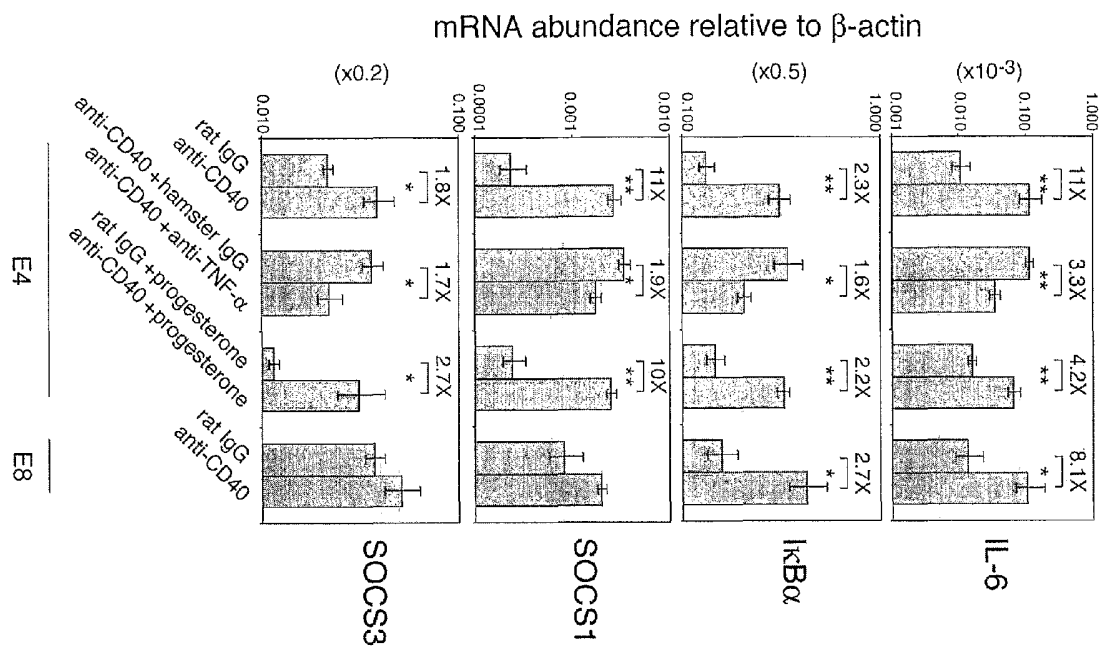
(43) International Publication Date
8 December 2005 (08.12.2005)

PCT

(10) International Publication Number
WO 2005/115456 A2

- (51) International Patent Classification⁷: **A61K 39/395**
- (21) International Application Number:
PCT/US2005/018790
- (22) International Filing Date: 27 May 2005 (27.05.2005)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/575,143 28 May 2004 (28.05.2004) US
- (71) Applicant (for all designated States except US): **PRESIDENT AND FELLOWS OF HARVARD COLLEGE** [US/US]; 1350 Massachusetts Avenue, Suite 727, Cambridge, MA 02138 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **ERLEBACHER, Adrian** [US/US]; 41 Orchard Street, Apt #2, Jamaica Plain, MA 02130 (US). **GLIMCHER, Laurie, H.** [US/US]; 51 Hampshire Street, West Newton, MA 02165 (US).
- (74) Agents: **MEGAN, E., Williams et al.**; Lahive & Cockfield, LLP, 28 State Street, Boston, MA 02109 (US).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHODS OF MODULATING THE REPRODUCTIVE ENDOCRINE SYSTEM BY MODULATION OF TNF α ACTIVITY



(57) Abstract: The present invention provides treatment methods, as well as prognostic and diagnostic methods of modulating the reproductive-endocrine system, e.g., inhibiting spontaneous abortion, by modulating TNF- α expression and/or activity.

ETHODS OF MODULATING THE REPRODUCTIVE ENDOCRINE SYSTEM BY MODULATION OF TNF- α ACTIVITY

Related Applications

This application claims the benefit of priority to U.S. Provisional Application Serial No. 60/575,143, filed May 28, 2004, the entire contents of which is incorporated herein by this reference.

Government Funding

Work described herein was supported, at least in part, by National Institutes of Health (NIH) under grants AI01650 and AI54370. The government may therefore have certain rights in this invention.

Background of the Invention

The mechanisms underlying immune-mediated pregnancy failure remain largely unknown (Laird, S.M., *et al.* (2003) *Hum Reprod Update* 9:163-174). In women with recurrent pregnancy loss, increased numbers and cellular activation of peripheral blood CD56⁺ natural killer (NK) cells have suggested an important role for the innate immune system (Aoki, K., *et al.* (1995) *Lancet* 345:1340-1342; Coulam, C.B., *et al.* (1995) *Am J Reprod Immunol* 33:40-46; Kwak, J.Y., *et al.* (1995) *Am J Reprod Immunol* 34:93-99; Emmer, P.M., *et al.* (2000) *Hum Reprod* 15:1163-1169; Ntrivalas, E.I., *et al.* (2001) *Hum Reprod* 16:855-861). Since NK cells produce the signature T helper-1 (Th1) cytokine IFN- γ , NK cell activation during pregnancy might explain the apparent Th1 bias also associated with recurrent pregnancy loss (Raghupathy, R. (1997) *Immunol Today* 18:478-482; Piccinni, M.P., *et al.* (1998) *Nat Med* 4:1020-1024). These associations, however, have not led to a clear understanding of the ultimate cause of fetal loss. Data from rodent studies have suggested that the major mechanism of immune-mediated pregnancy failure is immune activation at the maternal-fetal interface. Activation of decidual immune cells with attendant inflammatory cytokine production or activation of complement *via* the binding of anti-phospholipid antibodies is thought to directly damage the fetus and placenta or lead to derangements in decidual or placental hemostasis (Laird, S.M., *et al.* (2003) *Hum Reprod Update* 9:163-174; Gendron, R.L., *et al.* (1990) *J Reprod Fertil* 90:395-402; Clark, D.A., *et al.* (1998) *J Immunol* 160:545-549; Holers, V.M., *et al.* (2002) *J Exp Med* 195:211-220).

Endocrine failure is not thought to be an issue in recurring spontaneous abortion and the possibility that immune activation might cause pregnancy failure by inhibiting the reproductive endocrine system has been largely unexplored, despite indications that immune processes regulate reproductive endocrine function in non-

pregnant mammals. Inflammatory cytokines are thought to inhibit gonadotropin production at the level of the hypothalamus and pituitary in cases of chronic or acute illness (Rivest, S., and Rivier, C. (1995) *Endocr Rev* 16:177-199), and inhibit progesterone synthesis by the corpus luteum and promote luteal regression as part of the normal ovulatory cycle (Davis, J.S., and Rueda, B.R. (2002) *Front Biosci* 7:d1949-1978). During early gestation in rodents, progesterone production by the corpus luteum is driven primarily by pituitary-derived prolactin binding to its Janus kinase (JAK) 2/Signal transducer and activator of transcription (STAT) 5-coupled receptor expressed by corpus luteal cells (Risk, M., and Gibori, G. (2001) Mechanisms of luteal cell regulation by prolactin. In Prolactin. N.D. Horseman, editor. Boston: Kluwer Academic Publishers. 265-295).

The binding of progesterone to its nuclear receptor, in turn, is thought to maintain decidual viability and inhibit myometrial contractility (Deanesly, R. (1973) *J Reprod Fertil* 35:183-186; Jaffe, R.B. (1999). Neuroendocrine-metabolic regulation of pregnancy. In Reproductive Endocrinology. S.S.C. Yen, R.B. Jaffe, and R.L. Barbieri, editors. Philadelphia: W. B. Saunders Company. 751-784). In addition, there is strong evidence that lutenizing hormone (LH) produced by the pituitary is also critical for maintaining luteal function in rats early in pregnancy (Raj, H. G. and Moudgal, N.R. (1970) *Endocrinology* 86:874), and this is likely also to be the case in mice (Mednick, D.L., *et al.* (1980) *J. Reprod. Fertil.* 60:201). Thus, the reproductive endocrine system provides multiple potential points for inhibition by the immune system. However, it is unknown whether and how such pathways play a role during pregnancy.

Summary of the Invention

The present invention is based, at least in part, on the discovery that spontaneous abortion requires TNF- α . In particular, the present invention demonstrates that in a murine model of pregnancy loss employing anti-CD40 ligation, TNF- α acts on corpus luteal cells to induce the expression of the suppressor of cytokine signaling molecules, which in turn leads to decreased progesterone levels. Accordingly, the instant invention provides methods to modulate the reproductive-endocrine system. In one embodiment, these methods enable subjects, both human and animal subjects, to carry offspring to term by inhibiting spontaneous abortion.

In one aspect, the invention pertains to a method of inhibiting spontaneous abortion in a mammalian subject comprising administering to the mammalian subject a compound that inhibits TNF- α activity such that spontaneous abortion in the mammalian subject is inhibited.

In another aspect, the invention pertains to a method of enhancing the ability of a mammalian subject to carry at least one embryo to term, comprising administering to the mammalian a compound that inhibits TNF α activity such that the ability of the mammalian subject to carry at least one embryo to term is enhanced.

5 In one embodiment, the compound is an antibody that binds to TNF α .
In another embodiment, the antibody that binds to TNF α binds human TNF α .

In another embodiment, the antibody that binds to human TNF α is selected from the group consisting of: HUMIRA[®] and REMICADE[®].

10 In yet another embodiment, the compound is a soluble form of at least one TNF receptor.

In one embodiment, the soluble form of TNF receptor is selected from the group consisting of: ENBREL[®] and LENERCEPT[®].

15 In one embodiment, the compound is administered in an amount sufficient to prevent the upregulation of SOCS1 and SOCS3 expression such that spontaneous abortion is inhibited.

In another embodiment, the compound is administered in an amount sufficient to maintain progesterone levels in early pregnancy such that spontaneous abortion is inhibited.

20 In another embodiment, the method further comprises administering progesterone or a progesterone derivative.

In one embodiment, the mammalian subject has had a previous spontaneous abortion.

25 In one embodiment, the compound is administered to the mammalian subject prior to implantation of an embryo.

In one embodiment, the compound is administered to the mammalian subject after implantation of an embryo.

In one embodiment, the mammalian subject is human.

In another embodiment, the subject is a domesticated animal.

30 In one embodiment, the subject is an endangered species.

In another embodiment, the subject is a non-human animal being used to carry cloned, non-human animals.

In one aspect, the invention pertains to a prognostic method for determining whether a subject is at risk for having a spontaneous abortion comprising
35 detecting the presence or level of at least one of SOCS1, SOCS3 or I κ B α mRNA or polypeptide in a biological sample obtained from said subject to thereby determine whether the subject is at risk for having a spontaneous abortion, wherein if the level of at least one of SOCS1, SOCS3 or I κ B α mRNA or polypeptide is elevated relative to a

suitable control, the subject is at risk of having a spontaneous abortion.

In yet another aspect, the invention pertains to a prognostic method for determining whether a subject is at risk for having a spontaneous abortion comprising detecting the presence or level of mRNA or polypeptide of at least one of IL-6 and TNF α in a biological sample obtained from said subject, to thereby determining whether the subject is at risk for having a spontaneous abortion, wherein if the level of at least one of IL-6 and TNF α mRNA or polypeptide is elevated relative to a suitable control, the subject is at risk of having a spontaneous abortion.

In another aspect, the invention pertains to a diagnostic method for determining whether a subject has had a spontaneous abortion that would benefit from treatment with a compound that inhibits TNF α activity comprising detecting the presence or level of SOCS1, SOCS3 or I κ B α mRNA or polypeptide in a biological sample obtained from said subject to thereby determine whether the subject has had a spontaneous abortion that would benefit from treatment with a compound that inhibits TNF α activity, wherein if the level of at least one of SOCS1, SOCS3 or I κ B α mRNA or polypeptide is elevated relative to a suitable control, the subject has had a spontaneous abortion.

In another embodiment, the invention pertains to a diagnostic method for determining whether a subject has had a spontaneous abortion that would benefit from treatment with a compound that inhibits TNF α activity comprising detecting the presence or level of mRNA or polypeptide of at least one of IL-6 and TNF α in a biological sample obtained from said subject thereby determining whether the subject has had a spontaneous abortion that would benefit from treatment with a compound that inhibits TNF α activity, wherein if the level of at least one of IL-6 and TNF α mRNA or polypeptide is elevated relative to a suitable control, the subject has had a spontaneous abortion..

In still another embodiment, the invention pertains to a method for determining whether a subject is responding to treatment for recurring spontaneous abortions comprising detecting the presence or level of SOCS1, SOCS3 or I κ B α mRNA or polypeptide in a biological sample obtained from said subject to thereby determining whether the subject is responding to treatment for recurring spontaneous abortions, wherein if the level of at least one of SOCS1, SOCS3 or I κ B α mRNA or polypeptide is reduced relative to a suitable control, the subject is responding to treatment for recurring spontaneous abortions.

In another embodiment, the invention pertains to a method for determining whether a subject is responding to treatment for recurring spontaneous abortions comprising detecting the presence or level of mRNA or polypeptide of at least one of IL-6 and TNF α in a biological sample obtained from said subject to thereby

determining whether the subject is responding to treatment for recurring spontaneous abortions, wherein if the level of at least one of IL-6 and TNF α mRNA or polypeptide is reduced relative to a suitable control, the subject is responding to treatment for recurring spontaneous abortions.

5 In one embodiment, the method further comprises detecting the presence or level of mRNA or polypeptide of one or more of an immune cell surface molecule selected from the group consisting of: CD69, CD25, CD44, CD45RB, CD62L, CD80, CD86, CD40, MHC class II, and CD54.

10 In one embodiment, the method further comprises detecting the presence or level of marker mRNA or polypeptide, wherein the marker is selected from the group consisting of: luteinizing hormone, luteinizing hormone receptor, steroid acute regulatory protein, phosphorylated steroid acute regulatory protein, and 3 β -hydroxysteroid dehydrogenase.

15 In another embodiment, the method further comprises detecting the level of progesterone.

In one embodiment, the biological sample is selected from the group consisting of: a tissue sample, a cell sample, or a serum sample.

In one embodiment, the tissue sample is a chorionic villus sample or a placental sample.

20

Brief Description of the Drawings

Figures 1A-1E show that overt embryo resorption is preceded by decreased serum progesterone concentrations following systemic CD40 ligation.

25 *Figures 2A-2D* depict post-receptor prolactin signaling defects and luteal insufficiency following systemic CD40 ligation.

Figures 3A-3I depict rescue of CD40 ligation-induced pregnancy failure by exogenous progesterone or prolactin.

30 *Figures 4A-4E* depict components of immune activation acting upstream from endocrine failure.

Figures 5A-5D depict the involvement of TNF- α in anti-CD40-induced pregnancy failure.

Figure 6 depicts the ovarian expression of IL-6, I κ B α , SOCS1 and SOCS3 upon systemic CD40 ligation.

Detailed Description of the Invention

The present invention is based, at least in part, on the discovery that activation of the innate immune system and associated inflammatory cytokine production leads to pregnancy failure through inhibition of the reproductive-endocrine system. More specifically, utilizing an animal model in which pregnancy failure is induced by systemic activation of the CD40 immune costimulatory pathway, it was found that spontaneous abortion requires TNF- α . Without wishing to be bound by theory, TNF- α appears to act on corpus luteal cells to induce the expression of the suppressor of cytokine signaling molecules, SOCS1 and SOCS3, which in turn leads to decreased progesterone levels and spontaneous abortion.

Accordingly, the instant invention provides methods, *inter alia*, to modulate the reproductive endocrine system which inhibits spontaneous abortion in subjects and enables subjects, both human and animal subjects, to carry offspring to term.

Various aspects of the invention are described in further detail in the following subsections:

I. Definitions

The articles "a" and "an" are used herein to refer to one or to more than one (*i.e.* to at least one) of the grammatical object of the article. By way of example, "a TNF- α receptor" means one or more than one TNF- α receptor.

As used herein, "TNF- α " is a non-glycosylated protein of 17 kDa and a length of 157 amino acids which is observed as homotrimer under physiological conditions, but can also exist as a homodimer. The 17 kDa form of TNF- α is synthesized as a 26 kDa soluble precursor molecule and is processed to the 17 kDa form by TNF-alpha converting enzyme (TACE) (Jones, E. Y. *et al. Nature*, 1989, 338, 225-8).

Most of the cellular actions of TNF- α have been attributed to the activities of two distinct TNF- α receptor molecules, a type I receptor and a type II receptor. "TNFR1" (also known as, p55, CD120a, and TNFRSF1A) and "TNFR2" (p75, CD120b, and TNFRSF1B) (Bazzoni, F. and Beutler, B. N. *Engl. J. Med.*, 1996, 334, 1717-25) which are expressed ubiquitously. Binding of TNF- α to its membrane-bound receptors induces diverse effects in different organs and tissues. The extracellular portions of both TNF receptors can also be shed from the cell surface through proteolytic cleavage and exist in soluble form. These soluble receptors retain the ability to bind TNF- α and thus may act as physiological modulators of TNF activity *in vivo* (Engelmann, H.; *et al. J. Biol. Chem.*, 1989, 264, 11974-80, Seckinger, P. *et al. J. Exp.*

Med., 1988, 167, 1511-6).

The cytoplasmic domains of TNFRI bear a motif termed 'death domain' (DD). The DD is a protein-protein interaction motif that allows two proteins with DD to bind to each other. Binding of TNF- α to TNFRI induces recruitment of the DD-containing protein TRADD to the DD of TNFRI (Hsu, H. *et al.*, *Cell*, 1995, 81, 495-504). Overexpression of TRADD also induces TNF- α -regulated responses such as apoptosis and activation of the transcription factors NF- κ B and Jun kinase (Hsu, H. *et al.*, *Immunity*, 1996, 4, 387-96).

Recently several TNF receptor-associated proteins have been cloned. The cytoplasmic domains of the "TNF receptor-associated proteins" do not have any intrinsic enzymatic activity, and hence they signal by inducing aggregation of intracellular adaptor molecules.

TNF receptor-associated factors (TRAF) also interact with members of the TNFR family (Arch, R. H. *et al.* *Genes Dev.*, 1998, 12, 2821-30). Most of TRAF proteins interact with receptor molecules either directly, or indirectly through binding to other TRAF, or through binding to TRADD. TNFRII contains cytoplasmic TRAF binding motifs and is able to bind directly to TRAF proteins. Because TRAF2 can bind to TRADD, which in turn can associate with TNFRI, TRAF2 can indirectly participate in signaling from this receptor as well.

As used herein, the phrase "TNF- α activity" includes activities mediated by TNF- α , such as binding to a TNF receptor (*e.g.*, a type I or type II receptor, *e.g.*, TNFRI or TNFRII), transmission of a signal *via* such a receptor (*e.g.*, second messenger generation), modulation of gene transcription (*e.g.*, IL-6, SOCS1, SOCS3 or I κ B α), or downstream biological effects on a cell (*e.g.*, modulation of cytotoxicity, proliferation and/or apoptosis), or on an organism, *e.g.*, modulation of the reproductive endocrine system, *e.g.*, spontaneous abortion. Other exemplary TNF- α activities include: upmodulation of lymphoid activation markers, *e.g.*, CD69, CD25, CD44, CD45RB, and CD62L, upmodulation of SOCS1 and SCOS3 expression, upregulation of 20 α -HSD expression, downregulation of 3 β -HSD expression as well as downregulation of LHR expression, decreased prolactin receptor expression, and decreased progesterone production.

These or other activities of TNF- α can be assessed by one or more of several standard *in vitro* or *in vivo* assays known in the art. For example, the ability of a compound that modulates TNF- α activity or TNF- α receptor mediated signaling to modulate the presence or expression level of IL-6, SOCS1, SOCS3, and I κ B α can be assessed by semi-quantitative RT-PCR; the ability of an antibody to neutralize TNF- α activity can be assessed by inhibition of TNF- α -induced cytotoxicity of, for example, L929 cells; additionally, the ability of an antibody to inhibit TNF- α -induced expression

of, for example, ELAM-1 on HUVEC, as a measure of TNF- α -induced cellular activation, can be assessed.

As used herein, the phrase “reproductive endocrine system” includes the system of glands that have no ducts and that release their secretions, *e.g.*, hormones,
5 directly into the circulatory system and influence the reproductive system in female subjects, *e.g.*, the organs involved in producing eggs and in conceiving and carrying offspring. The glands of the reproductive endocrine system include, for example, the hypothalamus, pituitary, and the gonads. The organs of the reproductive system include, for example, in women, the ovaries, the fallopian tubes, the uterus, the cervix, and the
10 vagina.

As used herein, the term “hormone” includes a substance which is a product of living cells and that circulates in body fluids and produces a specific effect on the activity of cells remote from its point of origin. The term hormone, as used herein, also refers to synthetic versions thereof.

15 The terms “spontaneous abortion,” “miscarriage,” and “pregnancy loss,” used interchangeably herein, refer to the uninduced termination of a pregnancy. A spontaneous abortion as defined herein includes failure of a fertilized embryo to properly implant in the wall of the uterus of a subject or, once implanted, shedding of the embryo from the uterus of the subject, or reabsorption of an embryo by the subject,
20 and includes both recurrent loss and occult loss of a pregnancy.

As used herein the term “subject” includes mammalian subjects. A subject of the invention can be or can become naturally pregnant or can be or can become pregnant using assisted reproductive technologies, *e.g.*, *in vitro* fertilization, insemination, *etc.* In preferred embodiments, the subjects of the present invention are
25 human, although the claimed methods are also for use in other subjects such as domesticated animals, livestock, zoo animals, *etc.* In one embodiment, a subject of the invention is an endangered species. Non-limiting examples of endangered species, *e.g.*, endangered mammals, include Aye-aye, Banteng, Bighorn Sheep, Blue Whale, Bonobo, Common Chimpanzee, Chinese River Dolphin, Elephant, Fin Whale, Gelada, Giant
30 golden-crowned flyingfox, Giant Panda, Giant Pangolin, Golden Lio, Tamarin, Gorilla, Gray bat, Hawaiian Monk Seal, Indri, Kouprey, Leopard, Orangutan, Père David's Deer, Proboscis Monkey, Red Panda, Red Wolf, Sea Otter, Sei Whale, Snow Leopard, Steller's Sea Lion, Tiger, and Vaquita. In another embodiment, a subject is a non-human animal which is used for the purposes of carrying cloned non-human animals. Non-limiting
35 examples of subjects include humans, cows, cats, dogs, goats, horses, sheep, pigs, rats and mice.

In a preferred embodiment, a subject of the invention does not have detectable levels of anti-phospholipid antibodies (aPL). As used herein, "anti-phospholipid antibodies", are antibodies directed against phospholipids. Subjects with anti-phospholipid antibodies may develop antiphospholipid syndrome (APS) (also known as Hughes' syndrome) in which subjects may have blood clots, headaches, strokes, recurrent pregnancy loss, and thrombosis. Anti-phospholipid antibodies are often found in subjects with autoimmune disorders, such as systemic lupus erythematosus, however not all subjects with anti-phospholipid antibodies develop lupus. Non-limiting examples of anti-phospholipid antibodies are, lupus anticoagulant, anticardiolipin antibody, anti-beta 2 glycoprotein 1, and anti-prothrombin.

As used herein, the term "implantation" includes attachment of the fertilized egg to the uterine lining following a natural fertilization process or with the aid of assisted reproductive technology. As used herein "assisted reproductive technology" refers to any technically assisted method of reproduction such as, for example ovulation induction, *in vitro* fertilization, embryo transfer, and the like. In humans implantation usually occurs five to seven days after ovulation in the natural reproductive process.

As used herein, the term "maintain progesterone levels" includes maintaining such levels in the normal range for a pregnant female in order to maintain a pregnancy. Such levels can readily be determined by one of ordinary skill in the art. Exemplary guidelines for normal pregnant human progesterone levels are about 11.2 - 90.0 ng/mL in the first trimester, 25.6 - 89.4 ng/mL in the second trimester, and 48.4 - 422.5 ng/mL in the third trimester.

As used herein the term "embryo" includes a stage in the development of a multicellular organism between the time that the zygote is fertilized and the point at which the organism developing from that zygote becomes free-living.

As used herein, the various forms of the term "modulate" are intended to include upmodulation (*e.g.*, increasing or upregulating a particular response or activity) and downmodulation (*e.g.*, decreasing or downregulating a particular response or activity).

The term "interact" as used herein is meant to include detectable interactions between molecules, such as can be detected using, for example, a yeast two hybrid assay or coimmunoprecipitation. The term interact is also meant to include "binding" interactions between molecules. Interactions may be protein-protein or protein-nucleic acid in nature.

As used herein, the term "contacting" (*i.e.*, contacting a cell) includes incubating the compound and the cell together *in vitro* (*e.g.*, adding the compound to cells in culture) or administering the compound to a subject such that the compound and cells of the subject are contacted *in vivo*. The term "contacting" is not intended to

include exposure of cells to a modulator of TNF- α activity that may occur naturally in a subject (*i.e.*, exposure that may occur as a result of a natural physiological process).

As used herein, the term "test compound" includes a compound that has not previously been identified as, or recognized to be, a modulator of TNF- α activity and/or a modulator of reproductive endocrine function, *e.g.*, an inhibitor of spontaneous abortion.

The term "library of test compounds" is intended to refer to a panel comprising a multiplicity of test compounds.

As used herein, the term "cell free composition" includes an isolated composition which does not contain intact cells. Examples of cell free compositions include cell extracts and compositions containing isolated proteins.

As used herein, the term "immune cell" includes cells that are of hematopoietic origin and that play a role in the immune response. Immune cells include lymphocytes, such as B cells and T cells; dendritic cells; natural killer cells; and myeloid cells, such as monocytes, macrophages, eosinophils, mast cells, basophils, and granulocytes.

As used herein the term "innate immune system" includes natural or native immune mechanisms, *i.e.*, mechanisms that exist before infection, are capable of rapid responses to microbes, and react in essentially the same way to repeated infections.

As used herein, the term "adaptive immune system" or "specific immune system" includes immune mechanisms that are stimulated by exposure of infectious agents and increase in magnitude and defensive capabilities with each successive exposure to a particular microbe.

As used herein, "inflammation" is a local accumulation of fluid, plasma proteins and leukocytes (mostly neutrophils, macrophages and lymphocytes). Inflammation occurs after most kinds of tissue injuries or infections or immunologic stimulation as a defense against foreign or altered endogenous substances. Inflammation is normally a self-limiting episode. An inflammatory reaction is characterized by an initial increase in blood flow to the site of injury, enhanced vascular permeability, and the ordered and directional influx and selective accumulation of different effector cells from the peripheral blood at the site of injury.

Inflammation is also associated with the upmodulation of a number of cytokines, known collectively as pro-inflammatory cytokines. The major pro-inflammatory cytokines are IL1- α , IL1- β , IL6, and TNF- α . Other pro-inflammatory mediators include LIF, IFN- γ , OSM, CNTF, TGF- β , GM-CSF, IL11, IL12, IL17, IL18, IL8 and a variety of other chemokines that chemoattract inflammatory cells, and various neuromodulatory factors.

As used herein, "CD40" is a cell surface antigen that is a member of the TNF receptor superfamily. CD40 is also called Bp50 and TNFRSF5. CD40 is a transmembrane glycoprotein with a length of 277 amino acids (48 kDa). CD40 is phosphorylated and can be expressed as a homodimer. A soluble form of CD40 (28 kDa) has been described also. CD40 has a short cytoplasmic domain with limited homology to the conserved cytosolic death domain of the TNFRI receptor and APO-1. CD40 protein is expressed on all B-lymphocytes during various stages of development, activated T-cells and monocytes, follicular dendritic cells, thymic epithelial cells, and various carcinoma cell lines.

As used herein, the term "antibody", includes immunoglobulin molecules comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as HCVR or VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as LCVR or VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4.

The term antibody includes immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site which binds (immunoreacts with) an antigen, such as Fab and F(ab')₂ fragments, single chain antibodies, intracellular antibodies, scFv, Fd, or other fragments.

The term "antibody", as used herein, also includes antibodies that are prepared, expressed, created, or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell, antibodies isolated from a recombinant, combinatorial antibody library, antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic for human immunoglobulin genes (see *e.g.*, Taylor, L.D., *et al.* (1992) *Nucl. Acids Res.* 20:6287-6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of, for example, human immunoglobulin gene sequences to other DNA sequences. Such recombinant antibodies have, for example, variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant antibodies are subjected to *in vitro* mutagenesis (or, for example, when an

animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis), and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

Preferably, antibodies of the invention bind specifically or substantially specifically to TNF- α and/or TNF- α receptor molecules (*i.e.*, have little to no cross reactivity with non-TNF- α , non-TNF- α receptor molecules). The terms "monoclonal antibodies" and "monoclonal antibody composition", as used herein, refer to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope of an antigen, whereas the term "polyclonal antibodies" and "polyclonal antibody composition" refer to a population of antibody molecules that contain multiple species of antigen binding sites capable of interacting with a particular antigen. A monoclonal antibody composition thus typically display a single binding affinity for a particular antigen with which it immunoreacts.

An "isolated antibody", as used herein, is intended to refer to an antibody that is substantially free of other antibodies having different antigenic specificities (*e.g.*, an isolated antibody that specifically binds TNF- α or a TNF- α receptor and is substantially free of antibodies that specifically bind antigens other than TNF- α or a TNF- α receptor). An isolated antibody that specifically binds TNF- α or a TNF- α receptor may, however, have cross-reactivity to other antigens, such as TNF- α or TNF- α receptor molecules from other species. Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

A "neutralizing antibody", as used herein (or an "antibody that neutralizes TNF"), includes antibodies whose binding results in inhibition of the biological activity of TNF- α . This inhibition of the biological activity of TNF α can be assessed by measuring one or more indicators of TNF- α activity.

As used herein the term "soluble" with respect to TNF receptors includes forms of receptors which are not cell associated, *e.g.*, which lack transmembrane domains. Such soluble molecules may or may not be fusion proteins, *e.g.*, which incorporate amino acid sequences from a non-TNF receptor protein to improve desired characteristics, such as affinity, solubility, half-life, *etc.*

The term "treatment," as used herein, is defined as the application or administration of a therapeutic agent to a subject, or application or administration of a therapeutic agent to an isolated tissue or cell line from a subject, who has a disease, disorder, or infection, a symptom of a disease, disorder, or infection, or a predisposition toward a disease, disorder, or infection, with the purpose of curing, healing, alleviating, relieving, altering, remedying, ameliorating, improving or affecting the disease, disorder,

or infection, the symptoms of disease, disorder, or infection, or the predisposition toward a disease, disorder, or infection. A therapeutic agent includes agents which mediate TNF- α blockade (*i.e.*, inhibit TNF- α and/or TNF- α receptor activity) including, but not limited to, nucleic acid molecules, small molecules, peptides, peptidomimetics, antibodies, ribozymes, and sense and antisense oligonucleotides or nucleic acid molecules which mediate RNAi as described herein.

II. Methods of the Invention

A. Modulation of TNF- α Activity

The present invention demonstrates that activation of the innate immune system and associated inflammatory cytokine production leads to pregnancy failure through inhibition of the reproductive-endocrine system and that TNF- α is required for this failure. A number of changes in gene expression or cell surface expression are associated with spontaneous abortion (using an anti-CD40 ligation model), such as for example, upregulation of inflammatory cytokine production, *e.g.*, IL-6, modulated expression of cell surface lymphoid markers, *e.g.*, CD69, CD25, CD44, CD45RB, CD62L, CD80, CD86, CD40, MHC class II, and CD54, upregulation of SOCS1, SOCS3 and I κ B α , upregulated 20 α -HSD expression, downregulated 3 β -HSD expression as well as downregulated LHR expression, decreased prolactin receptor expression and decreased progesterone production.

Accordingly, in one aspect, the invention features methods of modulating the reproductive endocrine system, *e.g.*, inhibiting spontaneous abortion, comprising administering an agent that modulates TNF- α activity, *e.g.*, by modulating TNF- α expression or TNF- α receptor-mediated signaling. In one embodiment, spontaneous abortion is inhibited in a mammalian subject by administering an antibody to TNF- α or a TNF- α blocking antibody which binds to at least one TNF- α receptor but does not transmit a signal. In another embodiment, spontaneous abortion in a mammalian subject is inhibited by administering a soluble form of the TNF- α receptor. In another embodiment, the ability of a mammalian subject having low progesterone levels to carry at least one embryo to term is enhanced by administering an agent that modulates TNF- α activity in a subject. In a further embodiment, progesterone or a progesterone derivative (*e.g.*, the 19-nortestosterone derivatives (*e.g.*, norethisterone, levonorgestrel, desogestrel, gestodene, norgestimate), and the progesterone derivatives (*e.g.*, medroxyprogesterone acetate, cyproterone acetate, progesterone caproate (*N Engl J Med.* 2003 349:1087)), is additionally administered to the subject. In another embodiment, the ability of a mammalian subject having increased NK cell activation or NK cell infiltrates to carry at least one embryo to term is enhanced by administering an agent that modulates TNF- α activity to a subject. In a preferred embodiment, the agent

that modulates TNF- α activity is administered in an amount sufficient to prevent the upregulation of SOCS1 and SOC3 expression. In another preferred embodiment, the compound that modulates TNF- α activity is administered in an amount sufficient to maintain progesterone levels during pregnancy.

5 In one embodiment, TNF- α activity is modulated without modulating IL-1 activity (either IL-1 α or IL-1 β).

In one embodiment, TNF- α activity is modulated in a subject that does not have detectable levels of anti-phospholipid antibodies. In another embodiment, TNF- α activity is modulated in a subject in which pregnancy is characterized by
10 activation of the innate immune system and/or inflammatory cytokine production. In another embodiment, TNF- α activity is modulated in a subject in which pregnancy is not characterized by direct damage at the maternal-fetal interface, *e.g.*, the placental blood supply.

Agents useful for modulating TNF- α activity can be identified utilizing
15 the screening assays of the invention, or can be a known compounds that modulate TNF- α activity, described in further detail below.

The methods of the present invention also include prognostic and diagnostic methods and methods which determine whether treatment of a subject is having the desired effect (hereinafter "treatment monitoring methods") or whether a
20 subject is in need of treatment. Prognostic methods include methods which determine whether subjects are at risk for developing a spontaneous abortion treatable by modulation of TNF- α . Diagnostic methods include methods which determine whether a subject might be at risk for or has experienced a spontaneous abortion treatable by modulation of TNF- α .

25

1. Inhibitory Compounds for Blockade of TNF- α activity

Data presented herein demonstrate that an increase in TNF- α activity is associated with spontaneous abortion. Accordingly, compounds that downmodulate TNF- α and/or TNFR activity can be used to modulate the reproductive endocrine
30 system, *e.g.*, inhibit spontaneous abortion and/or enhance the ability of a subject to carry an embryo to term.

Inhibitory compounds of the invention can act extracellularly or intracellularly to specifically modulate TNF- α activity. Exemplary molecules that act extracellularly to inhibit TNF- α activity include antibodies that recognize TNF- α , antibodies that bind to
35 the TNF- α receptor but do not transmit a signal, soluble forms of the TNF- α receptor, and dominant negative TNF- α mutants. As used herein, the term "intracellular binding molecule" is intended to include molecules that act intracellularly to inhibit the expression or activity of a molecule that mediates a TNF- α activity by binding to the

protein or to a nucleic acid (*e.g.*, an mRNA molecule) that encodes a protein. Examples of intracellular binding molecules, described in further detail below, include antisense nucleic acids, nucleic acid molecules that mediate RNAi, intracellular antibodies, or certain chemical agents that specifically inhibit TNF- α activity, *e.g.*, by acting to decrease expression or activity of TNF- α , its receptor, or a molecule involved in transducing a signal upon the binding of TNF- α to its receptor.

a. Anti-TNF Antibodies

One type of inhibitory compound that can be used for blockade of TNF- α activity is an antibody that binds to TNF- α and inhibits its activity, *e.g.*, by inhibiting the binding of TNF- α to its receptor and activate inflammatory pathways, *e.g.*, cytokine production.

Antibodies to TNF- α can be known or can be made using standard techniques.

In one embodiment, the anti-TNF- α antibody is a commercially available (known) anti-TNF- α antibody.

In one embodiment, the anti-TNF- α antibody is Infliximab. Infliximab, also referred to as cA2, is marketed as REMICADE[®], and produced by Centocor, Malvern, PA. REMICADE[®] is indicated for the treatment of rheumatoid arthritis and Crohn's Disease. REMICADE[®] is a humanized (*e.g.*, chimeric) IgG1 κ monoclonal antibody with an approximate molecular weight of 149, 000 daltons. It is composed of human constant and murine variable regions. Infliximab neutralizes the biological activity of TNF- α by binding with high affinity to the soluble and transmembrane forms of TNF- α and inhibits binding of TNF- α with its receptors (American Thoracic Society, Centers for Disease Control and Prevention (2000) *Am J Respir Crit Care Med* 161:S221; Knight, D.M., *et al.* (1993) *Molec Immunol* 30:1443). Infliximab does not neutralize TNF- β . Biological compositions and methods for this antibody can be found in, for example, US Patent 6284471: *Anti-TNF- α antibodies and assays employing anti-TNF- α antibodies*, Le, Junming, *et al*; US Patent 6277969: *Anti-TNF antibodies and peptides of human tumor necrosis factor*, Le, Junming, *et al.*

In another embodiment, the anti-TNF- α antibody is Adalimumab. Adalimumab, also referred to as D2E7, is marketed as Humira[™], and is produced by Cambridge Antibody Technology, Great Britain. Humira[™] is indicated for the treatment of rheumatoid arthritis. Humira[™] is a recombinant IgG1 monoclonal antibody composed of human heavy and light chain variable regions and human IgG1 κ constant regions. Adalimumab binds specifically to TNF- α and blocks the interaction with p55 (type I) and p75 (type II) cell surface TNF- α receptors. Adalimumab does not neutralize TNF- β . Adalimumab also lyses surface TNF- α expressing cells *in vitro* in the presence of complement. Biological compositions and methods for this antibody can be

found in, for example, US Patents 6,090,382, 6,258,562, and 6,509,015.

Other non-limiting, exemplary antibodies that can be used in connection with the instant invention include CBOOO6, BAY x 1351, and afelimomab (Vincent, J.L. 2000 *Int. J. Clin. Pract.* 54:190) and CDP571, an engineered human antibody that
5 neutralizes human TNF- α (Rankin E.C., *et al.* 1995. *Br. J. Rheumatol.* 34:334).

In one embodiment, antibodies may be modified to improve their characteristics, *e.g.*, to increase their half-life in serum. For example, CDP870 is anti-TNF- α antibody fragment modified to obtain a prolonged plasma half-life (approximately 14 days) (Choy, E.H. *et al.* 2002 *Rheumatology* 41:1133).

10 In another embodiment, an antibody to TNF- α is made using methods known to those of skill in the art. Antibodies can be prepared by immunizing a suitable subject, (*e.g.*, rabbit, goat, mouse or other mammal), *e.g.*, with a TNF- α protein immunogen. An appropriate immunogenic preparation can contain, for example, recombinantly expressed protein or a chemically synthesized peptide. The preparation
15 can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or similar immunostimulatory compound. Antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975, *Nature* 256:495-497) (see also, Brown *et al.* (1981) *J. Immunol* 127:539-46; Brown *et al.* (1980) *J Biol Chem* 255:4980-83; Yeh *et al.* (1976) *PNAS* 76:2927-31; and Yeh *et al.* (1982) *Int. J. Cancer* 29:269-75). The technology for producing monoclonal antibody hybridomas is well known (see generally R. H. Kenneth, in *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum Publishing Corp., New York, New York (1980); E. A. Lerner (1981) *Yale J. Biol. Med.*, 54:387-402; M. L. Gefter *et al.* (1977) *Somatic Cell Genet.*, 3:231-36). Briefly, an immortal cell line (typically a myeloma) is
25 fused to lymphocytes (typically splenocytes) from a mammal immunized with a protein immunogen as described above, and the culture supernatants of the resulting hybridoma cells are screened to identify a hybridoma producing a monoclonal antibody that binds specifically, *e.g.*, to the TNF- α protein. Any of the many well known protocols used for
30 fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating a monoclonal antibody (see, *e.g.*, G. Galfre *et al.* (1977) *Nature* 266:550-52; Gefter *et al. Somatic Cell Genet.*, cited *supra*; Lerner, *Yale J. Biol. Med.*, cited *supra*; Kenneth, *Monoclonal Antibodies*, cited *supra*). Moreover, the ordinary skilled artisan will appreciate that there are many variations of such methods which also would be
35 useful. Typically, the immortal cell line (*e.g.*, a myeloma cell line) is derived from the same mammalian species as the lymphocytes. For example, murine hybridomas can be made by fusing lymphocytes from a mouse immunized with an immunogenic preparation of the present invention with an immortalized mouse cell line. Preferred

immortal cell lines are mouse myeloma cell lines that are sensitive to culture medium containing hypoxanthine, aminopterin and thymidine ("HAT medium"). Any of a number of myeloma cell lines can be used as a fusion partner according to standard techniques, *e.g.*, the P3-NS1/1- α g4-1, P3-x63- α g8.653 or Sp2/O- α g14 myeloma lines.

5 These myeloma lines are available from the American Type Culture Collection (ATCC), Rockville, Md. Typically, HAT-sensitive mouse myeloma cells are fused to mouse splenocytes using polyethylene glycol ("PEG"). Hybridoma cells resulting from the fusion are then selected using HAT medium, which kills unfused and unproductively fused myeloma cells (unfused splenocytes die after several days because they are not

10 transformed). Hybridoma cells producing a monoclonal antibody that specifically binds the protein are identified by screening the hybridoma culture supernatants for such antibodies, *e.g.*, using a standard ELISA assay.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody that binds to a protein can be identified and isolated by screening a

15 recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with the protein, or a peptide thereof, to thereby isolate immunoglobulin library members that bind specifically to the protein. Kits for generating and screening phage display libraries are commercially available (*e.g.*, the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAPTM Phage*

20 *Display Kit*, Catalog No. 240612). Additionally, examples of methods and compounds particularly amenable for use in generating and screening antibody display library can be found in, for example, Ladner *et al.* U.S. Patent No. 5,223,409; Kang *et al.* International Publication No. WO 92/18619; Dower *et al.* International Publication No. WO 91/17271; Winter *et al.* International Publication WO 92/20791; Markland *et al.*

25 International Publication No. WO 92/15679; Breitling *et al.* International Publication WO 93/01288; McCafferty *et al.* International Publication No. WO 92/01047; Garrard *et al.* International Publication No. WO 92/09690; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum Antibod Hybridomas* 3:81-85; Huse *et al.* (1989) *Science* 246:1275-1281; Griffiths *et al.* (1993) *EMBO J* 12:725-734; Hawkins *et al.*

30 (1992) *J Mol Biol* 226:889-896; Clarkson *et al.* (1991) *Nature* 352:624-628; Gram *et al.* (1992) *PNAS* 89:3576-3580; Garrard *et al.* (1991) *Bio/Technology* 9:1373-1377; Hoogenboom *et al.* (1991) *Nuc Acid Res* 19:4133-4137; Barbas *et al.* (1991) *PNAS* 88:7978-7982; and McCafferty *et al.* *Nature* (1990) 348:552-554.

In another embodiment, ribosomal display can be used to replace

35 bacteriophage as the display platform (see, *e.g.*, Hanes *et al.* 2000. *Nat. Biotechnol.* 18:1287; Wilson *et al.* 2001. *Proc. Natl. Acad. Sci. USA* 98:3750; or Irving *et al.* 2001 *J. Immunol. Methods* 248:31. In yet another embodiment, cell surface libraries can be screened for antibodies (Boder *et al.* 2000. *Proc. Natl. Acad. Sci. USA* 97:10701;

Daugherty *et al.* 2000 *J. Immunol. Methods* 243:211. Such procedures provide alternatives to traditional hybridoma techniques for the isolation and subsequent cloning of monoclonal antibodies.

Yet other embodiments of the present invention comprise the generation of substantially human antibodies in transgenic animals (*e.g.*, mice) that are incapable of endogenous immunoglobulin production (see *e.g.*, U.S. Pat. Nos. 6,075,181, 5,939,598, 5,591,669 and 5,589,369 each of which is incorporated herein by reference). For example, it has been described that the homozygous deletion of the antibody heavy-chain joining region in chimeric and germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of a human immunoglobulin gene array to such germ line mutant mice will result in the production of human antibodies upon antigen challenge. Another preferred means of generating human antibodies using SCID mice is disclosed in U.S. Pat. No. 5,811,524 which is incorporated herein by reference. It will be appreciated that the genetic material associated with these human antibodies can also be isolated and manipulated as described herein.

Yet another highly efficient means for generating recombinant antibodies is disclosed by Newman, *Biotechnology*, 10: 1455-1460 (1992). Specifically, this technique results in the generation of primatized antibodies that contain monkey variable domains and human constant sequences. This reference is incorporated by reference in its entirety herein. Moreover, this technique is also described in U.S. Pat. Nos. 5,658,570, 5,693,780 and 5,756,096 each of which is incorporated herein by reference.

Once a monoclonal antibody of has been identified (*e.g.*, either a hybridoma-derived monoclonal antibody or a recombinant antibody from a combinatorial library, including monoclonal antibodies that are already known in the art), DNAs encoding the light and heavy chains of the monoclonal antibody can be isolated by standard molecular biology techniques. For hybridoma derived antibodies, light and heavy chain cDNAs can be obtained, for example, by PCR amplification or cDNA library screening. For recombinant antibodies, such as from a phage display library, cDNA encoding the light and heavy chains can be recovered from the display package (*e.g.*, phage) isolated during the library screening process. Nucleotide sequences of antibody light and heavy chain genes from which PCR primers or cDNA library probes can be prepared are known in the art. For example, many such sequences are disclosed in Kabat, E.A., *et al.* (1991) *Sequences of Proteins of Immunological Interest, Fifth Edition*, U.S. Department of Health and Human Services, NIH Publication No. 91-3242 and in the "Vbase" human germline sequence database.

Once obtained, the antibody light and heavy chain sequences can be cloned and manipulated using standard methods. For example, in one embodiment, variable regions of the light and heavy chains can be linked by a flexible peptide linker (e.g., (Gly₄Ser)₃) and expressed as a single chain molecule.

5 In one embodiment, antibody of the invention may be modified to reduce their immunogenicity using art-recognized techniques. For example, antibodies can be humanized, deimmunized, or chimeric antibodies can be made. These types of antibodies are derived from a non-human antibody, typically a murine antibody, that retains or substantially retains the antigen-binding properties of the parent antibody, but
10 which is less immunogenic in humans. This may be achieved by various methods, including (a) grafting the entire non-human variable domains onto human constant regions to generate chimeric antibodies; (b) grafting at least a part of one or more of the non-human complementarity determining regions (CDRs) into a human framework and constant regions with or without retention of critical framework residues; or (c)
15 transplanting the entire non-human variable domains, but "cloaking" them with a human-like section by replacement of surface residues. Such methods are disclosed in Morrison *et al.*, *Proc. Natl. Acad. Sci.* 81: 6851-5 (1984); Morrison *et al.*, *Adv. Immunol.* 44: 65-92 (1988); Verhoeven *et al.*, *Science* 239: 1534-1536 (1988); Padlan, *Molec. Immun.* 28: 489-498 (1991); Padlan, *Molec. Immun.* 31: 169-217 (1994), and U.S. Pat.
20 Nos. 5,585,089, 5,693,761 and 5,693,762 all of which are hereby incorporated by reference in their entirety.

De-immunization can also be used to decrease the immunogenicity of an antibody. As used herein, the term "de-immunization" includes alteration of an antibody to modify T cell epitopes (see, e.g., WO9852976A1, WO0034317A2). For example,
25 VH and VL sequences from the starting antibody are analyzed and a human T cell epitope "map" from each V region showing the location of epitopes in relation to complementarity-determining regions (CDRs) and other key residues within the sequence. Individual T cell epitopes from the T cell epitope map are analyzed in order to identify alternative amino acid substitutions with a low risk of altering activity of the
30 final antibody. A range of alternative VH and VL sequences are designed comprising combinations of amino acid substitutions and these sequences are subsequently incorporated into a range of polypeptides of the invention that are tested for function. Typically, between 12 and 24 variant antibodies are generated and tested. Complete heavy and light chain genes comprising modified V and human C regions are then
35 cloned into expression vectors and the subsequent plasmids introduced into cell lines for the production of whole antibody. The antibodies are then compared in appropriate biochemical and biological assays, and the optimal variant is identified.

Those skilled in the art will appreciate that chimeric antibodies can also be produced. In the context of the present application the term "chimeric antibodies" will be held to mean any antibody wherein the immunoreactive region or site is obtained or derived from a first species and the constant region (which may be intact, partial or modified in accordance with the instant invention) is obtained from a second species. In preferred embodiments the target binding region or site will be from a non-human source (*e.g.* mouse) and the constant region is human. While the immunogenic specificity of the variable region is not generally affected by its source, a human constant region is less likely to elicit an immune response from a human subject than would the constant region from a non-human source.

Preferably, the variable domains in both the heavy and light chains are altered by at least partial replacement of one or more CDRs and, if necessary, by partial framework region replacement and sequence changing. Although the CDRs may be derived from an antibody of the same class or even subclass as the antibody from which the framework regions are derived, it is envisaged that the CDRs will be derived from an antibody of different class and preferably from an antibody from a different species. It may not be necessary to replace all of the CDRs with the complete CDRs from the donor variable region to transfer the antigen binding capacity of one variable domain to another. Rather, it may only be necessary to transfer those residues that are necessary to maintain the activity of the target binding site. Given the explanations set forth in U. S. Pat. Nos. 5,585,089, 5,693,761 and 5,693,762, it will be well within the competence of those skilled in the art, either by carrying out routine experimentation or by trial and error testing to obtain a functional antibody with reduced immunogenicity.

In another embodiment, the polypeptides described herein may be altered to provide for altered effector functionality that, *e.g.*, affects the biological profile of the administered antibody. For example, the deletion or inactivation (through point mutations or other means) of a constant region domain may reduce Fc receptor binding of the circulating modified antibody. In other cases it may be that constant region modifications consistent with the instant invention moderate complement binding and thus reduce the serum half life. Yet other modifications of the constant region may be used to modify disulfide linkages or oligosaccharide moieties that allow for enhanced localization due to increased antigen specificity or antibody flexibility. More generally, those skilled in the art will realize that antibodies modified as described herein may exert a number of subtle effects that may or may not be readily appreciated. However the resulting physiological profile, bioavailability and other biochemical effects of the modifications, such as serum half-life, may easily be measured and quantified using well known immunological techniques without undue experimentation.

In another embodiment, an antibody that recognizes a TNF- α receptor and does not transduce a signal can be made. Such an antibody can be selected using a screen which demonstrates that the antibody does not have one or more activities associated with the binding of TNF- α to a cell.

5 *b. Soluble TNF Receptor Molecules and Antibodies Thereto*

In another embodiment, a soluble form of a TNF receptor molecule can be used as a blockade or to inhibit TNF- α activity. Both type I and type II TNF- α receptors, *e.g.*, TNF receptor I (TNFRI, p55) and TNFRII (p75), have been found to mediate biological effects of TNF- α . Accordingly, soluble forms of either or both receptors can
10 be used to reduce circulating levels of TNF- α . Soluble TNF receptors are naturally produced and can be purified for use in the subject methods of can be made, *e.g.*, by engineering a form of the molecule lacking the transmembrane and cytoplasmic domains. Exemplary forms of soluble TNF receptors are also known in the art and are commercially available.

15 Antibodies to TNF- α receptors can be known or can be made using standard techniques, *e.g.*, such as those described supra. Preferably, such anti-TNF receptor antibodies do not transduce a signal to a cell resulting in a TNF- α activity.

In one embodiment, the anti-TNF- α receptor antibody is a commercially available (known) anti-TNF- α receptor antibody.

20 In one embodiment, the agent is Etanercept. Etanercept is also referred to as p75 TNFR:Fc, TNF receptor fusion protein, TNF receptor fusion Fc protein, TNFR:Fc, sTNFR:Fc, tumor necrosis factor receptor p75 Fc fusion protein, soluble tumor necrosis factor receptor, and TNF receptor (p80) Fc fusion protein. Marketed as ENBREL®, and produced by Immunex Corp., Seattle, WA, Etanercept is indicated for
25 the treatment of rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Etanercept is a soluble form of the TNF receptor which consists of two identical, soluble extracellular domains of the human p75 TNF receptor fused to the Fc fragment of human immunoglobulin G1 (IgG1). The Fc component of etanercept contains the CH2 domain, the CH3 domain and hinge region, but not the CH1 domain of
30 IgG1. Etanercept inhibits the binding of both TNF- α and TNF- β to cell surface receptors. The isolation and characterization of this drug is described in, for example, Eason *et al.*, *Transplantation* 61:224 (1996); Eason *et al.*, *Transplantation* 59:300 (1995); Fisher *et al.*, *New Eng. J. Med.* 334:1697 (1996); Heilig *et al.*, *Clin. Invest.* 70:22 (1992); Howard *et al.*, *Proc. Natl. Acad. Sci. USA* 90:2335 (1993); Mohler *et al.*,
35 *J. Immunol.* 151:1548 (1993); Moreland *et al.*, *J. Rheumatol.* 23:1849 (1996); Wooley *et al.*, *J. Immunol.* 151:6602 (1993).

In another embodiment, the agent is LENERCEPT®. LENERCEPT® is also referred to as Ro-45-2081 and is produced by Roche. It is a recombinant soluble TNF receptor p55 (type I) fused to an immunoglobulin heavy chain IgG1 (Renzetti, L. M., *et al. J. Pharmacol. Exp. Ther.* 278: 847-853, 1996; Abraham, E., *et al.* 1997.

5 J.A.M.A. 277: 1531-1538).

In yet another embodiment, the agent is onercept (Sandborn, J. *Best Pract Clin Gastroenterol.* 2003 48:35).

In one embodiment, such molecules can be modified to improve their characteristics, *e.g.*, to increase their half-life. For example, a recombinant C-terminal truncated form of the human soluble tumor necrosis factor receptor type I (sTNF-RI) has
10 been produced in *E. coli*. This soluble receptor contains the first 2.6 of the 4 domains of an intact sTNF-RI molecule. A monoPEGylated form of this molecule has been produced using a 30 kD methoxyPEG aldehyde with approximately 85% selectivity for the N-terminal amino group. This molecule was shown to be less immunogenic in
15 primates than the full length (4.0 domain) molecule or other versions of sTNF-RI which were either PEGylated at different sites or with different molecular weight PEGs. The 30 kD PEG also has a longer serum half-life to the molecule than lower molecular weight PEGs (Edwards, CK *et al.*, 2003. *Adv. Drug. Deliv. Rev.* 55:1315).

c. Nucleic Acid Molecules

20 Another type of inhibitory compound that can be used to inhibit TNF- α and/or TNFR activity is an antisense nucleic acid molecule that is complementary to a gene encoding TNF- α , TNF- α receptor, or intracellular signaling molecule, or to a portion of said gene, or a recombinant expression vector encoding such an antisense nucleic acid molecule. The use of antisense nucleic acid molecules to downregulate the expression
25 of a particular protein in a cell is well known in the art (see *e.g.*, Weintraub, H. *et al.*, Antisense RNA as a molecular tool for genetic analysis, *Reviews - Trends in Genetics*, Vol. 1(1) 1986; Askari, F.K. and McDonnell, W.M. (1996) *N. Eng. J. Med.* 334:316-318; Bennett, M.R. and Schwartz, S.M. (1995) *Circulation* 92:1981-1993; Mercola, D. and Cohen, J.S. (1995) *Cancer Gene Ther.* 2:47-59; Rossi, J.J. (1995) *Br. Med. Bull.*
30 51:217-225; Wagner, R.W. (1994) *Nature* 372:333-335). An antisense nucleic acid molecule comprises a nucleotide sequence that is complementary to the coding strand of another nucleic acid molecule (*e.g.*, an mRNA sequence) and accordingly is capable of hydrogen bonding to the coding strand of the other nucleic acid molecule. Antisense sequences complementary to a sequence of an mRNA can be complementary to a
35 sequence found in the coding region of the mRNA, the 5' or 3' untranslated region of the mRNA or a region bridging the coding region and an untranslated region (*e.g.*, at the junction of the 5' untranslated region and the coding region). Furthermore, an antisense nucleic acid can be complementary in sequence to a regulatory region of the gene

encoding the mRNA, for instance a transcription initiation sequence or regulatory element. Preferably, an antisense nucleic acid is designed so as to be complementary to a region preceding or spanning the initiation codon on the coding strand or in the 3' untranslated region of an mRNA.

5 Given the known nucleotide sequences for the coding strands of TNF- α , TNF- α receptors, and TNF- α signaling molecules, antisense nucleic acids of the invention can be designed according to the rules of Watson and Crick base pairing. The antisense nucleic acid molecule can be complementary to the entire coding region of an mRNA, but more preferably is an oligonucleotide which is antisense to only a portion of the
10 coding or noncoding region of an mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of an mRNA. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures
15 known in the art. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine
20 substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4- α -acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine,
25 N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6- α -adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil,
30 queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3- α -amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. To inhibit expression in cells in culture, one or more antisense oligonucleotides can be added to cells in culture media.

35 Known compositions and methods for the use of antisense can be found in, for example, US Patent 6228642 and US Patent 6080580.

Alternatively, an antisense nucleic acid can be produced biologically using an expression vector into which a cDNA has been subcloned in an antisense orientation (*i.e.*, nucleic acid transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest). Regulatory sequences operatively linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the expression of the antisense RNA molecule in a cell of interest, for instance promoters and/or enhancers or other regulatory sequences can be chosen which direct constitutive, tissue specific or inducible expression of antisense RNA. The antisense expression vector is prepared according to standard recombinant DNA methods for constructing recombinant expression vectors, except that the cDNA (or portion thereof) is cloned into the vector in the antisense orientation. The antisense expression vector can be in the form of, for example, a recombinant plasmid, phagemid or attenuated virus. The antisense expression vector is introduced into cells using a standard transfection technique.

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA to thereby inhibit expression of the protein, *e.g.*, by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of an antisense nucleic acid molecule of the invention includes direct injection at a tissue site. Alternatively, an antisense nucleic acid molecule can be modified to target selected cells and then administered systemically. For example, for systemic administration, an antisense molecule can be modified such that it specifically binds to a receptor or an antigen expressed on a selected cell surface, *e.g.*, by linking the antisense nucleic acid molecule to a peptide or an antibody which binds to a cell surface receptor or antigen. The antisense nucleic acid molecule can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

In yet another embodiment, the antisense nucleic acid molecule of the invention is an α -anomeric nucleic acid molecule. An α -anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β -units, the strands run parallel to each other (Gaultier *et al.* (1987) *Nucleic Acids Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise a 2'-O-methylribonucleotide (Inoue *et al.* (1987) *Nucleic Acids Res.* 15:6131-6148) or a

chimeric RNA-DNA analogue (Inoue *et al.* (1987) *FEBS Lett.* 215:327-330).

In still another embodiment, an antisense nucleic acid of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes (described in Haselhoff and Gerlach (1988) *Nature* 334:585-591)) can be used to catalytically cleave mRNA transcripts to thereby inhibit translation of mRNAs.

Known compositions and methods for ribozymes that are specific for TNF- α can be found in, for example, US Patent 5811300.

A ribozyme having specificity for a nucleic acid can be designed based upon the nucleotide sequence of the cDNA. For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in an mRNA. See, *e.g.*, Cech *et al.* U.S. Patent No. 4,987,071 and Cech *et al.* U.S. Patent No. 5,116,742. Alternatively, mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. See, *e.g.*, Bartel, D. and Szostak, J.W. (1993) *Science* 261:1411-1418.

Alternatively, gene expression can be inhibited by targeting nucleotide sequences complementary to a regulatory region of, *e.g.*, a TNF- α gene (*e.g.*, an TNF- α promoter and/or enhancer) to form triple helical structures that prevent transcription of the gene in target cells. See generally, Helene, C. (1991) *Anticancer Drug Des.* 6(6):569-84; Helene, C. *et al.* (1992) *Ann. N.Y. Acad. Sci.* 660:27-36; and Maher, L.J. (1992) *Bioassays* 14(12):807-15.

In one embodiment, a nucleic acid molecule of the invention is a compound that mediates RNA interference, RNAi. RNA interfering agents include, but are not limited to, nucleic acid molecules including RNA molecules which are homologous to the target gene or genomic sequence, *e.g.*, TNF- α or TNF- α receptor, or a fragment thereof, "short interfering RNA" (siRNA), "short hairpin" or "small hairpin RNA" (shRNA), and small molecules which interfere with or inhibit expression of a target gene by RNA interference (RNAi). RNA interference is a post-transcriptional, targeted gene-silencing technique that uses double-stranded RNA (dsRNA) to degrade messenger RNA (mRNA) containing the same sequence as the dsRNA (Sharp, P.A. and Zamore, P.D. 287, 2431-2432 (2000); Zamore, P.D., *et al.* *Cell* 101, 25-33 (2000). Tuschl, T. *et al.* *Genes Dev.* 13, 3191-3197 (1999)). The process occurs when an endogenous ribonuclease cleaves the longer dsRNA into shorter, 21- or 22-nucleotide-long RNAs, termed small interfering RNAs or siRNAs. The smaller RNA segments then mediate the degradation of the target mRNA. The antisense RNA strand of RNAi can be antisense to at least a portion of the coding region of TNF- α or a TNF- α receptor or to at

least a portion of the 5' or 3' untranslated region of the TNF- α or TNF- α receptor gene. In one embodiment, siRNA duplexes are composed of 21-nt sense and 21-nt antisense strands, paired in a manner to have a 2-nt 3' overhang. In one embodiment, siRNA sequences with TT in the overhang. The target region can be, *e.g.*, 50 to 100 nt downstream of the start codon, 3'-UTRs may also be targeted. In one embodiment, a 23-nt sequence motif AA(N19)TT (N, any nucleotide) can be searched for and hits with between about 30-70% G/C-content can be selected. If no suitable sequences are found, the search is extended using the motif NA(N21). SiRNAs are preferably chemically synthesized using appropriately protected ribonucleoside phosphoramidites and a conventional DNA/RNA synthesizer. SiRNAs are also available commercially from, *e.g.*, Dharmacon, Xeragon Inc, Proligo, and Ambion. Kits for synthesis of RNAi are commercially available from, *e.g.* New England Biolabs and Ambion. For example, Ambion catalog ID Nos: 3925, 4021, and 4115 are specific for TNF- α . In one embodiment one or more of the chemistries known in the art for use in antisense RNA can be employed.

d. Peptidic Compounds

In another embodiment, an inhibitory compound of the invention is a peptidic compound derived from TNF- α or a TNF- α receptor. As used herein, the term "peptide" includes relatively short chains of amino acids linked by peptide bonds. The term "peptidomimetic" includes compounds containing non-peptidic structural elements that are capable of mimicking or antagonizing peptides.

Preferably, the inhibitory compound(s) comprises a portion of TNF- α or the TNF- α receptor (or a peptidomimetic thereof) that mediates interaction of the two molecules such that the peptidic compound competitively inhibits the interaction of TNF- α and its receptor. For example, peptidic compounds for TNF receptors have been described in, for example, European Patent Application EP 568 925. In another embodiment, site-directed mutagenesis of TNF- α can be performed to generate dominant negative constructs in which amino acid changes result in decreased receptor binding and cellular activation (See, *e.g.*, Abraham, E. Sci STKE. 2003 11:PE51.)

The peptidic compounds of the invention can be made by recombinant synthesis in cells or by chemical synthesis using standard peptide synthesis techniques.

e. Other TNF- α Inhibitory Compounds

Other inhibitory compounds include those that interfere with signal transduction mediated by TNF- α . (See, *e.g.*, Rechless, J. *et al. Immunology* 2001. 103:244; Chandel *et al. J. Immunol.* 2000 165:1013; Manna SK. 2000. *J. Immunol.* 164:6509). In addition small molecule inhibitors that act on the TNF- α signaling cascade, *e.g.*, by blocking the activity of p38, JNK, ERK kinases, or activation of the transcription factor NF- κ B can be used. Additional compounds can be identified using screening assays

that select for such compounds, as described in detail below.

B. Prognostic and Diagnostic Assays

One embodiment of the present invention provides a method of
5 diagnosing whether a subject is at risk for or has had a spontaneous abortion that would benefit from treatment with a modulator of TNF- α activity, which includes determining the presence or level of TNF- α or IL-6 in a tissue, cell, or biological fluid sample from a subject (*e.g.*, a pregnant subject). In another embodiment, the present invention provides a method of diagnosing a subject who is at increased risk for or has had a spontaneous
10 abortion that would have benefited from modulation of TNF- α activity. For example, the method includes determining the presence or level of at least one of SOCS1, SOCS3 or I κ B α in a tissue, cell, or biological fluid sample from a subject (*e.g.*, a pregnant subject).

In yet another embodiment of the present invention, prognostic methods
15 are provided to determine whether a subject is at risk for having a spontaneous abortion that would benefit from modulation of TNF- α activity including detecting the presence or level of at least one of SOCS1, SOCS3 or I κ B α , in a tissue, cell, or biological fluid sample from a subject (*e.g.*, a pregnant subject). In another embodiment, the present invention provides a prognostic method of determining whether a subject is at risk for
20 having a spontaneous abortion that would benefit from treatment with a compound that inhibits TNF- α activity, which includes detecting the presence or level of one of TNF- α or IL-6 in a tissue, cell, or biological fluid sample from a subject (*e.g.*, a pregnant subject).

The diagnostic and prognostic methods can further comprise detecting the
25 presence or level of one or more immune cell surface molecules selected from the group consisting of CD69, CD25, CD44, CD45RB, CD62L, CD80, CD86, CD40, MHC class II, and CD54. In addition, the diagnostic and prognostic methods can further comprise detecting the presence or level of luteinizing hormone, luteinizing hormone receptor, 3 β -hydroxysteroid dehydrogenase, and/or StAR protein or phosphorylated StAR protein
30 (steroid acute regulatory protein; *J Biol Chem.* 1997, 272:32656), and, *e.g.*, in the case of endangered species, prolactin receptor, prolactin, and 20 α -hydroxysteroid dehydrogenase. The level of progesterone can also be determined in connection with a prognostic or diagnostic method of the invention.

Preferably, these determinations are made utilizing maternal serum or
35 blood. The presence or level of the above may also be determined from an amniotic fluid sample or from a tissue sample such as a chorionic villus sample or a placental bed sample.

In order to determine if the presence or level of TNF- α , IL-6, SOCS1, SOCS3, I κ B α , CD69, CD25, CD44, CD45RB, CD62L, CD80, CD86, CD40, MHC class II, CD54, luteinizing hormone, luteinizing hormone receptor, 3 β -hydroxysteroid dehydrogenase, and StAR protein and/or phosphorylated StAR protein, progesterone and/or leutinizing hormone receptor (and, *e.g.*, in the case of endangered species, prolactin receptor, prolactin, and 20 α -hydroxysteroid dehydrogenase) in a biological sample from a test subject is abnormal, the level of one or more of these molecules from the test subject is compared, for example, to the average level of those molecules determined from women who have had normal pregnancies.

Standard techniques can be used for determining the presence or level of one or more of the above-identified molecules in a sample. For example, in one embodiment, a biological sample can be contacted with an agent capable of detecting protein or nucleic acid molecules (*e.g.*, mRNA) such that the presence or level of a molecule can be determined by measuring protein molecules or nucleic acid molecules encoding a particular protein. One agent for detecting mRNA is a labeled or labelable nucleic acid probe capable of hybridizing specifically to the mRNA of a particular gene. The nucleic acid probe can be, for example, the full-length cDNA, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and is sufficiently complimentary to specifically hybridize under stringent conditions to the particular mRNA. As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% (65%, 70%, 75%, 80%, preferably 85%) identical to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in sections 6.3.1-6.3.6 of *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989). A preferred, non-limiting example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 50-65°C. Probes can be designed using the publicly available sequences, determined by searching Genbank using the following GI numbers :

gi:25952110 (human TNF- α nucleic acid) (SEQ ID NO.:30) (human TNF- α amino acid) (SEQ ID NO.:31); gi:23312372 (human TNFR1 nucleic acid) (SEQ ID NO.:32) (human TNFR1 amino acid) (SEQ ID NO.:33); gi:10834983 (human IL-6 nucleic acid) (SEQ ID NO.:34) (human IL-6 amino acid) (SEQ ID NO.:35); gi:10092618 (human I κ B α nucleic acid) (SEQ ID NO.:36) (human I κ B α amino acid) (SEQ ID NO.:37); gi:4507232 (human SOCS1 nucleic acid) (SEQ ID No.:38) (human SOCS1 amino acid) (SEQ ID No.:39); gi:45439351 (human SOCS3 nucleic acid) (SEQ ID No.:40) (human SOCS3 amino acid) (SEQ ID No.:41); gi:4504506 (human HSD3B1nucleic acid) (SEQ ID NO.:42) (human HSD3B1amino

acid) (SEQ ID NO.:43); gi:4504508 (human HSD3B2 nucleic acid) (SEQ ID NO.:44) (human HSD3B2 amino acid) (SEQ ID NO.:45); gi:4502680 (human CD69 nucleic acid) (SEQ ID NO.:46) (human CD69 amino acid) (SEQ ID NO.:47); gi:4557666 (human CD25 nucleic acid) (SEQ ID NO.:48) (human CD25 amino acid) (SEQ ID NO.:49); gi:5713320 (Human CD62L nucleic acid) (SEQ ID NO.:50) (human CD62L amino acid) (SEQ ID NO.:51); gi:31377790 human CD80 nucleic acid) (SEQ ID NO.:52) (human CD80 amino acid) (SEQ ID NO.:53); gi:29029570 (human CD86, variant 2, nucleic acid) (SEQ ID NO.:54) (human CD86, variant 2, amino acid) (SEQ ID NO.:55); gi:29029571 (human CD86, variant 1, nucleic acid) (SEQ ID NO.:56) (human CD86, variant 1, amino acid) (SEQ ID NO.:57); gi:23312369 (human CD40, variant 1, nucleic acid) (SEQ ID NO.:58) (human CD40, variant 1, amino acid) (SEQ ID NO.:59); gi:23312370 (human CD40, variant 2, nucleic acid) (SEQ ID NO.:60) (human CD40, variant 2, amino acid) (SEQ ID NO.:61); gi:4557877 (human CD54 nucleic acid) (SEQ ID NO.:62) (human CD54 amino acid) (SEQ ID NO.:63); gi:10834989 (human CD56, variant 1, nucleic acid) (SEQ ID NO.:64) (human CD56, variant 1, amino acid) (SEQ ID NO.:65); gi:41281936 (human CD56, variant 2, nucleic acid) (SEQ ID NO.:66) (human CD56, variant 2, amino acid) (SEQ ID NO.:67); gi:4557716 (human LHR nucleic acid) (SEQ ID NO.:68) (human LHR amino acid) (SEQ ID NO.:69); gi:15431286 (human LHB nucleic acid) (SEQ ID NO.:70) (human LHB amino acid) (SEQ ID NO.:71); gi:10800407 (human LHA nucleic acid) (SEQ ID NO.:72) (human LHA amino acid) (SEQ ID NO.:73); gi:40254435 (human PRLR nucleic acid) (SEQ ID NO.:74) (human PRLR amino acid) (SEQ ID NO.:75); gi:40254429 (human PRL nucleic acid) (SEQ ID NO.:76) (human PRL amino acid) (SEQ ID NO.:77); gi:4504500 (human HSD17B1 nucleic acid) (SEQ ID NO.:78) (human HSD17B1 amino acid) (SEQ ID NO.:79); gi:4504502 (human HSD17B2 nucleic acid) (SEQ ID NO.:80) (human HSD17B2 amino acid) (SEQ ID NO.:81); gi:18765714 (human HLA-DMA nucleic acid) (SEQ ID NO.:82) (human HLA-DMA amino acid) (SEQ ID NO.:83); gi:18641376 (human HLA-DMB nucleic acid) (SEQ ID NO.:84) (human HLA-DMB amino acid) (SEQ ID NO.:85); gi:34419636 (human HLA-DOA nucleic acid) (SEQ ID NO.:86) (human HLA-DOA amino acid) (SEQ ID NO.:87); gi:18641377 (human HLA-DOB nucleic acid) (SEQ ID NO.:88) (human HLA-DOB amino acid) (SEQ ID NO.:89); gi:18641378 (human HLA-DRA nucleic acid) (SEQ ID NO.:90) (human HLA-DRA amino acid) (SEQ ID NO.:91); gi:24797073 (human HLA-DPA1 nucleic acid) (SEQ ID NO.:92) (human HLA-DPA1 amino acid) (SEQ ID NO.:93); gi:21361192 (human CD44 nucleic acid) (SEQ ID NO.:94) (human CD44 amino acid) (SEQ ID NO.:95); gi:14714802 (human StAR nucleic acid) (SEQ ID NO.:96) (human StAR amino acid) (SEQ ID NO.:97); gi:34280 (human leukocyte common antigen (CD45) (SEQ ID NO.:98) nucleic acid) (human CD45 amino acid) (SEQ ID NO.:99); the entire contents of each of

these references is incorporated herein by reference.

Sequences for any of the aforementioned genes from species other than humans may be obtained by searching GenBank using the desired gene name and the name of the desired organism.

5 In a preferred embodiment, the presence or level of mRNA in a sample is determined using quantitative real-time RT-PCR, as described in the Examples. Gene specific primers and probes can be designed using the gene sequences described above by GenBank GI number.

10 In one embodiment, the expression pattern of one or more genes may form part of a "gene expression profile" or "transcriptional profile" which may be then be used in such an assessment. "Gene expression profile" or "transcriptional profile," as used herein, includes the pattern of mRNA expression of one or more genes obtained for a given tissue or cell type under a given set of conditions. Gene expression profiles may be generated, for example, by utilizing a differential display procedure, Northern
15 analysis and/or RT-PCR.

In another embodiment, the presence or level of a molecule of the invention can be detected using a labeled or labelable antibody, *e.g.*, a labeled or radiolabeled antibody, capable of binding to that specific protein. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof
20 (*e.g.*, Fab or F(ab')₂) can be used. The term "labeled or labelable", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance (*e.g.*, I¹²⁵) to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a
25 primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin. Exemplary techniques employing antibodies include, *e.g.*, enzyme linked immunosorbent assays (ELISAs), radioimmunoassays, Western blots, immunoprecipitations, immunofluorescence, and the like.

30 As used herein, the term "biological sample" refers to a sample of biological material isolated from a subject, preferably a human subject, or present within a subject, preferably a human subject. The "biological material" can include, for example, tissues, tissue samples, tumors, tumor samples, cells, biological fluids, and purified and/or partially-purified biological molecules. Preferably, the biological
35 material is maternal serum, maternal blood, amniotic fluid, a chorionic villus sample, or a placental bed sample. As used herein, the term "isolated", when used in the context of a biological sample, is intended to indicate that the biological sample has been removed from the subject. In one embodiment, a biological sample comprises a sample which

has been isolated from a subject and is subjected to a method of the present invention without further processing or manipulation subsequent to its isolation. In another embodiment, the biological sample can be processed or manipulated subsequent to being isolated and prior to being subjected to a method of the invention. For example, a sample can be refrigerated (*e.g.*, stored at 4°C), frozen (*e.g.*, stored at -20°C, stored at -135°C, frozen in liquid nitrogen, or cryopreserved using any one of many standard cryopreservation techniques known in the art). Furthermore, a sample can be purified subsequent to isolation from a subject and prior to subjecting it to a method of the present invention. As used herein, the term "purified" when used in the context of a biological sample, is intended to indicate that at least one component of the isolated biological sample has been removed from the biological sample such that fewer components, and consequently, purer components, remain following purification. For example, a serum sample can be separated into one or more components using centrifugation techniques known in the art to obtain partially-purified sample preparation. Furthermore, it is possible to purify a biological sample such that substantially only one component remains. For example, a tissue or tumor sample can be purified such that substantially only the protein or mRNA component of the biological sample remains.

Furthermore, it may be desirable to amplify a component of a biological sample such that detection of the component is facilitated. For example, the mRNA component of a biological sample can be amplified (*e.g.*, by RT-PCR) such that detection of mRNA is facilitated. As used herein, the term "RT-PCR" ("reverse transcriptase-polymerase chain reaction") includes subjecting mRNA to the reverse transcriptase enzyme resulting in the production of DNA which is complementary to the base sequences of the mRNA. Large amounts of selected cDNA can then be produced *via* the polymerase chain reaction which relies on the action of heat-stable DNA polymerase for its amplification action. Alternative amplification methods include, but are not limited to, self sustained sequence replication (Guatelli, J.C. *et al.*, 1990, *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh, D.Y. *et al.*, 1989, *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi, P.M. *et al.*, 1988, *Bio/Technology* 6:1197), or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. Preferably, the detection methods of the present invention can be used to detect protein or nucleic acid molecules in a biological sample *in vitro*.

In one embodiment, a subject is identified using a prognostic or diagnostic method of the invention based on a statistically significant difference between the level of at least one of the molecules set forth above.

In one embodiment, the level of expression of one or more of the molecules differs from the control level by at least about 1-10%. In another embodiment, the level of expression of one or more of the molecules differs from the control level by about 10-20%. In another embodiment, the level of expression of one or more of the molecules differs from the control level by about 30-40%. In another embodiment, the level of expression of one or more of the molecules differs from the control level by about 40-50%. In another embodiment, the level of expression of one or more of the molecules differs from the control level by about 50-100%. In another embodiment, the level of expression of one or more of the molecules differs from the control level by about 100-200%. In another embodiment, the level of expression of one or more of the molecules differs from the control level by about 200-400%. (*e.g.*, 2-fold to 4-fold), 4-fold to 10-fold, 10-fold to 100-fold, 100-fold or greater change in levels.

As set forth in the instant examples, TNF- α is required for spontaneous abortion which is characterized by increased levels of expression of TNF- α , IL-6, SOCS1, SOCS3, IkB α , CD69, CD25, CD44, CD45RB, CD62L, CD80, CD86, CD40, MHC class II, CD54, 20 α -hydroxysteroid dehydrogenase and decreased levels of luteinizing hormone, luteinizing hormone receptor, progesterone, 3 β -hydroxysteroid dehydrogenase, and StAR protein and/or phosphorylated StAR protein, and, *e.g.*, in the case of endangered species, prolactin receptor, prolactin, and 20 α -hydroxysteroid dehydrogenase. Accordingly, the level of one or more of these molecules can be measured and compared with that of an appropriate control to identify a subject as one at risk for a spontaneous abortion that would benefit from treatment with an agent that inhibits TNF- α activity.

It may also be desirable to use the methods of the present invention, as described above, to monitor the progress of treatment of a subject. For example, a subject (*e.g.*, a human) may be undergoing treatment for spontaneous abortion using any one of the methods of treatment described herein. Treatment of the subject can then be modified (*e.g.*, increased or decreased) depending on the results.

The treatment monitoring methods can be used alone or in conjunction with other methods. The "desired effect" includes at least one effect capable of providing an indication of the ability of the treatment methods of the invention to treat a subject.

For example, the desired effect may be modulation of the reproductive endocrine system. The desired effect may also be the prevention of spontaneous abortion or the ability of a subject to carry at least one embryo to term. In addition, the

desired effect may be a determination that the level of one or more of TNF- α , IL-6, SOCS1, SOCS3, I κ B α , CD69, CD25, CD44, CD45RB, CD62L, CD80, CD86, CD40, MHC class II, CD54, luteinizing hormone, luteinizing hormone receptor, progesterone, 3 β -hydroxysteroid dehydrogenase, StAR protein and/or phosphorylated StAR protein
 5 (and, *e.g.*, in the case of endangered species, prolactin receptor, prolactin, and 20 α -hydroxysteroid dehydrogenase) from a biological sample from the subject is normal or is normalizing.

In one embodiment, the invention also pertains to kits for detecting the level or presence of one or more of TNF- α , IL-6, SOCS1, SOCS3, I κ B α , CD69, CD25,
 10 CD44, CD45RB, CD62L, CD80, CD86, CD40, MHC class II, CD54, luteinizing hormone, luteinizing hormone receptor, progesterone, 3 β -hydroxysteroid dehydrogenase, StAR protein and/or phosphorylated StAR protein (and, *e.g.*, in the case of endangered species, prolactin receptor, prolactin, and 20 α -hydroxysteroid dehydrogenase) in a biological sample. For example, the kit can comprise a labeled or
 15 labelable agent capable of detecting one or more of the molecules in a biological sample and a control sample or a chart showing normal and abnormal ranges for the molecule(s). The kit can further comprise an agent for reducing the activity of TNF- α . The kit can further comprise instructions for use.

20 C. Screening Assays for the Identification of Novel Modulators of TNF- α Activity

In one aspect, the present invention provides methods (also referred to herein as "screening assays") for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptidomimetics, small molecules or other drugs) which modulate the reproductive-endocrine system, *e.g.*, inhibit spontaneous abortion, by
 25 modulating, TNF- α activity. For example one or more of the following may be modulated: the production of TNF- α mRNA or polypeptide; a TNF- α activity (*e.g.*, the ability to modulate IL-6, I κ B α , SOCS1 and/or SOCS3 mRNA or polypeptide production, modulation of progesterone levels, modulation of lymphoid activation markers, *e.g.*, CD69, CD25, CD44, CD45RB, and CD62L, and/or modulation of costimulatory
 30 molecules, *e.g.*, CD80, CD86, MHC class II, CD40, and CD54 on human dendritic cells; TNF- α -induced cytotoxicity (either *in vitro* or *in vivo*), TNF- α -induced cellular activation, TNF- α binding to TNF- α receptors). These assays are designed to identify compounds that modulate the function of TNF- α . Alternatively, such assays can be used for testing or optimizing the activity of such agents. In one embodiment, such
 35 agents bind to or interact with intracellular or extracellular proteins that interact with TNF- α or transduce a TNF- α -mediated signal. For example, such agents may interact with TNF α or a TNF receptor.

The subject screening assays can measure the activity of TNF- α directly or can measure a downstream event controlled by modulation of TNF- α .

In one embodiment, cell-based can be used to identify agents that modulate TNF- α expression or activity. For example, in one embodiment, the subject screening assays employ indicator compositions. These indicator compositions
5 comprise the components required for performing an assay that detects and/or measures a particular event. The indicator compositions of the invention provide a reference readout and changes in the readout can be monitored in the presence of one or more test compounds. A difference in the readout in the presence and the absence of the
10 compound indicates that the test compound is a modulator of the molecule(s) present in the indicator composition. The indicator composition used in the screening assay can be a cell that expresses a TNF- α polypeptide or a molecule in a signal transduction pathway involving TNF- α , *e.g.*, a TNF receptor molecule or a second messenger or mediator of a TNF- α -mediated signal. For example, a cell that naturally expresses or has been
15 engineered to express the protein by introducing into the cell an expression vector encoding the protein may be used. Preferably, the cell is a mammalian cell, *e.g.*, a human cell.

As set forth in more detail below, cell free assays can also be used to identify modulators of TNF- α activity. For example, the indicator composition can be a
20 cell-free composition that includes the protein (*e.g.*, a cell extract or a composition that includes *e.g.*, either purified natural or recombinant protein).

In another embodiment, an indicator composition comprises more than one polypeptide. For example, in one embodiment the subject assays are performed in the presence of TNF- α and a TNF receptor and/or a molecule in a signal transduction
25 pathway involving TNF- α .

Compounds that modulate the expression and/or activity of TNF- α identified using the assays described herein can be useful, *e.g.*, for treating a subject that would benefit from modulation of the reproductive endocrine system, *e.g.*, a subject at risk for a spontaneous abortion.

The subject screening assays can be performed in the presence or absence of other agents. In one embodiment, the subject assays are performed in the presence of an agent that provides a stimulatory signal to a cell. For example, in one embodiment, assays are performed in the presence of an agent that delivers or mimics a T cell receptor-mediated signal (*e.g.*, an antibody that recognizes the T cell receptor or an
30 associated molecule, *e.g.*, CD3, CD28, CD40 or PMA and Ionomycin).

In one embodiment, secondary assays can be used to confirm the activity of an agent. For example, compounds identified in a primary screening assay can be used in a secondary screening assay to determine whether the compound affects the

reproductive endocrine function, *e.g.*, spontaneous abortion. Accordingly, in another aspect, the invention pertains to a combination of two or more of the assays described herein. For example, a modulating agent can be identified using a cell-based or a cell-free assay, and the ability of the agent to modulate the activity of TNF- α can be confirmed *in vivo*, *e.g.*, in an animal such as, for example, in an animal model of a disorder, *e.g.*, reproductive-endocrine function, *e.g.*, spontaneous abortion, as described herein.

For example, in one aspect, the invention pertains to a mouse that is an animal model of spontaneous abortion. The invention provides a mouse, *e.g.*, an inbred mouse, and/or a transgenic mouse treated with an agent, *e.g.*, an anti-CD40 antibody such that the reproductive endocrine system of the mouse is modulated, *e.g.*, spontaneous abortion is enhanced.

This animal model of spontaneous abortion is characterized by increased spontaneous abortion, relative to a wild-type or untreated mice. The phenotype of the mice can further be characterized by: an increase in the level of mRNA and polypeptide of TNF- α , IL-6, I κ B α , SOCS1 and SOCS3. In addition, these animals exhibit upmodulation of various immune cell surface markers, *e.g.*, CD69, CD25, CD44, CD45RB, CD62L, CD80, CD86, CD40, MHC class II, and CD54, upmodulation of 20 α -hydroxysteroid dehydrogenase and a reduction in steriodogenic hormones, *e.g.*, luteinizing hormone, luteinizing hormone receptor, progesterone, 3 β -hydroxysteroid dehydrogenase, StAR protein and/or phosphorylated StAR protein (steroid acute regulatory protein; J Biol Chem. 1997, 272:32656) (and, *e.g.*, in the case of endangered species, prolactin receptor, prolactin, and 20 α -hydroxysteroid dehydrogenase) levels relative to an untreated mouse.

In the screening method, cells from the animal model of spontaneous abortion of the present invention can be contacted with a test compound and a biological response regulated by TNF- α can be measured. Modulation of spontaneous abortion (as compared to an appropriate control such as, for example, untreated animals) identifies or confirms a test compound as a modulator of the response. In another embodiment, cells from the animal are isolated and contacted with the test compound *ex vivo* to identify a test compound that modulates a response of spontaneous abortion, *e.g.*, modulation of one or more of the molecules described above.

The test compound can be administered to an animal model of spontaneous abortion of the present invention as a pharmaceutical composition. Such compositions typically comprise the test compound and a pharmaceutically acceptable carrier. As used herein the term "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal compounds, isotonic and absorption delaying compounds, and the like, compatible with pharmaceutical

administration. The use of such media and compounds for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or compound is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions. Pharmaceutical compositions are described in more detail below.

Additionally, gene expression patterns may be utilized to assess the ability of a compound to modulating the reproductive endocrine system. For example, the expression pattern of one or more genes may form part of a "gene expression profile" or "transcriptional profile" which may be then be used in such an assessment. "Gene expression profile" or "transcriptional profile", as used herein, includes the pattern of mRNA expression obtained for a given tissue or cell type under a given set of conditions. Gene expression profiles may be generated, for example, by utilizing a differential display procedure, Northern analysis and/or RT-PCR.

Gene expression profiles may be characterized for known states within the cell- and/or animal-based model systems. Subsequently, these known gene expression profiles may be compared to ascertain the effect a test compound has to modify such gene expression profiles, and to cause the profile to more closely resemble that of a more desirable profile.

Moreover, a modulator of TNF- α and/or TNFR expression and/or activity identified as described herein (*e.g.*, an antisense nucleic acid molecule, or a specific antibody, or a small molecule) may be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such a modulator. Alternatively, a modulator identified as described herein may be used in an animal model to determine the mechanism of action of such a modulator.

In one embodiment, the screening assays of the invention are high throughput or ultra high throughput (*e.g.*, Fernandes PB, *Curr Opin Chem Biol.* 1998 2:597; Sundberg SA, *Curr Opin Biotechnol.* 2000, 11:47).

Exemplary cell based and cell free assays of the invention are described in more detail below.

1. Cell Based Assays

In one embodiment, an indicator composition of the invention may be a cells that expresses TNF- α and/or TNFR. For example, a cell that naturally expresses endogenous polypeptide, or, a cell that has been engineered to express one or more exogenous polypeptides, *e.g.*, by introducing into the cell an expression vector encoding the protein may be used in a cell based assay.

The cells used in the instant assays can be eukaryotic or prokaryotic in origin. For example, in one embodiment, the cell is a bacterial cell. In another embodiment, the cell is a fungal cell, *e.g.*, a yeast cell. In another embodiment, the cell

is a vertebrate cell, *e.g.*, an avian or a mammalian cell (*e.g.*, a murine cell, or a human cell). In a preferred embodiment, the cell is a human cell.

In one embodiment, a cell is capable of producing progesterone, SOCS1, SOCS3, IL-6 and/or I κ B α (either naturally or upon expression or introduction of nucleic acid sequences). For example, a corpus leuteal cell is capable of producing SOCS1,
5 SOCS3, IL-6 and/or I κ B α .

Recombinant expression vectors that may be used for expression of polypeptides are known in the art. For example, the cDNA is first introduced into a recombinant expression vector using standard molecular biology techniques. A cDNA
10 can be obtained, for example, by amplification using the polymerase chain reaction (PCR) or by screening an appropriate cDNA library.

Following isolation or amplification of a cDNA molecule encoding the gene of interest, *e.g.*, TNF- α and/or TNFR, the DNA fragment is introduced into an expression vector. As used herein, the term "vector" refers to a nucleic acid molecule
15 capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*,
20 bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to
25 herein as "recombinant expression vectors" or simply "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral
30 vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

Exemplary recombinant expression vectors comprise a nucleic acid molecule in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory sequences,
35 selected on the basis of the host cells to be used for expression and the level of expression desired, which is operatively linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a

manner which allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" includes promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel; *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, CA (1990). Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cell, those which direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences) or those which direct expression of the nucleotide sequence only under certain conditions (*e.g.*, inducible regulatory sequences).

In one embodiment, *e.g.*, for measuring the effect of a compound on expression of TNF- α and/or TNFR, the expression of the gene is controlled by naturally-occurring regulatory elements.

When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma virus, adenovirus, cytomegalovirus and Simian Virus 40. Non-limiting examples of mammalian expression vectors include pCDM8 (Seed, B., (1987) *Nature* 329:840) and pMT2PC (Kaufman *et al.* (1987), *EMBO J.* 6:187-195). A variety of mammalian expression vectors carrying different regulatory sequences are commercially available. For constitutive expression of the nucleic acid in a mammalian host cell, a preferred regulatory element is the cytomegalovirus promoter/enhancer. Moreover, inducible regulatory systems for use in mammalian cells are known in the art, for example systems in which gene expression is regulated by heavy metal ions (see *e.g.*, Mayo *et al.* (1982) *Cell* 29:99-108; Brinster *et al.* (1982) *Nature* 296:39-42; Searle *et al.* (1985) *Mol. Cell. Biol.* 5:1480-1489), heat shock (see *e.g.*, Nouer *et al.* (1991) in *Heat Shock Response*, e.d. Nouer, L., CRC, Boca Raton, FL, pp167-220), hormones (see *e.g.*, Lee *et al.* (1981) *Nature* 294:228-232; Hynes *et al.* (1981) *Proc. Natl. Acad. Sci. USA* 78:2038-2042; Klock *et al.* (1987) *Nature* 329:734-736; Israel & Kaufman (1989) *Nucl. Acids Res.* 17:2589-2604; and PCT Publication No. WO 93/23431), FK506-related molecules (see *e.g.*, PCT Publication No. WO 94/18317) or tetracyclines (Gossen, M. and Bujard, H. (1992) *Proc. Natl. Acad. Sci. USA* 89:5547-5551; Gossen, M. *et al.* (1995) *Science* 268:1766-1769; PCT Publication No. WO 94/29442; and PCT Publication No. WO 96/01313). Still further, many tissue-specific regulatory sequences are known in the art, including the albumin promoter (liver-specific; Pinkert *et al.* (1987) *Genes Dev.* 1:268-277), lymphoid-specific promoters (Calame and Eaton (1988) *Adv. Immunol.* 43:235-275), in particular promoters of T cell receptors (Winoto and Baltimore (1989) *EMBO J.* 8:729-733) and immunoglobulins

(Banerji *et al.* (1983) *Cell* 33:729-740; Queen and Baltimore (1983) *Cell* 33:741-748), neuron-specific promoters (*e.g.*, the neurofilament promoter; Byrne and Ruddle (1989) *Proc. Natl. Acad. Sci. USA* 86:5473-5477), pancreas-specific promoters (Edlund *et al.* (1985) *Science* 230:912-916) and mammary gland-specific promoters (*e.g.*, milk whey promoter; U.S. Patent No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, for example the murine hox promoters (Kessel and Gruss (1990) *Science* 249:374-379) and the α -fetoprotein promoter (Campes and Tilghman (1989) *Genes Dev.* 3:537-546).

Vector DNA may be introduced into mammalian cells *via* conventional transfection techniques. As used herein, the various forms of the term "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (*e.g.*, DNA) into mammalian host cells, including calcium phosphate co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transfecting host cells can be found in Sambrook *et al.* (*Molecular Cloning: A Laboratory Manual*, 2nd Edition, Cold Spring Harbor Laboratory press (1989)), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (*e.g.*, resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable markers include those which confer resistance to drugs, such as G418, hygromycin and methotrexate. Nucleic acid encoding a selectable marker can be introduced into a host cell on a separate vector from that encoding the gene of interest or, more preferably, on the same vector. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker gene will survive, while the other cells die).

In one embodiment, within the expression vector coding sequences are operatively linked to regulatory sequences that allow for constitutive expression of the molecule in the indicator cell (*e.g.*, viral regulatory sequences, such as a cytomegalovirus promoter/enhancer, may be used). Use of a recombinant expression vector that allows for constitutive expression of the genes in the indicator cell is preferred for identification of compounds that enhance or inhibit the activity of the molecule. In an alternative embodiment, within the expression vector the coding sequences are operatively linked to regulatory sequences of the endogenous gene (*i.e.*, the promoter regulatory region derived from the endogenous gene). Use of a recombinant expression vector in which expression is controlled by the endogenous regulatory sequences is preferred for identification of compounds that enhance or inhibit

the transcriptional expression of the molecule.

For example, an indicator cell can express (or can be transfected with an expression vector comprising a nucleic acid molecule encoding TNF- α and/or TNFR and any appropriate regulatory elements) incubated in the presence and in the absence of
5 a test compound, and the effect of the compound on the expression of the molecule can be determined.

In another embodiment, the effect of the compound on one or more activities of TNF- α can be measured according to standard techniques. Activity can be a direct activity, such as an association with or binding to a TNF- α receptor protein.
10 Alternatively, activity may be a more downstream event associated with binding to a receptor and initiating signal transduction, such as, for example, generation of second messengers, or a biological effect on a cell or on an organism occurring as a result of the signaling cascade triggered by that interaction. For example, downstream activities of TNF- α described herein include the ability to: modulate the reproductive-endocrine
15 system, *e.g.*, inhibit spontaneous abortion, modulate cytokine production, *e.g.*, IL-6, modulate I κ B α , SOCS1 and/or SOCS3 mRNA or polypeptide production, and/or modulate progesterone production.

Compounds that modulate expression and/or activity of TNF- α or a molecule whose expression is regulated by TNF- α may be identified using various
20 "read-outs." For example, a variety of reporter genes are known in the art and are suitable for use in the screening assays of the invention.

As used herein, the term "reporter gene" includes genes that express a detectable gene product, which may be RNA or protein. Preferred reporter genes are those that are readily detectable. The reporter gene may also be included in a construct
25 in the form of a fusion gene with a gene that includes desired transcriptional regulatory sequences or exhibits other desirable properties. Examples of reporter genes include, but are not limited to CAT (chloramphenicol acetyl transferase) (Alton and Vapnek (1979), *Nature* 282: 864-869) luciferase, and other enzyme detection systems, such as beta-galactosidase; firefly luciferase (deWet, *et al.* (1987), *Mol. Cell. Biol.* 7:725-737);
30 bacterial luciferase (Engelbrecht and Silverman (1984), *Proc. Natl. Acad. Sci., USA* 1: 4154-4158; Baldwin, *et al.* (1984), *Biochemistry* 23: 3663-3667); alkaline phosphatase (Toh, *et al.* (1989) *Eur. J. Biochem.* 182: 231-238, Hall, *et al.* (1983) *J. Mol. Appl. Gen.* 2: 101), human placental secreted alkaline phosphatase (Cullen and Malim (1992) *Methods in Enzymol.* 216:362-368) and green fluorescent protein (U.S. Patent No.
35 5,491,084; WO 96/23898). Standard methods for measuring the activity of these gene products are known in the art.

To determine whether a test compound modulates expression, *in vitro* transcriptional assays can be performed. For example, mRNA or protein expression can be measured using methods well known in the art. For instance, one or more of Northern blotting, slot blotting, ribonuclease protection, quantitative RT-PCR, or
5 microarray analysis (*e.g.*, Current Protocols in Molecular Biology (1994) Ausubel FM *et al.*, eds., John Wiley & Sons, Inc.; Freeman WM *et al.*, Biotechniques 1999 26:112; Kallioniemi *et al.* 2001 *Ann. Med.* 33:142; Blohm and Guiseppi-Eli 2001 *Curr Opin Biotechnol.* 12:41) may be used to confirm that expression is modulated in cells treated with a modulating agent.

10 In another example, agents that modulate the expression of a TNF- α and/or TNFR can be identified by operably linking the upstream regulatory sequences (*e.g.*, the full length promoter and enhancer) of a TNF- α and/or TNFR or a gene whose expression is regulated by TNF- α to a reporter gene such as chloramphenicol acetyltransferase (CAT) or luciferase and introducing in into host cells. The ability of an
15 agent to modulate the expression of the reporter gene product as compared to control cells (*e.g.*, not exposed to the compound) can be measured.

As used interchangeably herein, the terms “operably linked” and “operatively linked” are intended to mean that the nucleotide sequence is linked to a regulatory sequence in a manner which allows expression of the nucleotide sequence in
20 a host cell (or by a cell extract). Regulatory sequences are art-recognized and can be selected to direct expression of the desired protein in an appropriate host cell. The term regulatory sequence is intended to include promoters, enhancers, polyadenylation signals and other expression control elements. Such regulatory sequences are known to those skilled in the art and are described in Goeddel, *Gene Expression Technology: Methods*
25 *in Enzymology* 185, Academic Press, San Diego, CA (1990). It should be understood that the design of the expression vector may depend on such factors as the choice of the host cell to be transfected and/or the type and/or amount of protein desired to be expressed.

In one embodiment, the level of expression of the reporter gene in the
30 indicator cell in the presence of the test compound is higher than the level of expression of the reporter gene in the indicator cell in the absence of the test compound and the test compound is identified as a compound that stimulates the expression of a cytokine gene. In another embodiment, the level of expression of the reporter gene in the indicator cell in the presence of the test compound is lower than the level of expression of the reporter
35 gene in the indicator cell in the absence of the test compound and the test compound is identified as a compound that inhibits the expression of a cytokine gene.

In another embodiment, protein expression may be measured. For example, standard techniques such as Western blotting, ELISA, or *in situ* detection can be used. In one embodiment, the ability of a compound to modulate expression of TNF- α or a cytokine whose expression is regulated by TNF- α can be determined by measuring the intracellular concentration of a cytokine (using intracellular cytokine FACS). In one embodiment, the ability of a compound to modulate cytokine production can be determined by measuring the concentration of the cytokine secreted by a cell. For example, IL-6 can be measured by measuring the effect of the supernatant on an indicator cell line (*e.g.*, on proliferation of the indicator cell line), or, *e.g.*, in an ELISA assay.

Standard methods for detecting mRNA of interest, such as reverse transcription-polymerase chain reaction (RT-PCR) and Northern blotting, are known in the art. Standard methods for detecting protein secretion in culture supernatants, such as enzyme linked immunosorbent assays (ELISA), are also known in the art. Proteins can also be detected using antibodies, *e.g.*, in an immunoprecipitation reaction or for staining and FACS analysis.

In one embodiment a downstream effect of modulation of cytokine production, *e.g.*, the effect of a compound on cell cytotoxicity, *e.g.*, immune cells, may be used as an indicator of modulation of TNF- α activity. For example, apoptosis can be monitored by measuring cytochrome C release from mitochondria during cell apoptosis and can be detected, *e.g.*, plasma cell apoptosis (as described in, for example, Bossy-Wetzel E. *et al.* (2000) *Methods in Enzymol.* 322:235-42). Other exemplary assays include: cytofluorometric quantitation of nuclear apoptosis induced in a cell-free system (as described in, for example, Lorenzo H.K. *et al.* (2000) *Methods in Enzymol.* 322:198-201); apoptotic nuclease assays (as described in, for example, Hughes F.M. (2000) *Methods in Enzymol.* 322:47-62); analysis of apoptotic cells, *e.g.*, apoptotic plasma cells, by flow and laser scanning cytometry (as described in, for example, Darzynkiewicz Z. *et al.* (2000) *Methods in Enzymol.* 322:18-39); detection of apoptosis by annexin V labeling (as described in, for example, Bossy-Wetzel E. *et al.* (2000) *Methods in Enzymol.* 322:15-18); transient transfection assays for cell death genes (as described in, for example, Miura M. *et al.* (2000) *Methods in Enzymol.* 322:480-92); and assays that detect DNA cleavage in apoptotic cells, *e.g.*, apoptotic plasma cells (as described in, for example, Kauffman S.H. *et al.* (2000) *Methods in Enzymol.* 322:3-15). Apoptosis can also be measured by propidium iodide staining or by TUNEL assay. In another embodiment, the transcription of genes associated with a cell signaling pathway involved in apoptosis (*e.g.*, JNK) can be detected using standard methods.

In another embodiment, mitochondrial inner membrane permeabilization can be measured in intact cells by loading the cytosol or the mitochondrial matrix with a dye that does not normally cross the inner membrane, *e.g.*, calcein (Bernardi *et al.* 1999. *Eur. J. Biochem.* 264:687; Lemasters, J., J. *et al.* 1998. *Biochem. Biophys. Acta* 1366:177. In another embodiment, mitochondrial inner membrane permeabilization can be assessed, *e.g.*, by determining a change in the mitochondrial inner membrane potential ($\Delta\Psi_m$). For example, cells can be incubated with lipophilic cationic fluorochromes such as DiOC6 (Gross *et al.* 1999. *Genes Dev.* 13:1988) (3,3'-dihexyloxacarbocyanine iodide) or JC-1 (5,5',6,6'-tetrachloro-1,1', 3,3'-tetraethylbenzimidazolylcarbocyanine iodide). These dyes accumulate in the mitochondrial matrix, driven by the Ψ_m . Dissipation results in a reduction of the fluorescence intensity (*e.g.*, for DiOC6 (Gross *et al.* 1999. *Genes Dev.* 13:1988) or a shift in the emission spectrum of the dye. These changes can be measured by cytofluorometry or microscopy.

The ability of the test compound to modulate binding of TNF- α or a TNF receptor or other TNF- α -interacting polypeptide can also be determined. For example, binding can be detected by determining the ability of the molecules to be coimmunoprecipitated or by coupling the target molecule (or TNF- α) with a detectable label (*e.g.*, a radioisotope or enzymatic label) such that binding of the molecules can be determined, *e.g.*, by detecting the labeled TNF- α target molecule in a complex.

Determining the ability of the test compound to bind to TNF- α can also be accomplished, for example, by coupling the compound with a radioisotope or enzymatic label such that binding of the compound can be determined by detecting the labeled compound in a complex. For example, targets can be labeled with ^{125}I , ^{35}S , ^{14}C , or ^3H , either directly or indirectly, and the radioisotope detected by direct counting of radioemission or by scintillation counting. Alternatively, compounds can be labeled, *e.g.*, with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

In another embodiment, fluorescence technologies can be used, *e.g.*, fluorescence polarization, time-resolved fluorescence, and fluorescence resonance energy transfer (Selvin PR, *Nat. Struct. Biol.* 2000 7:730; Hertzberg RP and Pope AJ, *Curr Opin Chem Biol.* 2000 4:445).

It is also within the scope of this invention to determine the ability of a compound to interact with TNF- α or the effect of a compound on the interaction of TNF- α with a TNF- α interacting molecule without the labeling of any of the interactants. For example, a microphysiometer may be used to detect the interaction of a compound with a TNF- α without the labeling of either the compound or the molecule

(McConnell, H. M. *et al.* (1992) *Science* 257:1906-1912). As used herein, a "microphysiometer" (*e.g.*, Cytosensor) is an analytical instrument that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate may be used as an indicator of the interaction
5 between compounds.

2. Cell-free assays

Alternatively, the indicator composition can be a cell-free composition that includes a TNF- α - and/or a TNF- α -interacting molecule (*e.g.*, TNF- α receptor protein) *e.g.*, a cell extract from a cell expressing the protein or a composition that
10 includes purified either natural or recombinant protein.

In one embodiment, the indicator composition is a cell free composition. Polypeptides expressed by recombinant methods in a host cells or culture medium can be isolated from the host cells, or cell culture medium using standard methods for protein purification. For example, ion-exchange chromatography, gel filtration
15 chromatography, ultrafiltration, electrophoresis, and immunoaffinity purification with antibodies may be used to produce a purified or semi-purified protein that may be used in a cell free composition. An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free
20 from chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of protein in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. Alternatively, a lysate or an extract of cells expressing the protein of interest can be prepared for use as cell-free composition. Cell
25 extracts with the appropriate post-translation modifications of proteins can be prepared using commercially available resources found at, for example Promega, Inc., and include but are not limited to reticulocyte lysate, wheat germ extract and *E. coli* S30 extract.

In one embodiment, compounds that specifically modulate the interaction of TNF- α with a target molecule to which TNF- α binds, *e.g.*, a TNF receptor. Suitable
30 assays are known in the art that allow for the detection of protein-protein interactions (*e.g.*, immunoprecipitations and the like). By performing such assays in the presence and absence of test compounds, these assays may be used to identify compounds that modulate the interaction of TNF- α with a target molecule.

In the methods of the invention for identifying test compounds that
35 modulate an interaction between a TNF- α -interacting protein and TNF- α , the complete TNF- α protein may be used in the method, or, alternatively, only portions of the protein may be used. For example, binding of TNF- α or a TNF- α -interacting polypeptide can be determined either directly or indirectly as described above. Determining the ability

of TNF- α or TNFR protein to bind to a test compound can also be accomplished using a technology such as real-time Biomolecular Interaction Analysis (BIA) (Sjolander, S. and Urbaniczky, C. (1991) *Anal. Chem.* 63:2338-2345; Szabo *et al.* (1995) *Curr. Opin. Struct. Biol.* 5:699-705). As used herein, "BIA" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (*e.g.*, BIAcore). Changes in the optical phenomenon of surface plasmon resonance (SPR) may be used as an indication of real-time reactions between biological molecules.

In one embodiment of the above assay methods, it may be desirable to immobilize either TNF- α or a TNF- α -interacting polypeptide for example, to facilitate separation of complexed from uncomplexed forms of one or both of the proteins, or to accommodate automation of the assay. Binding to a surface can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein can be provided in which a domain that allows one or both of the proteins to be bound to a matrix is added to one or more of the molecules. For example, glutathione-S-transferase fusion proteins or glutathione-S-transferase/target fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtitre plates, which are then combined with the test compound or the test compound and either the non-adsorbed target protein or TNF- α protein, and the mixture incubated under conditions conducive to complex formation (*e.g.*, at physiological conditions for salt and pH). Following incubation, the beads or microtitre plate wells are washed to remove any unbound components, the matrix is immobilized in the case of beads, and complex formation is determined either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, proteins may be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, antibodies which are reactive with protein or target molecules but which do not interfere with binding of the protein to its target molecule can be derivatized to the wells of the plate, and unbound target or TNF- α protein is trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with TNF- α or a TNF- α -interacting polypeptide.

3. Test Compounds

A variety of test compounds can be evaluated using the screening assays described herein. The term "test compound" includes any reagent or test agent which is employed in the assays of the invention and assayed for its ability to influence the production, expression and/or activity of TNF- α . More than one compound, *e.g.*, a plurality of compounds, can be tested at the same time in a screening assay. The term "screening assay" preferably refers to assays which test the ability of a plurality of compounds to influence the readout of choice rather than to tests which test the ability of one compound to influence a read-out. Preferably, the subject assays identify compounds not previously known to have the effect that the screening assay detects. In one embodiment, high throughput screening may be used to assay for the activity of a compound.

In certain embodiments, the compounds to be tested can be derived from libraries (*i.e.*, are members of a library of compounds). While the use of libraries of peptides is well established in the art, new techniques have been developed which have allowed the production of mixtures of other compounds, such as benzodiazepines (Bunin, *et al.* (1992). *J. Am. Chem. Soc.* 114:10987; DeWitt *et al.* (1993). *Proc. Natl. Acad. Sci., USA* 90:6909) peptoids (Zuckermann. (1994). *J. Med. Chem.* 37:2678) oligocarbamates (Cho, *et al.* (1993). *Science*.261:1303), and hydantoins (DeWitt *et al. supra*). An approach for the synthesis of molecular libraries of small organic molecules with a diversity of 10⁴-10⁵ as been described (Carell, *et al.* (1994). *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell, *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061).

The compounds of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries, synthetic library methods requiring de-convolution, the 'one-bead one-compound' library method, and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, K.S. (1997) *Anticancer Drug Des.* 12:145). Other exemplary methods for the synthesis of molecular libraries can be found in the art, for example in: Erb, *et al.* (1994). *Proc. Natl. Acad. Sci., USA* 91:11422; Horwell, *et al.* (1996) *Immunopharmacology* 33:68; and in Gallop, *et al.* (1994) *J. Med. Chem.* 37:1233.

Exemplary compounds which can be screened for activity include, but are not limited to, peptides, nucleic acids, carbohydrates, small organic molecules, and natural product extract libraries.

The term "small molecule" is a term of the art and includes molecules that are less than about 1000 molecular weight or less than about 500 molecular weight. In one embodiment, small molecules do not exclusively comprise peptide bonds. In another embodiment, small molecules are not oligomeric. Exemplary small molecule compounds which can be screened for activity include, but are not limited to, peptides, peptidomimetics, nucleic acids, carbohydrates, small organic molecules (*e.g.*, polyketides) (Cane, *et al.* 1998. *Science* 282:63), and natural product extract libraries. In another embodiment, the compounds are small, organic non-peptidic compounds. In a further embodiment, a small molecule is not biosynthetic. For example, a small molecule is preferably not itself the product of transcription or translation.

Candidate/test compounds include, for example, 1) peptides such as soluble peptides, including Ig-tailed fusion peptides and members of random peptide libraries (see, *e.g.*, Lam, K.S. *et al.* (1991) *Nature* 354:82-84; Houghten, R. *et al.* (1991) *Nature* 354:84-86) and combinatorial chemistry-derived molecular libraries made of D- and/or L- configuration amino acids; 2) phosphopeptides (*e.g.*, members of random and partially degenerate, directed phosphopeptide libraries, see, *e.g.*, Songyang, Z. *et al.* (1993) *Cell* 72:767-778); 3) antibodies (*e.g.*, antibodies (*e.g.*, intracellular, polyclonal, monoclonal, humanized, anti-idiotypic, chimeric, and single chain antibodies as well as Fab, F(ab')₂, Fab expression library fragments, and epitope-binding fragments of antibodies); 4) small organic and inorganic molecules (*e.g.*, molecules obtained from combinatorial and natural product libraries); 5) enzymes (*e.g.*, endoribonucleases, hydrolases, nucleases, proteases, synthetases, isomerases, polymerases, kinases, phosphatases, oxido-reductases and ATPases), and 6) mutant forms of molecules (*e.g.*, dominant negative mutant forms of TNF- α or a TNF- α -interacting protein).

The test compounds of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring de-convolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, K.S. (1997) *Anticancer Drug Des.* 12:145).

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt *et al.* (1993) *Proc. Natl. Acad. Sci., U.S.A.* 90:6909; Erb, *et al.* (1994) *Proc. Natl. Acad. Sci., USA* 91:11422; Zuckermann, *et al.* (1994) *J. Med. Chem.* 37:2678; Cho, *et al.* (1993) *Science* 261:1303; Carrell, *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carrell, *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and Gallop, *et al.* (1994) *J. Med. Chem.* 37:1233.

Libraries of compounds can be presented in solution (*e.g.*, Houghten (1992) *Biotechniques* 13:412-421), or on beads (Lam (1991) *Nature* 354:82-84), chips (Fodor (1993) *Nature* 364:555-556), bacteria (Ladner USP 5,223,409), spores (Ladner USP '409), plasmids (Cull *et al.* (1992) *Proc. Natl. Acad. Sci., USA* 89:1865-1869) or
5 phage (Scott and Smith (1990) *Science* 249:386-390; Devlin (1990) *Science* 249:404-406; Cwirla *et al.* (1990) *Proc. Natl. Acad. Sci.*, 87:6378-6382; Felici (1991) *J. Mol. Biol.* 222:301-310; Ladner *supra.*).

Compounds identified in the subject screening assays may be used, *e.g.*, in methods of modulating reproductive endocrine function, inhibiting spontaneous
10 abortion. It will be understood that it may be desirable to formulate such compound(s) as pharmaceutical compositions (described *supra*) prior to contacting them with cells.

Once a test compound is identified that directly or indirectly modulates TNF- α using a method known in the art or one of the variety of methods described herein, the selected test compound (or "compound of interest") can then be further
15 evaluated for its effect on cells or animals, and determining the effect of the compound of interest, as compared to an appropriate control.

The instant invention also pertains to compounds identified in the subject screening assays.

20 **III. Administration of Agents**

Administration of the compositions and/or agents described herein can be in any pharmacological form that includes a therapeutically active amount of an agent and optionally a pharmaceutically acceptable carrier. Administration of a therapeutically active amount of the subject agents and/or compositions is defined as an
25 amount effective, at dosages and for periods of time necessary to modulate the reproductive endocrine system, *e.g.*, to inhibit spontaneous abortion, preferably an amount which enables a subject to carry one or more embryos to term. A therapeutically active amount of an agent or composition may vary according to factors such as the age, and weight of the individual, and whether or not the individual has had a previous
30 spontaneous abortion. Such an amount can be readily determined by one of ordinary skill in the art.

The optimal course of administration of the agents and/or compositions may also vary depending upon the subject to be treated. For example in one embodiment, an agent which modulates the reproductive endocrine system, *e.g.*, inhibits
35 spontaneous abortion, is administered prior to fertilization. In another embodiment, the agent can be administered at the time of implantation (*e.g.*, natural or assisted implantation) or at the time of embryo transfer. In another embodiment, the agent can be administered after implantation of the embryo into the uterine wall. In one

embodiment, an agent which modulates the reproductive endocrine system, *e.g.*, inhibits spontaneous abortion, is administered throughout the course of the pregnancy, *e.g.*, beginning prior to fertilization, prior to implantation, or at about the time of implantation, and, *e.g.*, ending when the risk of spontaneous abortion has decreased or can be administered up to the time of delivery. In one embodiment an agent that modulates the reproductive endocrine system, *e.g.*, inhibits spontaneous abortion, is administered prior to, during, and/or after a procedure employed to promote fertility or pregnancy. For example, in one embodiment, an egg or a fertilized embryo is suspended in a composition comprising an agent that modulates the reproductive endocrine system, *e.g.*, inhibits spontaneous abortion, and is transferred into the uterus of a subject. In another embodiment, an agent that modulates the reproductive endocrine system, *e.g.*, inhibits spontaneous abortion, is administered to a subject, *e.g.*, is applied topically in the uterus prior to and/or after embryo transfer. In one embodiment, an agent that modulates the reproductive endocrine system, *e.g.*, inhibits spontaneous abortion, is administered systemically instead of or in addition to being administered directly to the uterus or vaginally. A dosage regime may be adjusted to provide the optimum therapeutic response for each subject without undue experimentation.

An agent that modulates the reproductive endocrine system, *e.g.*, inhibits spontaneous abortion, can be administered in the form of a pharmaceutical composition suitable for administration. Such compositions typically comprise the agent and a pharmaceutically acceptable carrier. As used herein the term "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, they may be used in the instant composition. Supplementary active compounds can also be incorporated into the compositions.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. For example, solutions or suspensions used for parenteral, intradermal, topical, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The

parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

In one embodiment an agent which modulates the reproductive endocrine system, *e.g.*, inhibits spontaneous abortion, is formulated into a suppository for vaginal use. These can be prepared by mixing the agent with a suitable non-irritating carrier which is solid at room temperature but liquid at rectal temperature and therefore will melt in the vagina to release the drug. Such materials include cocoa butter, beeswax, polyethylene glycols, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the vaginal cavity and release the active agent.

Compositions which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams, films, or spray compositions containing such carriers as are known in the art to be appropriate. The carrier employed in the should be compatible with vaginal administration. Combinations can be, *e.g.*, in solid, semi-solid and liquid dosage forms, such as douches, foams, films, ointments, creams, balms, gels, salves, pastes, slurries, vaginal suppositories, or sexual lubricants.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition will be sterile and should be fluid to the extent that easy syringability exists. Preferably, it will be stable under the conditions of manufacture and storage and will be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

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

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially, *e.g.*, from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of

active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active agent or composition for the treatment of individuals. Appropriate dosages can readily be determined by one of ordinary skill in the art.

In one embodiment, the compositions and/or agents described herein are administered to a subject at a dose level in the range of 1 mg to 300 mg per dose for as many doses as determined appropriate by one of ordinary skill in the art. A single dose may be administered or multiple doses may be administered.

In one embodiment, the compositions and/or agents described herein are administered subcutaneously to a subject at a dose level in the range of 1 mg to 300 mg per dose, e.g., with a dosage interval ranging from 1 day to 1 month.

In another embodiment, the compositions and/or agents described herein are administered intramuscularly to a subject at a dose level in the range of 1 mg to 300 mg per dose, e.g., with a dosage interval ranging from 1 day to 1 month.

In another embodiment, the compositions and/or agents described herein are administered intravenously to a subject at a dose level in the range of 1 mg to 300 mg per dose, e.g., with a dosage interval ranging from 1 day to 1 month.

In another embodiment, an anti-TNF- α antibody is administered intravenously at 3mg/kg-10mg/kg every 4-8 weeks), preferably 5mg/kg every 2-6 weeks.

In one embodiment, an anti-TNF- α antibody is administered subcutaneously with a dose of 40 mg every other week.

In one embodiment, an anti-TNF- α receptor antibody is administered subcutaneously with a dose of 50 mg every week.

In another embodiment, an anti-TNF- α receptor antibody is administered subcutaneously with a dose of 25 mg twice per week.

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of cell biology, cell culture, molecular biology, transgenic biology, microbiology, recombinant DNA, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature. See, for example, *Molecular Cloning A Laboratory Manual*, 2nd Ed., ed. by Sambrook, Fritsch and Maniatis (Cold Spring Harbor Laboratory Press: 1989); *DNA Cloning*, Volumes I and II (D. N. Glover ed., 1985); *Oligonucleotide Synthesis* (M. J. Gait ed., 1984); Mullis *et al.* U.S. Patent NO: 4,683,195; *Nucleic Acid Hybridization* (B. D. Hames & S. J.

- Higgins eds. 1984); Transcription And Translation (B. D. Hames & S. J. Higgins eds. 1984); Culture Of Animal Cells (R. I. Freshney, Alan R. Liss, Inc., 1987); Immobilized Cells And Enzymes (IRL Press, 1986); B. Perbal, A Practical Guide To Molecular Cloning (1984); the treatise, Methods In Enzymology (Academic Press, Inc., N.Y.);
- 5 Gene Transfer Vectors For Mammalian Cells (J. H. Miller and M. P. Calos eds., 1987, Cold Spring Harbor Laboratory); Methods In Enzymology, Vols. 154 and 155 (Wu *et al.* eds.), Immunochemical Methods In Cell And Molecular Biology (Mayer and Walker, eds., Academic Press, London, 1987); Handbook Of Experimental Immunology, Volumes I-IV (D. M. Weir and C. C. Blackwell, eds., 1986); Manipulating the Mouse
- 10 Embryo, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986).

EXAMPLES

- This invention is further illustrated by the following examples which
- 15 should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application are hereby incorporated by reference. Nucleotide and amino acid sequences deposited in public databases as referred to herein are also hereby incorporated by reference.

- 20 The following Materials and Methods were used in the Examples:

Mice, antibody and hormone treatments.

- CD40^{-/-} mice were the gift of R. Geha (Harvard Medical School, Boston, MA); C57BL/6 (B6), BALB/c, B6CBAF and B6129F1 (a strain-matched control for
- 25 CD40^{-/-} mice) were from The Jackson Laboratories; Rag2^{-/-} and Rag2^{-/-}γc^{-/-} mice were from Taconic Farms. Males were mated with individual females no more than once per week; B6CBAF1 females and B6 males were used in all experiments except when noted. The day of the copulation plug was counted as E0. All antibodies were given via intraperitoneal injection at the dose of 100 μg in 0.1 ml PBS. The FGK45 rat hybridoma
- 30 cell line was the gift of A. Groenewegen (Basel Institute for Immunology, Switzerland); antibodies were prepared from hybridoma supernatants by protein G chromatography either in house or by BioExpress (West Lebanon, NH). Polyclonal rat IgG antibodies were purchased from ICN (Aurora, OH). Mice received FGK45 or rat IgG antibodies between 0830 and 1200 h. For experiments evaluating the role of TNF-α, mice were
- 35 additionally injected two hours later with TN3-19.12, a hamster IgG monoclonal antibody that neutralizes murine TNF-α (Sheehan, K.C., *et al.* (1989) *J Immunol* 142:3884-3893), or 100 μg PIP, an irrelevant hamster IgG monoclonal antibody that recognizes glutathione s-transferase. Both of these antibodies were the gifts of R.

Schreiber (Washington University in St. Louis). Progesterone (Sigma, St. Louis, MO) was dissolved in sesame seed oil (Sigma) and 2 mg/0.1 ml was injected subcutaneously at the time of concurrent antibody injections. Ovine prolactin (NIDDK-oPRL-21) was dissolved in alkaline saline and 100 µg/0.1 ml was injected subcutaneously twice a day
 5 between 0800-0830 h and 1600-1630 h.

Serum hormone and cytokine measurements.

Serum was collected by retro-orbital eye bleeds. Progesterone concentrations were measured by enzyme-linked immunoassay (Alpco Diagnostics, Windham, NH), prolactin and luteinizing hormone (LH) concentrations were measured
 10 in the laboratory of the National Hormone and Peptide Program by radioimmunoassay, and cytokines were measured by the Searchlight assay (Pierce, Rockford, IL).

Flow cytometry.

Splenocyte forward scatter and cell surface marker expression was determined by flow cytometry using a Becton-Dickinson FACS Calibur and CellQuest software. The following antibodies were purchased from BD Biosciences (San Diego, CA) : CyChrome-conjugated anti-TCR-β (clone H57-597), FITC-anti-NK1.1 (PK136), PE-anti-B220 (RA3-6B2), PE-anti-CD69 (H1.2F3), APC-anti-CD11c (HL3), PE-anti-
 20 CD11b (M1/70), FITC-anti-CD80 (16-10A1), FITC-anti-CD86 (GL1), FITC-anti-MHC class II (AF6-120.1), FITC-anti-CD40 (HM40-3). Following an initial gating on all lymphoid cells based upon their forward and side scatter characteristics, T cells were identified as the TCRβ⁺NK1.1⁻ population, NK cells were identified as the TCRβ⁻NK1.1⁺ population, and B cells were identified as the TCRβ⁻NK1.1⁻ population. True
 25 B220⁺ B cells comprised 70-80% of this latter population in rat IgG-treated mice, and 85-95% of this latter population in FGK45-treated mice. Dendritic cells were identified and gated by virtue of their expression of CD11c, with an unused fluorescence channel was used to gate away autofluorescent cells.

30 *Histology and immunofluorescence microscopy.*

Tissue was fixed overnight at 4° C in 4% paraformaldehyde prior to routine paraffin embedding. For leukocyte visualization, sections were stained with biotin-conjugated antibodies against the common leukocyte antigen CD45 (clone 30-F11, BD Biosciences), using horseradish peroxidase-conjugated streptavidin as a
 35 secondary reagent (NEN, Boston, MA), biotin-tyramide amplification (NEN), and streptavidin-Alexa 954 (Molecular Probes, Eugene, OR) as the final fluorochrome. Sections were counterstained with DAPI (Sigma), and digitally photographed at 4x magnification. Composites were assembled in Adobe Photoshop (San Jose, CA). NF-

κB p65 was visualized with a goat primary antibody (C-20, Santa Cruz Biotechnology, Santa Cruz, CA), a biotin-conjugated horse anti-goat secondary antibody (Vector Laboratories, Burlingame, CA), and streptavidin-Alexa 954.

5 RNA analysis.

RNA was prepared from homogenized ovaries using the Trizol reagent (Invitrogen, Carlsbad, CA). Real-time RT-PCR was performed as described previously (Erlebacher, A., *et al.* (2002) *Proc Natl Acad Sci U S A* 99:16940-16945). All reactions were run in duplicate using cDNA template synthesized from 10 ng RNA. ΔC_T values were calculated relative to β -actin, and statistical analyses were performed on groups of raw ΔC_T values. Expression levels relative to β -actin were calculated as $2^{-\Delta C_T}$, with error bars extrapolated from the standard deviation of the ΔC_T mean for each group. All probes were dual-labeled with FAM and TAMRA. SYBRG was used for amplifications when a primer set was used without a probe. For all reactions, the approximate fold difference in amplification between plus and minus RT reactions was >1000x, except the SYBRG (SYBR Green) amplifications of β -actin (50x), STAT5a (100x), STAT5b (50x).

Real-time PCR primer and probe sets are listed 5' to 3' in the order of forward primer, reverse primer, and probe (when employed):

20 β -actin

Forward primer: 5'-GCTCTGGCTCCTAGCACCAT-3' (SEQ ID NO.:1)

Reverse primer: 5'-GCCACCGATCCACACCGCGT-3' (SEQ ID NO.:2)

Probe: 5'-TCAAGATCATTGCTCCTCCTGAGCGC-3' (SEQ ID NO.:3)

25 StAR

Forward primer: 5'-TCACTTGGCTGCTCAGTATTGAC-3' (SEQ ID NO.:4)

Reverse primer: 5'-TCTATCTGGGTCTGCGATAGGAC-3' (SEQ ID NO.:5)

P450scc

30 Forward primer: 5'-CGGTACTTGGGCTTTGGCT-3' (SEQ ID NO.:6)

Reverse primer: 5'-AGCAGATTGATAAGGAGGATGGTC-3' (SEQ ID NO.:7)

3 β -HSD

Forward primer: 5'-CCAGGCAGACCATCCTAGATGT-3' (SEQ ID NO.:8)

35 Reverse primer: 5'-AGATGAAGGCTGGCACACTTG-3' (SEQ ID NO.:9)

LHR

Forward primer: 5'-CGAGACGCTTTATTCTGCCAT-3' (SEQ ID NO.:10)

Reverse primer: 5'-AGCATCTGGTTCTGGAGTACATTG-3' (SEQ ID NO.:11)

5 20 α -HSD

Forward primer: 5'- GCTGATATGTTTAAGGCTCACCCCTAA-3' (SEQ ID NO.:12)

Reverse primer: 5'- AGAGTCCAGCATCACACAAAAGATC-3' (SEQ ID NO.:13)

PRLR

10 Forward primer: 5'- GGATGTGACTTACATTGTTGAACCA-3' (SEQ ID NO.:14)

Reverse primer: 5'- TACCCACAGATATGTTTTTTTGTCTTTT-3' (SEQ ID NO.:15)

STAT5a

Forward primer: 5'-TGGTCCCTGAGTTCGTCAATG-3' (SEQ ID NO.:16)

15 Reverse primer: 5'-GTTGAGGGCACACGACTGG-3' (SEQ ID NO.:17)

STAT5b

Forward primer: 5'- GCGCCACCTACATGGATCA-3' (SEQ ID NO.:18)

Reverse primer: 5'- GACGGAGTCCGGGTTGG-3' (SEQ ID NO.:19)

20

IL-6

Forward primer: 5'-TTCAACCAAGAGGTAAAAGATTTACATAA-3' (SEQ ID NO.:20)

Reverse primer: 5'-CACTCCTTCTGTGACTCCAGCTT-3' (SEQ ID NO.:21)

25

I κ B α

Forward primer: AGATGCTACCCGAGAGCGAG (SEQ ID NO.:22)

Reverse primer: TCATCATAGGGCAGCTCATCC (SEQ ID NO.:23)

30 SOCS1

Forward primer: 5'-TGTGCCGCAGCATTAAGTG-3' (SEQ ID NO.:24)

Reverse primer: 5'-GGCATCTCACCCCTCCACAAC-3' (SEQ ID NO.:25)

Probe: 5'-CCGCCTGGGTCGGAGGGAGT-3' (SEQ ID NO.:26)

35 SOSC3

Forward primer: 5'-TGCTGGCCAAAGAAATAACCA-3' (SEQ ID NO.:27)

Reverse primer: 5'-GGTCACCCCTTGCCACTCT-3' (SEQ ID NO.:28)

Probe: 5'-CCCCTGCCCAGCCTAGGTGAGGA-3' (SEQ ID NO.:29)

Statistical analysis.

Pregnancy rates were compared by Chi-square statistics; all other comparisons used Student's *t* test.

5 **Example 1. Systemic CD40 ligation in mice causes early pregnancy failure preceded by decreased serum progesterone concentrations.**

To determine the gestational effects of systemic CD40 ligation, the agonistic anti-CD40 monoclonal antibody FGK45 was injected (Rolink, A., *et al.* (1996) *Immunity* 5:319-330) at various times during pregnancy. Mice were treated with
10 control rat IgG or agonistic anti-CD40 antibodies (FGK45) either once on embryonic day (E) E4 and sacrificed 24 h later on E5, or daily on E4-7 and sacrificed on E8. Four daily injections of FGK45 from E4 to E7 dramatically reduced the percentage of pregnant mice per total mated mice to nearly 0% in females of all strains tested, with control pregnancy rates following treatment with polyclonal rat IgG varying between
15 40% and 100% depending upon the background strain (Table 1). The effect of FGK45 injection occurred in both syngeneic and allogeneic mating combinations and was restricted to this immediate post-implantation period, since similar daily injections on E8-11 did not reduce pregnancy rates or litter sizes. FGK45 injection also did not inhibit pregnancy in CD40^{-/-} females
20 (Castigli, E., *et al.* (1994) *Proc Natl Acad Sci U S A* 91:12135-12139) mated to wild-type males, ruling out the possibility that its abortifacient effect was non-specific, or due to embryonic or placental ligation of CD40. Rather, pregnancy failure required maternal CD40 expression.

Table 1. Systemic CD40 ligation causes murine pregnancy failure in the post-implantation period.

Treatment						Number Pregnant		Litter size	
period	Female	Male	Treatment	Sacrifice	n	rate (%)		(+/- SD)	
E4-7	BALB/c	BALB/c or						7.2 +/-	
		B6 ^a	rat IgG	E17	25	14	56	1.7	
			anti-CD40	E17	25	1	4 ^c	9	
	B6	B6	rat IgG	E14-17	12	5	42	8.6 +/-	
			anti-CD40	E14-17	11	0	0 ^d	0.9	
								NA	
	B6CBAF1	B6	rat IgG	E8	15	15	100	9.3 +/-	
			anti-CD40	E8	22	1	5 ^c	1.3	
								8	
E8-11	BALB/c	BALB/c or						6.5 +/-	
		B6 ^b	rat IgG	E17	11	4	36	1.7	
			anti-CD40	E17	12	6	50	7.0 +/-	
								1.8	
	B6CBAF1	B6	rat IgG	E12	7	6	86	6.9 +/-	
								2.3	
			anti-CD40	E12	6	6	100	7.9 +/-	
								1.1	

^aMales were divided between $n=12$ BALB/c and $n=13$ C57BL/6 (B6) mice for both treatment groups.

^bMales were divided between $n=5-6$ BALB/c and $n=5-6$ B6 mice for both treatment groups.

^c $P<0.0001$

^d $P<0.02$

Although CD40 is largely considered an immune stimulatory molecule, the timing of events leading to embryo loss suggested that the ultimate cause of pregnancy failure following CD40 ligation was endocrinological rather than immunological. Employing B6CBAF1 females to take advantage of their high natural pregnancy rate (Table 1), it was found that a single FGK45 injection on E4 dramatically reduced serum progesterone levels ($\pm$ SEM of $n=6$ mice per group) within 24 hours (Figure 1A; *, $P<0.001$), yet implantation sites from these mice showed no evidence of a pathological leukocyte infiltration that might be expected with a tissue rejection response. Rather, compared to controls (Figure 1B, whole mount uteri preparation; and Figure 1D, paraffin sections of implantation sites), implantation sites from FGK45-treated mice were only mildly reduced in size at E5 (Figure 1C, paraffin sections of implantation sites) and contained implanted embryos with the typical clearing of CD45⁺ leukocytes from the early primary maternal decidua (Figure 1E; immunostaining is representative of $n=2-3$ mice per group, encompassing a total of $n=15-20$ implantation sites in each group. Scale bar shows 0.5 mm). By E8, however, after daily E4-7 FGK45 injections, all implantation sites had been completely resorbed (see below) and serum progesterone levels remained low (Figure 1A). The mesometrial pole of each implantation site in Figures 1D and 1E is oriented toward the top of the panel, and a recently implanted embryo can be seen in the center of each section (arrowhead).

Since progesterone is the sole ovarian hormone required for the maintenance of post-implantation pregnancy (Rubinstein, L., and Forbes, T.R. (1963) *Proc Soc Exp Biol Med* 113:1043-1046), its reduced concentration in serum prior to overt embryo resorption suggested that CD40 ligation-induced abortion involved an inhibition of the hypothalamic-pituitary-gonadal axis. This possibility would also be consistent with the observation that pregnancy failure occurred in an all-or-nothing fashion, with the normal-sized litters in those few females maintaining pregnancy following E4-7 FGK45 treatment (Table 1) showing no evidence of piecemeal embryonic resorption.

Example 2. Pregnancy failure following CD40 ligation is due to luteal insufficiency associated with ovarian prolactin resistance and defective prolactin receptor signaling.

The mechanism of inhibition of ovarian function following CD40 ligation was investigated. Compared to paraffin control sections stained with hematoxylin and eosin (Figure 2A), there was little microscopic evidence that CD40 ligation caused the histological regression of corpora lutea (*i.e.* structural luteolysis), since these structures were still clearly present on E8 following daily E4-7 FGK45 injections and only showed a mild and variable increase in luteal cellularity (Figure 2B). Furthermore, quantitative

real-time RT-PCR analysis of ovarian RNA from FGK45-treated mice (Figure 2C) revealed no significant change on either E5 or E8 in the levels of mRNA encoding the steroidogenic enzymes Steroidogenic Acute Regulatory protein (StAR) and P450 side chain cleavage enzyme (P450ssc), and only transient 2-fold decreases on E5 alone in the mRNA levels of 3 β -hydroxysteroid dehydrogenase (3 β -HSD). Ovaries were collected from mice treated with control rat IgG or anti-CD40 antibodies (FGK45) either once on E4 and sacrificed 24 h later on E5 ($n=4$ mice per group; upper panel), or daily on E4-7 and sacrificed on E8 ($n=3$ mice per group; lower panel). Data represent mean $\pm$ SD.

On the other hand, CD40 ligation induced dramatic changes in the mRNA expression levels of the luteinizing hormone receptor (LHR) and 20 α -HSD, the two major transcriptional targets of prolactin receptor signaling in corpus luteal cells (Risk, M., and Gibori, G. (2001) Mechanisms of luteal cell regulation by prolactin. In Prolactin. N.D. Horseman, editor. Boston: Kluwer Academic Publishers. 265-295; Stocco, C., *et al.* (2001) *Endocrinology* 142:4158-4161) (Figure 2C). Normally, prolactin receptor signaling via JAK2/STAT5 induces the transcription of LHR and represses the transcription of 20 α -HSD (Risk, M., and Gibori, G. (2001) Mechanisms of luteal cell regulation by prolactin. In Prolactin. N.D. Horseman, editor. Boston: Kluwer Academic Publishers. 265-295). However, as shown in Figure 2C, on both E5 and E8, 20 α -HSD and LHR mRNA levels were increased and decreased, respectively (fold changes indicated by brackets in Figure 2C), whereas 3 β -HSD and PRLR mRNA levels were decreased on E5 only (*, $P<0.02$; **, $P<0.005$; ***, $P<0.001$). Prolactin and LH concentrations in FGK45-treated mice on E5 were significantly elevated compared to control mice (*, $P<0.05$; data represent mean $\pm$ SEM of $n=12$ mice per group), but there was no change in prolactin concentrations on E8 ($n=6$ mice per group). (Figure 2D). The limit of detection for LH was 0.2 ng/ml. Thus, a single FGK45 injection on E4 led to a 12-fold decrease the abundance of LHR mRNA and a 2-fold increase in 20 α -HSD mRNA within 24 h, which progressed after daily E4-7 FGK45 injections to a 13-fold decrease and a 15-fold increase in mRNA transcript levels, respectively, on E8 (Figure 2C).

Thus, CD40 ligation led to a functional luteal insufficiency associated with defective prolactin receptor target gene expression. Since 20 α -HSD catalyzes the intra-ovarian catabolism of newly synthesized progesterone (Risk, M., and Gibori, G. (2001) Mechanisms of luteal cell regulation by prolactin. In Prolactin. N.D. Horseman, editor. Boston: Kluwer Academic Publishers. 265-295), its derepression in FGK45-treated mice likely contributed to the decrease in serum progesterone concentrations.

Further molecular and hormonal analyses suggested that the defect in prolactin target gene expression was due to inhibition at the post-receptor level. Thus, serum levels of prolactin were actually modestly elevated from controls 24 hours after a

single FGK45 injection on E4 (Figure 2D), consistent with a loss of feedback inhibition by progesterone (Davis, J.S., and Rueda, B.R. (2002) *Front Biosci* 7:d1949-1978), and similar to controls on E8 after daily E4-7 injections. The overall decrease in serum prolactin levels at this latter time point is consistent with the known pattern of pituitary prolactin secretion during early mouse gestation (Markoff, E., and Talamantes, F. (1981) *Biol Reprod* 24:846-851), and unimpaired pituitary function was also suggested by the modestly elevated serum levels of LH seen on E5 (Figure 2D). Furthermore, we observed only a transient 3-fold decrease in prolactin receptor (PRLR) mRNA expression on E5 alone (due to proportionate decreases in mRNAs for the long and short isoforms) and normal expression levels on E8, with unaltered mRNA expression of STAT5a and STAT5b on both E5 and E8 (Figure 2C).

Collectively, these data implied that the deregulation of prolactin target genes was due to the presence of a dominant inhibitor of STAT5 signaling, a possibility we explore further below.

To directly evaluate whether luteal insufficiency was the ultimate cause of pregnancy failure, pregnant mice were treated with both FGK45 and progesterone. Strikingly, daily E4-7 progesterone administration, which led to serum concentrations of about 35 ng/ml 24 h after the E7 injection, almost completely prevented abortions caused by daily E4-7 FGK45 injection (Figure 3A). Implantation sites at E8 from dually-treated mice appeared completely normal both grossly (Fig. 3H) as well as histologically (Figure 3I), and showed no evidence of an altered distribution of CD45⁺ leukocytes compared to control mice treated with either rat IgG plus progesterone (Fig. 3F, 3G) or with rat IgG plus sesame seed oil vehicle (Figures 3B and 3C). In contrast, E8 uteri of mice treated with anti-CD40 antibodies plus vehicle showed no evidence of implantation (Figure 3D), occasionally contained debris in the uterine lumen (Figure 3E, arrowhead), and by this end stage were infiltrated with CD45⁺ leukocytes scattered throughout the uterine stroma. The CD45 staining intensity in these sections tended to be greater than that at viable implantation sites because they do not contain the high numbers of CD45^{dim} uterine natural killer cells present in the decidua. Immunostaining is representative of $n=2$ mice per group, encompassing a total of about $n=12$ implantation sites in each group. Scale bar shows 0.5 mm. Continued daily progesterone injection, up to E17, also maintained pregnancy in mice treated with FGK45 on E4-7 (6/6 mice).

In addition to progesterone, twice-daily coadministration of 100 µg ovine prolactin prevented CD40 ligation-induced abortion (Figure 3A), and implantation sites from these mice also showed no histological abnormalities. Prolactin injections raised serum progesterone concentrations above those seen in mice treated with FGK45 alone, however these levels still remained subphysiological (10.9±1.5 ng/ml [mean ± SEM]

on E8). Thus, although the corpora lutea of FGK45-treated mice were resistant to physiological or modestly elevated serum prolactin levels, this could be overcome by exogenous prolactin administration at high doses.

5 **Example 3. Induction of luteal insufficiency requires a lymphoid intermediate and TNF- α , and is associated with increased SOCS1 and SOCS3 expression.**

To understand how systemic CD40 ligation caused luteal insufficiency, flow cytometry was used first to determine that there was no significant CD40 staining of enzymatically dispersed E4 ovarian cell suspensions aside from a subset of CD45⁺ leukocytes. This ruled out the possibility that FGK45 treatment induced abortion via
10 direct ligation of CD40 on corpus luteal cells themselves. Furthermore, CD40 ligation induced abortion in Rag2^{-/-} mice, which lack B cells, T cells and NKT cells (Shinkai, Y., *et al.* (1992) *Cell* 68:855-867), yet had no effect on pregnancy in completely alymphoid Rag2^{-/-} γ_c ^{-/-} mice, which additionally lack NK cells (Cao, X., *et al.* (1995) *Immunity* 2:223-238) (Figure 4A). Mice were sacrificed on E8 following daily E4-7
15 treatment with rat IgG or anti-CD40 antibodies (FGK45). Data for control C57BL/6 matings are shown in Table 1. Thus, a lymphocyte population was required for the abortifacient effects of CD40 ligation, and NK cells were sufficient to perform this function.

20 Systemic CD40 ligation led to broad activation of lymphocytes and dendritic cells. Importantly, this activation was not affected by concurrent progesterone administration, suggesting that it lay entirely upstream to luteal insufficiency. Thus, the same degree of splenomegaly and elevated splenocyte numbers following FGK45 treatment in both groups ($P < 0.005$) (Figure 4B), increased lymphocyte cell size (Figure
25 4C), modulated expression of the lymphoid activation markers CD69 (Figure 4C), CD25, CD44, CD45RB, and CD62L, as well as upregulation of the costimulatory molecules CD80, CD86, MHC class II (Figure 4D), CD40 and CD54 on CD11c⁺ dendritic cells was found. The splenic CD11b⁺ CD11c⁻ macrophage population expressed low levels of CD40 and showed only modest changes in surface marker
30 expression after daily E4-7 FGK45 treatment. Flow cytometric analysis of cell size and surface activation marker expression is shown with the shaded histograms denoting rat IgG-treated mice, while open histograms show data from FGK45-treated mice. Data is representative of $n=3$ mice per group. Increased forward scatter indicating increased cell size (Figure 4C) and increased CD69 expression indicating cell activation (Figure 4D)
35 was seen in B cells, NK cells, and a fraction of T cells following FGK45 treatment in both groups. Dendritic cells were identified and gated by virtue of their expression of CD11c. Increased CD80, CD86 and MHC class II expression indicating cell activation was seen following FGK45 treatment in both groups.

Since FGK45 injection did not cause a significant leukocytic infiltration into the ovaries, luteal insufficiency following CD40 ligation was likely due to inflammatory cytokines produced by the immune system potentially acting at the systemic level. In contrast to unaltered serum levels of IL-1 β , IL-2, IL-4, IL-10, IL-12 or IFN- γ , a single FGK45 injection on E4 induced a transient increase after 24 h in the serum concentrations of TNF- α and its downstream target IL-6 (Figure 5A) (Ghosh, S., *et al.* (1998) *Annu Rev Immunol* 16:225-260). The limits of detection were 31.1 pg/ml TNF- α and 54.7 pg/ml IL-6. Indeed, TNF- α was critical for pregnancy failure, as its neutralization with a specific monoclonal antibody prevented FGK45-induced abortion (Figure 5B). Mice were sacrificed on E8-E10 after daily E4-7 injections of rat IgG and control hamster IgG monoclonal antibodies, FGK45 and control hamster IgG monoclonal antibodies, or FGK45 and TNF- α -neutralizing hamster IgG monoclonal. One mouse receiving FGK45 and TNF- α -neutralizing antibodies was allowed to carry its litter to term. In addition, administration of a single dose (100 μ g) of FGK45 and TNF- α -neutralizing antibodies at embryonic day (E) 4.5 also prevented FGK45-induced abortion (6/8 mice were pregnant).

Furthermore, immunohistochemical and biochemical studies suggested that the cytokine was acting directly on corpus luteal cells. Thus, the p65 subunit of NF- κ B, a transcriptional mediator of TNF receptor (TNFR) signaling present in the cytoplasm of unstimulated cells (Figure 5C), had assumed a nuclear distribution pattern in corpus luteal cells 12 h after FGK45 injection on E4 (Figure 5D; data is representative of immunostained ovaries from $n=3$ mice per group. Scale bar shows 50 μ m). FGK45 injection also led to 11-fold and 2-fold respective increases in the ovarian abundances of transcripts for IL-6 and the additional NF- κ B target I κ B α (Ghosh, S., *et al.* (1998) *Annu Rev Immunol* 16:225-260), and these increases could largely be inhibited by administration of TNF- α neutralizing antibodies (Figure 6). Collectively, these data show that TNF- α was required for FGK45-induced pregnancy failure, and that corpus luteal cells were functionally exposed to this cytokine during the course of FGK45-induced abortion. The ovary was also likely exposed to IL-6 as a secondary consequence of its systemic or local induction.

Both TNF- α and IL-6 are known to transcriptionally induce multiple SOCS family members (Alexander, W.S. (2002) *Nat Rev Immunol* 2:410-416; Shuai, K., and Liu, B. (2003) *Nat Rev Immunol* 3:900-911). While only assessed to date outside the context of pregnancy, SOCS induction is thought to be the major mechanism of cross-talk inhibition between JAK/STAT signaling cascades of the immune and endocrine system (Auernhammer, C.J., and Melmed, S. (2001) *J Clin Invest* 108:1735-1740; Alexander, W.S. (2002) *Nat Rev Immunol* 2:410-416; Shuai, K., and Liu, B. (2003) *Nat Rev Immunol* 3:900-911). By analogy, the ovarian exposures to TNF- α and

IL-6 directly suggested SOCS proteins as the dominant inhibitors of STAT5 signaling that was inferred to exist from our expression studies of ovarian steroidogenic enzymes and prolactin receptor signaling components (see above). Indeed, 12 h after a single FGK45 injection on E4, ovarian SOCS1 and SOCS3 mRNA expression was induced 11- fold and 2-fold, respectively (Fig. 5f), while SOCS2 mRNA levels remained unchanged. Mice treated with FGK45 plus TNF- α -neutralizing antibodies showed partially inhibited SOCS1 and SOCS3 induction on E4. Thus, SOCS1 and SOCS3 inducibility correlated with the E4-7 temporal window of sensitivity towards FGK45-induced abortion, since FGK45 injection on E8 did not significantly increase SOCS1 and SOCS3 mRNA expression (Figure 6; on E4, 12 hours after treatment, IL-6, I κ B α , SOCS1 and SOCS3 mRNA levels were increased following FGK45 injection (*, $P < 0.05$; **, $P < 0.005$; ***, $P < 0.0005$). Baseline ovarian SOCS1 and SOCS3 expression was higher at this later point in gestation. The failure to induce SOCS1 and SOCS3 was likely due to altered ovarian TNF- α responsiveness on E8 since the pattern of immune cell surface marker modulation following FGK45 injection was identical in the E8-11 and E4-7 periods, and similar levels of IL-6 and I κ B α mRNA induction were seen 12 h after FGK45 injection on E8 versus E4 (Figure 6). Lastly, progesterone treatment did not affect the FGK45-induced ovarian upregulation of IL-6, I κ B α , SOCS1, or SOCS3 expression, consistent with immune activation acting entirely upstream to luteal insufficiency. Together, these data suggest that the direct or indirect induction of SOCS1 and SOCS3 by TNF- α is a major mechanism of deregulated luteal prolactin target gene expression and decreased ovarian progesterone synthesis following systemic CD40 ligation. For ease of graphical representation, transcript levels for IL-6, I κ B α , and SOCS3 were multiplied by 1000, 2, and 5, respectively.

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.

What is claimed is:

1. A method of inhibiting spontaneous abortion in a mammalian subject comprising administering to the mammalian subject a compound that inhibits TNF- α activity such that spontaneous abortion in the mammalian subject is inhibited.
5
2. A method of enhancing the ability of a mammalian subject to carry at least one embryo to term, comprising administering to the mammalian a compound that inhibits TNF α activity such that the ability of the mammalian subject to carry at least one embryo to term is enhanced.
10
3. The method of claim 1 or 2, wherein the compound is an antibody that binds to TNF α .
- 15 4. The method of claim 3, wherein the antibody that binds to TNF α binds human TNF α .
5. The method of claim 4, wherein the antibody that binds to human TNF α is selected from the group consisting of: HUMIRA[®] and REMICADE[®].
20
6. The method of claim 1 or 2, wherein the compound is a soluble form of at least one TNF receptor.
7. The method of claim 1 or 2, wherein the compound is an antibody that binds to a human TNF receptor.
25
8. The method of claim 1 or 2, wherein the compound is administered in an amount sufficient to prevent the upregulation of SOCS1 and SOCS3 expression such that spontaneous abortion is inhibited.
30
9. The method of claim 1 or 2, wherein the compound is administered in an amount sufficient to maintain progesterone levels in early pregnancy such that spontaneous abortion is inhibited.
- 35 10. The method of claim 1 or 2, further comprising administering progesterone or a progesterone derivative.

11. The method of claim 1 or 2, wherein the mammalian subject has had a previous spontaneous abortion.
12. The method of claim 1 or 2, wherein the compound is administered to the mammalian subject prior to implantation of an embryo.
13. The method of claim 1 or 2, wherein the compound is administered to the mammalian subject after implantation of an embryo.
14. The method of claim 1 or 2, wherein said mammalian subject is human.
15. The method of claim 1 or 2, wherein the subject is a domesticated animal.
16. The method of claim 1 or 2, wherein the subject is an endangered species.
17. The method of claim 1 or 2, wherein the subject is a non-human animal being used to carry cloned, non-human animals.
18. A prognostic method for determining whether a subject is at risk for having a spontaneous abortion comprising detecting the presence or level of at least one of SOCS1, SOCS3 or I κ B α mRNA or polypeptide in a biological sample obtained from said subject to thereby determine whether the subject is at risk for having a spontaneous abortion, wherein if the level of at least one of SOCS1, SOCS3 or I κ B α mRNA or polypeptide is elevated relative to a suitable control, the subject is at risk of having a spontaneous abortion.
19. A prognostic method for determining whether a subject is at risk for having a spontaneous abortion comprising detecting the presence or level of mRNA or polypeptide of at least one of IL-6 and TNF α in a biological sample obtained from said subject, to thereby determining whether the subject is at risk for having a spontaneous abortion, wherein if the level of at least one of IL-6 and TNF α mRNA or polypeptide is elevated relative to a suitable control, the subject is at risk of having a spontaneous abortion.
20. A diagnostic method for determining whether a subject has had a spontaneous abortion that would benefit from treatment with a compound that inhibits TNF α activity comprising detecting the presence or level of SOCS1, SOCS3 or I κ B α mRNA or polypeptide in a biological sample obtained from said subject to thereby

determine whether the subject has had a spontaneous abortion that would benefit from treatment with a compound that inhibits TNF α activity, wherein if the level of at least one of SOCS1, SOCS3 or I κ B α mRNA or polypeptide is elevated relative to a suitable control, the subject has had a spontaneous abortion.

5

21. A diagnostic method for determining whether a subject has had a spontaneous abortion that would benefit from treatment with a compound that inhibits TNF α activity comprising detecting the presence or level of mRNA or polypeptide of at least one of IL-6 and TNF α in a biological sample obtained from said subject thereby
10 determining whether the subject has had a spontaneous abortion that would benefit from treatment with a compound that inhibits TNF α activity, wherein if the level of at least one of IL-6 and TNF α mRNA or polypeptide is elevated relative to a suitable control, the subject has had a spontaneous abortion.

15

22. A method for determining whether a subject is responding to treatment for recurring spontaneous abortions comprising detecting the presence or level of SOCS1, SOCS3 or I κ B α mRNA or polypeptide in a biological sample obtained from said subject to thereby determining whether the subject is responding to treatment for recurring spontaneous abortions, wherein if the level of at least one of SOCS1, SOCS3
20 or I κ B α mRNA or polypeptide is reduced relative to a suitable control, the subject is responding to treatment for recurring spontaneous abortions.

23. A method for determining whether a subject is responding to treatment for recurring spontaneous abortions comprising detecting the presence or level of mRNA
25 or polypeptide of at least one of IL-6 and TNF α in a biological sample obtained from said subject to thereby determining whether the subject is responding to treatment for recurring spontaneous abortions, wherein if the level of at least one of IL-6 and TNF α mRNA or polypeptide is reduced relative to a suitable control, the subject is responding to treatment for recurring spontaneous abortions.

30

24. The method of any one of claims 18-23, further comprising detecting the presence or level of mRNA or polypeptide of one or more of an immune cell surface molecule selected from the group consisting of: CD69, CD25, CD44, CD45RB, CD62L, CD80, CD86, CD40, MHC class II, and CD54.

35

25. The method of any one of claims 18-23, further comprising detecting the presence or level of marker mRNA or polypeptide, wherein the marker is selected from the group consisting of: luteinizing hormone,

λυτεϊνιζινγ ηορμονε ρεχεπτορ, στεροϊδ αχυτε ρεγυλατορψ προτειν, πηοσπηορψλ
ατεδ στεροϊδ αχυτε ρεγυλατορψ προτειν, ανδ 3β-hydroxysteroid dehydrogenase.

5 26. The method any one of claims 18-23, further comprising detecting level
of progesterone.

27. The method of claim any one of claims 18-23, wherein the biological
sample is selected from the group consisting of: a tissue sample, a cell sample, or a
10 serum sample.

28. The method of claim 27, wherein the tissue sample is a chorionic villus
sample or a placental sample.

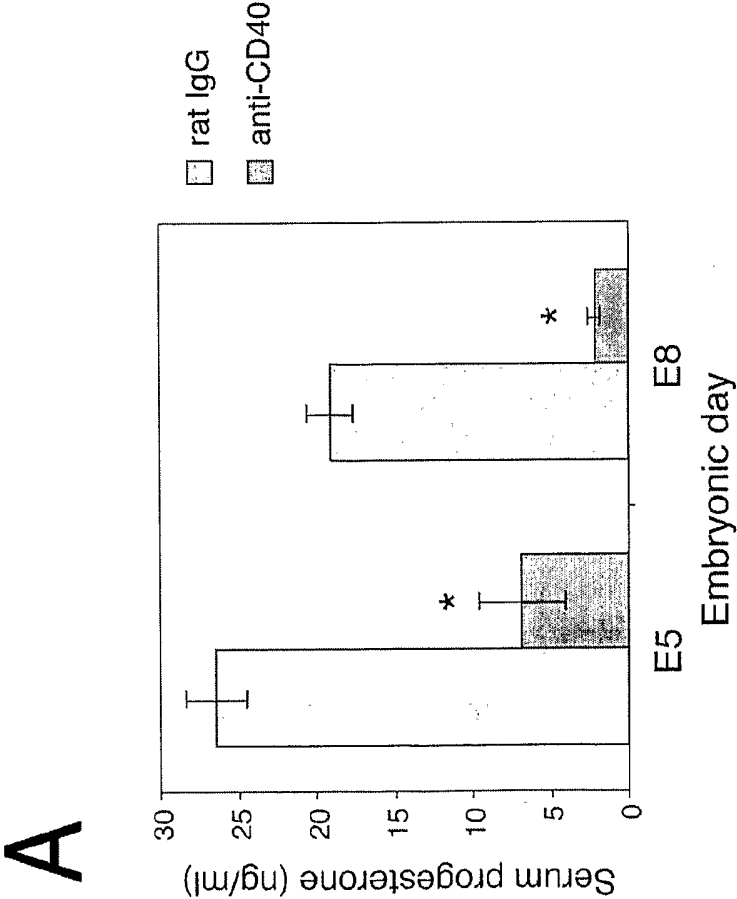
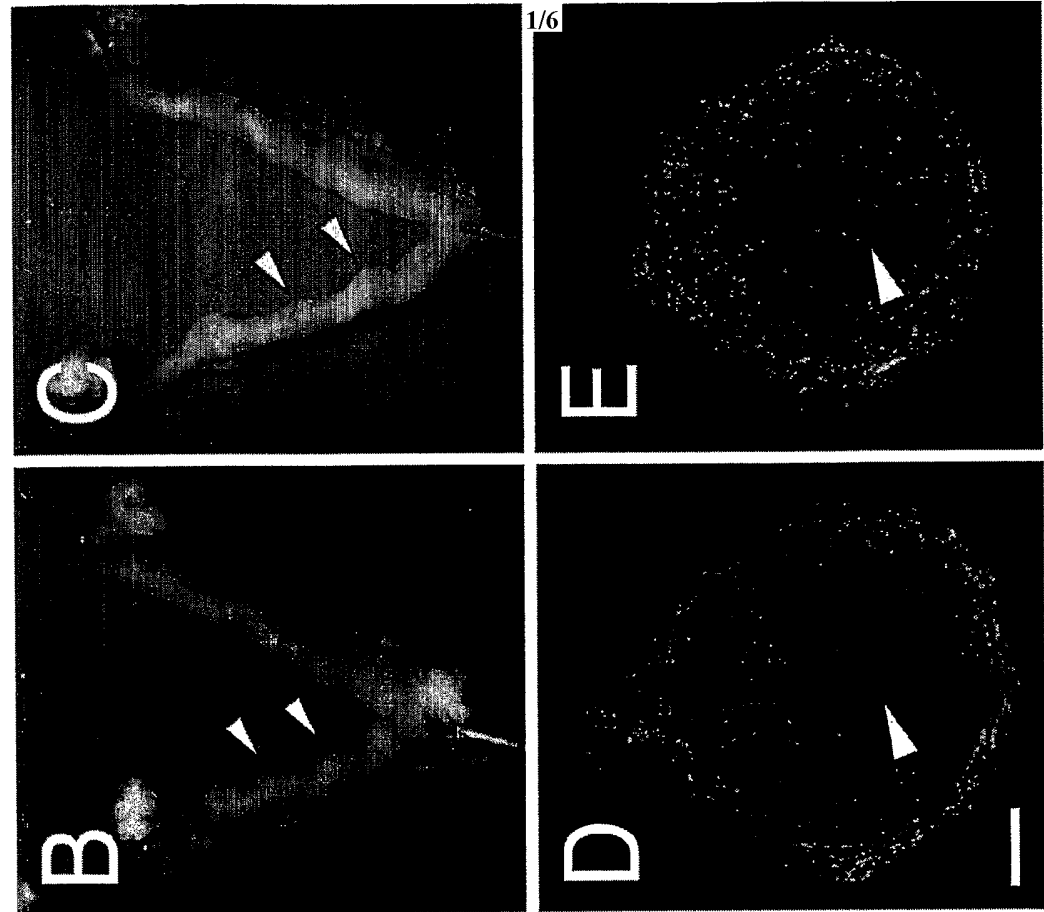
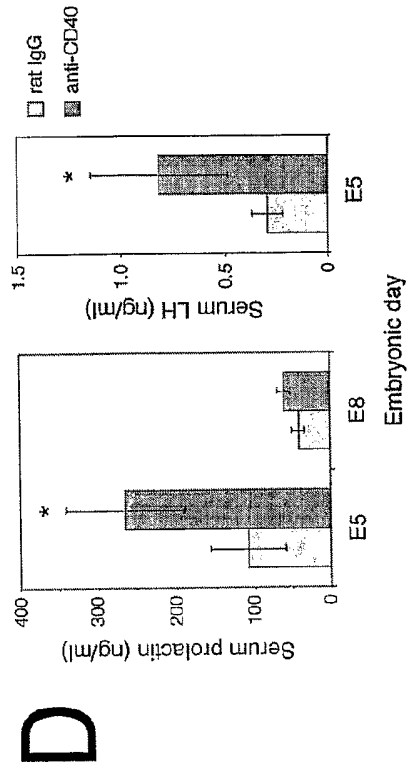
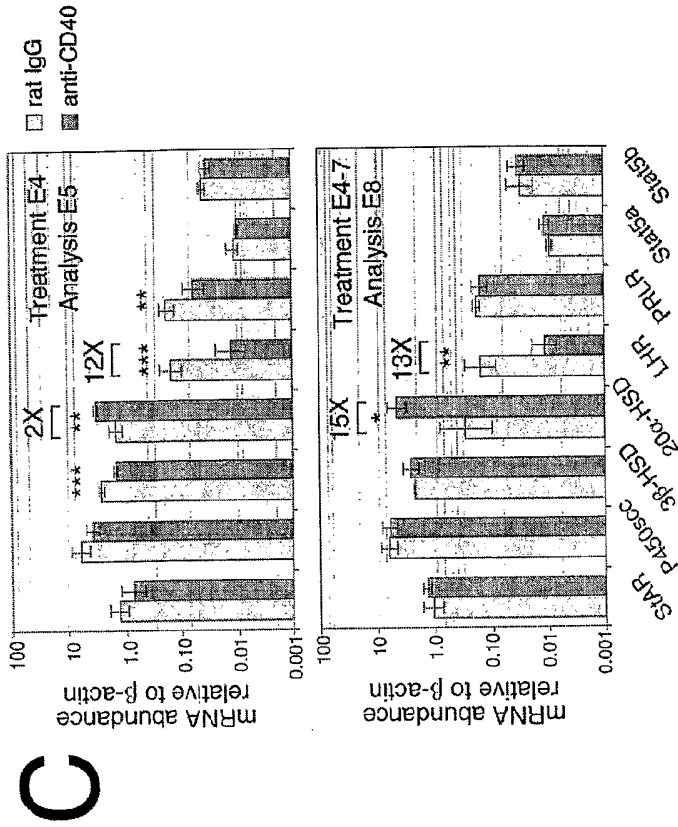
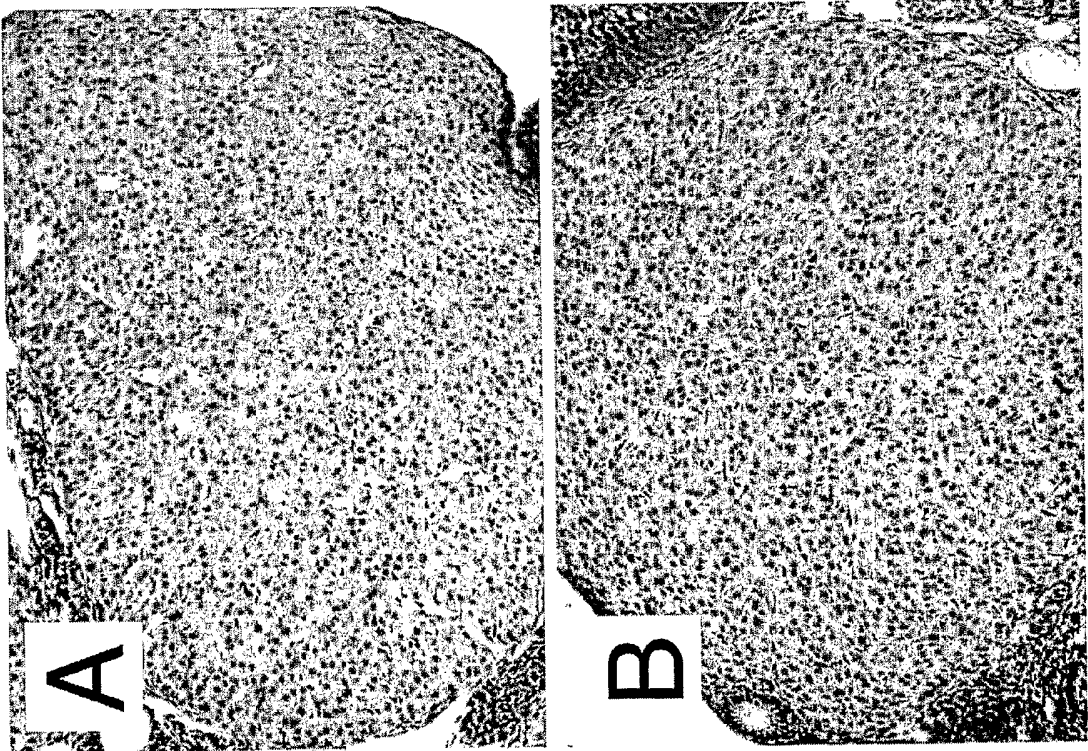


Figure 1



A

Treatment	Co-treatment	n	Number pregnant	Pregnancy rate (%)	Litter size (+/- SD)
rat IgG	vehicle	10	10	100	9.2 +/- 0.9
	progesterone	13	12	92	9.5 +/- 1.5
anti-CD40	vehicle	10	0	0	NA
	progesterone	13	12	92 ^a	9.2 +/- 1.5
anti-CD40	vehicle	5	0	0	8.6 +/- 0.9
	ovine prolactin	8	6	75 ^b	9.0 +/- 2.0

^aP <0.0001

^bP <0.01

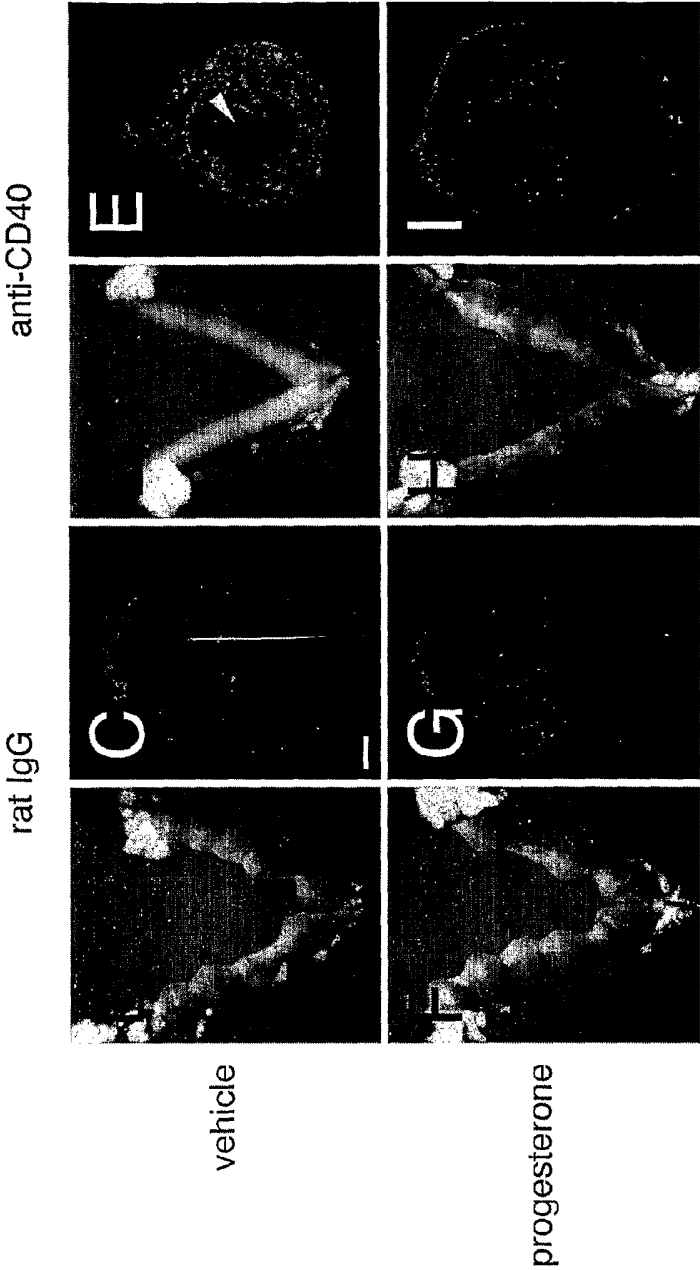
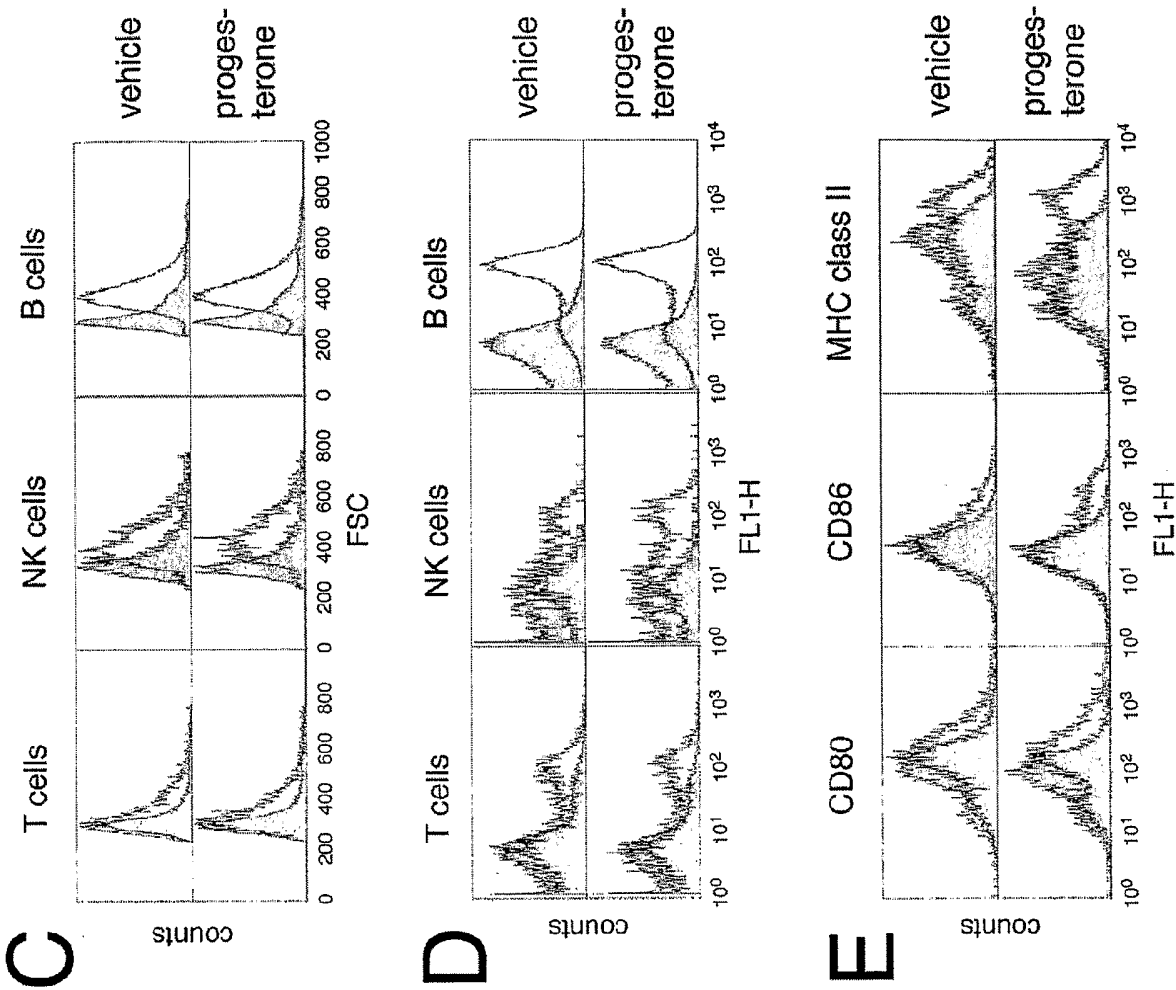


Figure 3



A

Female	Treatment	n	Number pregnant	Pregnancy rate (%)	Litter size (+/- SD)
Rag2 ^{-/-}	rat IgG	9	5	56	8.4 +/- 4.2
	anti-CD40	9	0	0 ^a	NA
Rag2 ^{-/-} γ _c ^{-/-}	rat IgG	6	4	67	8.0 +/- 2.4
	anti-CD40	5	4	80	8.0 +/- 1.6

^aP < 0.01; an equivalent effect was seen with Rag2^{-/-} females on a BALB/c background.

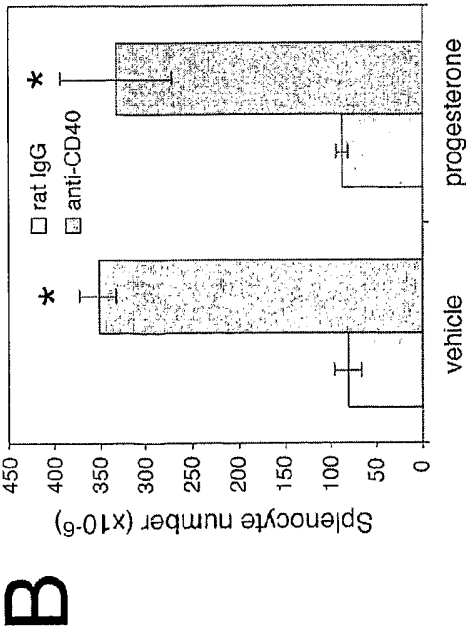
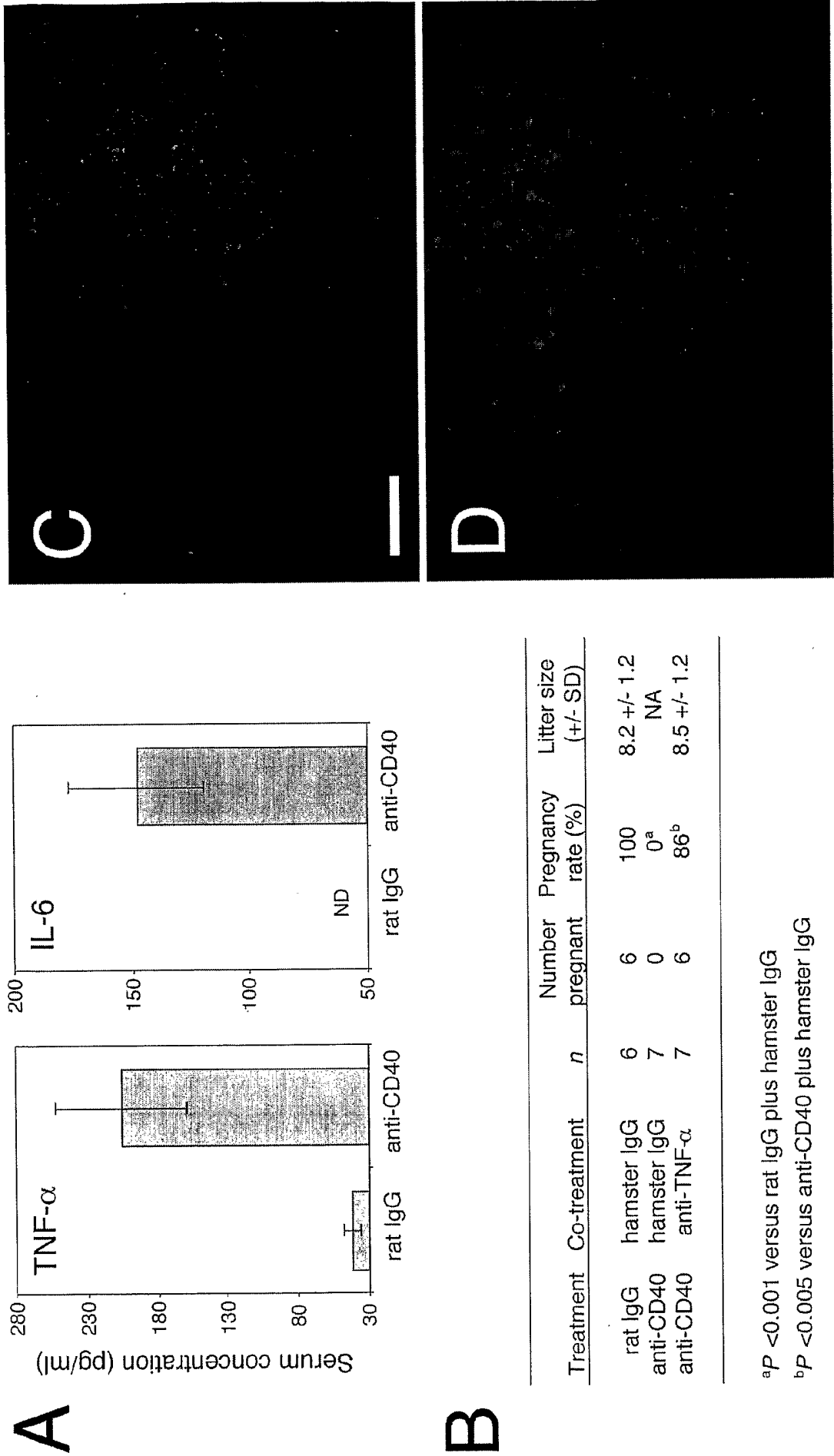
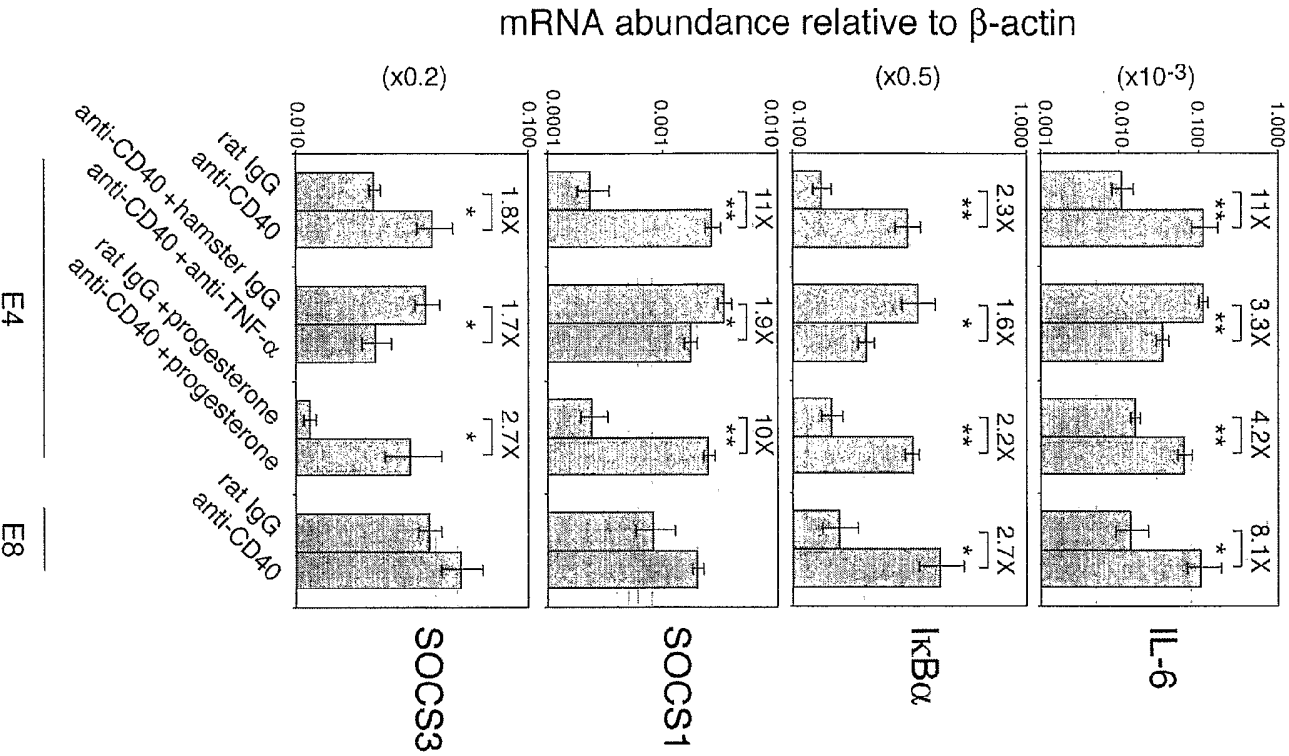


Figure 4



^a*P* <0.001 versus rat IgG plus hamster IgG
^b*P* <0.005 versus anti-CD40 plus hamster IgG

Figure 5



1/80

SEQUENCE LISTING

<110> PRESIDENT AND FELLOWS OF HARVARD COLLEGE

<120> METHODS OF MODULATING THE REPRODUCTIVE ENDOCRINE SYSTEM
BY MODULATION OF TNF-alpha ACTIVITY

<130> HUI-055PC

<140>

<141>

<150> 60/575,143

<151> 2004-05-28

<160> 99

<170> PatentIn 3.3

<210> 1

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic primer

<400> 1

gctctggctc ctagcaccat

20

<210> 2

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic primer

<400> 2

gccaccgatc cacaccgcgt

20

<210> 3

<211> 26

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic primer

<400> 3

tcaagatcat tgctcctcct gagcgc

26

<210> 4

<211> 23

<212> DNA

<213> Artificial Sequence

2/80

<220>

<223> Description of Artificial Sequence: Synthetic primer

<400> 4

tcacttggct gctcagtatt gac

23

<210> 5

<211> 23

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic primer

<400> 5

tctatctggg tctgcgatag gac

23

<210> 6

<211> 19

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic primer

<400> 6

cgggtacttgg gctttggct

19

<210> 7

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic primer

<400> 7

agcagattga taaggaggat ggtc

24

<210> 8

<211> 22

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic primer

<400> 8

ccaggcagac catcctagat gt

22

<210> 9

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic primer

3/80

<400> 9
agatgaaggc tggcacactt g 21

<210> 10
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 10
cgagacgctt tattctgcca t 21

<210> 11
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 11
agcatctggt tctggagtac attg 24

<210> 12
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 12
gctgatatgt ttaaggctca ccctaa 26

<210> 13
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 13
agagtccagc atcacacaaa agatc 25

<210> 14
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 14
ggatgtgact tacattgttg aacca 25

4/80

<210> 15
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 15
taccacaga tatgtttttt tgtctttt 28

<210> 16
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 16
tggtccctga gttcgtcaat g 21

<210> 17
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 17
gttgagggca cacgactgg 19

<210> 18
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 18
gcgccaccta catggatca 19

<210> 19
<211> 17
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 19
gacggagtcc gggttgg 17

5/80

<210> 20
<211> 29
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 20
ttcaaccaag aggtaaaaga ttacataa 29

<210> 21
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 21
cactccttct gtgactccag ctt 23

<210> 22
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 22
agatgctacc cgagagcgag 20

<210> 23
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 23
tcatcatagg gcagctcatc c 21

<210> 24
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 24
tgtgccgcag cattaagtg 19

6/80

<210> 25
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 25
ggcatctcac cctccacaac 20

<210> 26
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 26
ccgcctgggt cggaggagt 20

<210> 27
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 27
tgctggccaa agaaataacc a 21

<210> 28
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 28
ggtcaccctt tgccactct 19

<210> 29
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic primer

<400> 29
cccactgccc agcctaggtg agga 24

7/80

<210> 30
 <211> 1664
 <212> DNA
 <213> Homo sapiens

<400> 30
 tcagcaagga cagcagagga ccagctaaga gggagagaag caactacaga cccccctga 60
 aaacaaccct cagacgccac atccccctgac aagctgccag gcaggttctc ttccctctcac 120
 atactgaccc acggctccac cctctctccc ctggaaagga caccatgagc actgaaagca 180
 tgatccggga cgtggagctg gccgaggagg cgctcccaa gaagacaggg gggccccagg 240
 gctccaggcg gtgcttgctc ctcagcctct tctccttctc gatcgtggca ggcgccacca 300
 cgctcttctg cctgctgcac tttggagtga tcggcccca gaggaagag ttccccaggg 360
 acctctctct aatcagccct ctggcccagg cagtccagatc atcttctcga accccgagtg 420
 acaagcctgt agcccattgt gtagcaaacc ctcaagctga ggggcagctc cagtggctga 480
 accgccgggc caatgccctc ctggccaatg gcgtggagct gagagataac cagctgggtg 540
 tgccatcaga gggcctgtac ctcatctact ccagggtcct cttcaagggc caaggctgcc 600
 cctccaccca tgtgctcctc acccacacca tcagccgcat cgccgtctcc taccagacca 660
 aggtcaacct cctctctgcc atcaagagcc cctgccagag ggagaccca gagggggctg 720
 aggccaagcc ctggtatgag cccatctatc tgggaggggt cttccagctg gagaagggtg 780
 accgactcag cgctgagatc aatcggcccg actatctcga ctttgccgag tctgggcagg 840
 tctacttttg gatcattgcc ctgtgaggag gacgaacatc caaccttccc aaacgcctcc 900
 cctgccccaa tccctttatt acccctcctc tcagacaccc tcaacctctt ctgggtcaaa 960
 aagagaattg ggggcttagg gtccggaacc aagcttagaa ctttaagcaa caagaccacc 1020
 acttcgaaac ctgggattca ggaatgtgtg gcctgcacag tgaagtgtg gcaaccacta 1080
 agaattcaaa ctggggcctc cagaactcac tggggcctac agctttgatc cctgacatct 1140
 ggaatctgga gaccagggag cctttggctc tggccagaat gctgcaggac ttgagaagac 1200
 ctacacctaga aattgacaca agtggacctt aggccttctc ctctccagat gtttccagac 1260
 ttcccttgaga cacggagccc agccctcccc atggagccag ctccctctat ttatgtttgc 1320
 acttggtgatt atttattatt tattttattt ttattttatt acagatgaat gtattttatt 1380
 gggagaccgg ggtatcctgg gggacccaat gtaggagctg ccttggctca gacatgtttt 1440
 ccgtgaaaac ggagctgaac aataggctgt tcccatgtag cccctggcc tctgtgcctt 1500
 cttttgatta tgttttttaa aatattttat tgattaagtt gtctaaacaa tgctgatttg 1560
 gtgaccaact gtcactcatt gctgagcctc tgctccccag gggagtgtg tctgtaatcg 1620
 ccctactatt cagtggcgag aaataaagtt tgcttagaaa agaa 1664

<210> 31
 <211> 233
 <212> PRT
 <213> Homo sapiens

<400> 31
 Met Ser Thr Glu Ser Met Ile Arg Asp Val Glu Leu Ala Glu Glu Ala
 1 5 10 15
 Leu Pro Lys Lys Thr Gly Gly Pro Gln Gly Ser Arg Arg Cys Leu Phe
 20 25 30
 Leu Ser Leu Phe Ser Phe Leu Ile Val Ala Gly Ala Thr Thr Leu Phe
 35 40 45
 Cys Leu Leu His Phe Gly Val Ile Gly Pro Gln Arg Glu Glu Phe Pro
 50 55 60
 Arg Asp Leu Ser Leu Ile Ser Pro Leu Ala Gln Ala Val Arg Ser Ser
 65 70 75 80
 Ser Arg Thr Pro Ser Asp Lys Pro Val Ala His Val Val Ala Asn Pro
 85 90 95

8/80

Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg Ala Asn Ala Leu
 100 105 110

Leu Ala Asn Gly Val Glu Leu Arg Asp Asn Gln Leu Val Val Pro Ser
 115 120 125

Glu Gly Leu Tyr Leu Ile Tyr Ser Gln Val Leu Phe Lys Gly Gln Gly
 130 135 140

Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile Ser Arg Ile Ala
 145 150 155 160

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

Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Lys Pro Trp Tyr Glu
 180 185 190

Pro Ile Tyr Leu Gly Gly Val Phe Gln Leu Glu Lys Gly Asp Arg Leu
 195 200 205

Ser Ala Glu Ile Asn Arg Pro Asp Tyr Leu Asp Phe Ala Glu Ser Gly
 210 215 220

Gln Val Tyr Phe Gly Ile Ile Ala Leu
 225 230

<210> 32

<211> 2236

<212> DNA

<213> Homo sapiens

<400> 32

```

gctgttgcaa cactgcctca ctcttcccct cccaccttct ctccccctct ctctgcttta 60
atattctcag aattctctgg actgaggctc cagttctggc ctttgggggt caagatcact 120
gggaccaggc cgtgatctct atgcccagat ctcaaccctc aactgtcacc ccaaggcact 180
tgggacgtcc tggacagacc gagtcccggg aagccccagc actgccgctg ccacactgcc 240
ctgagcccaa atgggggagt gagaggccat agctgtctgg catgggcctc tccaccgtgc 300
ctgacctgct gctgccactg gtgctcctgg agctgttggt gggaatatac cctcagggg 360
ttattggact ggtccctcac ctaggggaca gggagaagag agatagtgtg tgtccccaag 420
gaaaatatac ccaccctcaa aataattcga tttgctgtac caagtgccac aaaggaacct 480
acttgtacaa tgactgtcca ggcccggggc aggatacgga ctgcaggagg tgtgagagcg 540
gctccttcac cgcttcagaa aaccacctca gacactgcct cagctgctcc aaatgccgaa 600
aggaaatggg tcagggtggag atctcttctt gcacagtgga ccgggacacc gtgtgtggct 660
gcaggaagaa ccagtaccgg cattattgga gtgaaaacct tttccagtgc ttcaattgca 720
gcctctgcct caatgggacc gtgcacctct cctgccagga gaaacagaac accgtgtgca 780
cctgccatgc aggttttctt ctaagagaaa acgagtgtgt ctctgtagt aactgtaaga 840
aaagcctgga gtgcacgaag ttgtgcctac ccagattga gaatgttaag ggcactgagg 900
actcaggcac cacagtgtg ttgcccctgg tcattttctt tggctcttgc cttttatccc 960
tcctcttcat tggtttaatg tctcgctacc aacggtggaa gtccaagctc tactccattg 1020
tttggtggaa atcgacacct gaaaaagagg gggagcttga aggaactact actaagcccc 1080
tggccccaaa cccaagcttc agtcccactc caggcttcac ccccaccctg ggcttcagtc 1140
ccgtgcccag ttccaccttc acctccagct ccacctatac ccccgggtgac tgtcccaact 1200
ttgcggtctc ccgcagagag gtggcaccac cctatcaggg ggtgacccc atccttgcca 1260
cagccctcgc ctccgacccc atccccaccc cccctcagaa gtgggaggac agcgcaccac 1320
agccacagag cctagacact gatgaccccg cgacgctgta cgccgtggtg gagaacgtgc 1380
ccccgttgcg ctggaaggaa ttcggtgcggc gcctagggct gagcgaccac gagatcgatc 1440

```

9/80

```

ggctggagct gcagaacggg cgctgcctgc gcgaggcgca atacagcatg ctggcgacct 1500
ggaggcggcg cacgccggcg cgcgaggcca cgctggagct gctgggacgc gtgctccgcg 1560
acatggacct gctgggctgc ctggaggaca tcgaggaggc gctttgcggc cccgccgccc 1620
tcccgcccg cccagtcctt ctcagatgag gctgcgcccc tgcgggcagc tctaaggacc 1680
gtcctgcgag atcgccttcc aaccccactt ttttctggaa aggaggggtc ctgcaggggc 1740
aagcaggagc tagcagccgc ctacttggtg ctaaccctc gatgtacata gcttttctca 1800
gctgcctgcg cgccgccgac agtcagcgct gtgcgcgcgg agagaggtgc gccgtgggct 1860
caagagcctg agtgggtggt ttgcgaggat gagggacgct atgcctcatg cccgttttgg 1920
gtgtcctcac cagcaaggct gctcgggggc cctgggttcg tccctgagcc ttttccacag 1980
tgcataagca gttttttttg tttttgtttt gttttgtttt gtttttaaat caatcatgtt 2040
acactaatag aaacttggca ctctgtgccc ctctgcctgg acaagcacat agcaagctga 2100
actgtcctaa ggcaggggcg agcacggaac aatggggcct tcagctggag ctgtggactt 2160
ttgtacatac actaaaattc tgaagttaaa gctctgctct tggaaaaaaa aaaaaaaaaa 2220
aaaaaaaaaa aaaaaa                                     2236

```

<210> 33

<211> 455

<212> PRT

<213> Homo sapiens

<400> 33

```

Met Gly Leu Ser Thr Val Pro Asp Leu Leu Leu Pro Leu Val Leu Leu
  1              5              10              15

Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile Gly Leu Val Pro
      20              25              30

His Leu Gly Asp Arg Glu Lys Arg Asp Ser Val Cys Pro Gln Gly Lys
      35              40              45

Tyr Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr Lys Cys His Lys
      50              55              60

Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Pro Gly Gln Asp Thr Asp
      65              70              75              80

Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu
      85              90              95

Arg His Cys Leu Ser Cys Ser Lys Cys Arg Lys Glu Met Gly Gln Val
      100             105             110

Glu Ile Ser Ser Cys Thr Val Asp Arg Asp Thr Val Cys Gly Cys Arg
      115             120             125

Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu Phe Gln Cys Phe
      130             135             140

Asn Cys Ser Leu Cys Leu Asn Gly Thr Val His Leu Ser Cys Gln Glu
      145             150             155             160

Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Phe Leu Arg Glu
      165             170             175

Asn Glu Cys Val Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu Cys Thr
      180             185             190

```

10/80

Lys Leu Cys Leu Pro Gln Ile Glu Asn Val Lys Gly Thr Glu Asp Ser
 195 200 205

Gly Thr Thr Val Leu Leu Pro Leu Val Ile Phe Phe Gly Leu Cys Leu
 210 215 220

Leu Ser Leu Leu Phe Ile Gly Leu Met Tyr Arg Tyr Gln Arg Trp Lys
 225 230 235 240

Ser Lys Leu Tyr Ser Ile Val Cys Gly Lys Ser Thr Pro Glu Lys Glu
 245 250 255

Gly Glu Leu Glu Gly Thr Thr Thr Lys Pro Leu Ala Pro Asn Pro Ser
 260 265 270

Phe Ser Pro Thr Pro Gly Phe Thr Pro Thr Leu Gly Phe Ser Pro Val
 275 280 285

Pro Ser Ser Thr Phe Thr Ser Ser Ser Thr Tyr Thr Pro Gly Asp Cys
 290 295 300

Pro Asn Phe Ala Ala Pro Arg Arg Glu Val Ala Pro Pro Tyr Gln Gly
 305 310 315 320

Ala Asp Pro Ile Leu Ala Thr Ala Leu Ala Ser Asp Pro Ile Pro Asn
 325 330 335

Pro Leu Gln Lys Trp Glu Asp Ser Ala His Lys Pro Gln Ser Leu Asp
 340 345 350

Thr Asp Asp Pro Ala Thr Leu Tyr Ala Val Val Glu Asn Val Pro Pro
 355 360 365

Leu Arg Trp Lys Glu Phe Val Arg Arg Leu Gly Leu Ser Asp His Glu
 370 375 380

Ile Asp Arg Leu Glu Leu Gln Asn Gly Arg Cys Leu Arg Glu Ala Gln
 385 390 395 400

Tyr Ser Met Leu Ala Thr Trp Arg Arg Arg Thr Pro Arg Arg Glu Ala
 405 410 415

Thr Leu Glu Leu Leu Gly Arg Val Leu Arg Asp Met Asp Leu Leu Gly
 420 425 430

Cys Leu Glu Asp Ile Glu Glu Ala Leu Cys Gly Pro Ala Ala Leu Pro
 435 440 445

Pro Ala Pro Ser Leu Leu Arg
 450 455

<210> 34

<211> 1125

<212> DNA

<213> Homo sapiens

<400> 34

ttctgccttc gagccacccg ggaacgaaag agaagctcta tctgcctcc aggagcccag 60

11/80

```

ctaigaactc cttctccaca agcgccttcg gtccagttgc cttctccctg gggctgctcc 120
tgggtgttgc tgctgccttc cctgccccag tacccccagg agaagattcc aaagatgtag 180
ccgccccaca cagacagcca ctcacctctt cagaacgaat tgacaaacaa attcggtaga 240
tcctcgacgg catctcagcc ctgagaaagg agacatgtaa caagagtaac atgtgtgaaa 300
gcagcaaaga ggcactggca gaaaacaacc tgaaccttcc aaagatggct gaaaaagatg 360
gatgcttcca atctggattc aatgaggaga ctgtgcctgg gaaaatcatc actggctctt 420
tggagtttga ggtataccta gagtacctcc agaacagatt tgagagtagt gaggaacaag 480
ccagagctgt gcagatgagt acaaaagtcc tgatccagtt cctgcagaaa aaggcaaaga 540
atctagatgc aataaccacc cctgacccaa ccacaaatgc cagcctgctg acgaagctgc 600
aggcacagaa ccagtggctg caggacatga caactcatct cattctgctg agctttaagg 660
agttcctgca gtccagcctg agggctcttc ggcaaagtga gcatgggcac ctcagattgt 720
tgttgtaaat gggcattcct tcttctggtc agaaacctgt ccactgggca cagaacttat 780
gttgttctct atggagaact aaaagtatga gcgttaggac actattttta ttatttttaa 840
tttattaata tttaaatag tgaagctgag ttaatttatg taagtcatat ttatattttt 900
aagaagtacc acttgaaaca ttttatgtat tagttttgaa ataataatgg aaagtggcta 960
tgcagtttga atatcctttg tttcagagcc agatcatttc ttggaaagtg taggcttacc 1020
tcaaataaat ggctaactta tacatatatt taaagaaata tttatattgt atttatataa 1080
tgtataaatg gtttttatac caataaatgg cattttaaaa aattc 1125

```

<210> 35

<211> 212

<212> PRT

<213> Homo sapiens

<400> 35

```

Met Asn Ser Phe Ser Thr Ser Ala Phe Gly Pro Val Ala Phe Ser Leu
  1                      5                      10                      15

```

```

Gly Leu Leu Leu Val Leu Pro Ala Ala Phe Pro Ala Pro Val Pro Pro
          20                      25                      30

```

```

Gly Glu Asp Ser Lys Asp Val Ala Ala Pro His Arg Gln Pro Leu Thr
          35                      40                      45

```

```

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

```

```

Ser Ala Leu Arg Lys Glu Thr Cys Asn Lys Ser Asn Met Cys Glu Ser
          65                      70                      75                      80

```

```

Ser Lys Glu Ala Leu Ala Glu Asn Asn Leu Asn Leu Pro Lys Met Ala
          85                      90                      95

```

```

Glu Lys Asp Gly Cys Phe Gln Ser Gly Phe Asn Glu Glu Thr Cys Leu
          100                      105                      110

```

```

Val Lys Ile Ile Thr Gly Leu Leu Glu Phe Glu Val Tyr Leu Glu Tyr
          115                      120                      125

```

```

Leu Gln Asn Arg Phe Glu Ser Ser Glu Glu Gln Ala Arg Ala Val Gln
          130                      135                      140

```

```

Met Ser Thr Lys Val Leu Ile Gln Phe Leu Gln Lys Lys Ala Lys Asn
          145                      150                      155                      160

```

```

Leu Asp Ala Ile Thr Thr Pro Asp Pro Thr Thr Asn Ala Ser Leu Leu
          165                      170                      175

```

12/80

Thr Lys Leu Gln Ala Gln Asn Gln Trp Leu Gln Asp Met Thr Thr His
 180 185 190

Leu Ile Leu Arg Ser Phe Lys Glu Phe Leu Gln Ser Ser Leu Arg Ala
 195 200 205

Leu Arg Gln Met
 210

<210> 36

<211> 1550

<212> DNA

<213> Homo sapiens

<400> 36

```

tgcgcgcgtc ccgcccgcga gcgccccagc gaggaagcag cgcgccagccc gcggcccagc 60
gcacccgcag cagcgcccgc agctcgtccg cgccatgttc caggcgggccg agcgccccca 120
ggagtgggccc atggagggcc cccgcgacgg gctgaagaag gagcgggtac tggacgaccg 180
ccacgacagc ggcctggact ccatgaaaga cgaggagtac gagcagatgg tcaaggagct 240
gcaggagatc cgcctcgagc cgcaggaggt gccgcgcggc tcggagccct ggaagcagca 300
gctcaccgag gacggggact cgttcctgca ctgtggccatc atccatgaag aaaaggcact 360
gaccatggaa gtgatccgcc aggtgaaggg agacctggct ttcctcaact tccagaacaa 420
cctgcagcag actccactcc acttggtgtg gatcaccaac cagccagaaa ttgctgaggc 480
acttctggga gctggctgtg atcctgagct ccgagacttt cgaggaaata ccccctaca 540
ccttgctgtg gagcagggct gcctggccag cgtgggagtc ctgactcagt cctgcaccac 600
cccgcacctc cactccatcc tgaaggctac caactacaat ggccacacgt gtctacactt 660
agcctctatc catggctacc tgggcatcgt ggagcttttg gtgtccttgg gtgctgatgt 720
caatgctcag gagccctgta atggccggac tgcccttcac ctgcagtggt acctgcaaaa 780
tctgacctg gtgtcactcc tgttgaagtg tggggctgat gtcaacagag ttacctacca 840
gggctattct ccctaccagc tcacctgggg ccgcccgaagc acccggtatc agcagcagct 900
gggccagctg acactagaaa accttcagat gctgccagag agtgaggatg aggagagcta 960
tgacacagag tcagagttca cggagttcac agaggacgag ctgccctatg atgactgtgt 1020
gtttggaggc cagcgtctga cgttatgagt gcaaaagggc tgaaagaaca tggacttgta 1080
tatttgtaca aaaaaaaagt tttatttttc taaaaaaaga aaaaagaaga aaaaatttaa 1140
aggtgtgact tatatccaca ctgcacactg cctagcccaa aacgtcttat tgtggttaga 1200
tcagccctca ttttgttgct tttgtgaact ttttgtaggg gacgagaaaag atcattgaaa 1260
ttctgagaaa acttctttta aacctcacct ttgtgggggt tttggagaag gttatcaaaa 1320
atttcatgga aggaccacat tttatatatta ttgtgcttcg agtgactgac cccagtggta 1380
tcctgtgaca tgtaacagcc aggagtgtta agcgttcagt gatgtggggt gaaaagttac 1440
tacctgtcaa ggtttgtgtt accctcctgt aaatgggtga cataatgtat tgttggtaat 1500
tattttggta cttttatgat gtatatatat taaagagatt tttacaaatg 1550

```

<210> 37

<211> 317

<212> PRT

<213> Homo sapiens

<400> 37

Met Phe Gln Ala Ala Glu Arg Pro Gln Glu Trp Ala Met Glu Gly Pro
 1 5 10 15

Arg Asp Gly Leu Lys Lys Glu Arg Leu Leu Asp Asp Arg His Asp Ser
 20 25 30

Gly Leu Asp Ser Met Lys Asp Glu Glu Tyr Glu Gln Met Val Lys Glu
 35 40 45

13/80

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

<210> 38

<211> 1216

<212> DNA

<213> Homo sapiens

<400> 38

ggcagctgca cggctcctgg ccccgagca tgcgcgagag ccgccccgga gcgccccgga 60

14/80

```

gccccccgcc gtccccgccg cgcccgcccc cgccccgccg ccagcgcacc cccggacgct 120
atggcccacc cctccggctg gcccttctct taggatggta gcacacaacc aggtggcagc 180
cgacaatgca gtctccacag cagcagagcc ccgacggcgg ccagaacctt cctcctcttc 240
ctcctcctcg ccccgggccc ccgcgcgccc gcggccgtgc cccgcggtcc cggccccggc 300
ccccggcgac acgcacttcc gcacattccg ttcgacgcgc gattaccggc gcatcacgcg 360
cgccagcgcg ctcttgagcg cctgcggatt ctactggggg cccctgagcg tgcacggggc 420
gcacgagcgg ctgcgcgcgc agcccgtggg caccttcctg gtgcgcgaca gccgccagcg 480
gaactgcttt ttgcgcccta gcgtgaagat ggcttcggga cccacgagca tccgcgtgca 540
ctttcaggcc ggccgctttc acctggatgg cagccgcgag agcttcgact gcctcttcga 600
gctgctggag cactacgtgg cgccgcgcgc ccgcatgctg ggggccccgc tgcgccagcg 660
ccgctgctgg ccgctgcagg agctgtgccg ccagcgcacg gtggccaccg tgggccgcga 720
gaacctggct cgcaccccc tcaaccccg cctccgcgac tacctgagct ccttccccct 780
ccagatttga ccggcagcgc ccgccgtgca cgcagcatta actgggatgc cgtgttattt 840
tgttattact tgcctggaac catgtgggta cctccccgg cctgggttgg agggagcgga 900
tgggtgtagg ggcgagggcg ctcccgcctc cgctggaga cgaggccgca gacccttct 960
cacctcttga gggggtcctc cccctcctgg tgctccctct gggccccctt ggttgttgta 1020
gcagcttaac tgtatctgga gccaggacct gaactcgcac ctctacctc ttcattgtta 1080
catataccca gtatctttgc acaaaccagg ggttggggga ggtctcttgg ctttattttt 1140
ctgctgtgca gaatcctatt ttatatTTTT taaagtcagt ttaggtaata aactttatta 1200
tgaaagTTTT tttttt                                     1216

```

<210> 39

<211> 211

<212> PRT

<213> Homo sapiens

<400> 39

```

Met Val Ala His Asn Gln Val Ala Ala Asp Asn Ala Val Ser Thr Ala
  1                      5                      10                      15

Ala Glu Pro Arg Arg Arg Pro Glu Pro Ser Ser Ser Ser Ser Ser Ser
      20                      25                      30

Pro Ala Ala Pro Ala Arg Pro Arg Pro Cys Pro Ala Val Pro Ala Pro
      35                      40                      45

Ala Pro Gly Asp Thr His Phe Arg Thr Phe Arg Ser His Ala Asp Tyr
      50                      55                      60

Arg Arg Ile Thr Arg Ala Ser Ala Leu Leu Asp Ala Cys Gly Phe Tyr
      65                      70                      75                      80

Trp Gly Pro Leu Ser Val His Gly Ala His Glu Arg Leu Arg Ala Glu
      85                      90                      95

Pro Val Gly Thr Phe Leu Val Arg Asp Ser Arg Gln Arg Asn Cys Phe
      100                      105                      110

Phe Ala Leu Ser Val Lys Met Ala Ser Gly Pro Thr Ser Ile Arg Val
      115                      120                      125

His Phe Gln Ala Gly Arg Phe His Leu Asp Gly Ser Arg Glu Ser Phe
      130                      135                      140

Asp Cys Leu Phe Glu Leu Leu Glu His Tyr Val Ala Ala Pro Arg Arg
      145                      150                      155                      160

```

15/80

Met Leu Gly Ala Pro Leu Arg Gln Arg Arg Val Arg Pro Leu Gln Glu
165 170 175

Leu Cys Arg Gln Arg Ile Val Ala Thr Val Gly Arg Glu Asn Leu Ala
180 185 190

Arg Ile Pro Leu Asn Pro Val Leu Arg Asp Tyr Leu Ser Ser Phe Pro
195 200 205

Phe Gln Ile
210

<210> 40

<211> 2746

<212> DNA

<213> Homo sapiens

<400> 40

```
ggctccgact tggactccct gctccgctgc tgcgcttcg gccccgcacg cagccagccg 60
ccagccgccc gcccgcccca gctcccgccg cggcccttg ccgcggtccc tctcctggtc 120
ccctcccggg tggctccggg gtgcgcaggg ggcagggcgg gcgcccaggg gaagctcgag 180
ggacgcgcgc gcgaaggctc ctttgtggac ttcacggccg ccaacatctg ggcgcagcgc 240
gggcccaccg tggcgtctc gccgcgcgt cgcttgggg acccgagggg gctcagcccc 300
aaggacggag acttcgattc gggaccagcc ccccgggatg cggtagcggc cgctgtgcgg 360
aggccgcgaa gcagctgcag ccgcgcgcgc gcagatccac gctggctccg tgcgccatgg 420
tcaccacacg caagtttccc gccgcgggga tgagccgccc cctggacacc agcctgcgcc 480
tcaagacctt cagctccaag agcgagtacc agctggtggt gaacgcagtg cgcaagctgc 540
aggagagcgg cttctactgg agcgagtgga ccggcggcga ggcgaacctg ctgctcagtg 600
ccgagcccgc cggcaccttt ctgatccgcg acagctcgga ccagcgccac ttcttcacgc 660
tcagcgtcaa gaccagctct gggaccaaga acctgcgcac ccagtgtgag gggggcagct 720
tctctctgca gagegatccc cggagcacgc agcccgtgcc ccgcttcgac tgcgtgctca 780
agctggtgca ccactacatg ccgccccctg gagccccctc cttcccctcg ccacctactg 840
aaccctcttc cgaggtgccc gagcagccgt ctgcccagcc actccctggg agtcccccca 900
gaagagccta ttacatctac tccgggggcg agaagatccc cctggtgttg agccggcccc 960
tctcctccaa cgtggccact cttcagcatc tctgtcggaa gaccgtcaac ggccacctgg 1020
actcctatga gaaagtcacc cagctgccgg ggccattcgg ggagttcctg gaccagtacg 1080
atgccccgct ttaaggggta aagggcgcaa agggcatggg tcgggagagg ggacgcaggc 1140
ccctctcctc cgtggcacat ggcacaagca caagaagcca accaggagag agtcctgtag 1200
ctctgggggg aaagagggcg gacaggcccc tccctctgcc ctctccctgc agaatgtggc 1260
aggcggacct ggaatgtgtt ggaggggaagg gggagtacca cctgagtctc cagcttctcc 1320
ggaggagcca gctgtcctgg tgggacgata gcaaccacaa gtggattctc cttcaattcc 1380
tcagcttccc ctctgcctcc aaacagggga cacttcggga atgctgaact aatgagaact 1440
gccagggaat cttcaaaact tccaacggaa cttgtttgct ctttgatttg gtttaaacct 1500
gagctggttg tggagcctgg gaaaggtgga agagagagag gtcctgaggg ccccgaggct 1560
gcgggctggc gaaggaaatg gtcacacccc ccgcccaccc caggcgagga tcctggtgac 1620
atgtcctctc ccctggctcc ggggagaagg gcttgggggtg acctgaaggg aacctcctg 1680
gtaccccaca tcctctcctc cgggacagtc accgaaaaca caggttccaa agtctacctg 1740
gtgcctgaga gccagggcc cttcctccgt tttaaggggg aagcaacatt tggaggggat 1800
ggatgggctg gtcagctggt ctccttttcc tactatact ataccttct gtacctgggt 1860
ggatggagcg ggaggtgga ggagacggga catctttcac ctcaggctcc tggtagagaa 1920
gacaggggat tctactctgt gcctcctgac tatgtctggc taagagattc gccttaaatg 1980
ctcctgttcc catggagagg gaccagcat aggaaagcca catactcagc ctggatgggt 2040
ggagaggctg agggactcac tggagggcac caagccagcc cacagccagg gaagtgggga 2100
ggggggggcg aaacccatgc ctcccagctg agcactggga atgtcagccc agtaagtatt 2160
ggccagtcag gcgcctcgtg gtcagagcag agccaccagg tcccaactgcc ccgagccctg 2220
cacagccctc cctcctgcct ggggtggggga ggctggaggt cattggagag gctggactgc 2280
tgccaccccg ggtgctcccg ctctgccata gcactgatca gtgacaattt acaggaatgt 2340
agcagcgatg gaattacctg gaacagtttt ttgtttttgt ttttgttttt gtttttgttg 2400
```

16/80

```

gggggggcaa ctaaacaac acaaagtatt ctgtgtcagg tattgggctg gacagggcag 2460
ttgtgtgttg ggggtggttt tttctctatt tttttgtttg tttcttggtt ttttaataatg 2520
tttacaatct gctcaatca ctctgtcttt tataaagatt ccacctccag tcctctctcc 2580
tccccctac tcaggccctt gaggtatatta ggagatgctt gaagaactca acaaaatccc 2640
aatccaagtc aaactttgca catatttata tttatattca gaaaagaaac atttcagtaa 2700
tttataataa agagcactat tttttaatga aaaaaaaaaa aaaaaa 2746

```

<210> 41

<211> 225

<212> PRT

<213> Homo sapiens

<400> 41

```

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

Asp Thr Ser Leu Arg Leu Lys Thr Phe Ser Ser Lys Ser Glu Tyr Gln
      20              25              30

Leu Val Val Asn Ala Val Arg Lys Leu Gln Glu Ser Gly Phe Tyr Trp
      35              40              45

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

Ala Gly Thr Phe Leu Ile Arg Asp Ser Ser Asp Gln Arg His Phe Phe
      65              70              75              80

Thr Leu Ser Val Lys Thr Gln Ser Gly Thr Lys Asn Leu Arg Ile Gln
      85              90              95

Cys Glu Gly Gly Ser Phe Ser Leu Gln Ser Asp Pro Arg Ser Thr Gln
      100              105              110

Pro Val Pro Arg Phe Asp Cys Val Leu Lys Leu Val His His Tyr Met
      115              120              125

Pro Pro Pro Gly Ala Pro Ser Phe Pro Ser Pro Pro Thr Glu Pro Ser
      130              135              140

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

Pro Arg Arg Ala Tyr Tyr Ile Tyr Ser Gly Gly Glu Lys Ile Pro Leu
      165              170              175

Val Leu Ser Arg Pro Leu Ser Ser Asn Val Ala Thr Leu Gln His Leu
      180              185              190

Cys Arg Lys Thr Val Asn Gly His Leu Asp Ser Tyr Glu Lys Val Thr
      195              200              205

Gln Leu Pro Gly Pro Ile Arg Glu Phe Leu Asp Gln Tyr Asp Ala Pro
      210              215              220

Leu
225

```

17/80

<210> 42
 <211> 1665
 <212> DNA
 <213> Homo sapiens

<400> 42
 actcttctgt ccagcttttta acaatctaac taatgccctc tccaggggtca ccctaggggtc 60
 accctagaat cagatctgct cccagcctc ttctgtttcc tgggtgagtga ttcttggtac 120
 tttggatggc catgacgggc tggagctgcc ttgtgacagg agcaggaggg ttcttggtac 180
 agaggatcat ccgcctcttg gtgaaggaga aggagctgaa ggagatcagg gtcttggtac 240
 aggccttcgg accagaattg agagaggaat ttcttaaact ccagaacaag accaagctga 300
 cagtgtgga aggagacatt ctggatgagc cattcctgaa gagagcctgc caggacgtct 360
 cggtcacat ccacaccgcc tgtatcattg atgtcttcgg tgtcactcac agagagtcta 420
 tcatgaatgt caatgtgaaa ggtacccagc tctgttaga ggcctgtgtc caagctagt 480
 tgccagtctt catctacacc agtagcatag aggtagccgg gcccaactcc tacaaggaaa 540
 tcatccagaa tggccatgaa gaagagcctc tggaaaacac atggcccgct ccataccac 600
 acagcaaaaa gcttgctgag aaggctgtac tggcggctaa cgggtggaat ctgaaaaacg 660
 gcggcaccct gtacacttgt gccttacgac ccatgtatat ctatggggaa ggaagccgat 720
 tcctttctgc tagtataaac gaggcctga acaacaatgg gatcctgtca agtggttgaa 780
 agttctccac tgttaaccca gtctatgttg gcaatgtggc ctgggcccac attctggcct 840
 tgagggccct gcaggacccc aagaaggccc caagcatccg aggacagttc tactatatct 900
 cagatgacac gcctcaccaa agctatgata accttaatta caccctgagc aaagagttcg 960
 gcctccgcct tgattccaga tggagctttc ctttatccct gatgtattgg attggcttcc 1020
 tgctggaaat agtgagcttc ctactcaggc caatttacac ctatcgaccg cccttcaacc 1080
 gccacatagt cacattgtca aatagcgtat tcaccttctc ttataagaag gctcagcgag 1140
 atctggcgta taagccactc tacagctggg aggaagccaa gcagaaaacg gtggagtggg 1200
 ttggttccct tgtggaccgg cacaaggaga ccctgaagtc caagactcag tgatttaagg 1260
 atgacagaga tgtgcatgtg ggtattgtta ggagatgtca tcaagctcca ccctcctggc 1320
 ctacacaga aagtgacaag ggcacaagct caggctcctgc tgcctccctt tcatacaatg 1380
 gccaaacttat tgtattcctc atgtcatcaa aacctgcgca gtcattggcc caacaagaag 1440
 gtttctgtcc taatcatata ccagagggaaa gaccatgtgg tttgtgttta ccaaactctca 1500
 gtagctgatt ctgaacaatt tagggactct tttaacttga gggctggttt gactactaga 1560
 gctccatttc tactcttaaa tgagaaagga ttccctttct ttttaattct ccattccttc 1620
 acatagtttg ataaaaagat caataaatgt ttgaatgtta aaaaa 1665

<210> 43
 <211> 373
 <212> PRT
 <213> Homo sapiens

<400> 43
 Met Thr Gly Trp Ser Cys Leu Val Thr Gly Ala Gly Gly Phe Leu Gly
 1 5 10 15
 Gln Arg Ile Ile Arg Leu Leu Val Lys Glu Lys Glu Leu Lys Glu Ile
 20 25 30
 Arg Val Leu Asp Lys Ala Phe Gly Pro Glu Leu Arg Glu Glu Phe Ser
 35 40 45
 Lys Leu Gln Asn Lys Thr Lys Leu Thr Val Leu Glu Gly Asp Ile Leu
 50 55 60
 Asp Glu Pro Phe Leu Lys Arg Ala Cys Gln Asp Val Ser Val Ile Ile
 65 70 75 80
 His Thr Ala Cys Ile Ile Asp Val Phe Gly Val Thr His Arg Glu Ser
 85 90 95

18/80

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

19/80

<210> 44
 <211> 1673
 <212> DNA
 <213> Homo sapiens

<400> 44
 gaggcagtaa ggacttggac tcctctgtcc agcttttaac aatctaagtt acgggttacct 60
 tcttctgggt cagcctagaa tcagatctgc tctccagcat cttctgtttc ctggcaagtg 120
 tttcctgcta ctttggattg gccacgatgg gctggagctg cttgtgaca ggagcaggag 180
 ggcttctggg tcagaggatc gtccgcctgt tggtggaaga gaaggaaactg aaggagatca 240
 gggccttggg caaggccttc agaccagaat tgagagagga attttctaag ctccagaaca 300
 ggaccaagct gactgtactt gaaggagaca ttctggatga gccattcctg aaaagagcct 360
 gccaggacgt ctcggtcgtc atccacaccg cctgtatcat tgatgtcttt ggtgtcactc 420
 acagagagtc catcatgaat gtcaatgtga aaggtaacca gctactgttg gaggcctgtg 480
 tccaagccag tgtgccagtc ttcatctaca ccagtagcat agaggtagcc gggcccaact 540
 cttacaagga aatcatccag aacggccacg aagaagagcc tctggaaaac acatggccca 600
 ctccataccc gtacagcaaa aagcttgctg agaaggctgt gctggcggct aatgggtgga 660
 atctaaaaaa tggtgatacc ttgtacactt gtgcgttaag acccacatat atctatgggg 720
 aaggaggccc attcctttct gccagtataa atgaggccct gaacaacaat gggatcctgt 780
 caagtgttgg aaagttctct acagtcaacc cagtctatgt tggcaacgtg gcctgggccc 840
 acattctggc cttgagggct ctgcgggacc ccaagaaggc cccaagtgtc cgaggtcaat 900
 tctattacat ctacagatgac acgcctcacc aaagctatga taaccttaat tacatcctga 960
 gcaaagagtt tggcctccgc cttgattcca gatggagcct tcctttaacc ctgatgtact 1020
 ggattggctt cctgctggaa gtagtgagct tcctactcag cccaatttac tcctatcaac 1080
 ccccttcaa ccgccacaca gtcacattat caaatagtgt gttcaccttc tcttacaaga 1140
 aggtcagcg agatctggcg tataagccac tctacagctg ggaggaaagg aagcagaaaa 1200
 ccgtggagtg ggttgggtcc cttgtggacc ggcacaagga gacctgaag tccaagactc 1260
 agtgatttaa ggatgacaga gatgtgcatg tgggtattgt taggaaatgt catcaaactc 1320
 caccacactg gcttcataca gaaggcaaca ggggcacaag cccaggtcct gctgcctctc 1380
 tttcacacaa tgcccaactt actgtcttct tcatgtcatc aaaatctgca cagtcaactg 1440
 cccaaccaga actttctgtc ctaatcatac accagaagac aaacaatatg atttctgttt 1500
 accaaatctc agtggctgat tctgaacaat tgtggtctct ctttaactga ggttctcttt 1560
 tgactaatag agctccattt cccctcttaa atgagaaagc atttcttttc tctttaatct 1620
 cctattcctt cacacagttc aacataaaga gcaataaatg ttttaatgct taa 1673

<210> 45
 <211> 372
 <212> PRT
 <213> Homo sapiens

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

20/80

Met Asn Val Asn Val Lys Gly Thr Gln Leu Leu Leu Glu Ala Cys Val
 100 105 110

Gln Ala Ser Val Pro Val Phe Ile Tyr Thr Ser Ser Ile Glu Val Ala
 115 120 125

Gly Pro Asn Ser Tyr Lys Glu Ile Ile Gln Asn Gly His Glu Glu Glu
 130 135 140

Pro Leu Glu Asn Thr Trp Pro Thr Pro Tyr Pro Tyr Ser Lys Lys Leu
 145 150 155 160

Ala Glu Lys Ala Val Leu Ala Ala Asn Gly Trp Asn Leu Lys Asn Gly
 165 170 175

Asp Thr Leu Tyr Thr Cys Ala Leu Arg Pro Thr Tyr Ile Tyr Gly Glu
 180 185 190

Gly Gly Pro Phe Leu Ser Ala Ser Ile Asn Glu Ala Leu Asn Asn Asn
 195 200 205

Gly Ile Leu Ser Ser Val Gly Lys Phe Ser Thr Val Asn Pro Val Tyr
 210 215 220

Val Gly Asn Val Ala Trp Ala His Ile Leu Ala Leu Arg Ala Leu Arg
 225 230 235 240

Asp Pro Lys Lys Ala Pro Ser Val Arg Gly Gln Phe Tyr Tyr Ile Ser
 245 250 255

Asp Asp Thr Pro His Gln Ser Tyr Asp Asn Leu Asn Tyr Ile Leu Ser
 260 265 270

Lys Glu Phe Gly Leu Arg Leu Asp Ser Arg Trp Ser Leu Pro Leu Thr
 275 280 285

Leu Met Tyr Trp Ile Gly Phe Leu Leu Glu Val Val Ser Phe Leu Leu
 290 295 300

Ser Pro Ile Tyr Ser Tyr Gln Pro Pro Phe Asn Arg His Thr Val Thr
 305 310 315 320

Leu Ser Asn Ser Val Phe Thr Phe Ser Tyr Lys Lys Ala Gln Arg Asp
 325 330 335

Leu Ala Tyr Lys Pro Leu Tyr Ser Trp Glu Glu Ala Lys Gln Lys Thr
 340 345 350

Val Glu Trp Val Gly Ser Leu Val Asp Arg His Lys Glu Thr Leu Lys
 355 360 365

Ser Lys Thr Gln
 370

21/80

<210> 46
 <211> 1702
 <212> DNA
 <213> Homo sapiens

<400> 46
 agactcaaca agagctccag caaagacttt cactgtagct tgacttgacc tgagattaac 60
 tagggaatct tgagaataaa gatgagctct gaaaattggt tcgtagcaga gaacagctct 120
 ttgcatccgg agagtggaca agaaaatgat gccaccagtc cccatttctc aacacgctcat 180
 gaaggggtcct tccaagttcc tgtcctgtgt gctgtaatga atgtgggtcct catcaccatt 240
 ttaatcatag ctctcattgc cttatcagtg ggccaataca attgtccagg ccaatacaca 300
 ttctcaatgc catcagacag ccatgtttct tcatgctctg aggactgggt tggctaccag 360
 aggaaatgct actttatttc tactgtgaag aggagctgga cttcagccca aaatgcttgt 420
 tctgaacatg gtgctactct tgctgtcatt gattctgaaa aggacatgaa ctttctaaaa 480
 cgatacgcag gtagagagga acactgggtt ggactgaaaa aggaacctgg tcacccatgg 540
 aagtgggtcaa atggcaaaga atttaacaac tggttcaacg ttacagggtc tgacaagtgt 600
 gtttttctga aaaacacaga ggtcagcagc atggaatgtg agaagaatct atactggata 660
 tgaacaaaac cttacaataa ataaggaaac atgttcactt attgactatt atagaatgga 720
 actcaaggaa atctgtgtca gtggatgctg ctctgtgggt cgaagtcttc catagagact 780
 ttgtgaaaaa aaattttata gtgtcttggg aattttcttc caaacagAAC tatggaaaaa 840
 aaggaagaaa ttccaggaaa atctgcactg tgggctttta ttgccatgag ctagaagcat 900
 cacagggtga ccaataacca tgcccaagaa tgagaagaat gactatgcaa cctttggatg 960
 cactttatat tattttgaat ccagaaataa tgaaataact aggcgtggac ttactattta 1020
 ttgtggaatg actaccaaca gtgagagccc ttcatgcatt tgcactactg gaaggagtta 1080
 gatgttggtg ctagatactg aatgtaaaca aaggaattat ggctggtaac ataggttttt 1140
 agtctaattg aatcccttaa actcaggagg catttataaa tggacaaatg cttatgaaac 1200
 taagatttgt aatatttctc tctttttaga gaaatttgcc aatttacttt gttatttttc 1260
 cccaaaaaga atgggatgat cgtgtattta tttttttact tcctcagctg tagacagggtc 1320
 cttttcgatg gtacataattt ctttgccttt ataatctttt atacagtgtc ttacagagaa 1380
 aagacataag caaagactat gaggaatatt tgcaagacat agaatagtgt tggaaaatgt 1440
 gcaatatgtg atgtggcaaa tctctatttag gaaatattct gtaatcttca gacctagaat 1500
 aatactagtc ttataaatagg tttgtgactt tcctaaatca attctattac gtgcaatact 1560
 tcaatacttc atttaaaata tttttatgtg caataaaatg tatttgtttg tattttgtgt 1620
 tcagtacaat tataagctgt ttttatatat gtgaaataaa agtagaataa acacaaaaaa 1680
 aaaaaaaaaa aaaaaaaaaa aa 1702

<210> 47
 <211> 199
 <212> PRT
 <213> Homo sapiens

<400> 47
 Met Ser Ser Glu Asn Cys Phe Val Ala Glu Asn Ser Ser Leu His Pro
 1 5 10 15
 Glu Ser Gly Gln Glu Asn Asp Ala Thr Ser Pro His Phe Ser Thr Arg
 20 25 30
 His Glu Gly Ser Phe Gln Val Pro Val Leu Cys Ala Val Met Asn Val
 35 40 45
 Val Phe Ile Thr Ile Leu Ile Ile Ala Leu Ile Ala Leu Ser Val Gly
 50 55 60
 Gln Tyr Asn Cys Pro Gly Gln Tyr Thr Phe Ser Met Pro Ser Asp Ser
 65 70 75 80

22/80

His Val Ser Ser Cys Ser Glu Asp Trp Val Gly Tyr Gln Arg Lys Cys
85 90 95

Tyr Phe Ile Ser Thr Val Lys Arg Ser Trp Thr Ser Ala Gln Asn Ala
100 105 110

Cys Ser Glu His Gly Ala Thr Leu Ala Val Ile Asp Ser Glu Lys Asp
115 120 125

Met Asn Phe Leu Lys Arg Tyr Ala Gly Arg Glu Glu His Trp Val Gly
130 135 140

Leu Lys Lys Glu Pro Gly His Pro Trp Lys Trp Ser Asn Gly Lys Glu
145 150 155 160

Phe Asn Asn Trp Phe Asn Val Thr Gly Ser Asp Lys Cys Val Phe Leu
165 170 175

Lys Asn Thr Glu Val Ser Ser Met Glu Cys Glu Lys Asn Leu Tyr Trp
180 185 190

Ile Cys Asn Lys Pro Tyr Lys
195

<210> 48

<211> 2308

<212> DNA

<213> Homo sapiens

<400> 48

gagagactgg atggacccac aagggtgaca gcccaggcgg accgatcttc ccatcccaca 60
tcctccggcg cgatgccaaa aagaggctga cggcaactgg gccttctgca gagaaagacc 120
tccgcttcac tgccccggct ggtcccaagg gtcaggaaga tggattcata cctgctgatg 180
tggggactgc tcacgttcat catggtgcct ggctgccagg cagagctctg tgacgatgac 240
ccgccagaga tcccacacgc cacattcaaa gccatggcct acaaggaagg aacctgttg 300
aactgtgaat gcaagagagg tttccgcaga ataaaaagcg ggctactcta tatgctctgt 360
acaggaaact ctagccactc gtcctgggac aaccaatgtc aatgcacaag ctctgccact 420
cggaacacaa cgaaacaagt gacacctcaa cctgaagaac agaaagaaag gaaaaccaca 480
gaaatgcaaa gtccaatgca gccagtggac caagcgagcc ttccagggtca ctgcagggaa 540
cctccaccat gggaaaatga agccacagag agaatttatc atttcgtggt ggggcagatg 600
gtttattatc agtgcgtcca gggatacagg gctctacaca gaggtcctgc tgagagcgtc 660
tgcaaaatga cccacgggaa gacaagggtg acccagcccc agctcatatg cacaggtgaa 720
atggagacca gtcagtttcc aggtgaagag aagcctcagg caagccccga aggccgtcct 780
gagagtgaga cttcctgcct cgtcacaaca acagattttc aaatacagac agaaatggct 840
gcaaccatgg agacgtccat atttacaaca gagtaccagg tagcagtggc cggctgtgtt 900
ttcctgctga tcagcgtcct cctcctgagt gggctcacct ggcagcggag acagaggaag 960
agtagaagaa caatctagaa aaccaaaaaga acaagaattt cttggtgaaga agccgggaac 1020
agacaacaga agtcatgaag cccaagtga atcaaagggtg ctaaattggtc gccaggaga 1080
catccgttgt gcttgctgc gttttggaag ctctgaagtc acatcacagg acacggggca 1140
gtggcaacct tgtctctatg ccagctcagt cccatcacag agcgagcgct acccacttct 1200
aaatagcaat ttcgccgttg aagaggaagg gcaaaaccac tagaactctc catcttattt 1260
tcatgtatat gtgtcatta aagcatgaat ggtatggaac tctctccacc ctatatgtag 1320
tataaagaaa agtaggttta cattcatctc attccaactt cccagtccag gagtcccaag 1380
gaaagcccca gcactaacgt aaatacacaa cacacacact ctaccctata caactggaca 1440
ttgtctgctg ggttctcttc tcagccgctt ctgactgctg attctcccgt tcacgttgcc 1500
taataaacat ccttcaagaa ctctgggctg ctaccagaa atcattttac ccttggctca 1560
atcctctaag ctaacccct tctactgagc cttcagtcct gaatttctaa aaaacagagg 1620
ccatggcaga ataattcttg ggtaacttca aaacggggca gccaaaccca tgaggcaatg 1680

23/80

```

tcaggaacag aaggatgaat gaggtccag gcagagaatc atacttagca aagttttacc 1740
tgtgcgttac taattggcct ctttaagagt tagtttcttt gggattgcta tgaatgatac 1800
cctgaatttg gcctgcacta atttgatgtt tacaggtgga cacacaaggt gcaaatacaat 1860
gcgtacgttt cctgagaagt gtctaaaaac accaaaaagg gatccgtaca ttcaatgttt 1920
atgcaaggaa ggaaagaaag aaggaagtga agagggagaa gggatggagg tcacactggg 1980
agaacgtaac cacggaaaag agcgcacatc gcctggcacg gtggctcagg cctataaccc 2040
cagctcccta ggagaccaag gcgggagcat ctcttgaggc caggagtgtg agaccagcct 2100
gggcagcata gcaagacaca tcctacaaa aaattagaaa ttggctggat gtggtggcat 2160
acgcctgtag tcctagccac tcaggaggct gaggcaggag gattgcttga gccaggagt 2220
tcgaggctgc agtcagtcac gatggcacca ctgcactcca gcctgggcaa cagagcaaga 2280
tcctgtcttt aaggaaaaaa agacaagg 2308

```

<210> 49

<211> 272

<212> PRT

<213> Homo sapiens

<400> 49

```

Met Asp Ser Tyr Leu Leu Met Trp Gly Leu Leu Thr Phe Ile Met Val
  1                      5                      10                      15

```

```

Pro Gly Cys Gln Ala Glu Leu Cys Asp Asp Asp Pro Pro Glu Ile Pro
          20                      25                      30

```

```

His Ala Thr Phe Lys Ala Met Ala Tyr Lys Glu Gly Thr Met Leu Asn
    35                      40                      45

```

```

Cys Glu Cys Lys Arg Gly Phe Arg Arg Ile Lys Ser Gly Ser Leu Tyr
    50                      55                      60

```

```

Met Leu Cys Thr Gly Asn Ser Ser His Ser Ser Trp Asp Asn Gln Cys
    65                      70                      75                      80

```

```

Gln Cys Thr Ser Ser Ala Thr Arg Asn Thr Thr Lys Gln Val Thr Pro
          85                      90                      95

```

```

Gln Pro Glu Glu Gln Lys Glu Arg Lys Thr Thr Glu Met Gln Ser Pro
    100                      105                      110

```

```

Met Gln Pro Val Asp Gln Ala Ser Leu Pro Gly His Cys Arg Glu Pro
    115                      120                      125

```

```

Pro Pro Trp Glu Asn Glu Ala Thr Glu Arg Ile Tyr His Phe Val Val
    130                      135                      140

```

```

Gly Gln Met Val Tyr Tyr Gln Cys Val Gln Gly Tyr Arg Ala Leu His
    145                      150                      155                      160

```

```

Arg Gly Pro Ala Glu Ser Val Cys Lys Met Thr His Gly Lys Thr Arg
          165                      170                      175

```

```

Trp Thr Gln Pro Gln Leu Ile Cys Thr Gly Glu Met Glu Thr Ser Gln
          180                      185                      190

```

```

Phe Pro Gly Glu Glu Lys Pro Gln Ala Ser Pro Glu Gly Arg Pro Glu
    195                      200                      205

```

24/80

Ser Glu Thr Ser Cys Leu Val Thr Thr Thr Asp Phe Gln Ile Gln Thr
 210 215 220

Glu Met Ala Ala Thr Met Glu Thr Ser Ile Phe Thr Thr Glu Tyr Gln
 225 230 235 240

Val Ala Val Ala Gly Cys Val Phe Leu Leu Ile Ser Val Leu Leu Leu
 245 250 255

Ser Gly Leu Thr Trp Gln Arg Arg Gln Arg Lys Ser Arg Arg Thr Ile
 260 265 270

<210> 50

<211> 2324

<212> DNA

<213> Homo sapiens

<400> 50

```

ctccctttgg gcaaggacct gagacccttg tgctaagtca agaggctcaa tgggctgcag 60
aagaactaga gaaggaccaa gcaaagccat gatatttcca tggaaatgtc agagcaccce 120
gagggactta tggaacatct tcaagttgtg ggggtggaca atgctctgtt gtgatttccct 180
ggcacatcat ggaaccgact gctggactta ccattattct gaaaaaccca tgaactggca 240
aagggtaga agattctgcc gagacaatta cacagattta gttgccatac aaaacaaggc 300
ggaaattgag tatctggaga agactctgcc ttccagtcgt tcttactact ggataggaat 360
ccggaagata ggaggaatat ggacgtgggt gggaaccaac aaatctctta ctgaagaagc 420
agagaactgg ggagatgggt agcccaacaa caagaagaac aaggaggact gcgtggagat 480
ctatatcaag agaaacaaag atgcaggcaa atggaacgat gacgcctgcc acaactaaa 540
ggcagccctc tgttacacag cttcttgcca gccctggcca tgcagtggcc atggagaatg 600
tgtagaaatc atcaataatt acacctgcaa ctgtgatgtg ggggtactatg ggccccagtg 660
tcagtttgtg attcagtggt agcctttgga ggccccagag ctgggtacca tggactgtac 720
tcaccctttg ggaaacttca gcttcagctc acagtgtgcc ttcagctgct ctgaaggaac 780
aaacttaact gggattgaag aaaccacctg tggaccattt ggaaactggt catctccaga 840
accaacctgt caagtgttc agtgtgagcc tctatcagca ccagatttgg ggatcatgaa 900
ctgtagccat cccctggcca gcttcagctt tacctctgca tgtaccttca tctgctcaga 960
aggaactgag ttaattggga agaagaaaac catttgtgaa tcatctggaa tctgggtcaa 1020
tcctagtcca atatgtcaaa aattggacaa aagtttctca atgattaagg aggggtgatta 1080
taacccctc ttcattccag tggcagtcac ggttactgca ttctctgggt tggcatttat 1140
catttggctg gcaaggagat taaaaaaagg caagaaatcc aagagaagta tgaatgacct 1200
atattaaatc gcccttggtg aaagaaaatt cttggaatac taaaaatcat gagatccttt 1260
aaatccttc atgaaacgtt ttgtgtgggt gcacctccta cgtcaaacat gaagtgtgtt 1320
tccttcagtg catctgggaa gatttctacc tgaccaacag ttccttcagc ttccatttcg 1380
ccctcattt atccctcaac cccagccca cagggtgttt tacagctcag ctttttgtct 1440
tttctgagga gaaacaaata agaccataaa gggaaaggat tcatgtggaa tataaagatg 1500
gctgactttg ctctttcttg actcttggtt tcagtttcaa ttcagtgtct tacttgatga 1560
cagacacttc taaatgaagt gcaaatttga tacatatgtg aatatggact cagttttctt 1620
gcagatcaaa tttcacgtcg tcttctgtat actgtggagg tacactctta tagaaagttc 1680
aaaaagtcta cgctctcctt tctttctaac tccagtgaag taatggggct ctgctcaagt 1740
tgaaagagtc ctatttgcac tgtagcctcg ccgtctgtga attggacat cctatttaac 1800
tggcttcagc ctccccacct tcttcagcca cctctctttt tcagttggct gacttcaca 1860
cctagcatct catgagtggc aagcaaaagg agagaagaga gaaatagcct gcgctgtttt 1920
ttagtttggg ggttttgtct tttcttttta tgagacccat tcctatttct tatagtcaat 1980
gtttctttta tcacgatatt attagtaaga aaacatcact gaaatgctag ctgcaagtga 2040
catctctttg atgtcatatg gaagagttaa aacagggtga gaaattcctt gattcacaat 2100
gaaatgctct ctttccctc gccccagac cttttatcca cttacctaga ttctacatat 2160
tctttaaatt tcatctcagg cctccctcaa cccaccact tcttttataa ctagtctttt 2220
actaatcaaa ccatgatga gctcctcttc ctggcttctt actgaaaggt taccctgtaa 2280
catgcaattt tgcatttgaa taaagcctgc tttttaagtg ttaa 2324

```

25/80

<210> 51

<211> 372

<212> PRT

<213> Homo sapiens

<400> 51

```

Met Ile Phe Pro Trp Lys Cys Gln Ser Thr Gln Arg Asp Leu Trp Asn
 1           5           10           15

Ile Phe Lys Leu Trp Gly Trp Thr Met Leu Cys Cys Asp Phe Leu Ala
      20           25           30

His His Gly Thr Asp Cys Trp Thr Tyr His Tyr Ser Glu Lys Pro Met
      35           40           45

Asn Trp Gln Arg Ala Arg Arg Phe Cys Arg Asp Asn Tyr Thr Asp Leu
      50           55           60

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

Pro Phe Ser Arg Ser Tyr Tyr Trp Ile Gly Ile Arg Lys Ile Gly Gly
      85           90           95

Ile Trp Thr Trp Val Gly Thr Asn Lys Ser Leu Thr Glu Glu Ala Glu
      100          105          110

Asn Trp Gly Asp Gly Glu Pro Asn Asn Lys Lys Asn Lys Glu Asp Cys
      115          120          125

Val Glu Ile Tyr Ile Lys Arg Asn Lys Asp Ala Gly Lys Trp Asn Asp
      130          135          140

Asp Ala Cys His Lys Leu Lys Ala Ala Leu Cys Tyr Thr Ala Ser Cys
      145          150          155          160

Gln Pro Trp Ser Cys Ser Gly His Gly Glu Cys Val Glu Ile Ile Asn
      165          170          175

Asn Tyr Thr Cys Asn Cys Asp Val Gly Tyr Tyr Gly Pro Gln Cys Gln
      180          185          190

Phe Val Ile Gln Cys Glu Pro Leu Glu Ala Pro Glu Leu Gly Thr Met
      195          200          205

Asp Cys Thr His Pro Leu Gly Asn Phe Ser Phe Ser Ser Gln Cys Ala
      210          215          220

Phe Ser Cys Ser Glu Gly Thr Asn Leu Thr Gly Ile Glu Glu Thr Thr
      225          230          235          240

Cys Gly Pro Phe Gly Asn Trp Ser Ser Pro Glu Pro Thr Cys Gln Val
      245          250          255

Ile Gln Cys Glu Pro Leu Ser Ala Pro Asp Leu Gly Ile Met Asn Cys
      260          265          270

```

26/80

Ser His Pro Leu Ala Ser Phe Ser Phe Thr Ser Ala Cys Thr Phe Ile
275 280 285

Cys Ser Glu Gly Thr Glu Leu Ile Gly Lys Lys Lys Thr Ile Cys Glu
290 295 300

Ser Ser Gly Ile Trp Ser Asn Pro Ser Pro Ile Cys Gln Lys Leu Asp
305 310 315 320

Lys Ser Phe Ser Met Ile Lys Glu Gly Asp Tyr Asn Pro Leu Phe Ile
325 330 335

Pro Val Ala Val Met Val Thr Ala Phe Ser Gly Leu Ala Phe Ile Ile
340 345 350

Trp Leu Ala Arg Arg Leu Lys Lys Gly Lys Lys Ser Lys Arg Ser Met
355 360 365

Asn Asp Pro Tyr
370

<210> 52

<211> 2824

<212> DNA

<213> Homo sapiens

<400> 52

```

aagtaacaga agttagaagg ggaaatgtcg cctctctgaa gattacccaa agaaaaagtg 60
at ttgtcatt gctttataga ctgtaagaag agaacatctc agaagtggag tcttaccctg 120
aatcaaagg atttaaagaa aaagtggaa ttttcttcag caagctgtga aactaaatcc 180
acaacctttg gagaccagg aacacctcc aatctctgtg tgttttgtaa acatcactgg 240
agggctctct acgtgagcaa ttggattgtc atcagccctg cctgttttgc acctgggaag 300
tgccctggtc ttacttgggt ccaaattggt ggctttcact ttgacccta agcatctgaa 360
gcatgaggcc acacacggag gcagggaaca tcaccatcca agtgtccata cctcaatttc 420
tttcagctct tgggtgctggc tgggtcttct cacttctgtt cagggtgttat ccacgtgacc 480
aaggaagtga aagaagtggc aacgctgtcc tgtggtcaca atgtttctgt tgaagagctg 540
gcacaaactc gcatctactg gcaaaaggag aagaaaatgg tgctgactat gatgtctggg 600
gacatgaata tatggcccga gtacaagaac cggaccatct ttgatatac taataacctc 660
tccattgtga tcctggctct gcgcccatct gacgagggca catacgagtg tgttgttctg 720
aagtatgaaa aagacgcttt caagcgggaa cacctggctg aagtgcggtt atcagtcгаа 780
gctgacttcc ctacacctag tatatctgac ttgaaattc caacttctaa tattagaagg 840
ataatttgct caacctctgg aggttttcca gagcctcacc tctcctgggt ggaaaatgga 900
gaagaattaa atgccatcaa cacaacagtt tccaagatc ctgaaactga gctctatgct 960
gttagcagca aactggattt caatatgaca accaaccaca gttcatgtg tctcatcaag 1020
tatggacatt taagagtga tccagacctc aactggaata caaccaagca agagcatttt 1080
cctgataacc tgctcccatc ctgggccatt acctaatct cagtaaattg aatttttgtg 1140
atatgctgcc tgacctactg ctttgcccca agatgcagag agagaaggag gaatgagaga 1200
ttgagaaggg aaagtgtacg ccctgtataa cagtgtccgc agaagcaagg ggctgaaaag 1260
atctgaagg ctacacctca tttgcaattg acctcttctg ggaacttcct cagatggaca 1320
agattacccc accttgccct ttacgtatct gctcttaggt gcttcttcac ttcagtgtgt 1380
ttgcaggaag tgtctagagg aatatggtgg gcacagaagt agctctggtg acctgatca 1440
aggggttttg aaatgcagaa ttcttgagtt ctggaaggga ctttagagaa taccagtgtt 1500
attaatgaca aaggcactga ggcccaggga ggtgacccga attataaagg ccagcgccag 1560
aaccagatt tcctaactct ggtgctcttt ccctttatca gtttgactgt ggccgtgtta 1620
ctggtatata catatatatg tcaggcaaag tgctgctgga agtagaattt gtccaataac 1680
aggtcaactt cagagactat ctgatttcct aatgtcagag tagaagattt tatgtgctgt 1740
tttacaaaag cccaatgtaa tgcataggaa gtatggcatg aacatcttta ggagactaat 1800
ggaaatatta ttggtgttta ccagtatct catttttttc atttgtgtct ctattgctgc 1860

```

27/80

```

tctctcactc ccccatgagg tacagcagaa aggagaacta tccaaaacta atttcctctg 1920
acatgtaaga cgaatgattt aggtacgtca aagcagtagt caaggaggaa agggatagtc 1980
caaagactta actggttcat attggactga taatctcttt aaatggcttt atgctagttt 2040
gacctcattt gtaaaatatt tatgagaaag ttctcattta aaatgagatc gttgtttaca 2100
gtgtatgtac taagcagtaa gctatcttca aatgtctaag gtagtaactt tccatagggc 2160
ctccttagat ccctaagatg gctttttctc cttgggtattt ctgggtcttt ctgacatcag 2220
cagagaactg gaaagacata gccaaactgct gttcatgtta ctcatgactc ctttctctaa 2280
aactgccttc cacaattcac tagaccagaa gtggacgcaa ctttaagctgg gataatcaca 2340
ttatcatctg aaaatctgga gttgaacagc aaaagaagac aacatttctc aaatgcacat 2400
ctcatggcag ctaagccaca tggctgggat ttaaaagcctt tagagccagc ccatggcttt 2460
agctacctca ctatgtctgt tcacaaacct tgctcctgtg taaaactata ttctcagtgt 2520
agggcagaga ggtctaacac caacataagg tactagcagt gtttcccgta ttgacaggaa 2580
tacttaactc aataattctt ttcttttcca tttagtaaca gttgtgatga ctatgtttct 2640
attctaagta attcctgtat tctacagcag atactttgtc agcaatacta agggaagaaa 2700
caaagttgaa ccgtttcttt aataaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2760
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2820
aaaa
2824

```

<210> 53

<211> 288

<212> PRT

<213> Homo sapiens

<400> 53

```

Met Gly His Thr Arg Arg Gln Gly Thr Ser Pro Ser Lys Cys Pro Tyr
  1              5              10              15

Leu Asn Phe Phe Gln Leu Leu Val Leu Ala Gly Leu Ser His Phe Cys
      20              25              30

Ser Gly Val Ile His Val Thr Lys Glu Val Lys Glu Val Ala Thr Leu
      35              40              45

Ser Cys Gly His Asn Val Ser Val Glu Glu Leu Ala Gln Thr Arg Ile
      50              55              60

Tyr Trp Gln Lys Glu Lys Lys Met Val Leu Thr Met Met Ser Gly Asp
      65              70              75              80

Met Asn Ile Trp Pro Glu Tyr Lys Asn Arg Thr Ile Phe Asp Ile Thr
      85              90              95

Asn Asn Leu Ser Ile Val Ile Leu Ala Leu Arg Pro Ser Asp Glu Gly
      100             105             110

Thr Tyr Glu Cys Val Val Leu Lys Tyr Glu Lys Asp Ala Phe Lys Arg
      115             120             125

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

Pro Ser Ile Ser Asp Phe Glu Ile Pro Thr Ser Asn Ile Arg Arg Ile
      145             150             155             160

Ile Cys Ser Thr Ser Gly Gly Phe Pro Glu Pro His Leu Ser Trp Leu
      165             170             175

```

28/80

Glu Asn Gly Glu Glu Leu Asn Ala Ile Asn Thr Thr Val Ser Gln Asp
 180 185 190
 Pro Glu Thr Glu Leu Tyr Ala Val Ser Ser Lys Leu Asp Phe Asn Met
 195 200 205
 Thr Thr Asn His Ser Phe Met Cys Leu Ile Lys Tyr Gly His Leu Arg
 210 215 220
 Val Asn Gln Thr Phe Asn Trp Asn Thr Thr Lys Gln Glu His Phe Pro
 225 230 235 240
 Asp Asn Leu Leu Pro Ser Trp Ala Ile Thr Leu Ile Ser Val Asn Gly
 245 250 255
 Ile Phe Val Ile Cys Cys Leu Thr Tyr Cys Phe Ala Pro Arg Cys Arg
 260 265 270
 Glu Arg Arg Arg Asn Glu Arg Leu Arg Arg Glu Ser Val Arg Pro Val
 275 280 285

<210> 54

<211> 2794

<212> DNA

<213> Homo sapiens

<400> 54

```

aggagcctta ggaggtacgg ggagctcgca aatactcctt ttggtttatt cttaccacct 60
tgcttctgtg ttccttgga atgctgctgt gcttatgcat ctggctctctt tttggagcta 120
cagtggacag gcatttggtga cagcactatg ggactgagta acattctctt tgtgatggcc 180
ttcctgctct ctggtgctgc tctctgaag attcaagctt atttcaatga gactgcagac 240
ctgccatgcc aatttgcaaa ctctcaaaac caaagcctga gtgagctagt agtattttgg 300
caggaccagg aaaacttgggt tctgaatgag gtatacttag gcaaagagaa atttgacagt 360
gttcattcca agtatatggg ccgcacaagt tttgattcgg acagttggac cctgagactt 420
cacaatcttc agatcaagga caagggcttg tatcaatgta tcatccatca caaaaagccc 480
acaggaatga ttgcgcatcca ccagatgaat tctgaactgt cagtgcctgc taacttcagt 540
caacctgaaa tagtaccaat ttctaataata acagaaaatg tgtacataaa tttgacctgc 600
tcatctatac acggttaccc agaacctaa aagatgagtg ttttgctaag aaccaagaat 660
tcaactatcg agtatgatgg tattatgcag aaatctcaag ataatgtcac agaactgtac 720
gacgtttcca tcagcttgctc tgtttcattc cctgatgtta cgagcaatat gaccatcttc 780
tgtattctgg aaactgacaa gacgcggcct ttatcttcac ctttctctat agagcttgag 840
gaccctcagc ctccccaga ccacattcct tggattacag ctgtacttcc aacagttatt 900
atatgtgtga tgggtttctg tctaattcta tggaaatgga agaagaagaa gcggcctcgc 960
aactcttata aatgtggaac caacacaatg gagaggggaag agagtgaaca gaccaagaaa 1020
agagaaaaaa tccatatacc tgaaagatct gatgaagccc agcgtgtttt taaaagtctg 1080
aagacatctt catgcgacaa aagtgtatata tgtttttaat taaagagtaa agcccataca 1140
agtattcatt ttttctaccc tttcctttgt aagttcctgg gcaacctttt tgatttcttc 1200
cagaaggcaa aaagacatta ccatgagtaa taagggggct ccaggactcc ctctaagtgg 1260
aatagcctcc ctgtaactcc agctctgctc cgtatgcaa gaggagactt taattctctt 1320
actgcttctt ttcacttcag agcacactta tgggccaagc ccagcttaat ggctcatgac 1380
ctggaaataa aatttaggac caatacctcc tccagatcag attcttctct taatttcata 1440
gattgtgttt ttttttaaag agacctctca atttctggaa aactgccttt tatctgcca 1500
gaattctaag ctggtgcccc actgaatctt gtgtacctgt gactaaacaa ctacctctc 1560
agtctgggtg ggacttatgt atttatgacc ttatagtgtt aatatcttga aacatagaga 1620
tctatgtact gtaatagtgt gattactatg ctctagagaa aagtctaccc ctgctaagga 1680
gtttctcatcc cctctgcagg gtcagtaagg aaaacgggtg ctaggggtac aggaacaat 1740
gagcagacca acctaaatgt ggggaaatta ggagaggcag agatagaacc tggagccact 1800
tctatctggg ctgttgctaa tattgaggag gcttgcccca cccaacaagc catagtggag 1860

```

29/80

```

agaactgaat aaacaggaaa atgccagagc ttgtgaaccc tgtttctctt gaagaactga 1920
ctagttagat ggcttgggga agctgtgaaa gaaccaaaag agatcacaat actcaaaaga 1980
gagagagaga gaaaaaagag agatcttgat ccacagaaat acatgaaatg tctgggtctgt 2040
ccaccccatc aacaagtctt gaaacaagca acagatggat agtctgtcca aatggacata 2100
agacagacag cagtttccct ggtggtcagg gaggggtttt ggtgataccc aagtatttgg 2160
gatgtcatct tcctggaagc agagctgggg agggagagcc atcaccttga taatgggatg 2220
aatggaagga ggcttaggac ttccactcc tggctgagag aggaagagct gcaacggaat 2280
taggaagacc aagacacaga tcaccgggg cttacttagc ctacagatgt cctacgggaa 2340
cgtgggctgg ccagcatag ggctagcaaa tttgagttgg atgattgttt ttgctcaagg 2400
caaccagagg aaacttgcac acagagacag atatactggg agaaatgact ttgaaaacct 2460
ggctctaagg tgggatcact aagggatggg gcagtctctg cccaaacata aagagaactc 2520
tgaggagcct gagccacaaa aatgttcctt tattttatgt aaacctcaa gggttataga 2580
ctgccatgct agacaagctt gtccatgtaa tattcccatg tttttaccct gccctgcct 2640
tgattagact cctagcacct ggctagtctt taacatgttt tgtgcagcac agtttttaat 2700
aatgcttgt tacattcaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2760
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaa                                     2794

```

<210> 55

<211> 323

<212> PRT

<213> Homo sapiens

<400> 55

```

Met Gly Leu Ser Asn Ile Leu Phe Val Met Ala Phe Leu Leu Ser Gly
  1             5             10            15

Ala Ala Pro Leu Lys Ile Gln Ala Tyr Phe Asn Glu Thr Ala Asp Leu
      20             25            30

Pro Cys Gln Phe Ala Asn Ser Gln Asn Gln Ser Leu Ser Glu Leu Val
      35             40            45

Val Phe Trp Gln Asp Gln Glu Asn Leu Val Leu Asn Glu Val Tyr Leu
      50             55            60

Gly Lys Glu Lys Phe Asp Ser Val His Ser Lys Tyr Met Gly Arg Thr
      65             70            75            80

Ser Phe Asp Ser Asp Ser Trp Thr Leu Arg Leu His Asn Leu Gln Ile
      85             90            95

Lys Asp Lys Gly Leu Tyr Gln Cys Ile Ile His His Lys Lys Pro Thr
      100            105           110

Gly Met Ile Arg Ile His Gln Met Asn Ser Glu Leu Ser Val Leu Ala
      115            120           125

Asn Phe Ser Gln Pro Glu Ile Val Pro Ile Ser Asn Ile Thr Glu Asn
      130            135           140

Val Tyr Ile Asn Leu Thr Cys Ser Ser Ile His Gly Tyr Pro Glu Pro
      145            150           155           160

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

Asp Gly Ile Met Gln Lys Ser Gln Asp Asn Val Thr Glu Leu Tyr Asp
      180            185           190

```

30/80

Val Ser Ile Ser Leu Ser Val Ser Phe Pro Asp Val Thr Ser Asn Met
 195 200 205

Thr Ile Phe Cys Ile Leu Glu Thr Asp Lys Thr Arg Leu Leu Ser Ser
 210 215 220

Pro Phe Ser Ile Glu Leu Glu Asp Pro Gln Pro Pro Pro Asp His Ile
 225 230 235 240

Pro Trp Ile Thr Ala Val Leu Pro Thr Val Ile Ile Cys Val Met Val
 245 250 255

Phe Cys Leu Ile Leu Trp Lys Trp Lys Lys Lys Lys Arg Pro Arg Asn
 260 265 270

Ser Tyr Lys Cys Gly Thr Asn Thr Met Glu Arg Glu Glu Ser Glu Gln
 275 280 285

Thr Lys Lys Arg Glu Lys Ile His Ile Pro Glu Arg Ser Asp Glu Ala
 290 295 300

Gln Arg Val Phe Lys Ser Ser Lys Thr Ser Ser Cys Asp Lys Ser Asp
 305 310 315 320

Thr Cys Phe

<210> 56

<211> 2781

<212> DNA

<213> Homo sapiens

<400> 56

```

ggaaggcttg cacaggggtga aagcttttgct tctctgctgc tgtaacaggg actagcacag 60
acacacggat gagggtgggtc atttccagat attaggtcac agcagaagca gccaaaatgg 120
atccccagtg cactatggga ctgagtaaca ttctctttgt gatggccttc ctgctctctg 180
gtgctgctcc tctgaagatt caagcttatt tcaatgagac tgcagacctg ccatgccaat 240
ttgcaaaatc tcaaaaccaa agcctgagtg agctagtagt attttggcag gaccaggaaa 300
acttggttct gaatgaggta tacttaggca aagagaaatt tgacagtgtt cattccaagt 360
atatgggccc cacaagtttt gattcggaca ttgggacct gagacttcac aatcttcaga 420
tcaaggacaa gggcttgtat caatgtatca tccatcacaa aaagcccaca ggaatgattc 480
gcatccacca gatgaattct gaactgtcag tgcttgctaa cttcagtcaa cctgaaatag 540
taccaatttc taatataaca gaaaatgtgt acataaattt gacctgctca tctatacacg 600
gttaccacga acctaagaag atgagtgttt tgctaagaac caagaattca actatcgagt 660
atgatggtat tatgcagaaa tctcaagata atgtcacaga actgtacgac gtttccatca 720
gcttgctctg ttcatccctt gatgttacga gcaatatgac catcttctgt attctggaaa 780
ctgacaagac gcggctttta tcttcacctt tctctataga gcttgaggac cctcagcctc 840
ccccagacca cattccttgg attacagctg tacttccaac agttattata tgtgtgatgg 900
ttttctgtct aattctatgg aaatggaaga agaagaagcg gcctcgcaac tcttataaat 960
gtggaaccaa cacaatggag agggaagaga gtgaacagac caagaaaaga gaaaaaatcc 1020
atatacctga aagatctgat gaagcccagc gtgtttttta aagttcgaag acatcttcat 1080
gcgacaaaag tgatacatgt ttttaattaa agagtaaagc ccatacaagt attcattttt 1140
tctacccttt ctttgtaag ttcctgggca acctttttga tttcttccag aaggcaaaaa 1200
gacattacca tgagtaataa gggggctcca ggactccctc taagtggaaat agcctccctg 1260
taactccagc tctgctccgt atgccaagag gagactttta ttctcttact gcttcttttc 1320
acttcagagc acacttatgg gccaaagcca gcttaatggc tcatgacctg gaaataaaa 1380
ttaggaccaa tacctcctcc agatcagatt tctctcttaa tttcatagat tgtgtttttt 1440
tttaaataga cctctcaatt tctggaaaac tgcctttttat ctgccagaa ttctaagctg 1500

```

31/80

```

gtgccccact gaatcttgtg tacctgtgac taaacaacta cctcctcagt ctgggtggga 1560
cttatgtatt tatgacctta tagtggtta atcttgaaac atagagatct atgtactgta 1620
atagtgtgat tactatgctc tagagaaaag tctacccttg ctaaggagtt ctcatccctc 1680
tgtcaggggtc agtaaggaaa acgggtggcct agggtagagg caacaatgag cagaccaacc 1740
taaatttggg gaaatttagga gaggcagaga tagaacctgg agccacttct atctgggctg 1800
ttgctaatat tgaggaggct tgccccaccc aacaagccat agtggagaga actgaataaa 1860
caggaaaatg ccagagcttg tgaacctgtt ttctcttgaa gaactgacta gtgagatggc 1920
ctggggaagc tgtgaaagaa caaaagaga tcacaatact caaaagagag agagagagaa 1980
aaaagagaga tcttgatcca cagaaataca tgaaatgtct ggtctgtcca ccccatcaac 2040
aagtcttgaa acaagcaaca gatggatagt ctgtccaaat ggacataaga cagacagcag 2100
tttccctggg ggtcagggag gggttttggg gatacccaag ttattgggat gtcactcttc 2160
tggaagcaga gctggggagg gagagccatc accttgataa tgggatgaat ggaaggaggc 2220
ttaggacttt ccactcctgg ctgagagagg aagagctgca acggaattag gaagaccaag 2280
acacagatca cccggggcct acttagccta cagatgtcct acgggaacgt gggctggccc 2340
agcatagggc tagcaaattt gagttggatg attgtttttg ctcaaggcaa ccagaggaaa 2400
cttgcataca gagacagata tactgggaga aatgactttg aaaacctggc tctaaggttg 2460
gatcataaag ggatggggca gtctctgccc aaacataaag agaactctgg ggagcctgag 2520
ccacaaaaat gttcctttat tttatgtaaa cctcaagggt ttatagactg ccatgctaga 2580
caagcttgct catgtaatat tcccatgttt ttaccctgcc cctgccttga ttagactcct 2640
agcacctggc tagtttctaa catgttttgt gcagcacagt ttttaataaa tgcttggttac 2700
attcaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2760
aaaaaaaaaa aaaaaaaaaa a 2781

```

<210> 57

<211> 329

<212> PRT

<213> Homo sapiens

<400> 57

```

Met Asp Pro Gln Cys Thr Met Gly Leu Ser Asn Ile Leu Phe Val Met
  1              5              10              15

Ala Phe Leu Leu Ser Gly Ala Ala Pro Leu Lys Ile Gln Ala Tyr Phe
      20              25              30

Asn Glu Thr Ala Asp Leu Pro Cys Gln Phe Ala Asn Ser Gln Asn Gln
      35              40              45

Ser Leu Ser Glu Leu Val Val Phe Trp Gln Asp Gln Glu Asn Leu Val
      50              55              60

Leu Asn Glu Val Tyr Leu Gly Lys Glu Lys Phe Asp Ser Val His Ser
      65              70              75              80

Lys Tyr Met Gly Arg Thr Ser Phe Asp Ser Asp Ser Trp Thr Leu Arg
      85              90              95

Leu His Asn Leu Gln Ile Lys Asp Lys Gly Leu Tyr Gln Cys Ile Ile
      100             105             110

His His Lys Lys Pro Thr Gly Met Ile Arg Ile His Gln Met Asn Ser
      115             120             125

Glu Leu Ser Val Leu Ala Asn Phe Ser Gln Pro Glu Ile Val Pro Ile
      130             135             140

Ser Asn Ile Thr Glu Asn Val Tyr Ile Asn Leu Thr Cys Ser Ser Ile
      145             150             155             160

```

32/80

His Gly Tyr Pro Glu Pro Lys Lys Met Ser Val Leu Leu Arg Thr Lys
 165 170 175
 Asn Ser Thr Ile Glu Tyr Asp Gly Ile Met Gln Lys Ser Gln Asp Asn
 180 185 190
 Val Thr Glu Leu Tyr Asp Val Ser Ile Ser Leu Ser Val Ser Phe Pro
 195 200 205
 Asp Val Thr Ser Asn Met Thr Ile Phe Cys Ile Leu Glu Thr Asp Lys
 210 215 220
 Thr Arg Leu Leu Ser Ser Pro Phe Ser Ile Glu Leu Glu Asp Pro Gln
 225 230 235 240
 Pro Pro Pro Asp His Ile Pro Trp Ile Thr Ala Val Leu Pro Thr Val
 245 250 255
 Ile Ile Cys Val Met Val Phe Cys Leu Ile Leu Trp Lys Trp Lys Lys
 260 265 270
 Lys Lys Arg Pro Arg Asn Ser Tyr Lys Cys Gly Thr Asn Thr Met Glu
 275 280 285
 Arg Glu Glu Ser Glu Gln Thr Lys Lys Arg Glu Lys Ile His Ile Pro
 290 295 300
 Glu Arg Ser Asp Glu Ala Gln Arg Val Phe Lys Ser Ser Lys Thr Ser
 305 310 315 320
 Ser Cys Asp Lys Ser Asp Thr Cys Phe
 325

<210> 58

<211> 1177

<212> DNA

<213> Homo sapiens

<400> 58

```

gccaaaggctg gggcagggga gtcagcagag gcctcgctcg ggcgcccagt ggtcctgccc 60
cctgggtctca cctcgctatg gttcgtctgc ctctgcagtg cgtcctcttg ggctgcttgc 120
tgaccgctgt ccatccagaa ccaccactg catgcagaga aaaacagtac ctaataaaca 180
gtcagtgtcg ttctttgtgc cagccaggac agaaactggt gactgactgc acagagttca 240
ctgaaacgga atgccttcct tgcggtgaaa gcgaattcct agacacctgg aacagagaga 300
cacactgcca ccagcacaaa tactgcgacc ccaacctagg gcttcggggtc cagcagaagg 360
gcacctcaga aacagacacc atctgcacct gtgaagaagg ctggcactgt acgagtgagg 420
cctgtgagag ctgtgtcctg caccgctcat gctcgcccgg ctttgggggtc aagcagattg 480
ctacaggggt ttctgatacc atctgcgagc cctgcccagt cggcttcttc tccaatgtgt 540
catctgcttt cgaaaaatgt cacccttgga caagctgtga gaccaaagac ctggttgtgc 600
aacaggcagg cacaaacaag actgatgttg tctgtggtcc ccaggatcgg ctgagagccc 660
tggtggtgat ccccatcatc ttcgggatcc tgtttgccat cctcttggtg ctggtcttta 720
tcaaaaagggt ggccaagaag ccaaccaata agggccccca cccaagcag gaacccagg 780
agatcaattt tcccgacgat ctctctggct ccaacactgc tgctccagtg caggagactt 840
tacatggatg ccaaccggtc acccaggagg atggcaaaga gactgcacat tcagtgcagg 900
agagacagtg aggtgcacc caccaggag tgtggccacg tgggcaaaca ggcagttggc 960
cagagagcct ggtgctgctg ctgctgtggc gtgaggggtg ggggctggca ctgactgggc 1020
atagctcccc gcttctgctt gcaccctgc agtttgagac aggagacctg gcactggatg 1080

```

33/80

cagaaacagt tcaccttgaa gaacctctca cttcaccctg gagcccatcc agtctcccaa 1140
 cttgtattaa agacagaggc agaaaaaaaa aaaaaaa 1177

<210> 59

<211> 277

<212> PRT

<213> Homo sapiens

<400> 59

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

34/80

Gly Cys Gln Pro Val Thr Gln Glu Asp Gly Lys Glu Ser Arg Ile Ser
 260 265 270

Val Gln Glu Arg Gln
 275

<210> 60

<211> 1115

<212> DNA

<213> Homo sapiens

<400> 60

```

gccaaggctg gggcagggga gtcagcagag gcctcgctcg ggcgcccagt ggtcctgccg 60
cctgggtctca cctcgctatg gttcgtctgc ctctgcagtg cgtcctctgg ggctgcttgc 120
tgaccgctgt ccatccagaa ccacccactg catgcagaga aaaacagtac ctaataaaca 180
gtcagtgtctg ttctttgtgc cagccaggac agaaactggt gactgactgc acagagttca 240
ctgaaaacgga atgccttcct tgcggtgaaa gcgaattcct agacacctgg aacagagaga 300
cacactgcc aacagacaaa tactgcgacc ccaacctagg gcttcgggtc cagcagaagg 360
gcacctcaga aacagacacc atctgcacct gtgaagaagg ctggcactgt acgagtgagg 420
cctgtgagag ctgtgtcctg caccgctcat gctcgcccg ctttggggtc aagcagattg 480
ctacaggggt ttctgatacc atctgcgagc cctgccaggt cggcttcttc tccaatgtgt 540
catctgcttt cgaaaaatgt cacccttgga caaggtcccc aggatcgggt gagagccctg 600
gtggtgatcc ccatcatctt cgggatcctg tttgccatcc tcttgggtgt ggtctttatc 660
aaaaagggtg ccaagaagcc aaccaataag gccccccacc ccaagcagga accccaggag 720
atcaattttc ccgacgatct tctgggtcc aacactgctg ctccagtcca ggagacttta 780
catggatgcc aaccggtcac ccaggaggat ggcaaagaga gtccgatctc agtgcaggag 840
agacagttag gctgcaccca cccaggagtg tggccacgtg ggcaaacagg cagttggcca 900
gagagcctgg tctgtctgct gctgtggcgt gagggtagg ggctggcact gactgggcat 960
agctccccgc ttctgcctgc acccctgcag tttagacag gagacctggc actggatgca 1020
gaaacagttc accttgaaga acctctcact tcaccctgga gcccatccag tctcccaact 1080
tgtattaaag acagaggcag aaaaaaaaaa aaaaaa 1115

```

<210> 61

<211> 203

<212> PRT

<213> Homo sapiens

<400> 61

```

Met Val Arg Leu Pro Leu Gln Cys Val Leu Trp Gly Cys Leu Leu Thr
  1             5             10             15

Ala Val His Pro Glu Pro Pro Thr Ala Cys Arg Glu Lys Gln Tyr Leu
      20             25             30

Ile Asn Ser Gln Cys Cys Ser Leu Cys Gln Pro Gly Gln Lys Leu Val
      35             40             45

Ser Asp Cys Thr Glu Phe Thr Glu Thr Glu Cys Leu Pro Cys Gly Glu
      50             55             60

Ser Glu Phe Leu Asp Thr Trp Asn Arg Glu Thr His Cys His Gln His
      65             70             75             80

Lys Tyr Cys Asp Pro Asn Leu Gly Leu Arg Val Gln Gln Lys Gly Thr
      85             90             95

Ser Glu Thr Asp Thr Ile Cys Thr Cys Glu Glu Gly Trp His Cys Thr
      100            105            110

```

35/80

Ser Glu Ala Cys Glu Ser Cys Val Leu His Arg Ser Cys Ser Pro Gly
 115 120 125

Phe Gly Val Lys Gln Ile Ala Thr Gly Val Ser Asp Thr Ile Cys Glu
 130 135 140

Pro Cys Pro Val Gly Phe Phe Ser Asn Val Ser Ser Ala Phe Glu Lys
 145 150 155 160

Cys His Pro Trp Thr Arg Ser Pro Gly Ser Ala Glu Ser Pro Gly Gly
 165 170 175

Asp Pro His His Leu Arg Asp Pro Val Cys His Pro Leu Gly Ala Gly
 180 185 190

Leu Tyr Gln Lys Gly Gly Gln Glu Ala Asn Gln
 195 200

<210> 62

<211> 2986

<212> DNA

<213> Homo sapiens

<400> 62

```

gcgccccagt cgacgctgag ctccctctgct actcagagtt gcaacctcag cctcgctatg 60
gctcccagca gcccccgcc cgcgctgccc gcactcctgg tctgctcgg ggctctgttc 120
ccaggacctg gcaatgccca gacatctgtg tccccctcaa aagtcaccc gccccgggga 180
ggctccgtgc tggtgacatg cagcacctcc tgtgaccagc ccaagttgtt gggcatagag 240
accccgttgc ctaaaaagga gttgctcctg cctgggaaca accggaaggt gtatgaactg 300
agcaatgtgc aagaagatag ccaaccaatg tgctattcaa actgccctga tgggcagtca 360
acagctaaaa ccttcctcac cgtgtactgg actccagaac ggggtggaact ggcacccctc 420
ccctcttggc agccagtggg caagaacctt accctacgct gccaggtgga ggggtgggga 480
ccccgggcca acctcaccgt ggtgctgctc cgtggggaga aggagctgaa acgggagcca 540
gctgtggggg agcccgtga ggtcacgacc acggtgctgg tgaggagaga tcaccatgga 600
gccaatctct cgtgccgcac tgaactggac ctgcggcccc aagggtgga gctgtttgag 660
aacacctcgg cccctacca gctccagacc ttgtctctgc cagcgactcc cccacaactt 720
gtcagcccc gggtctaga ggtggacacg caggggaccg tggctctgtt cctggacggg 780
ctgttcccag tctcggaggc ccaggtccac ctggcactgg gggaccagag gttgaacccc 840
acagtcacct atggcaacga ctcttctcgc gccaaggcct cagtcagtgt gaccgcagag 900
gacgagggca cccagcggct gacgtgtgca gtaatactgg ggaaccagag ccaggagaca 960
ctgcagacag tgaccatcta cagctttcgc gcgcccacg tgattctgac gaagccagag 1020
gtctcagaag ggaccgaggt gacagtgaag tgtgaggccc accctagagc caaggtgacg 1080
ctgaatgggg ttccagccca gccactgggc ccgagggccc agctcctgct gaaggccacc 1140
ccagaggaca acgggcgcag cttctcctgc tctgcaaccc tggaggtggc cggccagctt 1200
atacacaaga accagaccgg ggagcttcgt gtctgtatg gccccgact ggacgagag 1260
gattgtccgg gaaactggac gtggccagaa aattcccagc agactccaat gtgccaggct 1320
tgggggaacc cattgcccga gctcaagtgt cttaaaggat gcactttccc actgcccac 1380
ggggaatcag tgactgtcac tcgagatctt gagggcacct acctctgtcg gggcaggagc 1440
actcaagggg aggtcaccgg cgaggtgacc gtgaatgtgc tctccccccg gtatgagatt 1500
gtcatcatca ctgtggtagc agccgcagtc ataatgggca ctgcaggcct cagcacgtac 1560
ctctataacc gccagcggaa gatcaagaaa tacagactac aacaggccca aaaagggacc 1620
cccatgaaac cgaacacaca agccacgcct ccctgaacct atcccgggac agggcctctt 1680
cctcggcctt cccatattgg tggcagtggt gccacactga acagagtggg agacatatgc 1740
catgcagcta cacctaccgg ccctgggacg ccggaggaca gggcattgtc ctcagtcaga 1800
tacaacagca tttggggcca tggtagctgc acacctaaaa cactaggcca cgcactctgat 1860
ctgtagtcac atgactaagc caagaggaag gagcaagact caagacatga ttgatggatg 1920
ttaaagtcta gcctgatgag aggggaagtg gtgggggaga catagcccca ccatgaggac 1980

```

36/80

```

atacaactgg gaaatactga aacttgctgc ctattgggta tgctgaggcc cacagactta 2040
cagaagaagt ggccctccat agacatgtgt agcatcaaaa cacaaaggcc cacacttcct 2100
gacggatgcc agcttgggca ctgctgtcta ctgaccccaa cccttgatga tatgtattta 2160
ttcatttggt attttaccag ctatttattg agtgtctttt atgtaggcta aatgaacata 2220
ggtctctggc ctcacggagc tcccagtgca tgtcacattc aaggtcacca ggtacagttg 2280
tacaggttgt acactgcagg agagtgcctg gcaaaaagat caaatggggc tgggacttct 2340
cattggccaa cctgcctttc cccagaagga gtgatttttc tatcggcaca aaagcactat 2400
atggactggg aatggttcac aggttcagag attaccaggt gaggccttat tcctcccttc 2460
ccccaaaac tgacaccttt gttagccacc tcccaccca catacatttc tgccagtgtt 2520
cacaatgaca ctcagcggtc atgtctggac atgagtggcc agggaatatg cccaagctat 2580
gccttgctct cttgtcctgt ttgcatttca ctgggagcct gcactattgc agctccagtt 2640
tcctgcagtg atcagggtcc tgcaagcagt ggggaagggg gccaaaggtat tggaggactc 2700
cctcccagct ttggaagggt catccgcgtg tgtgtgtgtg tgtatgtgta gacaagctct 2760
cgctctgtca cccaggctgg agtgacgtgg tgcaatcatg gttcactgca gtcttgacct 2820
tttgggctca agtgatcctc ccacctcagc ctccctgagta gctgggacca taggctcaca 2880
acaccacacc tggcaaattt gatttttttt ttttttttca gagacggggt ctcgcaacat 2940
tgcccagact tcctttgtgt tagttaataa agctttctca actgcc 2986

```

<210> 63

<211> 532

<212> PRT

<213> Homo sapiens

<400> 63

```

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

Leu Gly Ala Leu Phe Pro Gly Pro Gly Asn Ala Gln Thr Ser Val Ser
      20              25              30

Pro Ser Lys Val Ile Leu Pro Arg Gly Gly Ser Val Leu Val Thr Cys
      35              40              45

Ser Thr Ser Cys Asp Gln Pro Lys Leu Leu Gly Ile Glu Thr Pro Leu
      50              55              60

Pro Lys Lys Glu Leu Leu Leu Pro Gly Asn Asn Arg Lys Val Tyr Glu
      65              70              75              80

Leu Ser Asn Val Gln Glu Asp Ser Gln Pro Met Cys Tyr Ser Asn Cys
      85              90              95

Pro Asp Gly Gln Ser Thr Ala Lys Thr Phe Leu Thr Val Tyr Trp Thr
      100             105             110

Pro Glu Arg Val Glu Leu Ala Pro Leu Pro Ser Trp Gln Pro Val Gly
      115             120             125

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

Asn Leu Thr Val Val Leu Leu Arg Gly Glu Lys Glu Leu Lys Arg Glu
      145             150             155             160

Pro Ala Val Gly Glu Pro Ala Glu Val Thr Thr Thr Val Leu Val Arg
      165             170             175

```

37/80

Arg Asp His His Gly Ala Asn Phe Ser Cys Arg Thr Glu Leu Asp Leu
 180 185 190

Arg Pro Gln Gly Leu Glu Leu Phe Glu Asn Thr Ser Ala Pro Tyr Gln
 195 200 205

Leu Gln Thr Phe Val Leu Pro Ala Thr Pro Pro Gln Leu Val Ser Pro
 210 215 220

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

Gly Leu Phe Pro Val Ser Glu Ala Gln Val His Leu Ala Leu Gly Asp
 245 250 255

Gln Arg Leu Asn Pro Thr Val Thr Tyr Gly Asn Asp Ser Phe Ser Ala
 260 265 270

Lys Ala Ser Val Ser Val Thr Ala Glu Asp Glu Gly Thr Gln Arg Leu
 275 280 285

Thr Cys Ala Val Ile Leu Gly Asn Gln Ser Gln Glu Thr Leu Gln Thr
 290 295 300

Val Thr Ile Tyr Ser Phe Pro Ala Pro Asn Val Ile Leu Thr Lys Pro
 305 310 315 320

Glu Val Ser Glu Gly Thr Glu Val Thr Val Lys Cys Glu Ala His Pro
 325 330 335

Arg Ala Lys Val Thr Leu Asn Gly Val Pro Ala Gln Pro Leu Gly Pro
 340 345 350

Arg Ala Gln Leu Leu Leu Lys Ala Thr Pro Glu Asp Asn Gly Arg Ser
 355 360 365

Phe Ser Cys Ser Ala Thr Leu Glu Val Ala Gly Gln Leu Ile His Lys
 370 375 380

Asn Gln Thr Arg Glu Leu Arg Val Leu Tyr Gly Pro Arg Leu Asp Glu
 385 390 395 400

Arg Asp Cys Pro Gly Asn Trp Thr Trp Pro Glu Asn Ser Gln Gln Thr
 405 410 415

Pro Met Cys Gln Ala Trp Gly Asn Pro Leu Pro Glu Leu Lys Cys Leu
 420 425 430

Lys Asp Gly Thr Phe Pro Leu Pro Ile Gly Glu Ser Val Thr Val Thr
 435 440 445

Arg Asp Leu Glu Gly Thr Tyr Leu Cys Arg Ala Arg Ser Thr Gln Gly
 450 455 460

Glu Val Thr Arg Glu Val Thr Val Asn Val Leu Ser Pro Arg Tyr Glu
 465 470 475 480

38/80

Ile Val Ile Ile Thr Val Val Ala Ala Ala Val Ile Met Gly Thr Ala
485 490 495

Gly Leu Ser Thr Tyr Leu Tyr Asn Arg Gln Arg Lys Ile Lys Lys Tyr
500 505 510

Arg Leu Gln Gln Ala Gln Lys Gly Thr Pro Met Lys Pro Asn Thr Gln
515 520 525

Ala Thr Pro Pro
530

<210> 64

<211> 2960

<212> DNA

<213> Homo sapiens

<400> 64

```

gaattcaggg atccgggtac catggcgcgt gaacgcagct cggtcgccgc tggcaggaaa 60
caattctgca aaaataatca tactcagcct ggcaattgtc tgcccctagg tctgtcgctc 120
agccgccgct cacactcgct gcaggggggg gggcacagaa ttaccgcgg caagaacatc 180
cctcccagcc agcagattac aatgctgcaa actaaggatc tcatctggac tttgtttttc 240
ctgggaactg cagtttctct gcaggtggat attgttccca gccaggggga gatcagcggt 300
ggagagtcca aattcttctt atgccaagtg gcaggagatg ccaaagataa agacatctcc 360
tggttctccc ccaatggaga aaagctcacc ccaaaccagc agcggatctc agtggtgtgg 420
aatgatgatt cctcctccac cctcaccatc tataacgcca acatcgacga cgccggcatt 480
tacaagtgtg tggttacagg cgaggatggc agtgagtcag aggccaccgt caacgtgaag 540
atctttcaga agctcatgtt caagaatgcg ccaacccac aggagtccg ggagggggaa 600
gatgccgtga ttgtgtgtga tgtggtcagc tccctccac caaccatcat ctggaaacac 660
aaaggccgag atgtcatcct gaaaaaagat gtccgattca tagtcctgtc caacaactac 720
ctgcagatcc ggggcataca gaaaacagat gagggcactt atcgctgtga gggcagaatc 780
ctggcacggg gggagatcaa cttcaaggac attcagggtc ttgtgaatgt gccacctacc 840
atccaggcca ggcagaatat tgtgaatgcc accgcccaacc tcggccagtc cgtcaccctg 900
gtgtgcatg ccgaaggctt cccagagccc accatgagct ggacaaagga tggggaacag 960
atagagcaag aggaagacga tgagaagtac atcttcagcg acgatagtcc ccagctgacc 1020
atcaaaaagg tggataagaa cgacgaggct gactacatct gcattgctga gaacaaggct 1080
ggcgagcagg atgcgaccat ccacctcaaa gtctttgcaa aacccaaaat cacatatgta 1140
gagaaccaga ctgccatgga attagaggag caggtcactc ttacctgtga agcctccgga 1200
gaccccatcc cctccatcac ctggaggact tctaccggga acatcagcag cgaagaaaag 1260
actctggatg ggcacatggt ggtgcgtagc catgcccgtg tgtcgctcgt gacctgaag 1320
agcatccagt acactgatgc cggagagtag atctgcaccg ccagcaacac catcgccag 1380
gactccagtc ccatgtacct tgaagtgcaa tatgccccaa agctacaggg ccctgtggct 1440
gtgtacactt gggaggggaa ccaggatgaac atcacctgcg aggtatattgc ctatccagtc 1500
gccacgatct catggtttcg ggatggccag ctgctgccaa gctccaatta cagcaatatc 1560
aagatctaca acacccctc tgccagctat ctggagggtg cccagactc tgagaatgat 1620
tttggaactt acaactgtac tgcagtgaac cgcattgggc aggagtcctt ggaattcatc 1680
cttgttcaag cagacacccc ctcttcacca tccatcgacc aggtggagcc atactccagc 1740
acagcccagg tgcagtttga tgaaccagag gccacagggt gggtgcccat cctcaaatac 1800
aaagctgagt ggagagcagt tgggtgaagaa gtatggcatt ccaagtggta tgatgccaag 1860
gaagccagca tggagggcac cgtcaccatc gtgggcctga agcccgaac aacgtacgcc 1920
gtaaggctgg cggcgtcaa tggcaaaggg ctgggtgaga tcagcgcggc ctccgagttc 1980
aagacgcagc cagtccaagg ggaacccagt gcacctaaag tcgaagggca gatgggagag 2040
gatggaaact ctattaaagt gaacctgatc aagcaggatg acggcggctc ccccatcaga 2100
cactatctgg tcaggatacc agcgtctctc tccgagtgga aaccagagat caggctcccg 2160
tctggcagtg accacgtcat gctgaagtcc ctggactgga atgctgagta tgaggtctac 2220
gtggtggctg agaaccagca aggaaaatcc aaggcgctc attttgtgtt caggacctcg 2280
gccagcccca cagccatccc agccaacgag agcccacct caggcctgag caccggggcc 2340
atcggtgggca tcctcatcgt catcttcgtc ctgctcctgg tggttgtgga catcacctgc 2400

```

39/80

```

tacttcctga acaagtgtgg cctgttcattg tgcattgcgg tcaacctgtg tggaaaagcc 2460
gggcccgggg ccaagggcaa ggacatggag gagggcaagg ccgccttctc gaaagatgag 2520
tccaaggagc ccatcgtgga ggttcgaacg gagggaggaga ggaccccaaa ccatgatgga 2580
gggaaacaca cagagcccaa cgagaccacg ccactgacgg agcccagaaa gggccccgta 2640
gaagcaaagc cagagtgccg ggagacagaa acgaagccag cgccagccga agtcaagacg 2700
gtccccaatg acgccacaca gacaaaggag aacgagagca aagcatgatg ggtgaagaga 2760
accgagcaaa gatcaaaata aaaagtgaca cagcagcttc accagagcat ttccaacacc 2820
acagacacac acacgcacac acacacacaa ttctaggcta gtttctgggc ttatcattga 2880
gttacagctt agtgcagatt ttaagacaaa acaaacaaac aaaaaaaaaa aaaaaccatg 2940
gtaccccgat cctcgaattc                                     2960

```

<210> 65

<211> 848

<212> PRT

<213> Homo sapiens

<400> 65

```

Met Leu Gln Thr Lys Asp Leu Ile Trp Thr Leu Phe Phe Leu Gly Thr
  1                      5                      10                     15

Ala Val Ser Leu Gln Val Asp Ile Val Pro Ser Gln Gly Glu Ile Ser
      20                      25                     30

Val Gly Glu Ser Lys Phe Phe Leu Cys Gln Val Ala Gly Asp Ala Lys
      35                      40                     45

Asp Lys Asp Ile Ser Trp Phe Ser Pro Asn Gly Glu Lys Leu Thr Pro
      50                      55                     60

Asn Gln Gln Arg Ile Ser Val Val Trp Asn Asp Asp Ser Ser Ser Thr
      65                      70                     75                     80

Leu Thr Ile Tyr Asn Ala Asn Ile Asp Asp Ala Gly Ile Tyr Lys Cys
      85                      90                     95

Val Val Thr Gly Glu Asp Gly Ser Glu Ser Glu Ala Thr Val Asn Val
      100                     105                    110

Lys Ile Phe Gln Lys Leu Met Phe Lys Asn Ala Pro Thr Pro Gln Glu
      115                     120                    125

Phe Arg Glu Gly Glu Asp Ala Val Ile Val Cys Asp Val Val Ser Ser
      130                     135                    140

Leu Pro Pro Thr Ile Ile Trp Lys His Lys Gly Arg Asp Val Ile Leu
      145                     150                    155                    160

Lys Lys Asp Val Arg Phe Ile Val Leu Ser Asn Asn Tyr Leu Gln Ile
      165                     170                    175

Arg Gly Ile Lys Lys Thr Asp Glu Gly Thr Tyr Arg Cys Glu Gly Arg
      180                     185                    190

Ile Leu Ala Arg Gly Glu Ile Asn Phe Lys Asp Ile Gln Val Ile Val
      195                     200                    205

Asn Val Pro Pro Thr Ile Gln Ala Arg Gln Asn Ile Val Asn Ala Thr
      210                     215                    220

```

40/80

Ala Asn Leu Gly Gln Ser Val Thr Leu Val Cys Asp Ala Glu Gly Phe
 225 230 235 240
 Pro Glu Pro Thr Met Ser Trp Thr Lys Asp Gly Glu Gln Ile Glu Gln
 245 250 255
 Glu Glu Asp Asp Glu Lys Tyr Ile Phe Ser Asp Asp Ser Ser Gln Leu
 260 265 270
 Thr Ile Lys Lys Val Asp Lys Asn Asp Glu Ala Glu Tyr Ile Cys Ile
 275 280 285
 Ala Glu Asn Lys Ala Gly Glu Gln Asp Ala Thr Ile His Leu Lys Val
 290 295 300
 Phe Ala Lys Pro Lys Ile Thr Tyr Val Glu Asn Gln Thr Ala Met Glu
 305 310 315 320
 Leu Glu Glu Gln Val Thr Leu Thr Cys Glu Ala Ser Gly Asp Pro Ile
 325 330 335
 Pro Ser Ile Thr Trp Arg Thr Ser Thr Arg Asn Ile Ser Ser Glu Glu
 340 345 350
 Lys Thr Leu Asp Gly His Met Val Val Arg Ser His Ala Arg Val Ser
 355 360 365
 Ser Leu Thr Leu Lys Ser Ile Gln Tyr Thr Asp Ala Gly Glu Tyr Ile
 370 375 380
 Cys Thr Ala Ser Asn Thr Ile Gly Gln Asp Ser Gln Ser Met Tyr Leu
 385 390 395 400
 Glu Val Gln Tyr Ala Pro Lys Leu Gln Gly Pro Val Ala Val Tyr Thr
 405 410 415
 Trp Glu Gly Asn Gln Val Asn Ile Thr Cys Glu Val Phe Ala Tyr Pro
 420 425 430
 Ser Ala Thr Ile Ser Trp Phe Arg Asp Gly Gln Leu Leu Pro Ser Ser
 435 440 445
 Asn Tyr Ser Asn Ile Lys Ile Tyr Asn Thr Pro Ser Ala Ser Tyr Leu
 450 455 460
 Glu Val Thr Pro Asp Ser Glu Asn Asp Phe Gly Asn Tyr Asn Cys Thr
 465 470 475 480
 Ala Val Asn Arg Ile Gly Gln Glu Ser Leu Glu Phe Ile Leu Val Gln
 485 490 495
 Ala Asp Thr Pro Ser Ser Pro Ser Ile Asp Gln Val Glu Pro Tyr Ser
 500 505 510
 Ser Thr Ala Gln Val Gln Phe Asp Glu Pro Glu Ala Thr Gly Gly Val
 515 520 525

41/80

Pro Ile Leu Lys Tyr Lys Ala Glu Trp Arg Ala Val Gly Glu Glu Val
 530 535 540

Trp His Ser Lys Trp Tyr Asp Ala Lys Glu Ala Ser Met Glu Gly Ile
 545 550 555 560

Val Thr Ile Val Gly Leu Lys Pro Glu Thr Thr Tyr Ala Val Arg Leu
 565 570 575

Ala Ala Leu Asn Gly Lys Gly Leu Gly Glu Ile Ser Ala Ala Ser Glu
 580 585 590

Phe Lys Thr Gln Pro Val Gln Gly Glu Pro Ser Ala Pro Lys Leu Glu
 595 600 605

Gly Gln Met Gly Glu Asp Gly Asn Ser Ile Lys Val Asn Leu Ile Lys
 610 615 620

Gln Asp Asp Gly Gly Ser Pro Ile Arg His Tyr Leu Val Arg Tyr Arg
 625 630 635 640

Ala Leu Ser Ser Glu Trp Lys Pro Glu Ile Arg Leu Pro Ser Gly Ser
 645 650 655

Asp His Val Met Leu Lys Ser Leu Asp Trp Asn Ala Glu Tyr Glu Val
 660 665 670

Tyr Val Val Ala Glu Asn Gln Gln Gly Lys Ser Lys Ala Ala His Phe
 675 680 685

Val Phe Arg Thr Ser Ala Gln Pro Thr Ala Ile Pro Ala Asn Gly Ser
 690 695 700

Pro Thr Ser Gly Leu Ser Thr Gly Ala Ile Val Gly Ile Leu Ile Val
 705 710 715 720

Ile Phe Val Leu Leu Leu Val Val Val Asp Ile Thr Cys Tyr Phe Leu
 725 730 735

Asn Lys Cys Gly Leu Phe Met Cys Ile Ala Val Asn Leu Cys Gly Lys
 740 745 750

Ala Gly Pro Gly Ala Lys Gly Lys Asp Met Glu Glu Gly Lys Ala Ala
 755 760 765

Phe Ser Lys Asp Glu Ser Lys Glu Pro Ile Val Glu Val Arg Thr Glu
 770 775 780

Glu Glu Arg Thr Pro Asn His Asp Gly Gly Lys His Thr Glu Pro Asn
 785 790 795 800

Glu Thr Thr Pro Leu Thr Glu Pro Glu Lys Gly Pro Val Glu Ala Lys
 805 810 815

Pro Glu Cys Gln Glu Thr Glu Thr Lys Pro Ala Pro Ala Glu Val Lys
 820 825 830

42/80

Thr Val Pro Asn Asp Ala Thr Gln Thr Lys Glu Asn Glu Ser Lys Ala
 835 840 845

<210> 66
 <211> 4050
 <212> DNA
 <213> Homo sapiens

<400> 66
 gcgcgtgaac gcagctcggc tgccgctggc aggaacaacat tctgcaaaaa taatcatact 60
 cagcctggca attgtctgcc cctaggtctg tcgctcagcc gccgtccaca ctgcgtgcag 120
 gggggggggg cacagaattht accgcggcaa gaacatccct ccagccagc agattacaat 180
 gctgcaaaact aaggatctca tctggacttt gtttttcctg ggaactgcag tttctctgca 240
 ggtggatatt gttcccagcc agggggagat cagcgttgga gaggccaaat tcttcttatg 300
 ccaagtggca ggagatgcca aagataaaga catctcctgg ttctcccca atggagaaaa 360
 gctcacccca aaccagcagc ggatctcagt ggtgtggaat gatgattcct cctccaccct 420
 caccatctat aacgccaaca tcgacgacgc cggcatttac aagtgtgtgg ttacaggcga 480
 ggatggcagt gaggcagagg ccaccgtcaa cgtgaagatc ttccagaagc tcatgttcaa 540
 gaatgcgcca accccacagg agttccggga gggggaagat gccgtgattg tgtgtgatgt 600
 ggtcagctcc ctcccaccaa ccatcatctg gaaacacaaa ggccgagatg tcatcctgaa 660
 aaaagatgtc cgattcatag tctgttccaa caactacctg cagatccggg gcatcaagaa 720
 aacagatgag ggcacttatc gctgtgaggg cagaatcctg gcacgggggg agatcaactt 780
 caaggacatt caggtcattg tgaatgtgcc acctaccatc caggccaggc agaataattgt 840
 gaatgccacc gccaaacctc gccagtcctg caccctggtg tgcgatgccg aaggcttccc 900
 agagcccacc atgagctgga caaaggatgg ggaacagata gagcaagagg aagacgatga 960
 gaagtacatc ttcagcgagc atagttccca gctgaccatc aaaaagggtg ataagaacga 1020
 cgaggctgag tacatctgca ttgctgagaa caaggctggc gagcaggatg cgaccatcca 1080
 cctcaaagtc tttgcaaaaac ccaaaatcac atatgtagag aaccagactg ccatggaatt 1140
 agaggagcag gtcactctta cctgtgaagc ctccggagac ccatttccct ccatcacctg 1200
 gaggacttct acccggaaca tcagcagcga agaaaaggct tcgtggactc gaccagagaa 1260
 gcaagagatt ctggatgggc acatggtggc gcgtagccat gccctgtgtg cgtcgtgac 1320
 cctgaagagc atccagtaca ctgatgccgg agagtacatc tgcaccgcca gcaaacccat 1380
 cggccaggac tcccagtcga tgtaccttga agtgcaatat gcccacaaagc tacaggggccc 1440
 tgtggctgtg tacacttggg aggggaacca ggtgaacatc acctgcgagg tatttgccta 1500
 tcccagtgcc acgatctcat ggtttcggga tggccagctg ctgccaagct ccaattacag 1560
 caatatcaag atctacaaca cccctctgct cagctatctg gagggtgaccc cagactctga 1620
 gaatgatttt gggaactaca actgtactgc agtgaaccgc attgggcagg agtccttggga 1680
 attcatcctt gttcaagcag acacccctc ttcaccatcc atcgaccagg tggagccata 1740
 ctccagcaca gccaggtgc agtttgatga accagaggcc acagggtggg tgcccatcct 1800
 caaatacaaaa gctgagtggg gagcagtggg tgaagaagta tggcattcca agtggtatga 1860
 tgccaaggaa gccagcatgg agggcatcgt caccatcgtg ggcctgaagc ccgaaacaac 1920
 gtacgccgta aggtctggcg cgtcaatgg caaagggtg ggtgagatca gcgcggcctc 1980
 cgagttcaag acgcagccag tccaagggga acccagtgca cctaagctcg aagggcagat 2040
 gggagaggat ggaaactcta ttaaagtga cctgatcaag caggatgacg gcggctcccc 2100
 catcagacac tatctggtca ggtaccgagc gctctcctcc gagtggaaac cagagatcag 2160
 gctcccgtct ggagtgacc acgtcatgct gaagtcctg gactggaatg ctgagtatga 2220
 ggtctacgtg gtggctgaga accagcaagg aaaatccaag gcggctcatt ttgtgttcag 2280
 gacctcggcc cagcccacag ccatcccagc caacggcagc ccacctcag gcctgagcac 2340
 cggggccatc gtgggcatcc tcatcgtcat ctctcgtcctg ctctcgtggg ttgtggacat 2400
 cacctgctac ttctgaaca agtgtggcct gttcatgtgc attgcggtca acctgtgtgg 2460
 aaaagccggg cccggggcca agggcaagga catggaggag ggcaaggccg cttctctgaa 2520
 agatgagtc aaggagccca tcgtggaggt tcgaacggag gaggagagga ccccaacca 2580
 tgatggaggg aaacacacag agcccaacga gaccacgcca ctgacggagc ccgagaaggg 2640
 ccccgtagaa gcaaagccag agtgccagga gacagaaacg aagccagcgc cagccgaagt 2700
 caagacgggc cccaatgacg ccacacagac aaaggagaac gagaacaaag catgatgggt 2760
 gaagagaacc gagcaaatga caaaataaaa agtgacacag cagcttcacc agagcatttc 2820
 caacaccaca gacacacaca cgcacgcaca cacacaaaca cacatgcaca cacacacatc 2880

43/80

```

tcattttctct agtgtctttt gccttttaaaa aaaactaaac agataaaaca tgggaatctc 2940
ctttttgtag gtttatagaa aggggtccctt tgttgcacac tcacttgtaa gaaaatgaga 3000
caaaaagggtt aaaccacag ccaactagg acactccgtt ccctgaaacc gtaaaaaaat 3060
caaacaaaag gaccccaaata taagaatcta ggaagctcag aaacgaaatc taggttcagg 3120
aagaccacac ttggtgttac ccgattggca cagaccagtt tcagagaaat actttcaggc 3180
actaagacta atcgaatgaa caaagtccac agttttatttt tatactttca gtcaagtttg 3240
aactctgtaa aacctcataa ataagttata atttctgttc actttgtatt tgttcagtat 3300
gcaaagtgtg tcaccctttc tagctgaatt caattcccac gtagactctt attttatagg 3360
acgaatgcc aattgcagct tctgggggta gatctcaatt tgcagtattc agacttcttt 3420
ttctttcttt tacattcttt tttctttctt tctttctgcc aactttgttt tccagtgttt 3480
acaagggtgac aaatgtttga ctttggttgt gtttaaatgt ccgtgtaaaa tagctgcctt 3540
ttatttttta aggtaacaaa taccacctag aggtaggtag gatcatccca cgcttgcttt 3600
agcacaggac aactttacaa aacatgattg tttacagctg ctcttccctt cttttctgat 3660
ctgcagtttt tgctgggtc ccaactcagg gaaaatccat ctattctgg aatggttttg 3720
cttttgaatt tttggttatt tttgtgtttc tttgggggtt agaccacttt ctgattagcc 3780
gccacctgcc tgcatctgtg aaaagggatc tgctcccagg cgttctcacc cttcttttga 3840
aggactcctt aggcctttgtt gaatgaagca gagaagattg tatagttggg gctgggtctt 3900
gtgaacacac attattaccc cacacatccc ctttgtgtag aaagccaaat aaaatctata 3960
cataccaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 4020
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 4050

```

<210> 67

<211> 858

<212> PRT

<213> Homo sapiens

<400> 67

```

Met Leu Gln Thr Lys Asp Leu Ile Trp Thr Leu Phe Phe Leu Gly Thr
  1                      5                      10                     15

Ala Val Ser Leu Gln Val Asp Ile Val Pro Ser Gln Gly Glu Ile Ser
      20                      25                     30

Val Gly Glu Ser Lys Phe Phe Leu Cys Gln Val Ala Gly Asp Ala Lys
      35                      40                     45

Asp Lys Asp Ile Ser Trp Phe Ser Pro Asn Gly Glu Lys Leu Thr Pro
      50                      55                     60

Asn Gln Gln Arg Ile Ser Val Val Trp Asn Asp Asp Ser Ser Ser Thr
      65                      70                     75                     80

Leu Thr Ile Tyr Asn Ala Asn Ile Asp Asp Ala Gly Ile Tyr Lys Cys
      85                      90                     95

Val Val Thr Gly Glu Asp Gly Ser Glu Ser Glu Ala Thr Val Asn Val
      100                     105                    110

Lys Ile Phe Gln Lys Leu Met Phe Lys Asn Ala Pro Thr Pro Gln Glu
      115                     120                    125

Phe Arg Glu Gly Glu Asp Ala Val Ile Val Cys Asp Val Val Ser Ser
      130                     135                    140

Leu Pro Pro Thr Ile Ile Trp Lys His Lys Gly Arg Asp Val Ile Leu
      145                     150                    155                    160

```

44/80

Lys Lys Asp Val Arg Phe Ile Val Leu Ser Asn Asn Tyr Leu Gln Ile
 165 170 175
 Arg Gly Ile Lys Lys Thr Asp Glu Gly Thr Tyr Arg Cys Glu Gly Arg
 180 185 190
 Ile Leu Ala Arg Gly Glu Ile Asn Phe Lys Asp Ile Gln Val Ile Val
 195 200 205
 Asn Val Pro Pro Thr Ile Gln Ala Arg Gln Asn Ile Val Asn Ala Thr
 210 215 220
 Ala Asn Leu Gly Gln Ser Val Thr Leu Val Cys Asp Ala Glu Gly Phe
 225 230 235 240
 Pro Glu Pro Thr Met Ser Trp Thr Lys Asp Gly Glu Gln Ile Glu Gln
 245 250 255
 Glu Glu Asp Asp Glu Lys Tyr Ile Phe Ser Asp Asp Ser Ser Gln Leu
 260 265 270
 Thr Ile Lys Lys Val Asp Lys Asn Asp Glu Ala Glu Tyr Ile Cys Ile
 275 280 285
 Ala Glu Asn Lys Ala Gly Glu Gln Asp Ala Thr Ile His Leu Lys Val
 290 295 300
 Phe Ala Lys Pro Lys Ile Thr Tyr Val Glu Asn Gln Thr Ala Met Glu
 305 310 315 320
 Leu Glu Glu Gln Val Thr Leu Thr Cys Glu Ala Ser Gly Asp Pro Ile
 325 330 335
 Pro Ser Ile Thr Trp Arg Thr Ser Thr Arg Asn Ile Ser Ser Glu Glu
 340 345 350
 Lys Ala Ser Trp Thr Arg Pro Glu Lys Gln Glu Thr Leu Asp Gly His
 355 360 365
 Met Val Val Arg Ser His Ala Arg Val Ser Ser Leu Thr Leu Lys Ser
 370 375 380
 Ile Gln Tyr Thr Asp Ala Gly Glu Tyr Ile Cys Thr Ala Ser Asn Thr
 385 390 395 400
 Ile Gly Gln Asp Ser Gln Ser Met Tyr Leu Glu Val Gln Tyr Ala Pro
 405 410 415
 Lys Leu Gln Gly Pro Val Ala Val Tyr Thr Trp Glu Gly Asn Gln Val
 420 425 430
 Asn Ile Thr Cys Glu Val Phe Ala Tyr Pro Ser Ala Thr Ile Ser Trp
 435 440 445
 Phe Arg Asp Gly Gln Leu Leu Pro Ser Ser Asn Tyr Ser Asn Ile Lys
 450 455 460

45/80

Ile Tyr Asn Thr Pro Ser Ala Ser Tyr Leu Glu Val Thr Pro Asp Ser
 465 470 475 480
 Glu Asn Asp Phe Gly Asn Tyr Asn Cys Thr Ala Val Asn Arg Ile Gly
 485 490 495
 Gln Glu Ser Leu Glu Phe Ile Leu Val Gln Ala Asp Thr Pro Ser Ser
 500 505 510
 Pro Ser Ile Asp Gln Val Glu Pro Tyr Ser Ser Thr Ala Gln Val Gln
 515 520 525
 Phe Asp Glu Pro Glu Ala Thr Gly Gly Val Pro Ile Leu Lys Tyr Lys
 530 535 540
 Ala Glu Trp Arg Ala Val Gly Glu Glu Val Trp His Ser Lys Trp Tyr
 545 550 555 560
 Asp Ala Lys Glu Ala Ser Met Glu Gly Ile Val Thr Ile Val Gly Leu
 565 570 575
 Lys Pro Glu Thr Thr Tyr Ala Val Arg Leu Ala Ala Leu Asn Gly Lys
 580 585 590
 Gly Leu Gly Glu Ile Ser Ala Ala Ser Glu Phe Lys Thr Gln Pro Val
 595 600 605
 Gln Gly Glu Pro Ser Ala Pro Lys Leu Glu Gly Gln Met Gly Glu Asp
 610 615 620
 Gly Asn Ser Ile Lys Val Asn Leu Ile Lys Gln Asp Asp Gly Gly Ser
 625 630 635 640
 Pro Ile Arg His Tyr Leu Val Arg Tyr Arg Ala Leu Ser Ser Glu Trp
 645 650 655
 Lys Pro Glu Ile Arg Leu Pro Ser Gly Ser Asp His Val Met Leu Lys
 660 665 670
 Ser Leu Asp Trp Asn Ala Glu Tyr Glu Val Tyr Val Val Ala Glu Asn
 675 680 685
 Gln Gln Gly Lys Ser Lys Ala Ala His Phe Val Phe Arg Thr Ser Ala
 690 695 700
 Gln Pro Thr Ala Ile Pro Ala Asn Gly Ser Pro Thr Ser Gly Leu Ser
 705 710 715 720
 Thr Gly Ala Ile Val Gly Ile Leu Ile Val Ile Phe Val Leu Leu Leu
 725 730 735
 Val Val Val Asp Ile Thr Cys Tyr Phe Leu Asn Lys Cys Gly Leu Phe
 740 745 750
 Met Cys Ile Ala Val Asn Leu Cys Gly Lys Ala Gly Pro Gly Ala Lys
 755 760 765

46/80

Gly Lys Asp Met Glu Glu Gly Lys Ala Ala Phe Ser Lys Asp Glu Ser
 770 775 780
 Lys Glu Pro Ile Val Glu Val Arg Thr Glu Glu Glu Arg Thr Pro Asn
 785 790 795 800
 His Asp Gly Gly Lys His Thr Glu Pro Asn Glu Thr Thr Pro Leu Thr
 805 810 815
 Glu Pro Glu Lys Gly Pro Val Glu Ala Lys Pro Glu Cys Gln Glu Thr
 820 825 830
 Glu Thr Lys Pro Ala Pro Ala Glu Val Lys Thr Val Pro Asn Asp Ala
 835 840 845
 Thr Gln Thr Lys Glu Asn Glu Asn Lys Ala
 850 855

<210> 68

<211> 2995

<212> DNA

<213> Homo sapiens

<400> 68

```

ggccgcccac gaagcagcgg ttctcggcgc tgcagctgct gaagctgctg ctgctgctgc 60
agccgcgcgt gccacgagcg ctgcgcgagg cgctctgccc tgagccctgc aactgcgtgc 120
ccgacggcgc cctgcgctgc cccggcccca cggcgggtct cactcgacta tcacttgctc 180
acctccctgt caaagtgatc ccatctcaag ctttcagagg acttaatgag gtcataaaaa 240
ttgaaatctc tcagattgat tccctggaaa ggatagaagc taatgccttt gacaacctcc 300
tcaatttgct tgaaatactg atccagaaca ccaaaaatct gagatacatt gagcccgagg 360
catttataaa tcttcccgga ttaaaatact tgagcatctg taacacaggc atcagaaagt 420
ttccagatgt tacgaaggtc ttctcctctg aatcaaattt cattctggaa atttgtgata 480
acttacacat aaccaccata ccaggaaatg cttttcaagg gatgaataat gaatctgtaa 540
cactcaaat atattggaat ggatttgaag aagtacaaag tcatgcattc aatgggacga 600
cactgacttc actggagcta aaggaaaacg tacatctgga gaagatgcac aatggagcct 660
tcctgtggggc cacaggggcg aaaaccttgg atatttcttc caccaaattg caggccctgc 720
cgagctatgg cctagagtcc attcagaggc taattgccac gtcatcctat tctctaaaaa 780
aattgccatc aagagaaaca tttgtcaatc tcctggaggc cacgttgact taccacagcc 840
actgctgtgc ttttagaaac ttgccaaaca aagaacagaa tttttcacat tccatttctg 900
aaaacttttc caaacaatgt gaaagcacag taaggaaagt gagtaacaaa acactttatt 960
cttccatgct tgctgagagt gaactgagt gctgggacta tgaatatggt ttctgcttac 1020
ccaagacacc ccgatgtgct cctgaaccag atgcttttaa tccctgtgaa gacattatgg 1080
gctatgactt ccttagggtc ctgatttggc tgattaatat tctagccatc atgggaaaca 1140
tgactgttct ttttgttctc ctgacaagtc gttacaaact tacagtgcct cgttttctca 1200
tgtgcaatct ctcttttgca gacttttgca tggggctcta tctgctgctc atagcctcag 1260
ttgattccca aaccaagggc cagtactata accatgccat agactggcag acagggagtg 1320
ggtgcagcac tgctggcttt ttactgtat tcgcaagtga actttctgtc tacacctca 1380
ccgtcatcac tctagaaaga tggcacacca tcacctatgc tattcacctg gaccaaaagc 1440
tgcgattaag acatgccatt ctgattatgc ttggaggatg gctcttttct tctctaattg 1500
ctatgttgcc ccttgtcggg gtcagcaatt acatgaaggt cagtatttgc ttccccatgg 1560
atgtggaaac cactctctca caagtctata tattaacat cctgattctc aatgtggtgg 1620
ccttcttcat aatttgtgct tgctacatta aaatttattt tgcagttcga aaccagaat 1680
taatggctac caataaagat acaaagattg ctaagaaaat ggcaatcctc atcttcaccg 1740
atttcacctg catggcacct atctcttttt ttgccatctc agctgccttc aaagtacctc 1800
ttatcacagt aaccaactct aaagttttac tggttctttt ttatcccatc aattcttgtg 1860
ccaatccatt tctgtatgca atatttacta agacattcca aagagatttc tttcttttgc 1920
tgagcaaat ttggtgctgt aaacgtcggg ctgaacttta tagaaggaaa gatttttcag 1980
cttacacctc caactgcaaa aatggcttca ctggatcaaa taagccttct caatccacct 2040

```

47/80

```

tgaagttgtc cacattgcac tgtcaaggta cagctctcct agacaagact cgctacacag 2100
agtgttaact gttacatcag taactgcatt attgaattgt tcttaaacct gtaaaaaaaa 2160
attacctgta ccagtaattt taacataaag ggttggattt aggaaattat ttatttttag 2220
gtacattagg caagagacct ctacctagta gaaagtgtag tctatgacca ctgccacacg 2280
taaaaactat ttgtcattgt tacatggcat aaatatgaag ttgagagtgt ttagaaattt 2340
ttatagaaat tttgacacag taattttgtt tgatgaatct tttaaaaaac agaggaggta 2400
ttttgcatat ctttttttca ttttcgtaat ttgtattgca ttctataaaa atattagttc 2460
ataacagatc agaaatttaa aataaggggc tttttcctca ggtagtttga aaaacacact 2520
ctagagatgc actgttcaat tcggtacgca ctaggccacat gtggctaaat taaaattaaa 2580
taaaatgaga aatgtagttt ctcaagtgtc ctacgtttca agttctcaat ggctacgtca 2640
agttctcaat ggctacgtgt gactagtgtt taccatactg gacagcacag acacagaata 2700
ttttcatcac cacagaaagt tctatctgtt ctattataga gacttttatg tatgccctat 2760
ctggattcta cttatttata atttaaggta aacatctgaa agcacatttc agcctatttg 2820
cttagtgaat cattaagctg tagactgtaa actcctcgtg agtaggaacc ctgtctcagt 2880
gcattttgtt ttctgtcttc ctacctcaag atcttggcaa tgggtacacta caaatgtgct 2940
gagttagaat tactctgaag ttatgaaaca tataatgaaa acaatttttc cggcc 2995

```

<210> 69

<211> 699

<212> PRT

<213> Homo sapiens

<400> 69

```

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

```

```

Leu Gln Pro Pro Leu Pro Arg Ala Leu Arg Glu Ala Leu Cys Pro Glu
              20              25              30

```

```

Pro Cys Asn Cys Val Pro Asp Gly Ala Leu Arg Cys Pro Gly Pro Thr
              35              40              45

```

```

Ala Gly Leu Thr Arg Leu Ser Leu Ala Tyr Leu Pro Val Lys Val Ile
  50              55              60

```

```

Pro Ser Gln Ala Phe Arg Gly Leu Asn Glu Val Ile Lys Ile Glu Ile
  65              70              75              80

```

```

Ser Gln Ile Asp Ser Leu Glu Arg Ile Glu Ala Asn Ala Phe Asp Asn
              85              90              95

```

```

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

```

```

Tyr Ile Glu Pro Gly Ala Phe Ile Asn Leu Pro Gly Leu Lys Tyr Leu
              115              120              125

```

```

Ser Ile Cys Asn Thr Gly Ile Arg Lys Phe Pro Asp Val Thr Lys Val
              130              135              140

```

```

Phe Ser Ser Glu Ser Asn Phe Ile Leu Glu Ile Cys Asp Asn Leu His
  145              150              155              160

```

```

Ile Thr Thr Ile Pro Gly Asn Ala Phe Gln Gly Met Asn Asn Glu Ser
              165              170              175

```

```

Val Thr Leu Lys Leu Tyr Gly Asn Gly Phe Glu Glu Val Gln Ser His
              180              185              190

```

48/80

Ala Phe Asn Gly Thr Thr Leu Thr Ser Leu Glu Leu Lys Glu Asn Val
 195 200 205
 His Leu Glu Lys Met His Asn Gly Ala Phe Arg Gly Ala Thr Gly Pro
 210 215 220
 Lys Thr Leu Asp Ile Ser Ser Thr Lys Leu Gln Ala Leu Pro Ser Tyr
 225 230 235 240
 Gly Leu Glu Ser Ile Gln Arg Leu Ile Ala Thr Ser Ser Tyr Ser Leu
 245 250 255
 Lys Lys Leu Pro Ser Arg Glu Thr Phe Val Asn Leu Leu Glu Ala Thr
 260 265 270
 Leu Thr Tyr Pro Ser His Cys Cys Ala Phe Arg Asn Leu Pro Thr Lys
 275 280 285
 Glu Gln Asn Phe Ser His Ser Ile Ser Glu Asn Phe Ser Lys Gln Cys
 290 295 300
 Glu Ser Thr Val Arg Lys Val Ser Asn Lys Thr Leu Tyr Ser Ser Met
 305 310 315 320
 Leu Ala Glu Ser Glu Leu Ser Gly Trp Asp Tyr Glu Tyr Gly Phe Cys
 325 330 335
 Leu Pro Lys Thr Pro Arg Cys Ala Pro Glu Pro Asp Ala Phe Asn Pro
 340 345 350
 Cys Glu Asp Ile Met Gly Tyr Asp Phe Leu Arg Val Leu Ile Trp Leu
 355 360 365
 Ile Asn Ile Leu Ala Ile Met Gly Asn Met Thr Val Leu Phe Val Leu
 370 375 380
 Leu Thr Ser Arg Tyr Lys Leu Thr Val Pro Arg Phe Leu Met Cys Asn
 385 390 395 400
 Leu Ser Phe Ala Asp Phe Cys Met Gly Leu Tyr Leu Leu Leu Ile Ala
 405 410 415
 Ser Val Asp Ser Gln Thr Lys Gly Gln Tyr Tyr Asn His Ala Ile Asp
 420 425 430
 Trp Gln Thr Gly Ser Gly Cys Ser Thr Ala Gly Phe Phe Thr Val Phe
 435 440 445
 Ala Ser Glu Leu Ser Val Tyr Thr Leu Thr Val Ile Thr Leu Glu Arg
 450 455 460
 Trp His Thr Ile Thr Tyr Ala Ile His Leu Asp Gln Lys Leu Arg Leu
 465 470 475 480
 Arg His Ala Ile Leu Ile Met Leu Gly Gly Trp Leu Phe Ser Ser Leu
 485 490 495

49/80

Ile Ala Met Leu Pro Leu Val Gly Val Ser Asn Tyr Met Lys Val Ser
500 505 510

Ile Cys Phe Pro Met Asp Val Glu Thr Thr Leu Ser Gln Val Tyr Ile
515 520 525

Leu Thr Ile Leu Ile Leu Asn Val Val Ala Phe Phe Ile Ile Cys Ala
530 535 540

Cys Tyr Ile Lys Ile Tyr Phe Ala Val Arg Asn Pro Glu Leu Met Ala
545 550 555 560

Thr Asn Lys Asp Thr Lys Ile Ala Lys Lys Met Ala Ile Leu Ile Phe
565 570 575

Thr Asp Phe Thr Cys Met Ala Pro Ile Ser Phe Phe Ala Ile Ser Ala
580 585 590

Ala Phe Lys Val Pro Leu Ile Thr Val Thr Asn Ser Lys Val Leu Leu
595 600 605

Val Leu Phe Tyr Pro Ile Asn Ser Cys Ala Asn Pro Phe Leu Tyr Ala
610 615 620

Ile Phe Thr Lys Thr Phe Gln Arg Asp Phe Phe Leu Leu Leu Ser Lys
625 630 635 640

Phe Gly Cys Cys Lys Arg Arg Ala Glu Leu Tyr Arg Arg Lys Asp Phe
645 650 655

Ser Ala Tyr Thr Ser Asn Cys Lys Asn Gly Phe Thr Gly Ser Asn Lys
660 665 670

Pro Ser Gln Ser Thr Leu Lys Leu Ser Thr Leu His Cys Gln Gly Thr
675 680 685

Ala Leu Leu Asp Lys Thr Arg Tyr Thr Glu Cys
690 695

<210> 70

<211> 523

<212> DNA

<213> Homo sapiens

<400> 70

```
gcaccaagga tggagatgct ccaggggctg ctgctgttgc tgctgctgag catgggcggg 60
gcatgggcat ccaggagacc gcttcggcca tggtgccacc ccatcaatgc catcctggct 120
gtcgagaagg agggctgccc agtgtgcatc accgtcaaca ccaccatctg tgccggctac 180
tgccccacca tgatgcgcgt gctgcaggcg gtctgcccgc cctgcctca ggtggtgtgc 240
acctaccgtg atgtgcgctt cgagtccatc cggctccctg gctgcccgcg tgggtgtggac 300
cccgtggtct ccttcctgtt ggctctcagc tgtcgctgtg gaccctgccg ccgcagcacc 360
tctgactgtg ggggtcccaa agaccacccc ttgacctgtg accaccccca actctcaggc 420
ctcctcttcc tctaaagacc ctccccgcag ccttccaagt ccatcccagc tcctggagcc 480
ctgacacccc gatcctccca caataaaggc ttctcaatcc gca 523
```

50/80

<210> 71
 <211> 141
 <212> PRT
 <213> Homo sapiens

<400> 71
 Met Glu Met Leu Gln Gly Leu Leu Leu Leu Leu Leu Ser Met Gly
 1 5 10 15
 Gly Ala Trp Ala Ser Arg Glu Pro Leu Arg Pro Trp Cys His Pro Ile
 20 25 30
 Asn Ala Ile Leu Ala Val Glu Lys Glu Gly Cys Pro Val Cys Ile Thr
 35 40 45
 Val Asn Thr Thr Ile Cys Ala Gly Tyr Cys Pro Thr Met Met Arg Val
 50 55 60
 Leu Gln Ala Val Leu Pro Pro Leu Pro Gln Val Val Cys Thr Tyr Arg
 65 70 75 80
 Asp Val Arg Phe Glu Ser Ile Arg Leu Pro Gly Cys Pro Arg Gly Val
 85 90 95
 Asp Pro Val Val Ser Phe Pro Val Ala Leu Ser Cys Arg Cys Gly Pro
 100 105 110
 Cys Arg Arg Ser Thr Ser Asp Cys Gly Gly Pro Lys Asp His Pro Leu
 115 120 125
 Thr Cys Asp His Pro Gln Leu Ser Gly Leu Leu Phe Leu
 130 135 140

<210> 72
 <211> 704
 <212> DNA
 <213> Homo sapiens

<400> 72
 gcagttactg agaactcata agacgaagct aaaatccctc ttcggatcca cagtcaaccg 60
 ccctgaacac atcctgcaaa aagcccagag aaaggagcgc catggattac tacagaaaat 120
 atgcagctat ctttctggtc acattgtcgg tgtttctgca tgttctccat tccgctcctg 180
 atgtgcagga ttgccagaa tgcacgctac aggaaaacc attcttctcc cagccgggtg 240
 ccccaatact tcagtgcatt ggctgctgct tctctagagc atatcccact ccactaaggt 300
 ccaagaagac gatgttggtc caaaagaacg tcacctcaga gtccacttgc tgtgtagcta 360
 aatcatataa cagggtcaca gtaatggggg gtttcaaagt ggagaaccac acggcgtgcc 420
 actgcagtac ttgttattat cacaaatctt aaatgtttta ccaagtgtct tcttgatgac 480
 tgctgatttt ctggaatgga aaattaagtt gtttagtggt tatggccttg tgagataaaa 540
 ctctcctttt ccttaccata ccactttgac acgcttcaag gatatactgc agctttactg 600
 ccttcctcct tatcctacag tacaatcagc agtctagttc ttttcatttg gaatgaatac 660
 agcattaagc ttgttccact gcaataaaag ccttttaaat catc 704

<210> 73
 <211> 116
 <212> PRT
 <213> Homo sapiens

51/80

<400> 73

Met Asp Tyr Tyr Arg Lys Tyr Ala Ala Ile Phe Leu Val Thr Leu Ser
 1 5 10 15

Val Phe Leu His Val Leu His Ser Ala Pro Asp Val Gln Asp Cys Pro
 20 25 30

Glu Cys Thr Leu Gln Glu Asn Pro Phe Phe Ser Gln Pro Gly Ala Pro
 35 40 45

Ile Leu Gln Cys Met Gly Cys Cys Phe Ser Arg Ala Tyr Pro Thr Pro
 50 55 60

Leu Arg Ser Lys Lys Thr Met Leu Val Gln Lys Asn Val Thr Ser Glu
 65 70 75 80

Ser Thr Cys Cys Val Ala Lys Ser Tyr Asn Arg Val Thr Val Met Gly
 85 90 95

Gly Phe Lys Val Glu Asn His Thr Ala Cys His Cys Ser Thr Cys Tyr
 100 105 110

Tyr His Lys Ser
 115

<210> 74

<211> 3162

<212> DNA

<213> Homo sapiens

<400> 74

agagccaccg ggctggggac cggggagcgg aggctgaaat cccagacgc cggttttctg 60
 ggctgggctt tctgccttac tcactccttc tccctctttc tggattttac cgaccgttcg 120
 cgaaacagct ttccacacaa tggagcttca tgtcctcgtg caggaagtac tcatcgactg 180
 atgtggcaga ctttgctccc tggcaaaact aaagaactct cctattcatg gaggcgaaca 240
 ctgaggatgc tttccacatg aaccctgaag tgaacttctg atacatttcc tgcagcaaga 300
 gaaggcagcc aacatgaagg aaaatgtggc atctgcaacc gttttcactc tgctactttt 360
 tctcaacacc tgccttctga atggacagtt acctcctgga aaacctgaga tctttaaatg 420
 togttctccc aataaggaaa cattcacctg ctggtggagg cctgggacag atggaggact 480
 tcctaccaat tattcactga cttaccacag ggaaggagag acactcatgc atgaatgtcc 540
 agactacata accggtggcc ccaactcctg ccactttggc aagcagtaca cctccatgtg 600
 gaggacatac atcatgatgg tcaatgccac taaccagatg ggaagcagtt tctcggatga 660
 actttatgtg gacgtgactt acatagttca gccagaccct cctttggagc tggctgtgga 720
 agtaaaacag ccagaagaca gaaaacccta cctgtggatt aaatgggtctc cacctaccct 780
 gattgactta aaaactgggt gggtcacgct cctgtatgaa attcgattaa aacccgagaa 840
 agcagctgag tgggagatcc attttgctgg gcagcaaaca gagtttaaga ttctcagcct 900
 acatccagga cagaaatacc ttgtccaggt tcgctgcaaa ccagaccatg gatactggag 960
 tgcattggagt ccagcgacct tcattcagat acctagtgc ttcaccatga atgatacaac 1020
 cgtgtggatc tctgtggctg tcctttctgc tgtcatctgt ttgattattg tctgggcagt 1080
 ggctttgaag ggctatagca tggtagcctg catctttccg ccagttcctg ggccaaaaat 1140
 aaaaggattt gatgctcatc tgttggagaa gggcaagtct gaagaactac tgagtgcctt 1200
 gggatgccaa gactttcctc ccacttctga ctatgaggac ttgctggtgg agtatttaga 1260
 agtagatgat agtgaggacc agcatcta at gtcagtccat tcaaaagaac acccaagtca 1320
 aggtatgaaa cccacatacc tggatcctga cactgactca ggccggggga gctgtgacag 1380
 ccttccctt ttgtctgaaa agtgtgagga accccagcc aatccctcca cattctatga 1440
 tccctaggctc attgagaagc cagagaatcc tgaaacaacc cacacctggg acccccagtg 1500
 cataagcatg gaaggcaaaa tccctatctt tcatgctggt ggatccaaat gttcaacatg 1560
 gcccttacca cagcccagcc agcacaaccc cagatcctct taccacaata ttactgatgt 1620

52/80

```

gtgtgagctg gctgtgggcc ctgcagggtgc accggccact ctgttgaatg aagcaggtaa 1680
agatgcttta aaatcctctc aaaccattaa gtctagagaa gagggaaagg caaccagca 1740
gagggaggta gaaagcttcc attctgagac tgaccaggat acgccctggc tgctgcccc 1800
ggagaaaacc ccctttggct ccgctaaacc cttggattat gtggagattc acaagggtcaa 1860
caaagatggt gcattatcat tgctaccaa acagagagag aacagcggca agcccaagaa 1920
gcccgggact cctgagaaca ataaggagta tgccaagggtg tccgggggtca tggataacaa 1980
catcctggtg ttggtgccag atccacatgc taaaaacgtg gcttgctttg aagaatcagc 2040
caaagaggcc ccaccatcac ttgaacagaa tcaagctgag aaagccctgg ccaacttcac 2100
tgcaacatca agcaagtgc ggctccagct gggtggtttg gattacctgg atcccgcatg 2160
ttttacacac tccttttact gatagcttga ctaatggaat gattggttaa aatgtgattt 2220
ttcttcaggt aacactacag agtacgtgaa atgctcaaga atgtagttag actgacacta 2280
ctaaagctcc cagctccttt catgctccat ttttaaccac ttgcctcttt ctccagcagc 2340
tgattccaga acaaatcatt atgtttccta actgtgattt gtagatttac tttttgctgt 2400
tagttataaa actatgtgtt caatgaaata aaagcacact gcttagtatt cttgaggggac 2460
aatgccaata ggtatatcct ctggaaaagg ctttcatgat ttgacatggg acagacggaa 2520
atgaaattgt caaaattgtt taccatagaa agatgacaaa agaaaatttt ccacatagga 2580
aaatgccatg aaaattgctt ttgaaaaaca actgcataac ctttactc ctgcgtccatt 2640
ttattaggat tacccaaata taaccattta aagaaagaat gcattccaga acaaattgtt 2700
tacataagtt cctatacctt actgacacat tgctgatatg caagtaagaa ataatgcctc 2760
caattttttt cttaaaatag tttagatatg ttaagcatgg attttcccc taaattctac 2820
tctaaagctt ctataaaata tagtttgtaa ataaaaatgt tcttacacaa ggggcaaagt 2880
aatttcatgt gaatcccttt aggatgtttt cctccttcat ttcagcatga tagataattt 2940
attatacacc ttagtctttc cttagttaaa aaaaaattcc ctaaagacta acttgaaaag 3000
aaaaccacag caggatgcta atggaattac tgccttactg tacatacaaa ttctacttta 3060
atataaaccc ataagtttaa ctgtattttt gaagactatt tttctatgac ttaggtaaaa 3120
taaaagacta ttttctattt tcccagaaaa aaaaaaaaaa aa 3162

```

<210> 75

<211> 622

<212> PRT

<213> Homo sapiens

<400> 75

```

Met Lys Glu Asn Val Ala Ser Ala Thr Val Phe Thr Leu Leu Leu Phe
  1                      5                      10                      15

Leu Asn Thr Cys Leu Leu Asn Gly Gln Leu Pro Pro Gly Lys Pro Glu
          20                      25                      30

Ile Phe Lys Cys Arg Ser Pro Asn Lys Glu Thr Phe Thr Cys Trp Trp
          35                      40                      45

Arg Pro Gly Thr Asp Gly Gly Leu Pro Thr Asn Tyr Ser Leu Thr Tyr
          50                      55                      60

His Arg Glu Gly Glu Thr Leu Met His Glu Cys Pro Asp Tyr Ile Thr
          65                      70                      75                      80

Gly Gly Pro Asn Ser Cys His Phe Gly Lys Gln Tyr Thr Ser Met Trp
          85                      90                      95

Arg Thr Tyr Ile Met Met Val Asn Ala Thr Asn Gln Met Gly Ser Ser
          100                      105                      110

Phe Ser Asp Glu Leu Tyr Val Asp Val Thr Tyr Ile Val Gln Pro Asp
          115                      120                      125

```

53/80

Pro Pro Leu Glu Leu Ala Val Glu Val Lys Gln Pro Glu Asp Arg Lys
 130 135 140
 Pro Tyr Leu Trp Ile Lys Trp Ser Pro Pro Thr Leu Ile Asp Leu Lys
 145 150 155 160
 Thr Gly Trp Phe Thr Leu Leu Tyr Glu Ile Arg Leu Lys Pro Glu Lys
 165 170 175
 Ala Ala Glu Trp Glu Ile His Phe Ala Gly Gln Gln Thr Glu Phe Lys
 180 185 190
 Ile Leu Ser Leu His Pro Gly Gln Lys Tyr Leu Val Gln Val Arg Cys
 195 200 205
 Lys Pro Asp His Gly Tyr Trp Ser Ala Trp Ser Pro Ala Thr Phe Ile
 210 215 220
 Gln Ile Pro Ser Asp Phe Thr Met Asn Asp Thr Thr Val Trp Ile Ser
 225 230 235 240
 Val Ala Val Leu Ser Ala Val Ile Cys Leu Ile Ile Val Trp Ala Val
 245 250 255
 Ala Leu Lys Gly Tyr Ser Met Val Thr Cys Ile Phe Pro Pro Val Pro
 260 265 270
 Gly Pro Lys Ile Lys Gly Phe Asp Ala His Leu Leu Glu Lys Gly Lys
 275 280 285
 Ser Glu Glu Leu Leu Ser Ala Leu Gly Cys Gln Asp Phe Pro Pro Thr
 290 295 300
 Ser Asp Tyr Glu Asp Leu Leu Val Glu Tyr Leu Glu Val Asp Asp Ser
 305 310 315 320
 Glu Asp Gln His Leu Met Ser Val His Ser Lys Glu His Pro Ser Gln
 325 330 335
 Gly Met Lys Pro Thr Tyr Leu Asp Pro Asp Thr Asp Ser Gly Arg Gly
 340 345 350
 Ser Cys Asp Ser Pro Ser Leu Leu Ser Glu Lys Cys Glu Glu Pro Gln
 355 360 365
 Ala Asn Pro Ser Thr Phe Tyr Asp Pro Glu Val Ile Glu Lys Pro Glu
 370 375 380
 Asn Pro Glu Thr Thr His Thr Trp Asp Pro Gln Cys Ile Ser Met Glu
 385 390 395 400
 Gly Lys Ile Pro Tyr Phe His Ala Gly Gly Ser Lys Cys Ser Thr Trp
 405 410 415
 Pro Leu Pro Gln Pro Ser Gln His Asn Pro Arg Ser Ser Tyr His Asn
 420 425 430

54/80

Ile Thr Asp Val Cys Glu Leu Ala Val Gly Pro Ala Gly Ala Pro Ala
 435 440 445
 Thr Leu Leu Asn Glu Ala Gly Lys Asp Ala Leu Lys Ser Ser Gln Thr
 450 455 460
 Ile Lys Ser Arg Glu Glu Gly Lys Ala Thr Gln Gln Arg Glu Val Glu
 465 470 475 480
 Ser Phe His Ser Glu Thr Asp Gln Asp Thr Pro Trp Leu Leu Pro Gln
 485 490 495
 Glu Lys Thr Pro Phe Gly Ser Ala Lys Pro Leu Asp Tyr Val Glu Ile
 500 505 510
 His Lys Val Asn Lys Asp Gly Ala Leu Ser Leu Leu Pro Lys Gln Arg
 515 520 525
 Glu Asn Ser Gly Lys Pro Lys Lys Pro Gly Thr Pro Glu Asn Asn Lys
 530 535 540
 Glu Tyr Ala Lys Val Ser Gly Val Met Asp Asn Asn Ile Leu Val Leu
 545 550 555 560
 Val Pro Asp Pro His Ala Lys Asn Val Ala Cys Phe Glu Glu Ser Ala
 565 570 575
 Lys Glu Ala Pro Pro Ser Leu Glu Gln Asn Gln Ala Glu Lys Ala Leu
 580 585 590
 Ala Asn Phe Thr Ala Thr Ser Ser Lys Cys Arg Leu Gln Leu Gly Gly
 595 600 605
 Leu Asp Tyr Leu Asp Pro Ala Cys Phe Thr His Ser Phe His
 610 615 620

<210> 76

<211> 1388

<212> DNA

<213> Homo sapiens

<400> 76

```

gggatacctta ttctatatct cttggtatct agtgtaaaaa ttttaaaatc tttacctagc 60
aatcttgagg aagaaacttg ataactgata atacatgaga ttgttaccta agtgaaatat 120
aatcctatat attcaacaaa ctttagagaa ataagataaa ttttaaagta aatgacttct 180
gtagttttat agatcctcca aaccaatcta gtctcagatc tcaccttcat catttctctc 240
atttcctttt ggcctaatta atcaaaatcc ttcctagaat gttcatttct ggccagtatg 300
tcttcctgaa tatgaataag aaataaaaata ccatttgatg ttgaaatta tgggggtaat 360
ctcaatgacg gaaatagatg accaggaaaa gggaaacgaa tgcctgattc attatattca 420
tgaagatatc aaaggtttat aaagccaata tctgggaaag agaaaaccgt gagacttcca 480
gatcttctct ggtgaagtgt gtttcctgca acgatcacga acatgaacat caaaggatcg 540
ccatggaaaag ggtccctcct gctgctgctg gtgtcaaacc tgctcctgtg ccagagcggtg 600
gcccccttgc ccactgtgcc cggcggggct gcccgatgcc aggtgacctt tcgagacctg 660
tttgaccgcg ccgctcgtcct gtcccactac atccataacc tctcctcaga aatgttcagc 720
gaattcgata aacggtatac ccattggcgg gggttcatta ccaaggccat caacagctgc 780
cacacttctt ccttgccac ccccgaaagc aaggagcaag cccaacagat gaatcaaaaa 840
gactttctga gcctgatagt cagcatattg cgatcctgga atgagcctct gtatcatctg 900
gtcacggaag tacgtggtat gcaagaagcc ccggaggcta tcctatccaa agctgtagag 960

```

55/80

```

attgaggagc aaaccaaacg gcttctagag ggcattggagc tgatagtcag ccagggttcat 1020
cctgaaacca aagaaaatga gatctaccct gtctggtcgg gacttccatc cctgcagatg 1080
gctgatgaag agtctcgctt ttctgcttat tataacctgc tccactgcct acgcagggat 1140
tcacataaaa tcgacaatta tctcaagctc ctgaagtgcc gaatcatcca caacaacaac 1200
tgctaagccc acatccatct catctatttc tgagaaggtc cttaatgacg cgttccattg 1260
caagcttctt ttagttgtat ctcttttgaa tccatgcttg ggtgtaacag gtctcctctt 1320
aaaaaataaa aactgactcc ttagagacat caaaatccaa aaaaaaaaaa aaaaaaaaaa 1380
aaaaaaaaa                                     1388

```

<210> 77

<211> 227

<212> PRT

<213> Homo sapiens

<400> 77

```

Met Asn Ile Lys Gly Ser Pro Trp Lys Gly Ser Leu Leu Leu Leu Leu
  1              5              10              15

```

```

Val Ser Asn Leu Leu Leu Cys Gln Ser Val Ala Pro Leu Pro Ile Cys
      20              25              30

```

```

Pro Gly Gly Ala Ala Arg Cys Gln Val Thr Leu Arg Asp Leu Phe Asp
    35              40              45

```

```

Arg Ala Val Val Leu Ser His Tyr Ile His Asn Leu Ser Ser Glu Met
    50              55              60

```

```

Phe Ser Glu Phe Asp Lys Arg Tyr Thr His Gly Arg Gly Phe Ile Thr
    65              70              75              80

```

```

Lys Ala Ile Asn Ser Cys His Thr Ser Ser Leu Ala Thr Pro Glu Asp
      85              90              95

```

```

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

```

```

Val Ser Ile Leu Arg Ser Trp Asn Glu Pro Leu Tyr His Leu Val Thr
    115              120              125

```

```

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

```

```

Val Glu Ile Glu Glu Gln Thr Lys Arg Leu Leu Glu Gly Met Glu Leu
    145              150              155              160

```

```

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

```

```

Val Trp Ser Gly Leu Pro Ser Leu Gln Met Ala Asp Glu Glu Ser Arg
    180              185              190

```

```

Leu Ser Ala Tyr Tyr Asn Leu Leu His Cys Leu Arg Arg Asp Ser His
    195              200              205

```

```

Lys Ile Asp Asn Tyr Leu Lys Leu Leu Lys Cys Arg Ile Ile His Asn
    210              215              220

```

56/80

Asn Asn Cys
225

<210> 78
<211> 2230
<212> DNA
<213> Homo sapiens

<400> 78
gggcctccca aagtgctggg attagaggca tgagccaccg tgcccagcct caaagcataat 60
tttaaaggat agaaataaac agccatatga agagatacag acagggcggt ctggaagggt 120
ccagagcagg agcttctatc tccatagagt tggggttacg tcaccctctg ggcacattct 180
gtcagcctcc acacgttcag ctctcagaag ctcccgaaac ctgtcctttg ggccttttat 240
ggagaactcc attggctgtc catgactgaa gcatggacaa ctgtgataat gtgattgggc 300
aaaaagggtc tgatctaagc ccagcaaggc cagtcagat tctttgggcc tttgtgcagc 360
attcctttct ccagggtatg gggcaaggac ccactctgga atgaggatcc tacaaccac 420
aatcagatta gagtctgtcc ttgggcagct gaaaagagga caggagaagg tcagagagac 480
gaaaggctgt tttttgaggc ctgaggcacc ccaacatgac aacgtaagac tgtaaccatg 540
gtcatgtgag ttatgagcta ggaaccttg acgaaaccaa cacatataca atcatctccc 600
acctcccaac gcctttactt tcacagcctc tgcagcaaac tgcggtcact ataatcgctc 660
ctgtggcaca gaggcatacc caggggaatc tgcccagggg gccactctgt gccacagtgg 720
gaaccacac ctgcttgtaa agcctcccc tctctgacc agcaaccagg acagtttgtt 780
gttccaagca gtgggctcat gtctgttttg gctcagaaca ggggtgggag agcggggcag 840
ggaccgcgag gaaggcttat ccttgagatt gcgtgggaga cacaacaagg ggtgggggcc 900
cgcaggcggg gcggggcgaa gcagggtgata tcaagccag agccccagcc tctccccaca 960
gtctcaccat ggccgcgacc gtggtgctca tcaccggctg ttcctcgggc atcggcctgc 1020
acttgccgt acgtctggct tcagatccat ccagagctt caaagtgtat gccacgttga 1080
gggacctgaa aacacagggc cggctgtggg aggcggcccg ggccttgga tgccctccg 1140
gatccctgga gacgttgca ctggacgtaa gggactcaaa atccgtggcc gctgcccggg 1200
aacgcgtgac tgagggccgc gtggacgtgc tgggtgtgaa cgcaggcctg ggcctgctgg 1260
ggcgcctgga ggcgctggg gaggacgccc tggcctctgt gctggacgtg aatgtagtag 1320
ggactgtgag gatgctgcag gccttcctgc cagacatgaa gaggcgcgt tcgggacgag 1380
tgttggtgac cgggagcgtg ggaggattga tggggctgcc tttcaatgac gtttattgag 1440
ccagcaagtt cgcgctcgaa ggcttatgag agagtctggc ggttctgctg ctgccctttg 1500
gggtccactt gagcctgatc gagtgcggcc cagtgcacac cgccttcagt gagaagggtg 1560
tgggcagccc agaggaggtg ctggaccgca cggacatcca caccttccac cgcttctacc 1620
aatacctcgc ccacagcaag caagtctttc gcgaggcggc gcagaacctt gaggaggtgg 1680
cggaggtctt cctcaccgct ttgcgcgccc cgaagccgac cctgcgctac ttcaccaccg 1740
agcgcttctt gcccctgctg cggatgcgcc tggacgacc cagcggctcc aactacgtca 1800
ccgcatgca ccgggaagtg ttccgacgac ttccggcaaa ggccgaggct ggggcccagg 1860
ctggggggcg ggccgggcct ggggcagagg acgaggccgg gcgcagtgcg gtgggggacc 1920
ctgagctcgg cgatcctccg gccgccccgc agtaaaggct tcctcagccg ctgtctcccg 1980
cgcccttctt tgtccctgg gtctgtgtgg tccttgggga tggggcggcg gtagcagctg 2040
tgggtggcta attagatag atcgcgttag ccagttttac cagcgcagct aggcgcgatg 2100
gctgtgcct gtaatgccag cgctttggga ggcggaggca ggaggatcgc tcaagccccg 2160
gagttggaga ccagccagag caacacagtg agacccccat ctctacaaaa ataaagaaaa 2220
tttaaaaatc 2230

<210> 79
<211> 328
<212> PRT
<213> Homo sapiens

<400> 79
Met Ala Arg Thr Val Val Leu Ile Thr Gly Cys Ser Ser Gly Ile Gly
1 5 10 15

57/80

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

58/80

Gly Asp Pro Pro Ala Ala Pro Gln
325

<210> 80
<211> 1427
<212> DNA
<213> Homo sapiens

<400> 80
ctgggaatat gattatgctt aatctatgct cagtcgaaaagg gggctggggc tgctttctcc 60
cctcccttct tgactctctg ttcacagaac tcaggctgcc tccagccagc ctttgccgc 120
tagactcact ggccctgagc acttgaaggc gcagcaagtc actgagaatg agcactttct 180
tctcggacac agcatggatc tgccctggctg tccccacagt actatgtggg acagtatttt 240
gcaaatacaa gaagagctca gggcagctgt ggagctggat ggtctgcctg gcaggcctct 300
gtgcagctctg cctgctcatc ctgtccctt tttggggctt gatcctcttc tcggtgtcat 360
gcttctcat gtatacttac ttatctggcc aagaattgtt acctgtggat cagaaggcag 420
tcctggtgac aggtgggtgat tgcgggcttg gccatgcttt gtgcaagtat ctggatgagc 480
tgggcttcac ggtattttgcc ggagttttga atgaaaatgg cccaggagct gaggaattgc 540
gaagaacctg ctctccgcgc ctctcggcgc tccaaatgga catcacgaag ccagtgcaga 600
taaaagatgc ttacagcaag gttgcagcaa tgctgcagga cagaggactg tgggctgtga 660
tcaacaatgc tggggtgctt ggctttccaa ctgatgggga gcttcttctt atgactgact 720
acaaacaatg catggccgtg aacttctttg gaactgtgga ggtcacaaag acgtttttgc 780
ctcttcttag aaaatccaaa gggaggcttg tgaatgtcag cagcatggga ggaggggccc 840
caatggaaag gctggcatct tatggctcat caaaggcggc tgtgacctg ttctcatcag 900
ttatgagact ggagctttcc aagtgggaa tttaaagttg tccatccaa cctggaggct 960
tcctaacaaa tatcgaggc accagtgaca agtgggaaaa gctggagaag gacattctg 1020
accacctccc cgctgaggtg caggaagact acggccagga ctacatctta gcacagcgga 1080
atttctcct attgatcaac tcgttagcca gcaaggactt ctctccggtg ctgcgggaca 1140
tccagcatgc tatcttggcg aagagccctt ttgcctatta cacgccaggg aaaggcgctt 1200
acttgtggat ctgccttgc cactatttgc ctattggcat atatgattac tttgctaaaa 1260
gacattttgg ccaagacaag cccatgcccc gagctctaag aatgcctaac tacaagaaaa 1320
aggccacctg ggcaatggaa gccctcaaag aagtcggaat gtcatagtct tgaatgaaa 1380
gggaaactgg gaaactgggt ttctcattaa agttgtttcc cactctg 1427

<210> 81
<211> 387
<212> PRT
<213> Homo sapiens

<400> 81
Met Ser Thr Phe Phe Ser Asp Thr Ala Trp Ile Cys Leu Ala Val Pro
1 5 10 15
Thr Val Leu Cys Gly Thr Val Phe Cys Lys Tyr Lys Lys Ser Ser Gly
20 25 30
Gln Leu Trp Ser Trp Met Val Cys Leu Ala Gly Leu Cys Ala Val Cys
35 40 45
Leu Leu Ile Leu Ser Pro Phe Trp Gly Leu Ile Leu Phe Ser Val Ser
50 55 60
Cys Phe Leu Met Tyr Thr Tyr Leu Ser Gly Gln Glu Leu Leu Pro Val
65 70 75 80
Asp Gln Lys Ala Val Leu Val Thr Gly Gly Asp Cys Gly Leu Gly His
85 90 95

59/80

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

60/80

<210> 82
 <211> 1100
 <212> DNA
 <213> Homo sapiens

<400> 82
 ctaaagctgg gttggtagct cctacctact gtgtggcaag aaggatatggg tcatgaacag 60
 aaccaaggag ctgcgctgct acagatgtta ccacttctgt ggctgctacc ccactcctgg 120
 gccgtccctg aagctcctac tccaatgtgg ccagatgacc tgcaaaacca cacattcctg 180
 cacacagtgt actgccagga tgggagtccc agtgtgggac tctctgaggc ctacgacgag 240
 gaccagcttt tcttcttcga cttttcccag aacactcggg tgcctcgctt gccgaattt 300
 gctgactggg ctcaggaaca gggagatgct cctgccattt tatttgacaa agagtctctg 360
 gagtggatga tccagcaaat agggccaaaa cttgatggga aaatcccggg gtccagaggg 420
 tttcctatcg ctgaagtgtt cacgctgaag cccctggagt ttggcaagcc caacactttg 480
 gtctgttttg tcagtaatct ctccccaccc atgctgacag tgaactggca gcatcattcc 540
 gtccctgtgg aaggatttgg gctactttt gtctcagctg tcgatggact cagcttccag 600
 gccttttctt acttaaaactt cacaccagaa ccttctgaca ttttctcctg cattgtgact 660
 cacgaaattg accgctacac agcaattgcc tattgggtac cccggaacgc actgccctca 720
 gatctgctgg agaattgtct gtgtggcgtg gcctttggcc tgggtgtgct gggcatcatc 780
 gtgggcattg ttctcatcat ctacttccgg aagccttgct caggtgactg attcttccag 840
 accagagttt gatgccagca gcttcggcca tccaaacaga ggatgctcag atttctcaca 900
 tcctgcccag gatctcctct tagggtagaa gaagtctctg ggacatccct ggggtgtgtg 960
 tgtagatttc ccacctgggg actctgctgt ccctgggctt gcatcccagg gatcccagag 1020
 tggcctgcct atcacaacca catcccttcc cccacaagg caataaatct catttcttta 1080
 aaaaaaaaaa aaaaaaaaaa 1100

<210> 83
 <211> 261
 <212> PRT
 <213> Homo sapiens

<400> 83
 Met Gly His Glu Gln Asn Gln Gly Ala Ala Leu Leu Gln Met Leu Pro
 1 5 10 15
 Leu Leu Trp Leu Leu Pro His Ser Trp Ala Val Pro Glu Ala Pro Thr
 20 25 30
 Pro Met Trp Pro Asp Asp Leu Gln Asn His Thr Phe Leu His Thr Val
 35 40 45
 Tyr Cys Gln Asp Gly Ser Pro Ser Val Gly Leu Ser Glu Ala Tyr Asp
 50 55 60
 Glu Asp Gln Leu Phe Phe Phe Asp Phe Ser Gln Asn Thr Arg Val Pro
 65 70 75 80
 Arg Leu Pro Glu Phe Ala Asp Trp Ala Gln Glu Gln Gly Asp Ala Pro
 85 90 95
 Ala Ile Leu Phe Asp Lys Glu Phe Cys Glu Trp Met Ile Gln Gln Ile
 100 105 110
 Gly Pro Lys Leu Asp Gly Lys Ile Pro Val Ser Arg Gly Phe Pro Ile
 115 120 125
 Ala Glu Val Phe Thr Leu Lys Pro Leu Glu Phe Gly Lys Pro Asn Thr
 130 135 140

61/80

Leu Val Cys Phe Val Ser Asn Leu Phe Pro Pro Met Leu Thr Val Asn
 145 150 155 160
 Trp Gln His His Ser Val Pro Val Glu Gly Phe Gly Pro Thr Phe Val
 165 170 175
 Ser Ala Val Asp Gly Leu Ser Phe Gln Ala Phe Ser Tyr Leu Asn Phe
 180 185 190
 Thr Pro Glu Pro Ser Asp Ile Phe Ser Cys Ile Val Thr His Glu Ile
 195 200 205
 Asp Arg Tyr Thr Ala Ile Ala Tyr Trp Val Pro Arg Asn Ala Leu Pro
 210 215 220
 Ser Asp Leu Leu Glu Asn Val Leu Cys Gly Val Ala Phe Gly Leu Gly
 225 230 235 240
 Val Leu Gly Ile Ile Val Gly Ile Val Leu Ile Ile Tyr Phe Arg Lys
 245 250 255
 Pro Cys Ser Gly Asp
 260

<210> 84

<211> 1358

<212> DNA

<213> Homo sapiens

<400> 84

```

cctgtttggg acactggact cccgtgagct ggaaggaaca gatttaatat ctaggggctg 60
ggtatcccca catcactcat ttgggggggtc aaggggaccg ggcaatatag tattctgctc 120
agtgtctgga gatcatctac ccaggctggg gcttctggga caggcgagga cccacggacc 180
ctggaagagc tgggtccagg gactgaactc ccggcatctt tacagagcag agcatgatca 240
cattcctgcc gctgctgctg gggctcagcc tgggctgcac aggagcaggt ggcttcgtgg 300
cccatgtgga aagcacctgt ctgttggatg atgctgggac tccaaaggat ttcacatact 360
gcatctcctt caacaaggat ctgctgacct gctgggatcc agaggagaat aagatggccc 420
cttgccaatt tgggtgctg aatagcttgg cgaatgtcct ctacacgcac ctcaaccaa 480
aagacaccct gatgcagcgc ttgcgcaatg ggcttcagaa ttgtgccaca cacaccagc 540
ccttctgggg atcactgacc aacaggacac ggccaccatc tgtgcaagta gccaaaacca 600
ctccttttaa cacgagggag cctgtgatgc tggcctgcta tgtgtggggc ttctatccag 660
cagaagtgac tatcagtgag aggaagaacg ggaagcttgt catgcctcac agcagtgcgc 720
acaagactgc ccagcccaat ggagactgga cataccagac cctctcccat ttagccttaa 780
ccccctctta cggggacact tacacctgtg tggtagagca cattgggggt cctgagccca 840
tccttcggga ctggacacct gggctgtccc ccatgcagac cctgaagggt tctgtgtctg 900
cagtgaactc gggcctgggc ctcatcatct tctctcttgg tgtgatcagc tggcggagag 960
ctggccactc tagttacact cctcttcctg ggtccaatta ttcagaagga tggcacattt 1020
cctagaggca gaatcctaca acttcactc caagttagaa ggagattcaa actcaatgat 1080
gtaaccatgc ctctccaaca tcttcaaccc cctgacatta tcttggatcc tatggtttct 1140
ccatccaatt ctttgaattt ccagctctcc cctatgtaaa acttagcaac ttgggggacc 1200
tcattcctgg gactatgctg taaccaaatt attgtccaag gctatatattc tgggatgaat 1260
ataatctgag gaagggagtt aaagaccctc ctgggggtct cagtgtgcca tagaggacag 1320
caactggtga ttgtttcaga gaaataaact ttggtgga 1358

```

62/80

<210> 85

<211> 263

<212> PRT

<213> Homo sapiens

<400> 85

```

Met Ile Thr Phe Leu Pro Leu Leu Leu Gly Leu Ser Leu Gly Cys Thr
 1           5           10           15

Gly Ala Gly Gly Phe Val Ala His Val Glu Ser Thr Cys Leu Leu Asp
          20           25           30

Asp Ala Gly Thr Pro Lys Asp Phe Thr Tyr Cys Ile Ser Phe Asn Lys
      35           40           45

Asp Leu Leu Thr Cys Trp Asp Pro Glu Glu Asn Lys Met Ala Pro Cys
 50           55           60

Glu Phe Gly Val Leu Asn Ser Leu Ala Asn Val Leu Ser Gln His Leu
 65           70           75           80

Asn Gln Lys Asp Thr Leu Met Gln Arg Leu Arg Asn Gly Leu Gln Asn
          85           90           95

Cys Ala Thr His Thr Gln Pro Phe Trp Gly Ser Leu Thr Asn Arg Thr
          100          105          110

Arg Pro Pro Ser Val Gln Val Ala Lys Thr Thr Pro Phe Asn Thr Arg
      115           120           125

Glu Pro Val Met Leu Ala Cys Tyr Val Trp Gly Phe Tyr Pro Ala Glu
 130           135           140

Val Thr Ile Thr Trp Arg Lys Asn Gly Lys Leu Val Met Pro His Ser
 145           150           155           160

Ser Ala His Lys Thr Ala Gln Pro Asn Gly Asp Trp Thr Tyr Gln Thr
          165          170          175

Leu Ser His Leu Ala Leu Thr Pro Ser Tyr Gly Asp Thr Tyr Thr Cys
      180           185           190

Val Val Glu His Ile Gly Ala Pro Glu Pro Ile Leu Arg Asp Trp Thr
      195           200           205

Pro Gly Leu Ser Pro Met Gln Thr Leu Lys Val Ser Val Ser Ala Val
      210           215           220

Thr Leu Gly Leu Gly Leu Ile Ile Phe Ser Leu Gly Val Ile Ser Trp
 225           230           235           240

Arg Arg Ala Gly His Ser Ser Tyr Thr Pro Leu Pro Gly Ser Asn Tyr
          245           250           255

Ser Glu Gly Trp His Ile Ser
      260

```

63/80

<210> 86
 <211> 2055
 <212> DNA
 <213> Homo sapiens

<400> 86
 atttgattaa agcaccagag tgtaatggcc ctcagagcag ggctggctct ggggttccac 60
 accctgatga ccctcctgag cccgcaggag gcagggggcca ccaaggctga ccacatgggc 120
 tcctacggac ccgccttcta ccagtcttac ggcgcctcgg gccagttcac ccatgaattt 180
 gatgaggaac agctgttctc tgtggacctg aagaaaagcg aggccgtgtg gcgtctgcct 240
 gagtttggcg actttgcccg ctttgacctg cagggcgggc tggccggcat cgccgcaatc 300
 aaagcccatc tggacatcct ggtggagcgc tccaaccgca gcagagccat caacgtgcct 360
 ccacgggtga ccgtgctccc caaatctcgg gtggagctgg gccagcccaa catcctcatc 420
 tgcatacgtg acaacatctt cccccctgtg atcaatatca cctggctgag caacggccaa 480
 actgtcactg agggagtgag ccagaccagc ttctattccc agcctgacca tttgttccgc 540
 aagttccact acctgcccct cgtgccctca gccgaggacg tctatgactg ccaggtggag 600
 cactggggcc tggatgcgac actcctcagg cattgggagc tccaggtgcc tattccacca 660
 ccagatgcca tggagaccct ggtctgtgcc ctgggcctgg ccacggcctt ggtgggcttc 720
 ctctgaggca ccgtcctcat catcatgggc acatatgtgt ccagtgtccc caggtaatga 780
 tccttctgag agaaatgact tgtgggagac accctgcaga tcctcatggg tttgtgacag 840
 ccctgcgtg ctacgtgccc ttttaagtga tcccgtgtg ctgactttga gtgggatcaa 900
 catctgtcct acgggtcccc tcttttttgg ccccgattat catggcaggg tttgttgagc 960
 acctactagc ttcccttccc attcaacaca cacacacatt ctgtctctac ccaaagctct 1020
 ggctggcagc actaaatgct ttggtggtgt ttgactgtg tcctttccag gccttgcca 1080
 gttcttccag gggtagagca tgtgtgtgctg gggattggca gccatcctgg ggccacaca 1140
 ggtgtgtctt gctccatttg gccattgtgt tgttaactttg tgaatgagcc atttcacatg 1200
 gacttcatga aatttgccctc ctgagttcag gtttaccctg aaagggatgc agattatcct 1260
 gttcctcacg acccctcag ctaacaacag ttctgaaggg tgctgggaca ggacaggctc 1320
 atggggactc cactcctgcc tgggtttact ctgtatgaag aggcactgg tatcctgcca 1380
 tgatgttatc tcctttttct acttttccct agagtcccat gcatgataaa gagaggccca 1440
 aggcttggat aaggtagcca ctccctcag tggagtcagt catgttaggt aggaggtggt 1500
 agagtcggtc tgcaggtat ctgtaagag gggagggtcca ctagacaca ctctaaatat 1560
 gtggcctaga agattttggt ctacttttct gtgaacagaa tttaaaacat acaaagagat 1620
 aaatcaccat accacatagt ttatgtcagg accaaaatga gcaatacaga ttacggtttt 1680
 caaaccagaa tgcacataag aactgcttgg gatcctttta aaagtacagg cattggcctg 1740
 gtgcagtggc tcattcctgt aatcccagca ctttgggagg ccaaggggac aggactgctt 1800
 gagggcaaga ggtggaacc atcttgggct acatagagag acccatctc tacaaagaaa 1860
 gatttaaaaa ttaaccagcc atgggtggct gcacctgtat tcccagccac tggggaggct 1920
 gagggcggag gagtgcctga gccaggagt tcaaggctgc agtgagccaa gattgcgcca 1980
 ctgcactcca gcctagggtga cagagtgaga ccctgtctct aaataataa ataaataaat 2040
 aaaaaaaaaa aaaaaa 2055

<210> 87
 <211> 250
 <212> PRT
 <213> Homo sapiens

<400> 87
 Met Ala Leu Arg Ala Gly Leu Val Leu Gly Phe His Thr Leu Met Thr
 1 5 10 15
 Leu Leu Ser Pro Gln Glu Ala Gly Ala Thr Lys Ala Asp His Met Gly
 20 25 30
 Ser Tyr Gly Pro Ala Phe Tyr Gln Ser Tyr Gly Ala Ser Gly Gln Phe
 35 40 45

64/80

Thr His Glu Phe Asp Glu Glu Gln Leu Phe Ser Val Asp Leu Lys Lys
 50 55 60

Ser Glu Ala Val Trp Arg Leu Pro Glu Phe Gly Asp Phe Ala Arg Phe
 65 70 75 80

Asp Pro Gln Gly Gly Leu Ala Gly Ile Ala Ala Ile Lys Ala His Leu
 85 90 95

Asp Ile Leu Val Glu Arg Ser Asn Arg Ser Arg Ala Ile Asn Val Pro
 100 105 110

Pro Arg Val Thr Val Leu Pro Lys Ser Arg Val Glu Leu Gly Gln Pro
 115 120 125

Asn Ile Leu Ile Cys Ile Val Asp Asn Ile Phe Pro Pro Val Ile Asn
 130 135 140

Ile Thr Trp Leu Arg Asn Gly Gln Thr Val Thr Glu Gly Val Ala Gln
 145 150 155 160

Thr Ser Phe Tyr Ser Gln Pro Asp His Leu Phe Arg Lys Phe His Tyr
 165 170 175

Leu Pro Phe Val Pro Ser Ala Glu Asp Val Tyr Asp Cys Gln Val Glu
 180 185 190

His Trp Gly Leu Asp Ala Pro Leu Leu Arg His Trp Glu Leu Gln Val
 195 200 205

Pro Ile Pro Pro Pro Asp Ala Met Glu Thr Leu Val Cys Ala Leu Gly
 210 215 220

Leu Ala Ile Gly Leu Val Gly Phe Leu Val Gly Thr Val Leu Ile Ile
 225 230 235 240

Met Gly Thr Tyr Val Ser Ser Val Pro Arg
 245 250

<210> 88

<211> 1322

<212> DNA

<213> Homo sapiens

<400> 88

aactcattct gaagaggetg acgattttac tgtctcattt ttttcctttc tccagaatgg 60
 gttctgggtg ggtcccctgg gtggtggctc tgctagtga tctgacccga ctggattcct 120
 ccatgactca aggcacagac tctccagaag attttgtgat tcaggcaaag gctgactgtt 180
 acttcaccaa cgggacagaa aaggtgcagt ttgtggtcag attcatcttt aacttgagg 240
 agtatgtacg tttcgacagt gatgtgggga tggttgtggc attgaccaag ctggggcagc 300
 cagatgctga gcagtggaa acgcggctgg atctcttga gaggagcaga caggccgtgg 360
 atgggggtctg tagacacaac tacaggctgg gcgcaccctt cactgtgggg agaaaagtgc 420
 aaccagaggt gacagtgtac ccagagagga cccactcct gcaccagcat aatctgctgc 480
 actgctctgt gacaggcttc tatccagggg atatcaagat caagtgggtc ctgaatgggc 540
 aggaggagag agctggggtc atgtccactg gccctatcag gaatggagac tggacctttc 600
 agactgtggt gatgctagaa atgactcctg aacttggaca tgtctacacc tgccttgtcg 660
 atcactccag cctgctgagc cctgtttctg tggagtggag agctcagtct gaattattct 720
 ggagaaagat gctgagtggc attgcagcct tctacttgg gctaattctt cttctggtgg 780

65/80

```

gaatcgtcac ccagctaagg gctcagaaaag gatatgtgag gacgcagatg tctggtaaatg 840
aggtctcaag agctgttctg ctccctcagt catgctaagg tcctcactga agcttctctc 900
tctggagcct gaagtagtga tgagtagtct gggccctggg tgaggtaaag gacattcatg 960
aggtcaatgt tctgggaata actctcttcc ctgacccctg gaggagcccg aactgattct 1020
ggagctctgt gttctgagat catgcatctc ccacccatct gcccttctcc cttctacgtg 1080
tacatcatta atccccattg ccaagggcat tgtccagaaa ctccccctgag accttactcc 1140
ttccagcccc aaatcattta cttttctgtg gtccagccct actcctataa gtcattgatct 1200
ccaaagcttt ctgtcttcca actgcagtct ccacagtctt cagaagacaa atgctcaggt 1260
agtcactgtt tcctttttcac tgttttttaa aaccttttat tgtcaaataa aatggagata 1320
ca 1322

```

<210> 89

<211> 273

<212> PRT

<213> Homo sapiens

<400> 89

```

Met Gly Ser Gly Trp Val Pro Trp Val Val Ala Leu Leu Val Asn Leu
  1             5             10             15

Thr Arg Leu Asp Ser Ser Met Thr Gln Gly Thr Asp Ser Pro Glu Asp
 20             25             30

Phe Val Ile Gln Ala Lys Ala Asp Cys Tyr Phe Thr Asn Gly Thr Glu
 35             40             45

Lys Val Gln Phe Val Val Arg Phe Ile Phe Asn Leu Glu Glu Tyr Val
 50             55             60

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

Gln Pro Asp Ala Glu Gln Trp Asn Ser Arg Leu Asp Leu Leu Glu Arg
 85             90             95

Ser Arg Gln Ala Val Asp Gly Val Cys Arg His Asn Tyr Arg Leu Gly
100            105            110

Ala Pro Phe Thr Val Gly Arg Lys Val Gln Pro Glu Val Thr Val Tyr
115            120            125

Pro Glu Arg Thr Pro Leu Leu His Gln His Asn Leu Leu His Cys Ser
130            135            140

Val Thr Gly Phe Tyr Pro Gly Asp Ile Lys Ile Lys Trp Phe Leu Asn
145            150            155            160

Gly Gln Glu Glu Arg Ala Gly Val Met Ser Thr Gly Pro Ile Arg Asn
165            170            175

Gly Asp Trp Thr Phe Gln Thr Val Val Met Leu Glu Met Thr Pro Glu
180            185            190

Leu Gly His Val Tyr Thr Cys Leu Val Asp His Ser Ser Leu Leu Ser
195            200            205

Pro Val Ser Val Glu Trp Arg Ala Gln Ser Glu Tyr Ser Trp Arg Lys
210            215            220

```

66/80

Met Leu Ser Gly Ile Ala Ala Phe Leu Leu Gly Leu Ile Phe Leu Leu
225 230 235 240

Val Gly Ile Val Ile Gln Leu Arg Ala Gln Lys Gly Tyr Val Arg Thr
245 250 255

Gln Met Ser Gly Asn Glu Val Ser Arg Ala Val Leu Leu Pro Gln Ser
260 265 270

Cys

<210> 90

<211> 1237

<212> DNA

<213> Homo sapiens

<400> 90

```

attcttgtct gttctgcctc actcccgagc tctactgact cccaaaagag cgcccaagaa 60
gaaaatggcc ataagtggag tccctgtgct aggatttttc atcatagctg tgcctgatgag 120
cgctcaggaa tcatgggcta tcaaagaaga acatgtgatc atccaggccg agttctatct 180
gaatcctgac caatcaggcg agtttatgtt tgactttgat ggtgatgaga ttttccatgt 240
ggatatggca aagaaggaga cggctctggcg gcttgaagaa tttggacgat ttgccagctt 300
tgaggctcaa ggtgcattgg ccaacatagc tgtggacaaa gccaacctgg aaatcatgac 360
aaagcgctcc aactatactc cgatcaccaa tgtacctcca gaggtaactg tgcctacgaa 420
cagccctgtg gaactgagag agcccaacgt cctcatctgt ttcactgaca agttcacccc 480
accagtggtc aatgtcacgt ggcttcgaaa tggaaaacct gtcaccacag gagtgtcaga 540
gacagtcttc ctgcccaggg aagaccacct tttccgcaag ttccactatc tccccttctc 600
gccctcaact gaggacgttt acgactgcag ggtggagcac tggggccttg atgagcctct 660
tctcaagcac tgggagtttg atgctccaag ccctctccca gagactacag agaacgtggt 720
gtgtgccttg ggcctgactg tgggtctggt gggcatcatt attgggacca tcttcatcat 780
caagggagtg cgcaaaagca atgcagcaga acgcaggggg cctctgtaag gcacatggag 840
gtgatgatgt ttcttagaga gaagatcact gaagaaactt ctgctttaat gactttacaa 900
agctggcaat attacaatcc ttgacctcag tgaaagcagt catcttcagc gttttccagc 960
cctatagcca ccccaagtgt ggttatgcct cctcgattgc tccgtactct aacatctagc 1020
tggttttccc tgtctattgc cttttcctgt atctattttc ctctatttcc tatcatttta 1080
ttatcaccat gcaatgcctc tggaataaaa catacaggag tctgtctctg ctatgggaatg 1140
ccccatgggg ctctcttctg tacttattgt ttaaggtttc ctcaaactgt gatttttctg 1200
aacacaataa actattttga tgatcttggg tggaaaa 1237

```

<210> 91

<211> 254

<212> PRT

<213> Homo sapiens

<400> 91

Met Ala Ile Ser Gly Val Pro Val Leu Gly Phe Phe Ile Ile Ala Val
1 5 10 15

Leu Met Ser Ala Gln Glu Ser Trp Ala Ile Lys Glu Glu His Val Ile
20 25 30

Ile Gln Ala Glu Phe Tyr Leu Asn Pro Asp Gln Ser Gly Glu Phe Met
35 40 45

Phe Asp Phe Asp Gly Asp Glu Ile Phe His Val Asp Met Ala Lys Lys
50 55 60

67/80

Glu Thr Val Trp Arg Leu Glu Glu Phe Gly Arg Phe Ala Ser Phe Glu
 65 70 75 80
 Ala Gln Gly Ala Leu Ala Asn Ile Ala Val Asp Lys Ala Asn Leu Glu
 85 90 95
 Ile Met Thr Lys Arg Ser Asn Tyr Thr Pro Ile Thr Asn Val Pro Pro
 100 105 110
 Glu Val Thr Val Leu Thr Asn Ser Pro Val Glu Leu Arg Glu Pro Asn
 115 120 125
 Val Leu Ile Cys Phe Ile Asp Lys Phe Thr Pro Pro Val Val Asn Val
 130 135 140
 Thr Trp Leu Arg Asn Gly Lys Pro Val Thr Thr Gly Val Ser Glu Thr
 145 150 155 160
 Val Phe Leu Pro Arg Glu Asp His Leu Phe Arg Lys Phe His Tyr Leu
 165 170 175
 Pro Phe Leu Pro Ser Thr Glu Asp Val Tyr Asp Cys Arg Val Glu His
 180 185 190
 Trp Gly Leu Asp Glu Pro Leu Leu Lys His Trp Glu Phe Asp Ala Pro
 195 200 205
 Ser Pro Leu Pro Glu Thr Thr Glu Asn Val Val Cys Ala Leu Gly Leu
 210 215 220
 Thr Val Gly Leu Val Gly Ile Ile Ile Gly Thr Ile Phe Ile Ile Lys
 225 230 235 240
 Gly Val Arg Lys Ser Asn Ala Ala Glu Arg Arg Gly Pro Leu
 245 250

<210> 92

<211> 1157

<212> DNA

<213> Homo sapiens

<400> 92

gctcacagtc atcaattata gacccacaaa catgcgccct gaagacagaa tgttccatat 60
 cagagctgtg atcttgagag ccctctcctt ggctttcctg ctgagtctcc gaggagctgg 120
 ggccatcaag gcggaccatg tgtcaactta tgccgcggtt gtacagacgc atagaccaac 180
 aggggagttt atgtttgaat ttgatgaaga tgagatgttc tatgtggatc tggacaagaa 240
 ggagaccgtc tggcatctgg aggagtttgg ccaagccttt tcctttgagg ctgagggcgg 300
 gctggctaac attgctatat tgaacaacaa cttgaatacc ttgatccagc gttccaacca 360
 cactcaggcc accaacgatc cccctgaggt gaccgtgttt cccaaggagc ctgtggagct 420
 gggccagccc aacaccctca tctgccacat tgacaagtgc ttcccaccag tgctcaacgt 480
 cacgtggctg tgcaacgggg agctgggtcac tgaggggtgtc gctgagagcc tcttcctgcc 540
 cagaacagat tacagcttcc acaagtccca ttacctgacc tttgtgccct cagcagagga 600
 cttctatgac tgcagggtgg agcactgggg cttggaccag ccgctcctca agcactggga 660
 ggcccaagag ccaatccaga tgcctgagac aacggagact gtgctctgtg ccctgggcct 720
 ggtgctgggc ctagtgcgga tcatcgtggg caccgtcctc atcataaagt ctctgcgttc 780
 tggccatgac ccccgggccc aggggacct gtgaaatact gtaaagggtg caaaatatct 840
 gaacagaaga ggacttagga gagatctgaa ctccagctgc cctacaaact ccatctcagc 900

68/80

```

ttttcttctc acttcatgtg aaaactactc cagtggctga ctgaattgct gacccttcaa 960
gctctgtcct tatccattac ctcaaagcag tcattcctta gtaaagtttc caacaaatag 1020
aaattaatga cactttggta gcactaatat ggagattatc ctttcattga gccttttatc 1080
ctctgttctc ctttgaagaa cccctcactg tcaccttccc gagaataccc taagaccaat 1140
aaataacttca gtatttcc                                     1157

```

<210> 93

<211> 260

<212> PRT

<213> Homo sapiens

<400> 93

```

Met Arg Pro Glu Asp Arg Met Phe His Ile Arg Ala Val Ile Leu Arg
 1             5             10             15

```

```

Ala Leu Ser Leu Ala Phe Leu Leu Ser Leu Arg Gly Ala Gly Ala Ile
      20             25             30

```

```

Lys Ala Asp His Val Ser Thr Tyr Ala Ala Phe Val Gln Thr His Arg
      35             40             45

```

```

Pro Thr Gly Glu Phe Met Phe Glu Phe Asp Glu Asp Glu Met Phe Tyr
      50             55             60

```

```

Val Asp Leu Asp Lys Lys Glu Thr Val Trp His Leu Glu Glu Phe Gly
      65             70             75             80

```

```

Gln Ala Phe Ser Phe Glu Ala Gln Gly Gly Leu Ala Asn Ile Ala Ile
      85             90             95

```

```

Leu Asn Asn Asn Leu Asn Thr Leu Ile Gln Arg Ser Asn His Thr Gln
      100            105            110

```

```

Ala Thr Asn Asp Pro Pro Glu Val Thr Val Phe Pro Lys Glu Pro Val
      115            120            125

```

```

Glu Leu Gly Gln Pro Asn Thr Leu Ile Cys His Ile Asp Lys Phe Phe
      130            135            140

```

```

Pro Pro Val Leu Asn Val Thr Trp Leu Cys Asn Gly Glu Leu Val Thr
      145            150            155            160

```

```

Glu Gly Val Ala Glu Ser Leu Phe Leu Pro Arg Thr Asp Tyr Ser Phe
      165            170            175

```

```

His Lys Phe His Tyr Leu Thr Phe Val Pro Ser Ala Glu Asp Phe Tyr
      180            185            190

```

```

Asp Cys Arg Val Glu His Trp Gly Leu Asp Gln Pro Leu Leu Lys His
      195            200            205

```

```

Trp Glu Ala Gln Glu Pro Ile Gln Met Pro Glu Thr Thr Glu Thr Val
      210            215            220

```

```

Leu Cys Ala Leu Gly Leu Val Leu Gly Leu Val Gly Ile Ile Val Gly
      225            230            235            240

```

69/80

Thr Val Leu Ile Ile Lys Ser Leu Arg Ser Gly His Asp Pro Arg Ala
 245 250 255

Gln Gly Thr Leu
 260

<210> 94

<211> 3091

<212> DNA

<213> Homo sapiens

<400> 94

```

gggagaccca agcttctaga gatccctcga cctcgagatc cattgtgctc taaagagcgg 60
accccagcct ctgccagggt cgggtccgcc tccctcgtccc gtccctccgcc ggccctcgcc 120
ccgcgcccag ggatcctcca gctcctttcg cccgcgccct ccgttcgctc cggacaccat 180
ggacaagttt tgggtggcacg cagcctgggg actctgcctc gtgccgctga gcctggcgca 240
gatcgatttg aatataacct gccgctttgc aggtgtattc cacgtggaga aaaatggtcg 300
ctacagcatc tctcggacgg aggcgctga cctctgcaag gctttcaata gcacctgcc 360
cacaatggcc cagatggaga aagctctgag catcggattt gagacctgca ggtatgggtt 420
catagaaggg catgtggtga ttccccggat ccaccccaac tccatctgtg cagcaaaca 480
cacaggggtg tacatcctca catacaacac ctcccagtat gacacatatt gcttcaatgc 540
ttcagctcca cctgaagaag attgtacatc agtcacagac ctgccaatg cctttgatgg 600
accaattacc ataactattg ttaaccgtga tggcaccgcg tatgtccaga aaggagaata 660
cagaacgaat cctgaagaca tctacccag caacctact gatgatgacg tgagcagcg 720
ctcctccagt gaaaggagca gcacttcagg aggttacatc ttttacacct tttctactgt 780
acaccccatc ccagacgaag acagtccctg gatcacgac agcacagaca gaatccctgc 840
taccactttg atgagcacta gtgctacagc aactgagaca gcaaccaaga ggcaagaagc 900
ctgggatttg ttttcatggt tgtttctacc atcagagtca aagaatcatc ttcacacaac 960
aacacaaatg gctggtacgt ctcaaatac catctcagca ggctgggagc caaatgaaga 1020
aatgaagat gaaagagaca gacacctcag tttttctgga tcaggcattg atgatgatga 1080
agatttttat tccagcacca tttcaaccac accacgggcc tttgaccaca caaaacagaa 1140
ccaggactgg acccagtgga acccaagcca ttcaaattcg gaagtgtctac ttcagacaac 1200
cacaaggatg actgatgtag acagaaatgg caccactgct tatgaaggaa actggaaccc 1260
agaagcacac cctcccctca ttcaccatga gcatcatgag gaagaagaga cccacattc 1320
tacaagcaca atccaggcaa ctctagtag tacaacggaa gaaacagcta ccagaagga 1380
acagtggttt ggcaacagat ggcattgagg atatcgccaa acacccagag aagactcca 1440
ttcgacaaca gggacagctg cagcctcagc tcataccagc catccaatgc aaggaaggac 1500
aacaccaagc ccagaggaca gttcctggac tgatttcttc aacccaatct cacaccccat 1560
gggacgaggt catcaagcag gaagaaggat ggatatggac tccagtcata gtacaacgct 1620
tcagcctact gcaaatccaa acacagggtt ggtggaaaaat ttggacagga caggacctct 1680
ttcaatgaca acgcagcaga gtaattctca gagcttctct acatcacatg aaggcttgga 1740
agaagataaa gaccatccaa caacttctac tctgacatca agcaatagga atgatgtcac 1800
aggtggaaga agagacccaa atcattctga aggtcactt actttactgg aaggttatac 1860
ctctcattac ccacacacga aggaaagcag gaccttcac ccagtgaact cagctaagac 1920
tgggtccttt ggagttactg cagttactgt tggagattcc aactctaatt tcaatcgttc 1980
cttatcagga gaccaagaca cattccaccc cagtgggggg tcccatacca ctcatggatc 2040
tgaatcagat ggacactcac atgggagtca agaagggtga gcaaacacaa cctctggtcc 2100
tataaggaca ccccaaattc cagaatggct gatcatcttg gcatccctct tggccttggc 2160
tttgattctt gcagtttgca ttgcagtcaa cagtcgaaga aggtgtgggc agaagaaaaa 2220
gctagtgatc aacagtggca atggagctgt ggaggacaga aagccaagtg gactcaacgg 2280
agaggccagc aagtctcagg aaatgggtga tttgggtgaac aaggagtcgt cagaaactcc 2340
agaccagttt atgacagctg atgagacaag gaacctgcag aatgtggaca tgaagattgg 2400
ggtgtaacac ctacaccatt atcttggaag gaaacaaccg ttggaaacat aaccattaca 2460
gggagctggg acacttaaca gatgcaatgt gctactgatt gtttcattgc gaatcttttt 2520
tagcataaaa ttttctactc tttttgtttt ttgtgttttg ttctttaaag tcaggtccaa 2580
tttgtaaaaa cagcattgct ttgtaaatta gggcccaatt aataatcagc aagaatttga 2640
tcgttcagtt ccacttgagg gccttcatcc tcgggtgtgc tatggatggc ttctaacaaa 2700
aactacacat atgtattcct gatcgccaac ctttcccca ccagctaagg acatttccca 2760

```

70/80

```

gggttaatag ggcctgggtcc ctgggaggaa atttgaatgg gtccattttg cccttccata 2820
gcctaataccc tgggcattgc tttccactga ggttgggggtg tactagttac acatcttcaa 2880
cagacccccct ctagaaattt ttcagatgct tctgggagac accaaagggg gaagctatatt 2940
atctgtagta aactatttat ctgtgttttt gaaatattaa accctggatc agtcctttga 3000
tcagtataat tttttaaagt tactttgtca gaggcacaaa agggttttaa ctgattcata 3060
ataaatatct gtacttcttc gatcttcaaa a 3091

```

<210> 95

<211> 742

<212> PRT

<213> Homo sapiens

<400> 95

```

Met Asp Lys Phe Trp Trp His Ala Ala Trp Gly Leu Cys Leu Val Pro
  1              5              10              15

```

```

Leu Ser Leu Ala Gln Ile Asp Leu Asn Ile Thr Cys Arg Phe Ala Gly
              20              25              30

```

```

Val Phe His Val Glu Lys Asn Gly Arg Tyr Ser Ile Ser Arg Thr Glu
      35              40              45

```

```

Ala Ala Asp Leu Cys Lys Ala Phe Asn Ser Thr Leu Pro Thr Met Ala
      50              55              60

```

```

Gln Met Glu Lys Ala Leu Ser Ile Gly Phe Glu Thr Cys Arg Tyr Gly
      65              70              75              80

```

```

Phe Ile Glu Gly His Val Val Ile Pro Arg Ile His Pro Asn Ser Ile
      85              90              95

```

```

Cys Ala Ala Asn Asn Thr Gly Val Tyr Ile Leu Thr Tyr Asn Thr Ser
      100              105              110

```

```

Gln Tyr Asp Thr Tyr Cys Phe Asn Ala Ser Ala Pro Pro Glu Glu Asp
      115              120              125

```

```

Cys Thr Ser Val Thr Asp Leu Pro Asn Ala Phe Asp Gly Pro Ile Thr
      130              135              140

```

```

Ile Thr Ile Val Asn Arg Asp Gly Thr Arg Tyr Val Gln Lys Gly Glu
      145              150              155              160

```

```

Tyr Arg Thr Asn Pro Glu Asp Ile Tyr Pro Ser Asn Pro Thr Asp Asp
      165              170              175

```

```

Asp Val Ser Ser Gly Ser Ser Ser Glu Arg Ser Ser Thr Ser Gly Gly
      180              185              190

```

```

Tyr Ile Phe Tyr Thr Phe Ser Thr Val His Pro Ile Pro Asp Glu Asp
      195              200              205

```

```

Ser Pro Trp Ile Thr Asp Ser Thr Asp Arg Ile Pro Ala Thr Thr Leu
      210              215              220

```

```

Met Ser Thr Ser Ala Thr Ala Thr Glu Thr Ala Thr Lys Arg Gln Glu
      225              230              235              240

```

71/80

Ala Trp Asp Trp Phe Ser Trp Leu Phe Leu Pro Ser Glu Ser Lys Asn
 245 250 255
 His Leu His Thr Thr Thr Gln Met Ala Gly Thr Ser Ser Asn Thr Ile
 260 265 270
 Ser Ala Gly Trp Glu Pro Asn Glu Glu Asn Glu Asp Glu Arg Asp Arg
 275 280 285
 His Leu Ser Phe Ser Gly Ser Gly Ile Asp Asp Asp Glu Asp Phe Ile
 290 295 300
 Ser Ser Thr Ile Ser Thr Thr Pro Arg Ala Phe Asp His Thr Lys Gln
 305 310 315 320
 Asn Gln Asp Trp Thr Gln Trp Asn Pro Ser His Ser Asn Pro Glu Val
 325 330 335
 Leu Leu Gln Thr Thr Thr Arg Met Thr Asp Val Asp Arg Asn Gly Thr
 340 345 350
 Thr Ala Tyr Glu Gly Asn Trp Asn Pro Glu Ala His Pro Pro Leu Ile
 355 360 365
 His His Glu His His Glu Glu Glu Glu Thr Pro His Ser Thr Ser Thr
 370 375 380
 Ile Gln Ala Thr Pro Ser Ser Thr Thr Glu Glu Thr Ala Thr Gln Lys
 385 390 395 400
 Glu Gln Trp Phe Gly Asn Arg Trp His Glu Gly Tyr Arg Gln Thr Pro
 405 410 415
 Arg Glu Asp Ser His Ser Thr Thr Gly Thr Ala Ala Ala Ser Ala His
 420 425 430
 Thr Ser His Pro Met Gln Gly Arg Thr Thr Pro Ser Pro Glu Asp Ser
 435 440 445
 Ser Trp Thr Asp Phe Phe Asn Pro Ile Ser His Pro Met Gly Arg Gly
 450 455 460
 His Gln Ala Gly Arg Arg Met Asp Met Asp Ser Ser His Ser Thr Thr
 465 470 475 480
 Leu Gln Pro Thr Ala Asn Pro Asn Thr Gly Leu Val Glu Asn Leu Asp
 485 490 495
 Arg Thr Gly Pro Leu Ser Met Thr Thr Gln Gln Ser Asn Ser Gln Ser
 500 505 510
 Phe Ser Thr Ser His Glu Gly Leu Glu Glu Asp Lys Asp His Pro Thr
 515 520 525
 Thr Ser Thr Leu Thr Ser Ser Asn Arg Asn Asp Val Thr Gly Gly Arg
 530 535 540

72/80

Arg Asp Pro Asn His Ser Glu Gly Ser Thr Thr Leu Leu Glu Gly Tyr
545 550 555 560

Thr Ser His Tyr Pro His Thr Lys Glu Ser Arg Thr Phe Ile Pro Val
565 570 575

Thr Ser Ala Lys Thr Gly Ser Phe Gly Val Thr Ala Val Thr Val Gly
580 585 590

Asp Ser Asn Ser Asn Val Asn Arg Ser Leu Ser Gly Asp Gln Asp Thr
595 600 605

Phe His Pro Ser Gly Gly Ser His Thr Thr His Gly Ser Glu Ser Asp
610 615 620

Gly His Ser His Gly Ser Gln Glu Gly Gly Ala Asn Thr Thr Ser Gly
625 630 635 640

Pro Ile Arg Thr Pro Gln Ile Pro Glu Trp Leu Ile Ile Leu Ala Ser
645 650 655

Leu Leu Ala Leu Ala Leu Ile Leu Ala Val Cys Ile Ala Val Asn Ser
660 665 670

Arg Arg Arg Cys Gly Gln Lys Lys Lys Leu Val Ile Asn Ser Gly Asn
675 680 685

Gly Ala Val Glu Asp Arg Lys Pro Ser Gly Leu Asn Gly Glu Ala Ser
690 695 700

Lys Ser Gln Glu Met Val His Leu Val Asn Lys Glu Ser Ser Glu Thr
705 710 715 720

Pro Asp Gln Phe Met Thr Ala Asp Glu Thr Arg Asn Leu Gln Asn Val
725 730 735

Asp Met Lys Ile Gly Val
740

<210> 96

<211> 1559

<212> DNA

<213> Homo sapiens

<400> 96

```

ggcagcagca gcgcgggcag cagcagcggc agcgacccca ccactgccac atttgccagg 60
aaacaatgct gctagcgaca ttcaagctgt gcgctgggag ctctacaga cacatgcgca 120
acatgaaggg gctgaggcaa caggctgtga tggccatcag ccaggagctg aaccggaggg 180
ccctgggggg ccccaccct agcacgtgga ttaaccaggt tcggcgggcg agctctctac 240
tcggttctcg gctggaagag actctctaca gtgaccagga gctggcctat ctccagcagg 300
gggaggaggc catgcagaag gccttgggca tccttagcaa ccaagagggc tggaagaagg 360
agagtcagca ggacaatggg gacaaagtga tgagtaaagt ggtcccagat gtgggcaagg 420
tggtccggct ggaggtcgtg gtggaccagc ccatggagag gctctatgaa gagctcgtgg 480
agcgcatgga agcaatgggg gagtggaaac ccaatgtcaa ggagatcaag gtcctgcaga 540
agatcggaag agatacatc attactcacg agctggctgc cgaggcagca ggaaacctgg 600
tggggccccc tgactttgtg agcgtgcgct tgccaagcg ccgaggctcc acctgtgtgc 660
tggttggtcat ggccacagac ttcggaaca tgcttgagca gaagggtgtc atcagggcgg 720
agcacggctc cacttgcatg gtgcttcacc cggtggctgg aagtcctctt aagaccaaac 780

```

73/80

```

ttacgtggct actcagcatc gacctcaagg ggtggctgcc caagagcatc atcaaccagg 840
tcctgtccca gaccaggtg gattttgcc accacctgcg caagcgctg gagtcccacc 900
ctgcctctga agccaggtgt tgaagaccag cctgctgttc ccaactgtgc ccagctgcac 960
tggtacacac gctcatcagg agaatcccta ctggaagcct gcaagtctaa gatctccatc 1020
tggtgacagt gggatgggtg ggggttcgtg ttagagtatg acactaggat tcagattggg 1080
gaaagttttt agtaccaaga aaacagggat gaggtccttg gattaaaagg taacttcatt 1140
cactgattag ctatgacatg agggttcagg cccctaaaat aattgtaaaa ctttttttct 1200
gggcccttat gtaccacatc aaaaccatct ttaaaatgct agtggctgat atgggtgtgg 1260
gggatgctaa ccacagggcc tgagaagtct tgctttatgg gctcaagaat gccatgcgct 1320
ggcagtacat gtgcacaaag cagaatctca gagggctctc tgcagccctc tgctcctccc 1380
ggccgctgca cagcaacacc acagaacaag cagcacccca cagtgggtgc cttccagaaa 1440
tatagtccaa gctttctctg tggaaaaaga caaaactcat tagtagacat gtttccctat 1500
tgctttcata ggcaccagtc agaataaaga atcataattc acacaaaaaa aaaaaaaaaa 1559

```

<210> 97

<211> 285

<212> PRT

<213> Homo sapiens

<400> 97

```

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

```

```

Met Arg Asn Met Lys Gly Leu Arg Gln Gln Ala Val Met Ala Ile Ser
      20                      25                      30

```

```

Gln Glu Leu Asn Arg Arg Ala Leu Gly Gly Pro Thr Pro Ser Thr Trp
    35                      40                      45

```

```

Ile Asn Gln Val Arg Arg Arg Ser Ser Leu Leu Gly Ser Arg Leu Glu
    50                      55                      60

```

```

Glu Thr Leu Tyr Ser Asp Gln Glu Leu Ala Tyr Leu Gln Gln Gly Glu
    65                      70                      75                      80

```

```

Glu Ala Met Gln Lys Ala Leu Gly Ile Leu Ser Asn Gln Glu Gly Trp
      85                      90                      95

```

```

Lys Lys Glu Ser Gln Gln Asp Asn Gly Asp Lys Val Met Ser Lys Val
    100                      105                      110

```

```

Val Pro Asp Val Gly Lys Val Phe Arg Leu Glu Val Val Val Asp Gln
    115                      120                      125

```

```

Pro Met Glu Arg Leu Tyr Glu Glu Leu Val Glu Arg Met Glu Ala Met
    130                      135                      140

```

```

Gly Glu Trp Asn Pro Asn Val Lys Glu Ile Lys Val Leu Gln Lys Ile
    145                      150                      155                      160

```

```

Gly Lys Asp Thr Phe Ile Thr His Glu Leu Ala Ala Glu Ala Ala Gly
    165                      170                      175

```

```

Asn Leu Val Gly Pro Arg Asp Phe Val Ser Val Arg Cys Ala Lys Arg
    180                      185                      190

```

```

Arg Gly Ser Thr Cys Val Leu Ala Gly Met Ala Thr Asp Phe Gly Asn
    195                      200                      205

```

74/80

Met Pro Glu Gln Lys Gly Val Ile Arg Ala Glu His Gly Pro Thr Cys
 210 215 220

Met Val Leu His Pro Leu Ala Gly Ser Pro Ser Lys Thr Lys Leu Thr
 225 230 235 240

Trp Leu Leu Ser Ile Asp Leu Lys Gly Trp Leu Pro Lys Ser Ile Ile
 245 250 255

Asn Gln Val Leu Ser Gln Thr Gln Val Asp Phe Ala Asn His Leu Arg
 260 265 270

Lys Arg Leu Glu Ser His Pro Ala Ser Glu Ala Arg Cys
 275 280 285

<210> 98

<211> 4315

<212> DNA

<213> Homo sapiens

<400> 98

```

ggaaattggt cctcgtctga taagacaaca gtggagaaag gacgcatgct gtttcttagg 60
gacacggctg gcttccagat atgaccatgt atttgtggct taaactcttg gcatttggct 120
ttgcctttct ggacacagaa gtatttgtga cagggcaaag cccaacacct tccccactg 180
gattgactac agcaaagatg cccagtgttc cactttcaag tgacccctta cctactcaca 240
ccactgcatt ctcacccgca agcacctttg aaagagaaaa tgacttctca gagaccacaa 300
cttctcttag tccagacaat acttccaccc aagtatcccc ggactctttg gataatgcta 360
gtgcttttaa taccacaggt gtttcatcag tacagacgcc tcaccttccc acgcacgcag 420
actcgcagac gccctctgct ggaactgaca cgcagacatt cagcggctcc gccgccaatg 480
caaaaactcaa ccctacccca ggcagcaatg ctatctcaga tgtcccagga gagaggagta 540
cagccagcac ctttcttaca gaccagttt ccccatgtac aaccaccctc agccttgcac 600
accacagctc tgctgcctta cctgcacgca cctccaacac caccatcaca gcgaacacct 660
cagatgccta ccttaatgcc tctgaaacaa cactctgag cccttctgga agcgtgttca 720
tttcaaccac aacaatagct actactccat ctaagccaac atgtgatgaa aaatatgcaa 780
acatcactgt ggattactta tataacaagg aaactaaatt atttacagca aagctaaatg 840
ttaatgagaa tgtggaatgt ggaaacaata cttgcacaaa caatgagggtg cataacctta 900
cagaatgtaa caatgcgtct gtttccatat atgtactgct cctgataaga 960
cattaatatt agatgtgcca ccaggggttg aaaagtttca gttacatgat tgtacacaag 1020
ttgaaaaagc agatactact atttgtttaa aatggaaaaa tattgaaacc tttacttgtg 1080
atacacagaa tattacctac agatttcagt gtggtaatat gatatttgat aataaagaaa 1140
ttaaattaga aaaccttgaa cccgaacatg agtataagtg tgactcagaa atactctata 1200
ataaccacaa gtttactaac gcaagtaaaa ttattaaaac agattttggg agtccaggag 1260
agcctcagat tattttttgt agaagtgaag ctgcacatca aggagtaatt acctggaatc 1320
cccctcaaag atcattttcat aattttaccc tctgttatat aaaagagaca gaaaaagatt 1380
gcctcaatct ggataaaaac ctgatcaaat atgatttgca aaatttaaaa cttatacaga 1440
aatatgtttt atcattacat gctacatca ttgcaaaagt gcaacgtaat ggaagtgtctg 1500
caatgtgtca tttcacaact aaaagtgtct ctccaagcca ggtctggaac atgactgtct 1560
ccatgacatc agataatagt atgcatgtca agtgtaggcc tcccagggac cgtaatggcc 1620
ccatgaacg ttaccatttg gaagttgaag ctggaaatac tctggttaga aatgagtcgc 1680
ataagaattg cgatttccgt gtaaaagatc ttcaatatcc aacagactac acttttaagg 1740
cctattttca caatggagac tatcctggag aaccctttat ttacatcat tcaacatctt 1800
ataattctaa ggactgata gcatttcttg catttctgat tattgtgaca tcaatagccc 1860
tgcttgttgt tctctacaaa atctatgatc tacataagaa aagatcctgc aatttagatg 1920
aacagcagga gcttgttgaa agggatgatg aaaaacaact gatgaatgtg gagccaatcc 1980
atgcagatat tttgttgtaa acttataaga ggaagattgc tgatgaagga agaccttttc 2040
tggctgaatt tcagagcatc ccgcggtgtg tcagcaagtt tcctataaag gaagctcgaa 2100

```

75/80

```

agccctttaa ccagaataaa aaccgttatg ttgacattct tccttatgat tataaccgtg 2160
ttgaactctc tgagataaac ggagatgcag ggtcaaacta cataaatgcc agctatatattg 2220
atggtttcaa agaaccagg aaatacattg ctgcacaagg tcccagggat gaaactgttg 2280
atgatttctg gaggatgatt tgggaacaga aagccacagt tattgtcatg gtcactcgat 2340
gtgaagaagg aaacaggaac aagtgtgcag aatactggcc gtcaatggaa gagggcactc 2400
gggcttttgg agatgttggt gtaaaagatca accagcacia aagatgtcca gattacatca 2460
ttcagaaatt gaacattgta aataaaaaag aaaaagcaac tggaagagag gtgactcaca 2520
ttcagttcac cagctggcca gaccacgggg tgccctgagga tcctcacttg ctccctcaaac 2580
tgagaaggag agtgaatgcc ttcagcaatt tcttcagtgg tcccattgtg gtgcactgca 2640
gtgctggtgt tgggctgcaca ggaacctata tcggaattga tgccatgcta gaaggcttg 2700
aagccgagaa caaagtggat gtttatgggt atgttgtcaa gctaaggcga cagagatgcc 2760
tgatggttca agtagaggcc cagtacatct tgatccatca ggctttggtg gaatacaatc 2820
agtttgagaa aacagaagtg aatttgtctg aattacatcc atatctacat aacatgaaga 2880
aaagggatcc acccagtgag ccgtctccac tagaggctga attccagaga ctcccttcat 2940
ataggagctg gaggacacag cacattggaa atcaagaaga aaataaaagt aaaaacagga 3000
attctaattg catcccata gactataaca gactgccact taaacatgag ctggaaatga 3060
gtaaaagagag tgagcatgat tcagatgaat cctctgatga tgacagtgat tcagaggaac 3120
caagcaataa catcaatgca tcttttataa tgagctactg gaaacctgaa gtgatgattg 3180
ctgctcaggg accactgaag gagaccattg gtgacttttg gcagatgatc ttccaaagaa 3240
aagtcaaaag tattgttatg ctgacagaac tgaacatgg agaccaggaa atctgtgctc 3300
agtactgggg agaaggaaag caaacatatg gagatattga agttgacctg aaagacacag 3360
acaaatcttc aacttatacc cttcgtgtct ttgaaactgag acattccaag aggaaagact 3420
ctcgaactgt gtaccagtac caatatacaa actggagtggt ggagcagctt cctgcagaac 3480
ccaagggaatt aatctctatg attcaggctg tcaaacaata acttcccag aagaattcct 3540
ctgaagggaa caagcatcac aagagtacac ctctactcat tcactgcagg gatggatctc 3600
agcaaacggg aatattttgt gctttgttaa atctcttaga aagtgcggaa acagaagagg 3660
tagtggatat ttttcaagtg gtaaaagctc tacgcaaagc taggctaggc atggtttcca 3720
cattcgagca atatcaattc ctatatgacg tcattgccag cacctacctt gctcagaatg 3780
gacaagtaaa gaaaaacaac catcaagaag ataaaattga atttgataat gaagtggaca 3840
aagtaaagca ggatgcta at tgtgttaatc cacttggtgc cccagaaaag ctccctgaag 3900
caaaggaaca ggctgaagg tctgaaccac cgagtggcac tgaggggcca gaacattctg 3960
tcaatgggtcc tgcaagtcca gcttttaatc aagggttcata ggaaaagaca taaatgagga 4020
aactccaaac ctctgttag ctgttatttc tatttttgta gaagtaggaa gtgaaaatag 4080
gtatacagtg gattaattaa atgcagcgaa ccaatatttg tagaagggtt atattttact 4140
actgtggaaa aatattttaag atagttttgc cagaacagtt tgtacagacg tatgcttatt 4200
ttaaaatttt atctcttatt cagtaaaaaa caacttcttt gtaatcgta tgagtgtata 4260
tgtatgtgtg tatgggtgtg tgtttgtgtg agagacagag aaagagagag aattc 4315

```

<210> 99

<211> 1304

<212> PRT

<213> Homo sapiens

<400> 99

```

Met Tyr Leu Trp Leu Lys Leu Leu Ala Phe Gly Phe Ala Phe Leu Asp
  1             5             10             15

```

```

Thr Glu Val Phe Val Thr Gly Gln Ser Pro Thr Pro Ser Pro Thr Gly
          20             25             30

```

```

Leu Thr Thr Ala Lys Met Pro Ser Val Pro Leu Ser Ser Asp Pro Leu
      35             40             45

```

```

Pro Thr His Thr Thr Ala Phe Ser Pro Ala Ser Thr Phe Glu Arg Glu
      50             55             60

```

```

Asn Asp Phe Ser Glu Thr Thr Thr Ser Leu Ser Pro Asp Asn Thr Ser
      65             70             75             80

```

76/80

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

77/80

Thr Asp Phe Gly Ser Pro Gly Glu Pro Gln Ile Ile Phe Cys Arg Ser
 385 390 395 400
 Glu Ala Ala His Gln Gly Val Ile Thr Trp Asn Pro Pro Gln Arg Ser
 405 410 415
 Phe His Asn Phe Thr Leu Cys Tyr Ile Lys Glu Thr Glu Lys Asp Cys
 420 425 430
 Leu Asn Leu Asp Lys Asn Leu Ile Lys Tyr Asp Leu Gln Asn Leu Lys
 435 440 445
 Pro Tyr Thr Lys Tyr Val Leu Ser Leu His Ala Tyr Ile Ile Ala Lys
 450 455 460
 Val Gln Arg Asn Gly Ser Ala Ala Met Cys His Phe Thr Thr Lys Ser
 465 470 475 480
 Ala Pro Pro Ser Gln Val Trp Asn Met Thr Val Ser Met Thr Ser Asp
 485 490 495
 Asn Ser Met His Val Lys Cys Arg Pro Pro Arg Asp Arg Asn Gly Pro
 500 505 510
 His Glu Arg Tyr His Leu Glu Val Glu Ala Gly Asn Thr Leu Val Arg
 515 520 525
 Asn Glu Ser His Lys Asn Cys Asp Phe Arg Val Lys Asp Leu Gln Tyr
 530 535 540
 Ser Thr Asp Tyr Thr Phe Lys Ala Tyr Phe His Asn Gly Asp Tyr Pro
 545 550 555 560
 Gly Glu Pro Phe Ile Leu His His Ser Thr Ser Tyr Asn Ser Lys Ala
 565 570 575
 Leu Ile Ala Phe Leu Ala Phe Leu Ile Ile Val Thr Ser Ile Ala Leu
 580 585 590
 Leu Val Val Leu Tyr Lys Ile Tyr Asp Leu His Lys Lys Arg Ser Cys
 595 600 605
 Asn Leu Asp Glu Gln Gln Glu Leu Val Glu Arg Asp Asp Glu Lys Gln
 610 615 620
 Leu Met Asn Val Glu Pro Ile His Ala Asp Ile Leu Leu Glu Thr Tyr
 625 630 635 640
 Lys Arg Lys Ile Ala Asp Glu Gly Arg Pro Phe Leu Ala Glu Phe Gln
 645 650 655
 Ser Ile Pro Arg Val Phe Ser Lys Phe Pro Ile Lys Glu Ala Arg Lys
 660 665 670
 Pro Phe Asn Gln Asn Lys Asn Arg Tyr Val Asp Ile Leu Pro Tyr Asp
 675 680 685

78/80

Tyr	Asn	Arg	Val	Glu	Leu	Ser	Glu	Ile	Asn	Gly	Asp	Ala	Gly	Ser	Asn	690	695	700	
Tyr	Ile	Asn	Ala	Ser	Tyr	Ile	Asp	Gly	Phe	Lys	Glu	Pro	Arg	Lys	Tyr	705	710	715	720
Ile	Ala	Ala	Gln	Gly	Pro	Arg	Asp	Glu	Thr	Val	Asp	Asp	Phe	Trp	Arg	725	730	735	
Met	Ile	Trp	Glu	Gln	Lys	Ala	Thr	Val	Ile	Val	Met	Val	Thr	Arg	Cys	740	745	750	
Glu	Glu	Gly	Asn	Arg	Asn	Lys	Cys	Ala	Glu	Tyr	Trp	Pro	Ser	Met	Glu	755	760	765	
Glu	Gly	Thr	Arg	Ala	Phe	Gly	Asp	Val	Val	Val	Lys	Ile	Asn	Gln	His	770	775	780	
Lys	Arg	Cys	Pro	Asp	Tyr	Ile	Ile	Gln	Lys	Leu	Asn	Ile	Val	Asn	Lys	785	790	795	800
Lys	Glu	Lys	Ala	Thr	Gly	Arg	Glu	Val	Thr	His	Ile	Gln	Phe	Thr	Ser	805	810	815	
Trp	Pro	Asp	His	Gly	Val	Pro	Glu	Asp	Pro	His	Leu	Leu	Leu	Lys	Leu	820	825	830	
Arg	Arg	Arg	Val	Asn	Ala	Phe	Ser	Asn	Phe	Phe	Ser	Gly	Pro	Ile	Val	835	840	845	
Val	His	Cys	Ser	Ala	Gly	Val	Gly	Arg	Thr	Gly	Thr	Tyr	Ile	Gly	Ile	850	855	860	
Asp	Ala	Met	Leu	Glu	Gly	Leu	Glu	Ala	Glu	Asn	Lys	Val	Asp	Val	Tyr	865	870	875	880
Gly	Tyr	Val	Val	Lys	Leu	Arg	Arg	Gln	Arg	Cys	Leu	Met	Val	Gln	Val	885	890	895	
Glu	Ala	Gln	Tyr	Ile	Leu	Ile	His	Gln	Ala	Leu	Val	Glu	Tyr	Asn	Gln	900	905	910	
Phe	Gly	Glu	Thr	Glu	Val	Asn	Leu	Ser	Glu	Leu	His	Pro	Tyr	Leu	His	915	920	925	
Asn	Met	Lys	Lys	Arg	Asp	Pro	Pro	Ser	Glu	Pro	Ser	Pro	Leu	Glu	Ala	930	935	940	
Glu	Phe	Gln	Arg	Leu	Pro	Ser	Tyr	Arg	Ser	Trp	Arg	Thr	Gln	His	Ile	945	950	955	960
Gly	Asn	Gln	Glu	Glu	Asn	Lys	Ser	Lys	Asn	Arg	Asn	Ser	Asn	Val	Ile	965	970	975	
Pro	Tyr	Asp	Tyr	Asn	Arg	Val	Pro	Leu	Lys	His	Glu	Leu	Glu	Met	Ser	980	985	990	

79/80

Lys Glu Ser Glu His Asp Ser Asp Glu Ser Ser Asp Asp Asp Ser Asp
 995 1000 1005
 Ser Glu Glu Pro Ser Lys Tyr Ile Asn Ala Ser Phe Ile Met Ser Tyr
 1010 1015 1020
 Trp Lys Pro Glu Val Met Ile Ala Ala Gln Gly Pro Leu Lys Glu Thr
 1025 1030 1035 1040
 Ile Gly Asp Phe Trp Gln Met Ile Phe Gln Arg Lys Val Lys Val Ile
 1045 1050 1055
 Val Met Leu Thr Glu Leu Lys His Gly Asp Gln Glu Ile Cys Ala Gln
 1060 1065 1070
 Tyr Trp Gly Glu Gly Lys Gln Thr Tyr Gly Asp Ile Glu Val Asp Leu
 1075 1080 1085
 Lys Asp Thr Asp Lys Ser Ser Thr Tyr Thr Leu Arg Val Phe Glu Leu
 1090 1095 1100
 Arg His Ser Lys Arg Lys Asp Ser Arg Thr Val Tyr Gln Tyr Gln Tyr
 1105 1110 1115 1120
 Thr Asn Trp Ser Val Glu Gln Leu Pro Ala Glu Pro Lys Glu Leu Ile
 1125 1130 1135
 Ser Met Ile Gln Val Val Lys Gln Lys Leu Pro Gln Lys Asn Ser Ser
 1140 1145 1150
 Glu Gly Asn Lys His His Lys Ser Thr Pro Leu Leu Ile His Cys Arg
 1155 1160 1165
 Asp Gly Ser Gln Gln Thr Gly Ile Phe Cys Ala Leu Leu Asn Leu Leu
 1170 1175 1180
 Glu Ser Ala Glu Thr Glu Glu Val Val Asp Ile Phe Gln Val Val Lys
 1185 1190 1195 1200
 Ala Leu Arg Lys Ala Arg Leu Gly Met Val Ser Thr Phe Glu Gln Tyr
 1205 1210 1215
 Gln Phe Leu Tyr Asp Val Ile Ala Ser Thr Tyr Pro Ala Gln Asn Gly
 1220 1225 1230
 Gln Val Lys Lys Asn Asn His Gln Glu Asp Lys Ile Glu Phe Asp Asn
 1235 1240 1245
 Glu Val Asp Lys Val Lys Gln Asp Ala Asn Cys Val Asn Pro Leu Gly
 1250 1255 1260
 Ala Pro Glu Lys Leu Pro Glu Ala Lys Glu Gln Ala Glu Gly Ser Glu
 1265 1270 1275 1280
 Pro Thr Ser Gly Thr Glu Gly Pro Glu His Ser Val Asn Gly Pro Ala
 1285 1290 1295

80/80

Ser Pro Ala Leu Asn Gln Gly Ser
1300