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(54) Titre : ANTICORPS TRX1 ET UTILISATIONS ASSOCIEES
(54) Title: CD4-SPECIFIC ANTIBODY TRX1 AND USES THEREFOR

(57) Abrégé/Abstract:
Inducing tolerance in a primate by use of a compound that has certain characteristics when tested in vitro. The compound is preferably the CD4-specific antibody TRX1 and the compound is preferably used in accordance with a specified dosing regimen.

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(54) Title: CD4-SPECIFIC ANTIBODY TRX1 AND USES THEREFOR

(57) Abstract: Inducing tolerance in a primate by use of a compound that has certain characteristics when tested *in vitro*. The compound is preferably the CD4-specific antibody TRX1 and the compound is preferably used in accordance with a specified dosing regimen.

TRX1 ANTIBODY AND USES THEREFOR

The present invention is applicable to inhibiting, preventing or ameliorating an immune response against an antigen(s). Such inhibiting, preventing, or ameliorating an immune response against an antigen(s) includes inducing tolerance to the antigen(s). This invention also relates to tolerance induction and/or preventing or inhibiting T cell activation and proliferation and, more particularly, to inducing tolerance in a primate.

BACKGROUND OF THE INVENTION

Tolerance to foreign antigen or tissue, or self antigen or tissue is a state whereby an otherwise normal, mature immune system is specifically unable to respond aggressively to that antigen/tissue which it therefore treats like a normal (non-diseased) body tissue/component, yet at the same time it can respond aggressively to foreign or diseased antigens/tissues to which it has not been specifically made tolerant by the natural process of self tolerance or by creating a tolerance-permissive environment *in vivo*.

SUMMARY OF THE INVENTION

In accordance with one aspect of the present invention there is provided a process for inducing tolerance by use of a compound that has certain characteristics when tested *in vitro*, with such compound in a preferred embodiment being a CD4 antibody.

In accordance with another aspect of the present invention there is provided a novel CD4 antibody and uses therefor.

In accordance with a further aspect of the invention there is provided a process for inducing tolerance in a primate by use of a compound with certain characteristics (preferably an antibody and more preferably a CD4 antibody) by use of a dosing regimen that induces such tolerance in a primate.

In accordance with a further aspect of the present invention, there is provided a screen or test for identifying compounds that are useful for inducing tolerance against one or more antigens.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 shows the amino acid sequences of the heavy and light chains of the first embodiment of TRX1 antibody, as well as the CDR and framework regions of the heavy and light chains.

Figure 2 shows the amino acid sequences of the heavy and light chains of another embodiment of the TRX1 antibody, as well as the CDR and framework regions of the heavy and light chains.

Figure 3 shows the amino acid sequences of the heavy and light chains of another embodiment of the TRX1 antibody, as well as the CDR and framework regions of the heavy and light chains.

Figure 4 shows the amino acid sequences of the heavy and light chains of another embodiment of the TRX1 antibody, as well as the CDR and framework regions of the heavy and light chains.

Figure 5 shows the immune response to antivenin for the first 68 days (i.e., the tolerization phase) of a study of groups of baboons which were given antivenin alone or in combination with TRX1 antibody.

Figure 6 shows the immune response to antivenin, subsequent to an antivenin and sheep red blood cell challenge, to groups of baboons which were given antivenin, alone or in combination with TRX1 antibody, 68 days before the challenge.

Figure 7 shows the immune response to antivenin, subsequent to each of three antivenin challenges, to groups of baboons which were given antivenin, alone or in combination with TRX1 antibody, 68 days before the first challenge.

Figure 8 is a chart depicting immune response to sheep red blood cells after TRX1 tolerization against antivenin.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with an aspect of the present invention, there is provided a process for tolerizing a primate against an antigen(s) by use of a compound as hereinafter described. The compound is administered in an amount and in accordance with a dosage regimen that is effective for inducing tolerance in a primate. The compound is a compound that when present in a primary mixed lymphocyte reaction (MLR) as compared to a mixed lymphocyte reaction in the absence of the compound reduces the amount of cells that are positive for both CD4 and CD25 (CD4+CD25+cells) that result from the mixed lymphocyte reaction. In a preferred embodiment, the compound is a compound that reduces the amount of such CD4+CD25+cells by at least 40% and preferably by at least 60% and still more preferably by at least 70%.

In a preferred embodiment, such a compound produces a cell population that inhibits a primary mixed lymphocyte reaction (performed with cells that have not been previously exposed to the compound) by reducing the CD4+ CD25+ cells produced in the primary MLR. In a preferred embodiment, there is at least a 10% reduction and preferably at least a 20% reduction. Protocols for performing the hereinabove described mixed lymphocyte reactions are described in Example 5.

In addition, in a preferred embodiment, the compound is a compound that reduces the amount of CD4+ CD25+cells produced in a primary mixed lymphocyte reaction and generates a cell population in such primary mixed lymphocyte reaction which cell population inhibits a secondary mixed lymphocyte reaction. In a preferred embodiment, the cells are generated in a primary mixed lymphocyte reaction that is performed in the presence of the compound, which cells when added to the secondary mixed lymphocyte reaction preferably reduce the CD4+ CD25+ cells generated in such secondary mixed lymphocyte reaction, as compared to a secondary mixed lymphocyte reaction in the absence of the added cells by at least 20% more preferably by at least 35%, and more preferably by at least 50%.

An inhibition of either a primary or secondary MLR by such a cell population is evidenced by a reduction in the amount of CD4+ CD25+cells produced in the MLR as compared to the MLR performed in the absence of such a cell population.

Thus, in accordance with an aspect of the present invention, a primate is treated with a compound having the characteristics as hereinabove described (reduction of the amount of CD4+ CD25+cells produced in an in vitro primary MLR, with such primary MLR generating a cell population that reduces the amount of CD4+ CD25+cells produced in vitro in a primary and/or secondary MLR and that preferably effects such reduction in both a primary and secondary MLR).

In one embodiment, the cells generated in the primary MLR in the presence of the compound are cells which when added to a secondary MLR (as compared to a secondary MLR without the added cells) reduces and/or eliminates the generation of one or more of cytokines; in particular, one or more of IL-2, IL-4 and IL-12 in the secondary MLR. In general, such reduction of at least one of IL-2, IL-4 and IL-12 is at least 40%, preferably by at least 60%.

Thus, a preferred compound is one that generates cells in a primary MLR that in a secondary MLR, as compared to control, reduces production of $CD_4^+CD_{25}^+$ cells or one or more or all (preferably all) of IL-2, IL-4 and IL-12 and preferably reduces production of both such cells and such cytokines.

In accordance with an additional aspect, there is provided a screen or test in which, in vitro, T cells are exposed to a material(s) or compound(s) under conditions which stimulate and cause the T cells to proliferate, with such exposure being effected in the presence of a compound(s) that is to be tested for its ability to induce tolerance. The T cell proliferation test may be a mixed lymphocyte reaction or a test in which T cells are caused to proliferate by a non-antigen specific stimulation through the T cell receptor (TCR) or a component of the TCR complex, for example a CD3 component. Typically, an anti-CD3 monoclonal antibody is used to stimulate T cells and cause them to proliferate. In addition to stimulation through the TCR complex, co-stimulatory signals sometimes are provided by addition of antibodies which bind co-stimulatory molecules such as CD28. The T cells that have been caused to proliferate, in the presence and absence of the compound that is being tested, are examined to determine a subset of T cells that are CD4 positive ($CD4^+$) and CD25 positive ($CD25^+$) in order to determine whether the presence of the compound inhibited the production of such T cell subset.

The in vitro test that is used to test a compound(s) for tolerance-inducing activity is preferably a mixed lymphocyte reaction (MLR). Mixed lymphocyte reactions are generally known in the art, and a protocol therefor is described in Example 5, however, the scope of the invention is not to be limited thereby.

The cell population produced in the initial test may then be tested in at least one further test in which T cells, in vitro are caused to proliferate in order to determine whether such cell population inhibits production of $CD4^+$ $CD25^+$ cells.

The at least one further test may be a mixed lymphocyte reaction (a primary or secondary mixed lymphocyte reaction) or a test in which T cells are caused to proliferate in response to a non-antigen specific stimulation through the T cell receptor (TCR) or a component of the TCR complex or with co-stimulation which mimics an antigen specific stimulation thorugh TCR.

A protocol for such a test is described in Example 5; however, the scope of the invention is not to be limited thereby.

In a preferred embodiment, the screen or test for determining a compound to be used for inducing tolerance involves both the initial test to determine whether the compound in an in vitro T cell proliferation test, such as an MLR, reduces the production of $CD4^+$ $CD25^+$ cells and a subsequent test to determine whether cells produced in the first test inhibit the production of $CD4^+$ $CD25^+$ cells in a second T cell proliferation test, such as a primary and/or secondary MLR and, in particular, a secondary MLR and/or cytokine production in a secondary MLR.

In accordance with a preferred embodiment, a compound selected for inducing tolerance is one that causes reduction of production of $CD4^+$ $CD25^+$ cells in the initial test and produces a cell population therein that reduces production of such T cell subset in a second test, as hereinabove described and/or that reduces cytokine production and, in particular, one or more of IL-2, IL-4 and IL-12 in a second test.

Thus, in accordance with an aspect of the invention, the selected compound is a compound that when present in a T cell proliferation assay such as a primary mixed lymphocyte reaction (MLR) as compared to a mixed lymphocyte reaction

in the absence of the compound reduces the amount of cells that are positive for both CD4 and CD25 (CD4+CD25+cells) that result from the mixed lymphocyte reaction. In a preferred embodiment, the compound is a compound that reduces the amount of such CD4+CD25+cells by at least 40% and preferably by at least 60% and still more preferably by at least 70%.

In addition, in a preferred embodiment, the selected compound is a compound that reduces the amount of CD4+ CD25+cells produced in a primary mixed lymphocyte reaction and generates a cell population in such primary mixed lymphocyte reaction which cell population inhibits a secondary mixed lymphocyte reaction. In a preferred embodiment, the cells are generated in a primary mixed lymphocyte reaction that is performed in the presence of the compound, which cells when added to the secondary mixed lymphocyte reaction preferably reduce the CD4+ CD25+ cells generated in such secondary mixed lymphocyte reaction, (as compared to a secondary mixed lymphocyte reaction in the absence of the added cells) by at least 20% more preferably by at least 35% and more preferably by at least 50%. In a preferred embodiment, such cells in the secondary MLR, as compared to a control, reduce the production of at least one of IL-2, IL-4 and IL-12 by at least 40% and preferably by at least 60%.

An inhibition of either a primary or secondary MLR by such a cell population is evidenced by a reduction in the amount of CD4+ CD25+cells produced in the MLR as compared to the MLR performed in the absence of such a cell population, and with respect to the secondary MLR, may be evidenced by reduction of $CD4^+CD25^+$ cells or reduced cytokine production and preferably by both.

In one embodiment, the compound that is used to induce tolerance in a primate is an antibody (or fragment thereof); however, the present invention is not limited to such antibody use.

As used herein, the term “tolerize” or “tolerant” with respect to an antigen means that, without requiring a therapeutic or effective level of an immunosuppressant, the primate does not produce an adverse immune response to the antigen over a period of time after treatment is stopped even when subsequently challenged with the antigen and/or when the antigen

remains present in the primate, but is capable of providing an immune response against other antigens.

The antigen(s) as to which tolerance is induced may be a self antigen or a foreign antigen.

The foreign antigen may be one or more of the following types of antigens:

(i) a foreign antigen present on transplanted tissue or cells, including tissue or cells present in an organ wherein the transplant may be allogeneic or xenogeneic;

(ii) a therapeutic agent (which also includes therapeutic agents used for disease prevention) that produces an immune response in a primate, which immune response diminishes the ability of the agent to function as a therapeutic agent. Such agents include, but are not limited to, delivery vehicles, such as vectors used in gene therapy; active agents such as proteins delivered to the primate, such as recombinant proteins such as monoclonal antibodies, enzymes, clotting factors and some small molecule drugs, or proteins produced from an agent delivered to the primate, such as in gene therapy.

The foreign antigens against which tolerance is induced in accordance with the present invention are not foreign antigens as present in disease-causing bacteria, fungi, viruses, etc. that infect a host, i.e., the term foreign antigen does not include a foreign antigen as part of an organism that infects a primate and causes a disease or disorder.

In accordance with one aspect, a primate is treated to produce tolerance against an antigen(s) by treating the primate with at least one CD4 antibody or fragment thereof in an amount and for a time that is effective for providing such tolerance, with the antibody being present in the primate at a time when such antigen is also present in the primate, with such treatment resulting in the primate being tolerant to the antigen. Such CD4 antibody has the hereinabove described characteristics when tested in vitro in an MLR (reduces the amount of CD4+ CD25+ cells produced in a primary MLR, with the cell population produced in the primary MLR when tested in vitro in at least one of a primary or a secondary MLR reduces the amount of CD4+ CD25+ cells produced therein).

The CD4 antibody is preferably a monoclonal antibody (or fragment thereof that retains the ability to bind to CD4). The antibody may be a human antibody or a non-human antibody, with non-human antibodies including humanized antibodies, chimeric antibodies, murine antibodies, etc.

The CD4 antibody or appropriate fragment thereof is administered to a primate in an amount and for a time effective to induce tolerance against a foreign or self-antigen and preferably a foreign antigen.

In accordance with a preferred embodiment, the CD4 antibody or appropriate fragment thereof is administered over a period of time in order to maintain in the primate appropriate levels of such antibody or fragment over a period of time that is sufficient to induce tolerance.

In general, the antibody (or fragment thereof) is administered in an initial dose of at least about 40 mg, preferably at least about 50 mg and more preferably in an amount of at least about 70 mg.

In one preferred embodiment, the initial dose is at least 400 mg, preferably at least about 500 mg and in a particular embodiment in an amount of at least about 700 mg.

The initial dose may be administered in one or more doses over a twenty-four hour period and preferably in one dose over twenty-four hours.

As used herein in reference to a dosage amount a dose is the total amount of antibody administered over a twenty-four hour period, even if administered more than once in 24 hours.

In most cases, after the initial dose, the CD4 antibody (or appropriate fragment thereof) is administered in one or more follow-up doses over several day(s), with each follow-up dose being administered in one or more doses in a twenty-four hour period. The follow-up dose(s) is generally provided in an amount to return serum levels of the antibody to those that were achieved by the initial dose.

In a preferred embodiment, the minimum follow-up dose or doses is in an amount that is at least equal to the amounts hereinabove described and may or may not be identical to the dose given as the original or initial dose. Thus, a follow-up dose is generally at least 40 mg, preferably at least 50 mg, and more preferably at least 70 mg. As hereinabove described, in one preferred embodiment, the follow-up dose(s) is at least 400 mg, preferably at least 500 mg, and in a particular embodiment at least 700 mg. In some cases, the follow-up dose or doses may be less than the minimum amount.

If there is more than one follow-up dose, each such additional follow-up dose over a 24-hour period may be the same or different than another follow-up dose.

The number of follow-up doses will vary, but in a preferred embodiment, there is generally at least one follow-up dose and in most cases there is no more than seven follow-up doses, i.e., the total number of doses generally does not exceed eight doses.

The total period over which the antibody is administered generally does not exceed four weeks and more preferably does not exceed three weeks. In many cases, tolerance can be achieved by using an initial dose and one or more follow-up doses over a period that does not exceed two weeks.

Although, in accordance with the present invention, initial tolerance to an antigen(s) can be achieved in a primate in a period of no more than four weeks, in some cases, periodic follow-up treatments with the antibody may be required in order to maintain tolerance.

As hereinabove described, at least one CD4 antibody (or appropriate fragment thereof) is delivered in an amount that is at least sufficient to induce tolerance in a primate against an antigen(s) and in a preferred embodiment against a foreign antigen. The maximum amount is of course limited by safety considerations. In general, the daily dosage of antibody would be less than 6000 mg.

The number of follow-up doses and the spacing thereof will be determined, in part, by the half-life of the at least one CD4 antibody. Although the present invention is not to be limited thereby, it is believed that the CD4 antibody

should be initially delivered in an amount to achieve antibody serum levels that exceed the amount required to saturate all of the CD4 of the primate being treated, with follow-up doses being given at times to maintain such excess over a period that induces tolerance in the primate against the antigen(s).

In a preferred embodiment, the CD4 antibody is a CD4 antibody that would have a reduced effector (i.e. lytic) function as compared to human IgG1. As representative examples of antibodies that would have reduced effector function, there may be mentioned antibodies that have an Fc portion that is aglycosylated and/or that has reduced binding to the Fc receptor and/or is non-lytic.

In one embodiment, a CD4 antibody with a reduced effector function is a non-depleting CD4 antibody. As used herein, "a non-depleting CD4 antibody" is a CD4 antibody that depletes less than 50% of CD4 cells and preferably less than 10% of CD4 cells.

In treating a primate and in particular a human, the CD4 antibody may be employed in combination with a pharmaceutically acceptable carrier. A composition that contains a CD4 antibody may include other ingredients, for example, stabilizers and/or other active agents.

The use of a CD4 antibody to induce tolerance against an antigen(s) in a primate in accordance with the present invention provides tolerance against one or more antigens and the primate is capable of immunologically responding to other antigens. Thus, in this respect, the primate is made tolerant to one or more antigens, and the immune system is capable of providing an immune response against other foreign antigens whereby the primate is not immunocompromised.

In the preferred embodiment where tolerance is induced against an antigen, the CD4 antibody is administered to the primate prior to, in conjunction with or subsequent to the antigen being delivered to the primate. In a preferred embodiment, the primate is provided with the CD4 antibody at a time such that the antibody is present in the primate. In a particularly preferred embodiment, the CD4 antibody (or fragment thereof) is delivered to the primate prior to the primate coming into contact with the antigen to which the primate is to be tolerized or within a few hours or less than one day thereafter. In a preferred

embodiment, the antibody is administered to the primate no more than about two, preferably no more than one day prior to the primate receiving the antigen.

As hereinabove indicated, in one embodiment, a primate is tolerized against a therapeutic protein that is to be used in treating the primate. Such therapeutic protein may be a therapeutic antibody (other than the CD4 antibody), which therapeutic antibody may be a human antibody, humanized antibody, chimeric antibody or a non-human antibody; an enzyme such as one used for replacement therapy; a hormone; clotting factor; a protein produced in gene therapy; a gene therapy delivery vehicle such as a vector used in gene therapy (for example, an adenovirus vector).

The foreign antigen(s) may be present in a transplanted organ, or in transplanted cells used in cell therapy, or in other tissue transplants, such as skin.

The treatment of a primate, in particular, a human, in order to tolerize the primate against a foreign antigen(s) by use of a CD4 antibody may be accomplished in some cases without adjunct therapy, such as a bone marrow transplant to promote acceptance of a foreign antigen and/or T-cell depletion and/or immunosuppression.

In some cases, adjunct therapy may also be employed. For example, as part of a transplant procedure, immunosuppression with an appropriate immunosuppressant may be used but by employing the present invention, chronic immunosuppression is not required. In addition, if used after or during the tolerizing procedure, in some cases, the immunosuppressant may be used with less than the amount required to provide for effective immunosuppression.

In one non-limiting embodiment, the antibody is preferably a TRX1 antibody (as hereinafter described) or one that binds to the same epitope as TRX1, as hereinafter described, and such antibody is preferably used with the dosing regimen as hereinabove described.

In accordance with an aspect of the present invention, there is provided a molecule (preferably a humanized antibody or fragment thereof) which binds to the same epitope (or a portion thereof) on human lymphocytes as the humanized antibody selected from the group consisting of the humanized

antibody shown in Figure 1 and the humanized antibody shown in Figure 2 and the humanized antibody of Figure 3 and the humanized antibody shown in Figure 4.

The antibody is hereinafter sometimes referred to as TRX1. The term "molecule" or "antibody that binds the same epitope as TRX1" includes TRX1. The term "TRX1" includes the antibody shown in Figure 1 , the antibody shown in Figure 2 and the one of Figure 3, and the one of Figure 4, and those identical thereto which may be produced, for example, by recombinant technology.

Although the preferred antibody is TRX1, from the teachings herein, one skilled in the art can produce antibodies that are equivalent to TRX1. As representative but non-limiting examples of such equivalent TRX1 antibodies there may be mentioned:

1) humanized antibodies that bind to the same epitope as TRX1;

2) humanized antibodies that have the same CDRs as TRX1 but which have a different humanized framework and/or a different human constant region;

3) humanized antibodies that bind to the same epitope as TRX1 in which one or more amino acids of one or more of the CDRs of TRX1 have been changed (preferably but not necessarily a conservative amino acid substitution) and in which the framework may be the same framework as TRX1 or have a different humanized framework or in which one or more of the amino acids of the framework region of TRX1 have been changed and/or in which the constant region may be the same as or different from TRX1;

4) humanized antibodies that bind to the same epitope as TRX1 wherein the antibody does not bind to the Fc region of the receptor.

5) humanized antibodies that bind to the same epitope as TRX1 wherein the CDRs thereof do not include a glycosylation site;

6) humanized antibodies that bind to the same epitope as TRX1 and that do not bind to the Fc region of the receptor and the CDRs do not include a glycosylation site;

7) a chimeric antibody that binds to the same epitope as TRX1; and

8) a murine antibody that binds to the same epitope as TRX1.

The antibodies that are equivalent to TRX1 may be used in the same manner and for the same purposes as TRX1.

The molecules or antibodies of the present invention may be used in a method for treating an animal, in particular a human, especially for use in inhibiting, ameliorating, or reducing an immune response to an antigen, which may be a foreign antigen or a self antigen, including inducing tolerance to an antigen. The molecules or antibodies may be used to inhibit, ameliorate, or reduce an immune response to a Class I presented antigen and/or to a Class II presented antigen. The molecules or antibodies may be used to inhibit, ameliorate, or reduce an immune response to such antigens. In the case of a transplant, for example, Class I and Class II major histocompatibility (MHC) antigens and non-MHC or minor histocompatibility antigens may be presented. Apart from transplantation antigens, the molecules or antibodies may be used to inhibit, ameliorate, or reduce an immune response to globular proteins, glycoproteins such as immunoglobulins, materials carried on particles such as pollen proteins, polypeptides intended for therapeutic use such as interferon, Interleukin-2 or tumor necrosis factor, or hormone replacements such as lutenizing hormone, its analogues and antagonists. Further specific antigens to which an immune response can be inhibited, ameliorated, or reduced include synthetic peptide analogues of protein therapeutic agents which are used to aid in receptor blocking, and alloantigens. Alloantigens may be responsible for rejection of foreign tissue in tissue transplants or skin grafts. The term "antigen" as used herein is a compound or material that induces an immune response in an animal, in particular a human animal. The immune response may be a T-cell response which may or may not be accompanied by a humoral response.

The molecules or antibodies of the present invention inhibit and/or alter T-cell activation and proliferation and Applicant has found that such inhibition can be effected when adding the molecule or antibody either before or after an agent which stimulates T-cell activation.

The molecules or antibodies of the present invention have the characteristics of binding to an epitope of a CD4 antigen (CD4 positive human T-cells), but it is to be understood, however, that although the antibody is believed to function by binding to a CD4 antigen on T-cells, the antibody may function by binding to a CD4 antigen on other cells; e.g., monocytes. As a result, the ability of such molecules or antibodies to inhibit and/or alter T-cell activation or proliferation may or may not be effected through binding to CD4 positive cells, although Applicant presently believes that the mechanism of action involves binding of the molecule or antibody to CD4 positive cells.

In accordance with another aspect of the present invention, there is provided a method of preventing and/or inhibiting an on-going immune response in human patients through the administration to the patient of an antibody, hereafter referred to as TRX1 (or fragment or derivative thereof) or any molecule that mimics such antibody or derivative or fragment thereof, i.e., binds to the same epitope as TRX1.

Although Applicants do not want to limit the invention to any theoretical reasoning, it is believed that the mechanism which enables the monoclonal antibody of this invention to inhibit or prevent or reduce or ameliorate the severity of an immune response, and to inhibit and/or alter the activation and proliferation of effector T cells, is the fact that the TRX1 antibody either decreases the density of CD4 expressed on T-cell surfaces which are capable of participating in an immune reaction, and thus decreases the number of functional CD4 +effector T lymphocytes; and/or affects signal transduction and thus decreases the number of functional CD4 + effector T lymphocytes. It is believed that these mechanisms of action are responsible for not only the prevention of immune responses, but also the reduction in severity of on-going immune responses. In addition, the TRX1 antibody inhibits natural killer (NK) cell activity in vitro. This is pertinent to the present invention because it is believed that a non-MHC restricted cytotoxic mechanism such as NK cell activity has been implicated in graft versus host disease.

The term "inhibit" as used herein throughout this application is intended to mean prevention, or inhibition, or reduction in severity, or amelioration of an immune response to one or more antigens. The antigen may be a foreign antigen or a self antigen. The term "graft" as used herein for purposes of this application shall mean any and all transplantation, including but not limited to, allograft and xenograft transplantation. Such transplantation may by way of example include, but not be limited to, transplantation of cells, bone marrow, tissue, solid-organ, bone, etc.

The term "immune response(s)" as used herein is intended to mean immune responses dependent upon T cell activation and proliferation which includes both cellular effects and T cell dependent antibodies which may be elicited in response to, by way of example and not limitation: (i) grafts, (ii) graft versus host disease, and (iii) autoantigens resulting in autoimmune diseases, which by way of example include but are not limited to rheumatoid arthritis, systemic lupus, multiple sclerosis, diabetes mellitus, etc.

The molecule employed in the present invention is one which binds to the same epitope (or a part of that epitope) as the TRX1 humanized antibody. The term "binds to the same epitope as TRX1 humanized antibody" is intended to describe not only the TRX1 humanized antibody but also describes other antibodies, fragments or derivatives thereof or molecules which bind to the same such epitope as the TRX1 humanized antibody.

Such molecules are preferably antibodies. In a preferred embodiment, the antibody does not bind to Fc receptors through the Fc region of the antibody and the CDRs do not include a glycosylation site.

The constant region may or may not include a glycosylation site. In one embodiment, the constant region includes a glycosylation site. An example of a heavy chain sequence which includes a glycosylation site is shown in Figures 1D and 1F and Figures 3D and 3F. In another embodiment, the constant region does not include a glycosylation site. An example of a heavy chain sequence which does not include a glycosylation site is shown in Figures 2D and 2F and in Figures 4D and 4F.

Such other antibodies include, by way of example and not by limitation, rat, murine, porcine, bovine, human, chimeric, humanized antibodies, or fragments or derivatives thereof.

The term "fragment" as used herein means a portion of an antibody, by way of example such portions of antibodies shall include but not be limited to CDR, Fab, or such other portions, which bind to the same epitope or any portion thereof as recognized by TRX1.

The term "antibody" as used herein includes polyclonal and monoclonal antibodies as well as antibody fragments and derivatives, as well as antibodies prepared by recombinant techniques, such as chimeric or humanized antibodies, single chain or bispecific antibodies which bind to the same epitope or a portion thereof as recognized by the humanized antibody TRX1. The term "molecules" includes by way of example and not limitation, peptides, oligonucleotides or other such compounds derived from any source which mimic the antibody or binds to the same epitope or a portion thereof as the antibody fragment or derivative thereof.

Another embodiment of the present invention provides for a method of treating a patient who is to receive or has received a graft transplant with an effective amount of at least one member selected from the group consisting of TRX1 antibody, or an antibody, or derivative or fragment thereof or molecules which bind to the same epitope (or a portion thereof) as the TRX1 antibody. The treatment is preferably effected with the whole or intact TRX1 antibody.

In one embodiment, the antibody is TRX1 which is a humanized antibody that includes modified constant regions of a human antibody, and light and heavy chain framework and CDR regions, in which the framework regions of the light and heavy chain variable regions correspond to the framework regions of the light and heavy chain variable region of a human antibody, and the CDRs derived from a mouse monoclonal antibody designated NSM4.7.2.4. The TRX1 antibody is shown in Figure 1. Figure 1A shows the amino acid and DNA sequences for the TRX1 light chain. Figure 1B shows the TRX1 light chain nucleic acid sequence. Figure1C shows the TRX1 light chain amino acid sequence with the CDRs highlighted. Figure 1D shows the amino acid and DNA sequences for the TRX1 heavy chain which includes a glycosylation site. Figure 1E shows the TRX1 heavy chain nucleotide sequence. Figure 1F shows

the TRX1 heavy chain amino acid sequences, which include a glycosylation site, with the CDRs highlighted.

In another embodiment, the antibody is TRX1 which is a humanized antibody that includes modified constant regions of a human antibody, and light and heavy chain framework and CDR regions, in which the framework regions of the light and heavy chain variable regions correspond to the framework regions of the light and heavy chain variable region of a human antibody, and the CDRs derived from a mouse monoclonal antibody designated NSM4.7.2.4. The TRX1 antibody is shown in Figure 3. Figure 3A shows the amino acid and DNA sequences for the TRX1 light chain. Figure 3B shows the TRX1 light chain nucleic acid sequence. Figure 3C shows the TRX1 light chain amino acid sequence with the CDRs highlighted. Figure 3D shows the amino acid and DNA sequences for the TRX1 heavy chain which includes a glycosylation site. Figure 3E shows the TRX1 heavy chain nucleotide sequence. Figure 3F shows the TRX1 heavy chain amino acid sequences, which include a glycosylation site, with the CDRs highlighted.

Another embodiment of the TRX1 antibody is shown in Figure 2. Figure 2A shows the amino acid and DNA sequences for the light chain. Figure 2B shows the light chain nucleic acid sequence. Figure 2C shows the light chain amino acid sequence with the CDRs highlighted. Figure 2D shows the amino acid and DNA sequences for the heavy chain. Figure 2E shows the heavy chain nucleotide sequence. Figure 2F shows the heavy chain amino acid sequences with the CDRs highlighted.

Another embodiment of the TRX1 antibody is shown in Figure 4. Figure 4A shows the DNA and amino acid sequences for the light chain. Figure 4B shows the light chain nucleic acid sequence. Figure 4C shows the light chain amino acid sequence with the CDRs highlighted. Figure 4D shows the amino acid and DNA sequences for the heavy chain. Figure 4E shows the heavy chain nucleotide sequence. Figure 4F shows the heavy chain amino acid sequences with the CDRs highlighted.

In the figures, amino acid residue 1 is the first amino acid, in each of the heavy and light chains, after the leader sequence. It also is the first residue in FR1 in the sequences.

The preparation of TRX1 humanized antibody suitable for the purposes of the present invention should be apparent to those skilled in the art from the teachings herein. Such antibody may be prepared by recombinant techniques known to those skilled in the art.

The antibodies of the present invention may be used to inhibit an immune response in an animal by administering the antibody (or fragment thereof) in an amount effective to inhibit such immune response.

For example, in some cases, treatment with a therapeutic agent includes an immune response against the therapeutic agent. As representative examples of such therapeutic agents there may be mentioned monoclonal antibodies such as ReoPro and OKT3, enzymes for replacement therapy such as, but not limited to, glucocerebrosidase for Gaucher's disease and clotting factors such as Factor VIII, and products of gene therapy and gene therapy delivery vehicles such as adenovirus derived vectors.

In accordance with an aspect of the present invention, an antibody as hereinabove described (or fragment of such antibody) is administered to a patient that is to be treated with such therapeutic agent, with the antibody (or fragment) being administered in an amount effective to inhibit the immune response against the therapeutic agent. The antibody may be administered prior to, in combination with, or subsequent to administration of the therapeutic agent. The method of administration is dependent on a variety of factors, including, but not limited to, the specific indication, specific therapeutic agent and optimal dosing schedule If administered prior to the administration of the therapeutic agent, the antibody is administered from about 1 hour to about 10 days prior to the administration of the therapeutic agent, preferably from about 1 hour to about 24 hours prior to the administration of the therapeutic agent. If administered after the administration of the therapeutic agent, the antibody is administered from about 1 hour to about 10 days after the administration of the therapeutic agent, preferably from about 1 hour to about 24 hours after the administration of the therapeutic agent.

The amount of antibody administered, the dosing schedule and the number of times that the antibody is administered is dependent upon the therapeutic agent and the regimen used for treating a patient with the therapeutic agent.

In general, the antibody may be used in an amount from 0.1 milligram to 3 grams per dose.

The antibody of the present invention may also be used to inhibit an immune response against a self-antigen and/or a foreign antibody, e.g., against a transplant (for example, transplant rejection) and/or to inhibit or ameliorate an immune response of a graft against a host.

The antibody of the present invention may also be used to inhibit an immune response against gene therapy products as well as an immune response against gene therapy delivery vehicles such as adenovirus derived vectors which limit the effectiveness of the gene therapy.

Thus, an immune response to an antigen in a host can be inhibited, ameliorated, or reduced by administering TRX1 antibody along with the antigen. A patient may be given a tissue transplant such as an organ transplant or a bone marrow transplant and may be given TRX1 antibody along with the transplant to inhibit rejection thereof. Also, tolerance may be induced to an antigen already possessed by a patient. Long-term specific tolerance can be induced to a self-antigen or antigens in order to treat autoimmune diseases.

Persistent or periodic antigen presence is required to maintain tolerance. A tissue graft, for example, supplies the antigen to maintain tolerance to itself. In the case of extraneous foreign antigens such as allergens, antigen "reminders" can be given at regular intervals.

An antibody or fragment thereof or molecule of the type hereinabove described may be administered in vivo in accordance with the present invention to inhibit the activation and proliferation of T-cells, and decrease the density of functional CD4 expression on the cell surface and/or affect signal transduction thereby reducing the functionality of CD4+ T lymphocytes and/or the number of $CD4^+$ T lymphocytes.

Thus, for example, in an in vivo procedure, such antibodies are administered to prevent and/or inhibit an immune response and thereby inhibit T cell activation and proliferation.

An antibody or fragment thereof or molecule of the type hereinabove described may be administered ex vivo in accordance with the present invention to decrease the density of functional $CD4^+$ expression on the cell surface and/or affect signal transduction, thus reducing the functionality of CD4+ T lymphocytes and/or the number of $CD4^+$ cells of the donor cells. By way of example and not limitation, in an ex vivo procedure, such antibodies or fragments or derivatives thereof or molecules would be infused into donor bone marrow prior to transplantation to prevent the onset of graft versus host disease upon transplantation.

The antibody or fragment thereof is generally administered in a pharmaceutically acceptable carrier. As representative examples of such carriers, there may be mentioned normal saline solution, buffers, etc. Such pharmaceutical carriers are well known in the art and the selection of a suitable carrier is deemed to be within the scope of those skilled in the art from the teachings contained herein.

The TRX1 antibody or other antibody of the present invention may be administered in vivo intravenously, subcutaneously, or by intramuscular administration, etc.

As hereinabove indicated, TRX1 antibody or other antibody of the present invention is administered in vivo in an amount effective to inhibit an immune response against an antigen(s). The term "an effective amount" for purposes of this Application shall mean that amount of antibody capable of producing the desired effect. In general, such antibody is administered in an amount of at least 0.1 milligram per dose. It is to be understood that lower amounts could be used. In addition after the initial treatment, the hereinabove described amounts may be reduced for subsequent treatments, if any. Thus the scope of the invention is not limited by such amounts.

The TRX1 antibody or other antibody of the present invention may be employed to induce tolerance to an antigen. The term "tolerance", as used herein, means that a T-cell non-response persists against an antigen after stopping the antibody treatment, even in the case of challenge. If needed, however, booster or reinforcing doses of the antibody may be given in order to maintain such tolerance.

The techniques of the present invention for inhibiting the activation of T-cells may be employed alone or in combination with other techniques, drugs or compounds for inhibiting the activation of T-cells or inhibiting graft rejection or graft versus host disease or in treating various autoimmune diseases Examples may include drugs such as rapamycin and cyclosporin, or other immunomodulatory compounds including monoclonal antibodies directed against co-stimulatory molecules such as CD2, CD8 and CD28, as well as monoclonal antibodies directed against adhesion molecules.

The antibodies of the present invention also may be employed in a method of selecting for or determining the presence of CD4 positive cells in a sample, such a blood sample, for example. In such method, a sample is contacted with the molecule or antibody, and the presence of CD4 positive cells is determined, and/or CD4 positive cells then can be selected or isolated form the sample.

In a preferred embodiment, the TRX1 antibody or an antibody that binds to the same epitope as TRX1 is employed to induce tolerance against an antigen(s) in a primate (in particular a human).

EXAMPLES

The invention now will be described with respect to the following examples; however, the scope of the present invention is not intended to be limited thereby.

EXAMPLE 1

A cDNA library was constructed from the mouse hybridoma NSM 4.7.2.4 using the Superscript plasmid system (Gibco/BRL, cat. no. 82485A) according to the manufacturer's suggested protocol. Heavy and light chain cDNAs were cloned from the library by DNA hybridization using as probes rat heavy and light chain gene cDNAs from the rat hybridoma YTS 177.

The rat heavy and light chain gene cDNAs of YTS 177 were isolated from the expression vector pHA Pr-1 as BamH1/Sal 1 fragments and labeled with ^{32}P and used independently to screen the NSM 4.7.2.4. cDNA library using standard molecular biology techniques (Sambrook, et al., Molecular Cloning, A. Laboratory Manual, 3rd edition, Cold Spring Harbor Laboratory Press, Cold

Spring Harbor, New York (2001); Ausubel, et al., Current Protocols in Molecular Biology, John Wiley & Sons, New York (2001).) Sequence analysis of the cDNAs derived from the NSM 4.7.2.4 cDNA library confirmed the NSM 4.7.2.4 heavy chain to be mouse gamma-1 subclass and the NSM 4.7.2.4 light chain to be kappa. The NSM 4.7.2.4 heavy and light V regions (VH and VL, respectively) were reshaped to the human VH and VL regions with the "best fit" or highest sequence similarity in the framework regions to that of the mouse. For the light chain, human antibody HSIGKAW (from EMBL) with a sequence similarity of 79%, was used (LA Spatz et al., 1990 *J. Immunol.* 144:2821-8). The sequence of HSIGKAW VL is:

MVLQTQVFISLLLWISGAYG**D**IVMTQSPDSLAVSLGERATINCKSSQSLLYS
SNNKNYLAWYQQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISS
LQAEDVAVYYCQQYYSTPPMFG**Q**GTKVEIKRT

D start of framework 1
Q changed to G

For the heavy chain, human antibody A32483 (From GenBank) with a sequence similarity of 74%, was used (Larrick, et al., Biochem. Biophys. Res. Comm., Vol. 160, pgs. 1250-1256 (1989)). The sequence of A32483 VH is:

LLAVAPGAHS**Q**VQLVQSGAEVKKPGASVKVSCKASGYTFTNYYMHWVRQ
APGQGLEWMGIINPSGNSTNYAQKFQGRVTMTRDTSTSTVYMELSSLRSE
DTAVYYCAREKLATTIFGVLI ITGMDYWGQGTLV**T**VSSGSASA

Q start of framework 1

For the humanization process, anti-CD4 light chain clone 77.53.1.2 (insert size 1kb) and anti-CD4 heavy chain clone 58.59.1 (insert size 1.7kb) were chosen from the cDNA library and inserts isolated from the pSport vector as Sal I/Not I fragments and cloned into M13mp18 vector to produce single stranded DNA for sequencing and template for mutagenesis. The humanization of NSM 4.7.2.4 was performed by site-directed mutagenesis of the mouse cDNA using a kit from Amersham International (RPN 1523) according to the manufacturer's suggested protocol.

Mutagenesis of the VL gene framework regions was performed using five oligonucleotides ranging in length from 29 to 76 bases. The oligos used were:

Primer #1998 76 bases
5'-TGA CAT TGT GAT GAC CCA ATC TCC AGA TTC TTT GGC TGT
GTC TCT AGG TGA GAG GGC CAC CAT CAA CTG CAA GGC
C

Primer #1999 29 bases
5'-TGA ACT GGT ATC AAC AGA AAC CAG GAC AG

Primer #2000 28 bases
5'-AGA GTC TGG GGT CCC AGA CAG GTT TAG T

Primer #2001 42 bases
5'-GTC TTC AGG ACC CTC CGA CGT TCG GTG GAG GTA CCA AGC
TGG

Primer #2008 52 bases
5'-CAC CCT CAC CAT CAG TTC TCT GCA GGC GGA GGA TGT TGC
AGT CTA TTA GTG T

The oligos were phosphorylated and mutagenesis performed in three steps using no more than two oligos per step to introduce changes according to the following procedure:

(1) Annealing phosphorylated mutant oligos to ssDNA template
(2) Polymerization
(3) Filtration to remove single-stranded DNA
(4) Nicking non mutant strand with Nci I
(5) Digestion of non-mutant strand with Exo III
(6) Repolymerization of gapped DNA
(7) Transformation of competent JM101
(8) Sequencing of clones

Mutations were confirmed by single strand DNA sequencing using M13 primers -20 and -40 and also the mutagenic primers # 1999 and # 2000.

A Sal I site at the 5' end of the variable region was changed to Hind III by linker oligos #2334 and #2335 to allow cloning of the variable region as a Hind III/Kpn I fragment into the light chain constant region of CAMPATH-1H.

Primer #2334 24 bases

5'-AGC TTT ACA GTT ACT GAG CAC ACA

Primer #2335 24 bases

5'-TCG ATG TGT GCT CAG TAA CTG TAA

Mutagenesis of the VH gene framework regions was performed using five oligonucleotides ranging in length from 24 to 75 bases. The oligos used were:

Primer #2003 75 bases

5'-GGT TCA GCT GGT GCA GTC TGG AGC TGA AGT GAA GAA GCC TGG GGC TTC AGT GAA GGT GTC CTG TAA GGC TTC TGG

Primer # 2004 52 bases

5'-AGC TGG GTG AGG CAG GCA CCT GGA CAG GGC CTT GAG TGG ATG GGA GAG ATT T

Primer #2005 60 bases

5'-CAA GGG CAG GGT CAC AAT GAC TAG AGA CAC ATC CAC CAG CAC AGT CTA CAT GGA ACT CAG

Primer #2006 44 bases

5'CAG CCT GAG GTC TGA GGA CAC TGC GGT CTA TTA CTG TGC AAG A

Primer #2007 24 bases

5′-GCC AAG GGA CAC TAG TCA CTG TGT

Mutagenesis was carried out as described above for the light chain again using no more than two oligos at a time to introduce the changes. Mutations were confirmed by single strand DNA sequencing using M13 primers -20 and -40 as well as the mutagenic primers #2002 and #2004.

Primer #2002 was used to correct a reading frame error in starting clone 58.59.1.

Primer #2002 39 bases

5′-ACT CTA ACC ATG GAA TGG ATC TGG ATC TTT CTC CTC ATC

Primer #2380 was used to correct extra mutation added by #2004 which was missed in the first sequencing.

Primer #2380 39 bases

5′-TCA CTG CCT ATG TTA TAA GCT GGG TGA GGC AGG CAC CTG

As with the light chain, the heavy chain 5' Sal I site was changed to Hind III using linker oligo's #2334 and #2335 to allow cloning of the heavy chain variable region as Hind III/ Spe I (site introduced by primer #2007) fragment into the heavy chain constant region of CAMPATH-1H.

Construction of heavy chain

The following samples of DNA were used

1. Plasmid 1990

Human gamma-1 heavy chain constant region gene cloned into pUC18 (obtained from Martin Sims, Wellcome Foundation Ltd).

2. Plasmid 2387

Reshaped heavy chain of NSM 4.7.2.4 containing human framework regions and mouse gamma 1 constant region.

A Sal I site in the reshaped CD4 heavy chain was altered to a Hind III site. The variable region gene was excised by digestion with Hind III/Spe I and ligated with the constant region gene in plasmid 1990 to give a complete humanized heavy chain (plasmid 2486). The heavy chain gene was cut out of this plasmid with Hind III/EcoR I and ligated with the expression vector pEE6.

Construction of light chain

The following samples of DNA were used.

1. Plasmid 2028

CAMPATH-1H light chain gene cloned into M13mp18 at Sal I/BamH I restriction site.

2. Plasmid 2197

Reshaped light chain of NSM 4.7.2.4 containing human framework regions and mouse kappa constant region. A Kpn I site already had been introduced between variable and constant portions of this gene.

A Kpn I restriction site was introduced into the CAMPATH 1H light chain gene corresponding to the site in plasmid 2197 and an EcoR I site was introduced at the 3' end of the constant region. The constant region gene was excised from this plasmid (2502) by digestion with Hind III/Kpn I.

Meanwhile a Sal I site in plasmid 2197 was changed to a Hind III site (this step had to be repeated because a frame-shift mutation inadvertently was introduced the first time). The new plasmid (2736) was digested with Hind III/Kpn I. The CD4 variable region fragment was cloned into a plasmid containing the kappa constant region gene from plasmid 2502 to give a complete humanized light chain (plasmid 2548). The light chain gene was cut out from this plasmid with Hind III/EcoR I and ligated with the expression vector pEE12 to give plasmid 2798.

Ligation of heavy and light chains and expression in NSO cells

The heavy chain gene was excised from the pEE6 vector by digestion with Sal I/Bgl II and cloned into the light chain pEE12 vector which had been digested with BamH I/Sal I.

The final vector construct was checked by restriction digests with Hind III, EcoR I, Sal I, BamH I, Bgl II and Spe I for the presence of the expected fragments, including 700 bp light chain, 1400 bp heavy chain, 2300 bp fragment of pEE6 and 7000 bp fragment of pEE12.

The pEE12 vector was linearised by digestion with Sal I and transferred into NSO cells by electroporation, following a standard protocol (Celltech 1991) except that the selection medium was slightly modified, being based on IMDM rather than DMEM. Transfectants were selected in medium lacking glutamine, supplemented with dialysed FCS, ribonucleosides, glutamic acid, and asparagine as recommended.

The transfection mixes were cultured in three 96-well plates, and of 36 growing wells which were tested, 5 were strongly positive for production of human heavy and light chains (18 others were positive for one or other, or weakly positive for both).

A clone, designated SDG/B7B.A.7 was selected and stored frozen but no further characterization has been done on this wild type antibody.

Construction of mutant IgG1 antibody designated to abolish effector functions

Due to concerns about side effects of other CD4 antibodies reported in various clinical trials, it was considered desirable to avoid the possibility of engaging Fc receptors. Human IgG4 is thought to have minimal Fc binding or complement-activating ability. However, experiments have show that it does engage Fc receptors in some individuals (Greenwood et al., Eur. J. Immunol., Vol. 23, pgs. 1098-1104, 1993), and clinical studies with a human IgG4 variant to CAMPATH-1H have demonstrated an ability to kill cells *in vivo* (Isaacs et al., Clin. Exp. Immunol., Vol. 106, pgs. 427-433 (1996)). To eliminate the possibility of binding Fc receptors, constructs were made with mutations in the IgG1 heavy chain constant region.

TRX 1 has the mutations Leu^{236} to Ala and Gly^{238} to Ala, as shown in Figures 1D and 1E and Figures 3D and 3E. These particular residues were chosen because they were predicted to disrupt maximally binding to all three types of human Fc receptors for IgG. Either mutation is sufficient to reduce binding to Fc(RI (Woof, et al., Mol. Immunol, Vol. 332, pgs. 563-564, 1986; Duncan, et al., Nature, Vol. 332, pgs. 563-564 1988; Lund, et al., J. Immunol, Vol. 147, pgs. 2657-2662 1991) or Fc(RII (Lund et al., 1991; Sarmay et al., Mol. Immunol., Vol. 29, pgs. 633-639 1992) whereas Gly^{238} to Ala has the biggest effect on binding to Fc(RIII (Sarmay et al., 1992).

The following samples of DNA were used.

1. Plasmid 2555 and Plasmid 2555 Mut.

Humanized V_H region of NSM 4.7.2.4 cloned into pEE6 expression vector at a Hind III/Spe I restriction site. Plasmid 2555 then was mutated by site directed mutagenesis such that amino acid residue Asn^{101} was changed to Asp^{101}, as shown in Figures 1D and 1E and Figures 3D and 3E. The resulting plasmid is plasmid 2555 Mut.

2. Plasmid 2798

Humanized V_H region of NSM 4.7.2.4 joined to human kappa constant regions to give approx 700 bp fragment cloned into pEE12 expression vector at a Hind III/EcoR I.

3. Plasmid MF4260

Human IgG1 heavy chain associated with the humanized CD18 V_H region, having the mutations Leu^{236} to Ala and Gly^{238} to Ala as well as a Spe I restriction site introduced into framework region 4, cloned into pUC18.

The purpose of the Spe I restriction site is to allow separation and recombination of different variable regions.

The CD18 V_H region gene was excised from plasmid MF 4260 by digestion with Spe I and Hind III and the remaining vector, now having only the relevant heavy chain constant region, was purified using Geneclean. It was ligated with the humanized V_H region DNA of NSM 4.7.2.4 which had been isolated from plasmid 2555 Mut in the same way. The product was used to transform "Sure"

cells and colonies were checked for the presence of the expected 1400 bp complete heavy chain insert.

The complete V_H and constant region insert was excised from the pUC vector by digestion with Hind III and EcoR I. The 1400 bp fragment was purified using QiaexII (Qiagen) and then ligated in turn into the vector pEE6, which had previously been cut with the same enzymes.

The next step was to excise the CD4 heavy chain genes from the pEE6 vector and clone them into pEE12, already containing the humanized CD4 light chain gene (plasmid 2798). The pEE6 vector was digested with Sal I and Bgl II and the pEE12 vector was digested with Sal I and BamH I to create the appropriate sites for re-ligation.

The final vector construct was checked by restriction digests with Hind III, EcoR I, Sal I and Spe I for the presence of the expected fragment, *i.e.*, 700 bp light chain, 1400 bp heavy chain, 2300 bp fragment of pEE6, and 7000 bp fragment of pEE12.

The pEE12 vector was linearized by digestion with Sal I and transfected into NSO cells by electroporation as above. The transfection mixes were cultured in six 96-well plates, and of 90 growing wells which were tested, all were positive for production of human heavy and light chains. At this stage a sample of the pEE12 vector DNA was digested with Sal I, precipitated with ethanol and transferred to the Therapeutic Antibody Centre (TAC).

Target Cells For Final Transfection

NSO cells were obtained directly from the ECACC (clone CB1782, accession number 85110503). A master cell bank (MCB) was prepared at the Therapeutic Antibody Centre, Churchill Hospital, Oxford, England.

Transfection and Selection Of Final Transfectant

The pEE12 vector was transfected into NSO cells from the MCB by electroporation as hereinabove described. A total of $2x10^7$ cells were transfected with 80 μg of linearized plasmid DNA in a final volume of 2.0ml. The transfection mix was plated out in twelve 96-well plates and fed with selective medium according to the standard protocol (The Cell Tech Glutamine

Synthetase Gene Expression System, Version 2 - Expression from Myeloma Cells, Revision 6.) Six plates received selective medium containing 10(M methionine sulfoximine (MSX). .

Purification of the antibody

Culture supernatant is purified by using a Biopilot chromatography system (Pharmacia) in three steps as follows:

(1) Affinity chromatography on a column of Protein A-Sepharose Fast Flow

(2) Ion exchange chromatography on S-Sepharose Fast Flow

(3) Size exclusion chromatography on Superdex 20.

The purified product was filtered and pooled into a single biocontainer.

Throughout the purification process, precautions are taken to ensure that the system remains aseptic. All buffers and reagents are passed through a 0.2 micron membrane filter and the purified product is also passed through a 0.2 micron filter before being pooled. After a batch of antibody has been processed, the entire chromatography system and columns are sanitized with 0.5M NaOH, washed with sterile PBS and stored in 20% ethanol. Before it is used again, the ethanol is washed out with sterile PBS and a complete trial run is carried out. Samples of buffers and column eluates are checked for endotoxin level.

Example 2

Construction of TRX1 Antibody Starting from Nucleotide Sequence

Cloning of Human Constant Regions

Heavy Chain Constant Region

The human gamma 1 heavy chain constant region (IgG1) is amplified from human leukocyte cDNA (QUICK-Clone™ cDNA Cat. No. 7182-1, Clontech) using the following primer set and cloned into pCR-Script (Stratagene). The

plasmid containing the human gamma 1 heavy chain constant region in pCR-Script is designated pHCγ-1.

primer hcγ-1

Spe I
5' primer: 5'- *ACT AGT* CAC AGT CTC CTC AGC

primer hcγ-2

EcoR I
3' primer: 5'- *GAA TTC* ATT TAC CCG GAG ACA G

Non-Fc binding mutations (Leu^{236}Ala, Gly^{238}Ala) are made in the heavy chain constant region by site-directed mutagenesis using the following primer and the Transformer^{TM} Site-Directed Mutagenesis Kit from Clontech (Cat. No. K1600-1). The plasmid containing the human gamma 1 heavy chain non-Fc binding mutant constant region in pCR-Script is designated pHCγ-1Fcmut.

primer hcγ-3

Fc mut oligo: 5'- CCG TGC CCA GCA CCT GAA CTC
GCG GGG GCA CCG TCA GTC TTC
CTC CCC C

Light Chain Constant Region

The human kappa light chain constant region is amplified from human leukocyte cDNA (QUICK-Clone^{TM} cDNA Cat. No. 7182-1, Clontech) using the following primer set and cloned into pCR-Script (Stratagene). The plasmid containing the human kappa light chain constant region in pCR-Script is designated pLCκ-1.

primer lcκ-1

Kpn I
5' primer: 5'- *GGT ACC* AAG GTG GAA ATC AAA CGA AC

primer lcκ-2

Hind III
3' primer: 5'- *AAG CTT* CTA ACA CTC TCC CCT GTT G

Synthesis, Contruction and Cloning of TRX1 Variable Regions

The heavy and light chain variable regions are constructed from a set of partially overlapping and complementary synthetic oligonucleotides encompassing the entire variable regions. The oligonucleotide set used for each variable region is shown below.

Heavy Chain Variable Region Synthetic Oligonucleotides

Coding Strand Heavy Chain Variable Region Primers

***primer hv-1* (1 – 72) + 6 nucleotide linker**
5'- *aagctt* ATG GAA TGG ATC TGG ATC TTT CTC CTC ATC CTG TCA GGA ACT CGA GGT GTC CAG TCC CAG GTT CAG CTG GTG

***primer hv-2* (120 – 193)**
5'- C TGT AAG GCT TCT GGA TAC ACA TTC ACT GCC TAT GTT ATA AGC TGG GTG AGG CAG GCA CCT GGA CAG GGC CTT G

***primer hv-3* (223 – 292)**
5'- GGT AGT AGT TAT TAT AAT GAG AAG TTC AAG GGC AGG GTC ACA ATG ACT AGA GAC ACA TCC ACC AGC ACA G

***primer hv-4* (322 – 399)**
5'- GAG GAC ACT GCG GTC TAT TAC TGT GCA AGA TCC GGG GAC GGC AGT CGG TTT GTT TAC TGG GGC CAA GGG ACA CTA GT

Non-Coding Strand Heavy Chain Variable Region Primers

***primer hv-5* (140 – 51)**
5'- GTG TAT CCA GAA GCC TTA CAG GAC ACC TTC ACT GAA GCC CCA GGC TTC TTC ACT TCA GCT CCA GAC TGC ACC AGC TGA ACC TGG GAC TGG

***primer hv-6* (246 – 170)**
5'- CTT CTC ATT ATA ATA ACT ACT ACC GCT TCC AGG ATA AAT CTC TCC CAT CCA CTC AAG GCC CTG TCC AGG TGC CTG CC

***primer hv-7* (342 – 272)**
5'- GTA ATA GAC CGC AGT GTC CTC AGA CCT CAG GCT GCT GAG TTC CAT GTA GAC TGT GCT GGT GGA TGT GTC TC

Light Chain Variable Region Synthetic Oligonucleotides

Coding Strand Light Chain Variable Region Primers

***primer lv-1* (1 - 63) + 6 nucleotide linker**
5'- gaattc ATG GAG ACA GAC ACA ATC CTG CTA TGG GTG CTG CTG CTC TGG GTT CCA GGC TCC ACT GGT GAC

***primer lv-2* (93 - 158)**
5'- GGC TGT GTC TCT AGG TGA GAG GGC CAC CAT CAA CTG CAA GGC CAG CCA AAG TGT TGA TTA TGA TGG

***primer lv-3* (184 - 248)**

5'- CAG AAA CCA GGA CAG CCA CCC AAA CTC CTC ATC TAT GTT GCA TCC AAT CTA GAG TCT GGG GTC CC

primer lv-4 **(275 - 340)**
5'- GGA CAG ACT TCA CCC TCA CCA TCA GTT CTC TGC AGG CGG AGG ATG TTG CAG TCT ATT ACT GTC AGC

Non-Coding Strand Light Chain Variable Region Primers

primer lv-5 **(109-43)**
5'- CAC CTA GAG ACA CAG CCA AAG AAT CTG GAG ATT GGG TCA TCA CAA TGT CAC CAG TGG AGC CTG GAA C

primer lv-6 **(203-138)**
5'- GGT GGC TGT CCT GGT TTC TGT TGA TAC CAG TTC ATA TAA CTA TCA CCA TCA TAA TCA ACA CTT TGG

primer lv-7 **(294-228)**
5'- GGT GAG GGT GAA GTC TGT CCC AGA CCC ACT GCC ACT AAA CCT GTC TGG GAC CCC AGA CTC TAG ATT G

primer lv-8 **(378-319)**
5'- GGT ACC TCC ACC GAA CGT CGG AGG GTC CTG AAG ACT TTG CTG ACA GTA ATA GAC TGC AAC

After HPLC purification and removal of organic solvents the oligonucleotides are resuspended in TE pH8.0 and phosphorylated. An aliquot of each oligonucleotide in the respective variable region set then are combined in equal molar amounts. The oligonucleotide mixtures are heated to 68°C for 10 minutes and allowed to cool slowly to room temperature. The annealed oligonuceotides then are extended to produce double stranded variable region DNA fragments. For the extension, dNTPs are added to a final concentration of 0.25 mM followed by an appropriate volume of 5X T4 DNA polymerase buffer [165 mM Tris acetate, pH 7.9, 330 mM sodium acetate, 50mM magnesium acetate, 500 (g/ml BSA, 2.5mM DTT] and 4 units of T4 DNA polymerase. The mixture is incubated at 37°C for 1 hour followed by heat inactivation of the T4 DNA polymerase at 65°C for 5 minutes.

The double stranded DNA is ethanol precipitated and resuspended in the same volume of TE pH 8.0. An appropriate volume of 5X T4 DNA ligase buffer [250mM Tris-HCl, pH7.6, 50mM $MgCl_2$, 5mM ATP, 5mM DTT, 25% w/v polyethylene glycol-8000] then is added to the double stranded DNA followed by 2 units of T4 DNA ligase and the mixture incubated for 1 hour at 37°C to

ligate the extended fragments. The T4 DNA ligase then is heat inactivated at 65°C for 10 minutes. The variable region DNA fragments then are phenol extracted, ethanol precipitated, and resuspended in TE, pH 8.0 and cloned into pCR-Script (Stratagene). The resulting plasmid containing the heavy chain variable region is designated pHV-1 and the plasmid containing the light chain variable region was designated pLV-1.

The final heavy and light chain expression vectors are constructed in pcDNA 3.1 (Invitrogen). For the heavy chain expression vector, the Fc mutated constant region is released from plasmid pHC-1Fcmut by digestion with Spe I and EcoR I and isolated by agarose gel electrophoresis. The heavy chain variable region is released from plasmid pHV-1 by digestion with Hind III and Spe I and isolated by agarose gel electrophoresis. The two fragments in equal molar amounts are ligated into the Hind III/EcoR I sites of pcDNA3.1(+) (Invitrogen) using standard molecular biology techniques. The resulting TRX1 heavy chain expression vector is designated pTRX1/HC.

Similarly, for the light chain expression vector, the light chain constant region is released from plasmid pLC-1 by digestion with Kpn I and Hind III followed by agarose gel purification. The light chain variable region is released from pLV-1 by digestion with EcoR I and Kpn I followed by agarose gel purification. The two light chain fragments in equal molar amounts are ligated into the EcoR I/Hind III sites of pcDNA3.1(-) (Invitrogen) using standard molecular biology techniques yielding the TRX1 light chain expression vector pTRX1/LC.

For production of TRX1 antibody, the TRX1 heavy chain and TRX1 light chain expression plasmids are cotransfected into CHO cells using standard molecular biology techniques.

Example 3

A humanized antibody is shown in Figures 2A, 2C, 2D, and 2F is produced by a procedure similar to that of Example 1. The humanized antibody is an aglycosylated antibody.

Example 4

A humanized antibody as shown in Figures 4A, 4C, 4D and 4F is produced by a procedure similar to that of Example 1. The humanized antibody is an aglycosylated antibody.

Example 5

A mixed lymphocyte reaction (MLR) is used to generate human lymphocytes primed to recognize foreign human histocompatibility antigens. To generate this reaction human peripheral blood lymphocytes are isolated from heparinized whole blood from two different individuals (Donor A and Donor B) using Ficoll density gradient centrifugation or a similar method. Lymphocytes from Donor B are adjusted to 10^7/ml in RPMI 1640 media with no serum but containing 50ug/ml of mitomycin C. The cells are incubated at 37°C for 30 minutes and are then washed out of the media with mitomycin C in three centrifugations in RPMI 1640 with 10% Donor A plasma. Cells from Donor A, which have not been treated with mitomycin C, are adjusted to 4 x 10^6/ml in RPMI 1640 with 10% Donor A plasma. After washing, the mitomycin C treated lymphocytes from Donor B are adjusted to 4 x 10^6/ml in RPMI with 10% Donor A plasma. Equal volumes of Donor A and Donor B cells are combined and placed into the compound to be tested ("Test Compound") suitably sized tissue culture flasks. Flasks with and without Test Compound are then incubated at 37°C in 5% CO_2 in air for 7-10 days. This is the primary mixed lymphocyte reaction.

It can be observed that the cells in the primary MLR will become activated and begin to divide between days 3-7 and following a period of active proliferation, the cells will return to a more resting state. The time of this can vary, however, cells will usually return to rest between days 7-10. Once cells appear to be at rest, cells from primary MLR flasks with and without Test Compound can be recovered by centrifugation and resuspended in RPMI 1640 with 10% Donor A plasma at 4 x 10^6/ml. Fresh PBL can be prepared by Ficoll density centrifugation from heparinized whole blood from Donor B and again inactivated with mitomycin C, the inactivated Donor B cells are adjusted to 4 x

10^6/ml in RPMI 1640 with 10% Donor A plasma. For the second MLR, equal volumes of primary MLR cells (cells from the primary MLR which was performed in the absence of Test Compound) are mixed with mitomycin C inactivated Donor B cells.

If the primary MLR cells (cells obtained from an MLR which was performed in the absence of Test Compound) are labeled with CFSE, a green fluorescent dye which is imported into living cells where it is acted upon by an enzyme and then reacts with cellular proteins, the number of cell divisions experienced over time by the labeled cells is reflected in the reduction of green label associated with each cell. If CFSE labeled MLR cells are stimulated in a secondary MLR to which has been added cells derived from the Test Compound treated primary MLR at a ratio of 2:1 to 10:1 MLR to Test Compound derived MLR cells, inhibition of the proliferation of the CFSE labeled MLR cells will be observed in the secondary MLR within 3-4 days of stimulation when compared with proliferation of CFSE labeled MLR cells stimulated in the secondary MLR inthe absence of the Test Compound derived cells.

The cells produced in the primary MLR and secondary MLR (as well as cells provided in control MLRs) are analyzed for CD4+ CD25+ cells as hereinabove described.

When TRX1 was tested as hereinabove described, as compared to control, CD4+ CD25+ cells were reduced by more than 60% in the primary MLR and by more than 20% in the secondary MLR, and in the secondary MLR, as compared to control, the production of IL-2, IL-4 and IL-12 was essentially eliminated and the production of IL-5,IL-13, IFN, gamma and TNF alpha was reduced by more than 50%.

Example 6

The induction of antigen specific immunological tolerance in non-human primates by the use of the non-depleting anti-CD4 monoclonal antibody, TRX1, was demonstrated in the following study. Baboons (*Papio anubus*) were

randomly divided into seven groups of three animals. The seven groups were comprised of four experimental groups designated Groups 4, 6, 7 and 8 and three control groups designated Groups 1, 5, and 9. The study was comprised of 2 phases, an Immunization/Tolerization phase followed by a Challenge phase.

For the Immunization/Tolerization phase of the study, Groups 4, 6, 7 and 8 were immunized with 3 doses of Antigen 1 (10 mg/kg in saline), one dose each on day 0, day 4, and day 8. Antigen 1 is polyvalent aggregated horse IgG (Antivenin) given intravenously (i.v.) for the first dose and subcutaneously (SC) for all subsequent doses. During this phase of the protocol: groups 4, 6, 7 & 8 also received 4 doses i.v. of the non-depleting anti-CD4 monoclonal antibody, TRX1, as follows: Group 4 received 4 doses of 20 mg/kg at day –1, day 4, day 8 and day 12; Group 6 received 1 mg/kg of TRX 1 on day –1, day 3, day 8, and day 12. Group 7 received 10 mg/kg on day –1, day 3, day 8 and day 12. Group 8 received 40 mg/kg on day –1, day 3, day 8, and day 12.

Control Groups 1 and 5 were treated as follows during the Immunization/Tolerization phase of the protocol: Group 1 received 3 doses of Antigen 1 at 10 mg/kg, one dose each on day 0, day 4, and day 8. Group 5 received 4 doses i.v. of TRX1 antibody, 20 mg/kg, one dose each on day –1, day 4, day 8, and day 12. Group 9 received four doses IV of TRX 1 antibody, 40 mg/kg, one dose each on day –1, day 4, day 8, and day 12.

Blood was collected prior to each injection of Antigen 1 and/or TRX1 and weekly thereafter to assess serum level of TRX1 by ELISA, the pharmacodynamic effects of TRX1 treatment on the level of circulating lymphocyte subsets, as well as the percentage of CD4 receptor occupancy by flow cytometry, and the baboon antibody response to Antigen 1 by ELISA.

The immune response to antivenin for the first 68 days of the study for Groups 1, 4, 6, 7, and 8, as measured in antibody titer, is shown in Figure 5.

The Challenge phase of the study was initiated once the serum levels of TRX 1 reached undetectable levels. For the Challenge phase, all animals in all groups were challenged (Day 68) with Antigen 1 (10 mg/kg, SC) and Antigen 2 (1.7 ml/kg). Antigen 2 is a 10% saline solution of sheep red blood cells given IV for one dose. Challenges with Antigen 1 were repeated on day 95 and day 135 for Control Groups 5 and 9 and Test Groups 4 and 8. Blood was collected prior to each challenge to assess for serum levels of Antigen 1, TRX1, and the baboon antibody response to Antigen 1 and Antigen 2.

Figure 6 shows the immune response to antivenin, as measured in antibody titer, for all groups after the first challenge (days 68-95). Figure 7 shows the immune response to antivenin, as measured in antibody titer, for Groups 1, 4, 5, 8, and 9, after Challenge 1, Challenge 2, and Challenge 3.

The results of the immune response of groups 1, 4 and 5 to sheep red-blood cells is shown in Figure 8.

The disclosures of all patents, publications (including published patent applications), depository accession numbers, and database accession numbers are hereby incorporated by reference to the same extent as if each patent, publication, depository accession number, and database accession number were specifically and individually incorporated herein by reference.

It is to be understood, however, that the scope of the present invention is not to be limited to the specific embodiments described above. The invention may be practiced other than as particularly described and still be within the scope of the accompanying claims.

SEQUENCE LISTING

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cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 1020

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa 1080

gggcagcccc gagaaccaca ggtgtacacc ctgccccat cccgggatga gctgaccaag 1140

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag 1200

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc 1260

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1320

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1380

ctctccctgt ctccgggtaa atga 1404

<210> 9

<211> 467

<212> PRT

<213> Homo sapiens

<400> 9

Met Glu Trp Ile Trp Ile Phe Leu Leu Ile Leu Ser Gly Thr Arg Gly
1 5 10 15

Val Gln Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

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

Glu Trp Met Gly Glu Ile Tyr Pro Gly Ser Gly Ser Ser Tyr Tyr Asn
65 70 75 80

Glu Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
85 90 95

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Ser Gly Asp Gly Ser Arg Phe Val Tyr Trp Gly
115 120 125

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
130 135 140

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145 150 155 160

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
165 170 175

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
180 185 190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
195 200 205

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
210 215 220

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
225 230 235 240

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Ala Gly
245 250 255

Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
260 265 270

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
275 280 285

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
290 295 300

```
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
305                 310                 315                 320

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                325                 330                 335

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            340                 345                 350

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

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

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
385                 390                 395                 400

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                405                 410                 415

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            420                 425                 430

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        435                 440                 445

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    450                 455                 460

Pro Gly Lys
465
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<210> 10

<211> 448

<212> PRT

<213> Homo sapiens

<400> 10

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ala Tyr
            20                  25                  30

Val Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
```

```
Gly Glu Ile Tyr Pro Gly Ser Gly Ser Ser Tyr Tyr Asn Glu Lys Phe
    50                  55                  60

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

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Ser Gly Asp Gly Ser Arg Phe Val Tyr Trp Gly Gln Gly Thr
            100                 105                 110

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

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Ala Gly Ala Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            260                 265                 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320
```

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

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

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 11

<211> 717

<212> DNA

<213> Homo sapiens

<400> 11
atggagacag acacaatcct gctatgggtg ctgctgctct gggttccagg ctccactggt 60

gacattgtga tgacccaatc tccagattct ttggctgtgt ctctaggtga gagggccacc 120

atcaactgca aggccagcca aagtgttgat tatgatggtg atagttatat gaactggtat 180

caacagaaac caggacagcc acccaaactc ctcatctatg ttgcatccaa tctagagtct 240

ggggtcccag acaggtttag tggcagtggg tctgggacag acttcaccct caccatcagt 300

tctctgcagg cggaggatgt tgcagtctat tactgtcagc aaagtcttca ggaccctccg 360

acgttcggtg gaggtaccaa ggtggaaatc aaacgaactg tggctgcact atctgtcttc 420

atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg 480

aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg 540

ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc 600

agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc 660

acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgttag 717

<210> 12

<211> 238

<212> PRT

<213> Homo sapiens

<400> 12

Met Glu Thr Asp Thr Ile Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

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

Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Gln Ser
35 40 45

Val Asp Tyr Asp Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
50 55 60

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

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
85 90 95

Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys
100 105 110

Gln Gln Ser Leu Gln Asp Pro Pro Thr Phe Gly Gly Gly Thr Lys Val
115 120 125

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

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

Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
165 170 175

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

Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala
195 200 205

Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
210 215 220

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 13

<211> 717

<212> DNA

<213> Homo sapiens

<400> 13
atggagacag acacaatcct gctatgggtg ctgctgctct gggttccagg ctccactggt 60

gacattgtga tgacccaatc tccagattct ttggctgtgt ctctaggtga gagggccacc 120

atcaactgca aggccagcca aagtgttgat tatgatggtg atagttatat gaactggtat 180

caacagaaac caggacagcc acccaaactc ctcatctatg ttgcatccaa tctagagtct 240

ggggtcccag acaggtttag tggcagtggg tctgggacag acttcaccct caccatcagt 300

tctctgcagg cggaggatgt tgcagtctat tactgtcagc aaagtcttca ggaccctccg 360

acgttcggtg gaggtaccaa ggtggaaatc aaacgaactg tggctgcact atctgtcttc 420

atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg 480

aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg 540

ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc 600

agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc 660

acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgttag 717

<210> 14

<211> 238

<212> PRT

<213> Homo sapiens

<400> 14
Met Glu Thr Asp Thr Ile Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

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

Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Gln Ser
35 40 45

Val Asp Tyr Asp Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
50 55 60

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

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
85 90 95

Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys
100 105 110

Gln Gln Ser Leu Gln Asp Pro Pro Thr Phe Gly Gly Gly Thr Lys Val
115 120 125

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

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

Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
165 170 175

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

Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala
195 200 205

Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
210 215 220

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 15

<211> 218

<212> PRT

<213> Homo sapiens

<400> 15

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

Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
20 25 30

Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Val Ala Ser Asn Leu Glu Ser Gly Val Pro Asp
50 55 60

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

Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Ser Leu
85 90 95

Gln Asp Pro Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

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

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 16

<211> 1404

<212> DNA

<213> Homo sapiens

<400> 16
atggaatgga tctggatctt tctcctcatc ctgtcaggaa ctcgaggtgt ccagtcccag 60

gttcagctgg tgcagtctgg agctgaagtg aagaagcctg gggcttcagt gaaggtgtcc 120

tgtaaggctt ctggatacac attcactgcc tatgttataa gctgggtgag gcaggcacct 180

ggacagggcc ttgagtggat gggagagatt tatcctggaa gcggtagtag ttattataat 240

gagaagttca agggcagggt cacaatgact agagacacat ccaccagcac agtctacatg 300

gaactcagca gcctgaggtc tgaggacact gcggtctatt actgtgcaag atccggggac 360

ggcagtcggt ttgtttactg gggccaaggg acactagtca cagtctcctc agcctccacc 420

aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 480

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 540

ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 600

tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 660

aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt 720

gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc 780

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 840

tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac 900

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacgc cagcacgtac 960

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 1020

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa 1080

gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggatga gctgaccaag 1140

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag 1200

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc 1260

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1320

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1380

ctctccctgt ctccgggtaa atga 1404

<210> 17

<211> 467

<212> PRT

<213> Homo sapiens

<400> 17

Met Glu Trp Ile Trp Ile Phe Leu Leu Ile Leu Ser Gly Thr Arg Gly
1 5 10 15

Val Gln Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

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

Glu Trp Met Gly Glu Ile Tyr Pro Gly Ser Gly Ser Ser Tyr Tyr Asn
65 70 75 80

```
Glu Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
                85                  90                  95

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Ser Gly Asp Gly Ser Arg Phe Val Tyr Trp Gly
        115                 120                 125

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
    130                 135                 140

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145                 150                 155                 160

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
                165                 170                 175

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
            180                 185                 190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
        195                 200                 205

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
    210                 215                 220

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
225                 230                 235                 240

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
                245                 250                 255

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            260                 265                 270

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        275                 280                 285

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    290                 295                 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr
305                 310                 315                 320

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                325                 330                 335

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            340                 345                 350
```

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

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

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
385 390 395 400

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
405 410 415

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
420 425 430

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
435 440 445

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
450 455 460

Pro Gly Lys
465

<210> 18

<211> 1404

<212> DNA

<213> Homo sapiens

<400> 18
atggaatgga tctggatctt tctcctcatc ctgtcaggaa ctcgaggtgt ccagtcccag 60

gttcagctgg tgcagtctgg agctgaagtg aagaagcctg gggcttcagt gaaggtgtcc 120

tgtaaggctt ctggatacac attcactgcc tatgttataa gctgggtgag gcaggcacct 180

ggacagggcc ttgagtggat gggagagatt tatcctggaa gcggtagtag ttattataat 240

gagaagttca agggcagggt cacaatgact agagacacat ccaccagcac agtctacatg 300

gaactcagca gcctgaggtc tgaggacact gcggtctatt actgtgcaag atccggggac 360

ggcagtcggt ttgtttactg gggccaaggg acactagtca cagtctcctc agcctccacc 420

aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 480

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 540

ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 600

tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 660

aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt 720

gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc 780

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 840

tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac 900

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacgc cagcacgtac 960

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 1020

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa 1080

gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggatga gctgaccaag 1140

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag 1200

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc 1260

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1320

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1380

ctctccctgt ctccgggtaa atga 1404

<210> 19

<211> 467

<212> PRT

<213> Homo sapiens

<400> 19

Met Glu Trp Ile Trp Ile Phe Leu Leu Ile Leu Ser Gly Thr Arg Gly
1 5 10 15

Val Gln Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

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

Glu Trp Met Gly Glu Ile Tyr Pro Gly Ser Gly Ser Ser Tyr Tyr Asn
65 70 75 80

Glu Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
85 90 95

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Ser Gly Asp Gly Ser Arg Phe Val Tyr Trp Gly
115 120 125

```
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
    130                 135                 140

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145                 150                 155                 160

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
                165                 170                 175

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
            180                 185                 190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
        195                 200                 205

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
    210                 215                 220

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
225                 230                 235                 240

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
                245                 250                 255

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            260                 265                 270

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        275                 280                 285

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    290                 295                 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr
305                 310                 315                 320

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                325                 330                 335

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            340                 345                 350

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

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

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
385                 390                 395                 400
```

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
405 410 415

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
420 425 430

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
435 440 445

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
450 455 460

Pro Gly Lys
465

<210> 20

<211> 448

<212> PRT

<213> Homo sapiens

<400> 20

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ala Tyr
20 25 30

Val Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Glu Ile Tyr Pro Gly Ser Gly Ser Ser Tyr Tyr Asn Glu Lys Phe
50 55 60

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

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Gly Asp Gly Ser Arg Phe Val Tyr Trp Gly Gln Gly Thr
100 105 110

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

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140

```
Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            260                 265                 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
                325                 330                 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

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

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                405                 410                 415
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Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 21

<211> 717

<212> DNA

<213> Homo sapiens

<400> 21
atggagacag acacaatcct gctatgggtg ctgctgctct gggttccagg ctccactggt 60

gacattgtga tgacccaatc tccagattct ttggctgtgt ctctaggtga gagggccacc 120

atcaactgca aggccagcca aagtgttgat tatgatggtg atagttatat gaactggtat 180

caacagaaac caggacagcc acccaaactc ctcatctatg ttgcatccaa tctagagtct 240

ggggtcccag acaggtttag tggcagtggg tctgggacag acttcaccct caccatcagt 300

tctctgcagg cggaggatgt tgcagtctat tactgtcagc aaagtcttca ggaccctccg 360

acgttcggtg gaggtaccaa ggtggaaatc aaacgaactg tggctgcact atctgtcttc 420

atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg 480

aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg 540

ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc 600

agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc 660

acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgttag 717

<210> 22

<211> 238

<212> PRT

<213> Homo sapiens

<400> 22

Met Glu Thr Asp Thr Ile Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

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

Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Gln Ser
35 40 45

Val Asp Tyr Asp Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
50 55 60

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

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
85 90 95

Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys
100 105 110

Gln Gln Ser Leu Gln Asp Pro Pro Thr Phe Gly Gly Gly Thr Lys Val
115 120 125

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

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

Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
165 170 175

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

Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala
195 200 205

Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
210 215 220

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 23

<211> 717

<212> DNA

<213> Homo sapiens

<400> 23
atggagacag acacaatcct gctatgggtg ctgctgctct gggttccagg ctccactggt 60

gacattgtga tgacccaatc tccagattct ttggctgtgt ctctaggtga gagggccacc 120

atcaactgca aggccagcca aagtgttgat tatgatggtg atagttatat gaactggtat 180

caacagaaac caggacagcc acccaaactc ctcatctatg ttgcatccaa tctagagtct 240

ggggtcccag acaggtttag tggcagtggg tctgggacag acttcaccct caccatcagt 300

tctctgcagg cggaggatgt tgcagtctat tactgtcagc aaagtcttca ggaccctccg 360

acgttcggtg gaggtaccaa ggtggaaatc aaacgaactg tggctgcact atctgtcttc 420

atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg 480

aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg 540

ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc 600

agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc 660

acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgttag 717

<210> 24

<211> 238

<212> PRT

<213> Homo sapiens

<400> 24

Met Glu Thr Asp Thr Ile Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

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

Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Gln Ser
35 40 45

Val Asp Tyr Asp Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
50 55 60

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

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
85 90 95

Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys
100 105 110

Gln Gln Ser Leu Gln Asp Pro Pro Thr Phe Gly Gly Gly Thr Lys Val
115 120 125

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

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

Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
165 170 175

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

Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala
195 200 205

Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
210 215 220

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 25

<211> 218

<212> PRT

<213> Homo sapiens

<400> 25

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

Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
20 25 30

Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Val Ala Ser Asn Leu Glu Ser Gly Val Pro Asp
50 55 60

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

Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Ser Leu
85 90 95

Gln Asp Pro Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

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

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 26

<211> 1404

<212> DNA

<213> Homo sapiens

<400> 26
atggaatgga tctggatctt tctcctcatc ctgtcaggaa ctcgaggtgt ccagtcccag 60

gttcagctgg tgcagtctgg agctgaagtg aagaagcctg gggcttcagt gaaggtgtcc 120

tgtaaggctt ctggatacac attcactgcc tatgttataa gctgggtgag gcaggcacct 180

ggacagggcc ttgagtggat gggagagatt tatcctggaa gcggtagtag ttattataat 240

gagaagttca agggcagggt cacaatgact agagacacat ccaccagcac agtctacatg 300

gaactcagca gcctgaggtc tgaggacact gcggtctatt actgtgcaag atccggggac 360

ggcagtcggt ttgtttactg gggccaaggg acactagtca cagtctcctc agcctccacc 420

aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 480

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 540

ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 600

tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 660

aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt 720

gacaaaactc acacatgccc accgtgccca gcacctgaac tcgcgggggc accgtcagtc 780

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 840

tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac 900

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac 960

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 1020

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa 1080

gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggatga gctgaccaag 1140

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag 1200

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc 1260

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1320

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1380

ctctccctgt ctccgggtaa atga 1404

<210> 27

<211> 467

<212> PRT

<213> Homo sapiens

<400> 27

Met Glu Trp Ile Trp Ile Phe Leu Leu Ile Leu Ser Gly Thr Arg Gly
1 5 10 15

Val Gln Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

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

Glu Trp Met Gly Glu Ile Tyr Pro Gly Ser Gly Ser Ser Tyr Tyr Asn
65 70 75 80

Glu Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
85 90 95

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Ser Gly Asp Gly Ser Arg Phe Val Tyr Trp Gly
115 120 125

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
130 135 140

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145 150 155 160

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
165 170 175

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
180 185 190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
195 200 205

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
210 215 220

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
225 230 235 240

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Ala Gly
245 250 255

Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
260 265 270

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
275 280 285

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
290 295 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
305 310 315 320

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
325 330 335

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
340 345 350

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

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

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
385 390 395 400

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
405 410 415

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
420 425 430

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
435 440 445

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
450 455 460

Pro Gly Lys
465

<210> 28

<211> 1404

<212> DNA

<213> Homo sapiens

<400> 28
atggaatgga tctggatctt tctcctcatc ctgtcaggaa ctcgaggtgt ccagtcccag 60

gttcagctgg tgcagtctgg agctgaagtg aagaagcctg gggcttcagt gaaggtgtcc 120

tgtaaggctt ctggatacac attcactgcc tatgttataa gctgggtgag gcaggcacct 180

ggacagggcc ttgagtggat gggagagatt tatcctggaa gcggtagtag ttattataat 240

gagaagttca agggcagggt cacaatgact agagacacat ccaccagcac agtctacatg 300

gaactcagca gcctgaggtc tgaggacact gcggtctatt actgtgcaag atccggggac 360

ggcagtcggt ttgtttactg gggccaaggg acactagtca cagtctcctc agcctccacc 420

aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 480

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 540

ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 600

tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 660

aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt 720

gacaaaactc acacatgccc accgtgccca gcacctgaac tcgcgggggc accgtcagtc 780

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 840

tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac 900

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac 960

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 1020

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa 1080

gggcagcccc gagaaccaca ggtgtacacc ctgccccccat cccgggatga gctgaccaag 1140

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag 1200

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc 1260

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1320

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1380

ctctccctgt ctccgggtaa atga 1404

<210> 29

<211> 467

<212> PRT

<213> Homo sapiens

<400> 29

Met Glu Trp Ile Trp Ile Phe Leu Leu Ile Leu Ser Gly Thr Arg Gly
1 5 10 15

Val Gln Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

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

Glu Trp Met Gly Glu Ile Tyr Pro Gly Ser Gly Ser Ser Tyr Tyr Asn
65 70 75 80

Glu Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
85 90 95

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Ser Gly Asp Gly Ser Arg Phe Val Tyr Trp Gly
115 120 125

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
130 135 140

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145 150 155 160

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
165 170 175

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
180 185 190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
195 200 205

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
210 215 220

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
225 230 235 240

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Ala Gly
245 250 255

Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
260 265 270

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
275 280 285

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
290 295 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
305 310 315 320

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
325 330 335

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
340 345 350

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

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

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
385 390 395 400

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
405 410 415

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
420 425 430

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
435 440 445

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
450 455 460

Pro Gly Lys
465

<210> 30

<211> 448

<212> PRT

<213> Homo sapiens

<400> 30

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ala Tyr
20 25 30

Val Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Glu Ile Tyr Pro Gly Ser Gly Ser Ser Tyr Tyr Asn Glu Lys Phe
50 55 60

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

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Gly Asp Gly Ser Arg Phe Val Tyr Trp Gly Gln Gly Thr
100 105 110

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

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Ala Gly Ala Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
290 295 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

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

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 31

<211> 717

<212> DNA

<213> Homo sapiens

<400> 31
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gacattgtga tgacccaatc tccagattct ttggctgtgt ctctaggtga gagggccacc 120

atcaactgca aggccagcca aagtgttgat tatgatggtg atagttatat gaactggtat 180

caacagaaac caggacagcc acccaaactc ctcatctatg ttgcatccaa tctagagtct 240

ggggtcccag acaggtttag tggcagtggg tctgggacag acttcaccct caccatcagt 300

tctctgcagg cggaggatgt tgcagtctat tactgtcagc aaagtcttca ggaccctccg 360

acgttcggtg gaggtaccaa ggtggaaatc aaacgaactg tggctgcacc atctgtcttc 420

atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg 480

aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg 540

ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc 600

agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc 660

acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgttag 717

<210> 32

<211> 238

<212> PRT

<213> Homo sapiens

<400> 32

Met Glu Thr Asp Thr Ile Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

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

Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Gln Ser
35 40 45

Val Asp Tyr Asp Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
50 55 60

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

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
85 90 95

Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys
100 105 110

Gln Gln Ser Leu Gln Asp Pro Pro Thr Phe Gly Gly Gly Thr Lys Val
115 120 125

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

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

Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
165 170 175

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

Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala
195 200 205

Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
210 215 220

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 33

<211> 716

<212> DNA

<213> Homo sapiens

<400> 33
atggagacag acacaatcct gctatgggtg ctgctgctct gggttccagg ctccactggt 60

gacattgtga tgacccaatc tccagattct ttggctgtgt ctctaggtga gagggccacc 120

atcaactgca aggccagcca aagtgttgat tatgatggtg atagttatat gaactggtat 180

caacagaaac caggacagcc acccaaactc ctcatctatg ttgcatccaa tctagagtct 240

ggggtcccag acaggtttag tggcagtggg tctgggacag acttcaccct caccatcagt 300

tctctgcagg cggaggatgt tgcagtctat tactgtcagc aaagtcttca ggaccctccg 360

acgttcggtg gaggtaccaa ggtggaaatc aaacgaactg tggctgcacc atctgtcttc 420

atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg 480

aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg 540

ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc 600

acaccctgac gctgagcaaa gcagactacg agaaacacaa agtctacgcc tgcgaagtca 660

cccatcaggg cctgagctcg cccgtcacaa agagcttcaa caggggagag tgttag 716

<210> 34

<211> 238

<212> PRT

<213> Homo sapiens

<400> 34

Met Glu Thr Asp Thr Ile Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

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

Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Gln Ser
35 40 45

Val Asp Tyr Asp Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
50 55 60

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

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
85 90 95

Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys
100 105 110

Gln Gln Ser Leu Gln Asp Pro Pro Thr Phe Gly Gly Gly Thr Lys Val
115 120 125

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

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

Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn
165 170 175

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

Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala
195 200 205

Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly
210 215 220

Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> 35

<211> 218

<212> PRT

<213> Homo sapiens

<400> 35

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

Glu Arg Ala Thr Ile Asn Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
20 25 30

Gly Asp Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Val Ala Ser Asn Leu Glu Ser Gly Val Pro Asp
50 55 60

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

Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Ser Leu
85 90 95

Gln Asp Pro Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
100 105 110

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

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
130 135 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145 150 155 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 36

<211> 1404

<212> DNA

<213> Homo sapiens

<400> 36
atggaatgga tctggatctt tctcctcatc ctgtcaggaa ctcgaggtgt ccagtcccag 60

gttcagctgg tgcagtctgg agctgaagtg aagaagcctg gggcttcagt gaaggtgtcc 120

tgtaaggctt ctggatacac attcactgcc tatgttataa gctgggtgag gcaggcacct 180

ggacagggcc ttgagtggat gggagagatt tatcctggaa gcggtagtag ttattataat 240

gagaagttca agggcagggt cacaatgact agagacacat ccaccagcac agtctacatg 300

gaactcagca gcctgaggtc tgaggacact gcggtctatt actgtgcaag atccggggac 360

ggcagtcggt ttgtttactg gggccaaggg acactagtca cagtctcctc agcctccacc 420

aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 480

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 540

ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 600

tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 660

aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt 720

gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc 780

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 840

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ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacgc cagcacgtac 960

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 1020

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa 1080

gggcagcccc gagaaccaca ggtgtacacc ctgccccccat cccgggatga gctgaccaag 1140

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag 1200

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc 1260

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1320

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1380

ctctccctgt ctccgggtaa atga 1404

<210> 37

<211> 467

<212> PRT

<213> Homo sapiens

<400> 37

Met Glu Trp Ile Trp Ile Phe Leu Leu Ile Leu Ser Gly Thr Arg Gly
1 5 10 15

Val Gln Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

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

Glu Trp Met Gly Glu Ile Tyr Pro Gly Ser Gly Ser Ser Tyr Tyr Asn
65 70 75 80

Glu Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
85 90 95

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Ser Gly Asp Gly Ser Arg Phe Val Tyr Trp Gly
115 120 125

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
130 135 140

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145 150 155 160

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
165 170 175

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
180 185 190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
195 200 205

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
210 215 220

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
225 230 235 240

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
245 250 255

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
260 265 270

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
275 280 285

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
290 295 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr
305 310 315 320

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
325 330 335

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
340 345 350

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

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

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
385 390 395 400

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
405 410 415

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
420 425 430

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
435 440 445

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
450 455 460

Pro Gly Lys
465

<210> 38

<211> 1404

<212> DNA

<213> Homo sapiens

<400> 38
atggaatgga tctggatctt tctcctcatc ctgtcaggaa ctcgaggtgt ccagtcccag 60

gttcagctgg tgcagtctgg agctgaagtg aagaagcctg gggcttcagt gaaggtgtcc 120

tgtaaggctt ctggatacac attcactgcc tatgttataa gctgggtgag gcaggcacct 180

ggacagggcc ttgagtggat gggagagatt tatcctggaa gcggtagtag ttattataat 240

gagaagttca agggcagggt cacaatgact agagacacat ccaccagcac agtctacatg 300

gaactcagca gcctgaggtc tgaggacact gcggtctatt actgtgcaag atccggggac 360

ggcagtcggt ttgtttactg gggccaaggg acactagtca cagtctcctc agcctccacc 420

aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 480

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 540

ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 600

tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 660

aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt 720

gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc 780

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 840

tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac 900

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacgc cagcacgtac 960

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 1020

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa 1080

gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggatga gctgaccaag 1140

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag 1200

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc 1260

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1320

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1380

ctctccctgt ctccgggtaa atga 1404

<210> 39

<211> 467

<212> PRT

<213> Homo sapiens

<400> 39

Met Glu Trp Ile Trp Ile Phe Leu Leu Ile Leu Ser Gly Thr Arg Gly
1 5 10 15

Val Gln Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

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

Glu Trp Met Gly Glu Ile Tyr Pro Gly Ser Gly Ser Ser Tyr Tyr Asn
65 70 75 80

Glu Lys Phe Lys Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
85 90 95

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Ser Gly Asp Gly Ser Arg Phe Val Tyr Trp Gly
115 120 125

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
130 135 140

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
145 150 155 160

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
165 170 175

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
180 185 190

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
195 200 205

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
210 215 220

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
225 230 235 240

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
245 250 255

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
260 265 270

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
275 280 285

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
290 295 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr
305 310 315 320

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
325 330 335

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
340 345 350

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

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

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
385 390 395 400

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
405 410 415

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
420 425 430

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
435 440 445

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
450 455 460

Pro Gly Lys
465

<210> 40

<211> 448

<212> PRT

<213> Homo sapiens

<400> 40

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ala Tyr
20 25 30

Val Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Glu Ile Tyr Pro Gly Ser Gly Ser Ser Tyr Tyr Asn Glu Lys Phe
50 55 60

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

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Gly Asp Gly Ser Arg Phe Val Tyr Trp Gly Gln Gly Thr
100 105 110

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

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
130 135 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145 150 155 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
165 170 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
180 185 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
195 200 205

Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr
210 215 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225 230 235 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
245 250 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
260 265 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
275 280 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val
290 295 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305 310 315 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
325 330 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
340 345 350

Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys
355 360 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
370 375 380

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

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
405 410 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
420 425 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 41

<211> 135

<212> PRT

<213> Homo sapiens

<400> 41

Met Val Leu Gln Thr Gln Val Phe Ile Ser Leu Leu Leu Trp Ile Ser
1 5 10 15

Gly Ala Tyr Gly Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala
20 25 30

Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser
35 40 45

Leu Leu Tyr Ser Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln
50 55 60

Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg
65 70 75 80

Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
85 90 95

Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr
100 105 110

Tyr Cys Gln Gln Tyr Tyr Ser Thr Pro Pro Met Phe Gly Gln Gly Thr
115 120 125

Lys Val Glu Ile Lys Arg Thr
130 135

<210> 42

<211> 142

<212> PRT

<213> Homo sapiens

<400> 42

Leu Leu Ala Val Ala Pro Gly Ala His Ser Gln Val Gln Leu Val Gln
1 5 10 15

Ser Gly Ala Glu Val Lys Lys Pro Gly Ala Ser Val Lys Val Ser Cys
20 25 30

Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Tyr Met His Trp Val Arg
35 40 45

Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Ile Ile Asn Pro Ser
50 55 60

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

Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr Met Glu Leu Ser Ser Leu
85 90 95

Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Glu Lys Leu Ala
100 105 110

Thr Thr Ile Phe Gly Val Leu Ile Ile Thr Gly Met Asp Tyr Trp Gly
115 120 125

Gln Gly Thr Leu Val Thr Val Ser Ser Gly Ser Ala Ser Ala
130 135 140

<210> 43

<211> 76

<212> DNA

<213> ARTIFICIAL SEQUENCE

<220>

<223> PCR Primer

<400> 43
tgacattgtg atgacccaat ctccagattc tttggctgtg tctctaggtg agagggccac 60

catcaactgc aaggcc 76

<210> 44

<211> 29

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 44
tgaactggta tcaacagaaa ccaggacag 29

<210> 45

<211> 28

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 45
agagtctggg gtcccagaca ggtttagt 28

<210> 46

<211> 42

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 46
gtcttcagga ccctccgacg ttcggtggag gtaccaagct gg 42

<210> 47

<211> 52

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 47
caccctcacc atcagttctc tgcaggcgga ggatgttgca gtctattagt gt 52

<210> 48

<211> 24

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 48
agctttacag ttactgagca caca 24

<210> 49

<211> 24

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 49
tcgatgtgtg ctcagtaact gtaa 24

<210> 50

<211> 75

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 50
ggttcagctg gtgcagtctg gagctgaagt gaagaagcct ggggcttcag tgaaggtgtc 60

ctgtaaggct tctgg 75

<210> 51

<211> 52

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 51
agctgggtga ggcaggcacc tggacagggc cttgagtgga tgggagagat tt 52

<210> 52

<211> 60

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 52
caagggcagg gtcacaatga ctagagacac atccaccagc acagtctaca tggaactcag 60

<210> 53

<211> 43

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 53
cagcctgagg tctgaggaca ctgcggtcta ttactgtgca aga 43

<210> 54

<211> 24

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 54
gccaagggac actagtcact gtgt 24

<210> 55

<211> 39

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 55
tcactgccta tgttataagc tgggtgaggc aggcacctg 39

<210> 56

<211> 39

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 56
actctaacca tggaatggat ctggatcttt ctcctcatc 39

<210> 57

<211> 21

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 57
actagtcaca gtctcctcag c 21

<210> 58

<211> 22

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 58
gaattcattt acccggagac ag 22

<210> 59

<211> 49

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 59
ccgtgcccag cacctgaact cgcgggggca ccgtcagtct tcctccccc 49

<210> 60

<211> 26

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 60
ggtaccaagg tggaaatcaa acgaac 26

<210> 61

<211> 25

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 61
aagcttctaa cactctcccc tgttg 25

<210> 62

<211> 78

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 62
aagcttatgg aatggatctg gatctttctc ctcatcctgt caggaactcg aggtgtccag 60

tcccaggttc agctggtg 78

<210> 63

<211> 74

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 63
ctgtaaggct tctggataca cattcactgc ctatgttata agctgggtga ggcaggcacc 60

tggacagggc cttg 74

<210> 64

<211> 70

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 64
ggtagtagtt attataatga gaagttcaag ggcagggtca caatgactag agacacatcc 60

accagcacag 70

<210> 65

<211> 77

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 65
gaggacactg cggtctatta ctgtgcaaga tccggggacg gcagtcggtt tgtttactgg 60

ggccaaggga cactagt 77

<210> 66

<211> 90

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 66
gtgtatccag aagccttaca ggacaccttc actgaagccc caggcttctt cacttcagct 60

ccagactgca ccagctgaac ctgggactgg 90

<210> 67

<211> 77

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 67
cttctcatta taataactac taccgcttcc aggataaatc tctcccatcc actcaaggcc 60

ctgtccaggt gcctgcc 77

<210> 68

<211> 71

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 68
gtaatagacc gcagtgtcct cagacctcag gctgctgagt tccatgtaga ctgtgctggt 60

ggatgtgtct c 71

<210> 69

<211> 69

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 69
gaattcatgg agacagacac aatcctgcta tgggtgctgc tgctctgggt tccaggctcc 60

actggtgac 69

<210> 70

<211> 66

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 70
ggctgtgtct ctaggtgaga gggccaccat caactgcaag gccagccaaa gtgttgatta 60

tgatgg 66

<210> 71

<211> 65

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 71
cagaaaccag gacagccacc caaactcctc atctatgttg catccaatct agagtctggg 60

gtccc 65

<210> 72

<211> 66

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 72
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gtcagc 66

<210> 73

<211> 67

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 73
cacctagaga cacagccaaa gaatctggag attgggtcat cacaatgtca ccagtggagc 60

ctggaac 67

<210> 74

<211> 66

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 74
ggtggctgtc ctggtttctg ttgataccag ttcatataac tatcaccatc ataatcaaca 60

ctttgg 66

<210> 75

<211> 67

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 75
ggtgagggtg aagtctgtcc cagacccact gccactaaac ctgtctggga ccccagactc 60

tagattg 67

<210> 76

<211> 60

<212> DNA

<213> Artificial sequence

<220>

<223> PCR Primer

<400> 76
ggtacctcca ccgaacgtcg gagggtcctg aagactttgc tgacagtaat agactgcaac 60

WHAT IS CLAIMED IS:

1. A process for treating a primate to induce tolerance to at least one antigen comprising:

treating a primate by administering to a primate at least one compound, said compound being a compound that in a primary mixed lymphocyte reaction in vitro reduces the amount of CD4+ CD25+ cells produced in said mixed lymphocyte reaction and that generates in said primary mixed lymphocyte reaction a cell population that reduces at least one of (x) the amount of CD4+ CD25+cells produced in vitro in at least one of a primary and secondary mixed lymphocyte reaction, and (y) the amount of at least one of IL-2, IL-4 and IL-12 in a secondary mixed lymphocyte reaction, said compound being administered in an amount and for a time effective to induce tolerance against said at least one antigen, said compound being present in said primate when said at least one antigen is present in said primate.

2. The process of Claim 1 wherein the compound reduces the amount of $CD24^+$ $CD25^+$ cells in a primary mixed lymphocyte reaction by at least 40%.

3. The process of Claim 2 wherein the compound reduces the amount of $CD24^+$ $CD25^+$ cells in a primary mixed lymphocyte reaction by at least 60%.

4. The process of Claim 2 wherein said cell population produced in the primary mixed lymphocyte reaction reduces the amount of $CD24^+$ $CD25^+$ cells produced in a secondary mixed lymphocyte reaction.

5. The process of Claim 4 wherein the $CD24^+$ $CD25^+$ cells produced in the secondary mixed lymphocyte reaction are reduced by at least 20%.

6. The process of Claim 5 wherein the $CD24^+$ $CD25^+$ cells produced in the secondary mixed lymphocyte reaction are reduced by at least 35%.

7. The process of Claim 5 wherein in the secondary mixed lymphocyte reaction the generation of at least one of IL-2, IL-4 and IL-12 is reduced by at least 40%.

8. The process of Claim 7 wherein said compound is an antibody.

9. The process of Claim 8 wherein said antibody is a CD4 antibody

10. A process for treating a primate to induce tolerance to at least one antigen comprising:

treating a primate by administering to a primate at least one CD4 antibody or CD4 binding fragment thereof in an amount and for a time effective to induce tolerance against at least one antigen, said CD4 antibody or fragment being present in said primate when said antigen is present in said primate and being administered in an initial dose of at least 40 mg, said treating inducing tolerance against said at least one antigen.

11. The process of Claim 10 wherein the initial dose is at least 70 mg.

12. The process of Claim 11 wherein the initial dose is at least 400 mg.

13. The process of Claim 12 wherein the initial dose is at least 500 mg.

14. The process of Claim 10 wherein said at least one CD4 antibody is administered in at least one followup dose and said followup dose is at least 40 mg.

15. The process of Claim 10 wherein said at least one antigen is a foreign antigen.

16. The process of Claim 15 wherein the CD4 antibody has an aglycosylated Fc portion.

17. The process of Claim 10 wherein the antibody is a CD4 antibody that binds to the same epitope as an antibody selected from the group consisting of the antibody shown in Figure 1, the antibody shown in Figure 2 and the antibody shown in Figure 3 and the antibody shown in Figure 4.

18. The process of Claim 17 wherein the antibody is a humanized antibody or fragment thereof.

19. The process of Claim 18 wherein the antibody does not bind to the Fc receptor.

20. The process of Claim 19 wherein the initial dose is at least 70 mg.

21. The process of Claim 20 wherein the initial dose is at least 400 mg.

22. An antibody that binds to the same epitope as a humanized antibody selected from the group consisting of the humanized antibody shown in Figure 1 and the humanized antibody shown in Figure 2 and the humanized antibody shown in Figure 3 and the humanized antibody shown in Figure 4.

23. The antibody of Claim 22 wherein said antibody is a humanized antibody or fragment thereof.

24. The antibody of Claim 22 wherein said antibody does not bind to the Fc receptor.

25. The antibody of Claim 22 wherein said antibody includes CDRs that are free of a glycosylation site.

26. The antibody of Claim 22 wherein said antibody is a humanized antibody identical to the humanized antibody shown in Figure 1.

27. The antibody of Claim 22 wherein said antibody is a humanized antibody having the same CDRs as the antibody shown in Figure 1.

28. The antibody of Claim 22 wherein said antibody is a chimeric antibody that includes the CDRs shown in Figure 1.

29. The antibody of Claim 22 wherein said antibody is a humanized antbody identical to the humanized antibody shown in Figure 2.

30. The antibody of Claim 22 wherein said antibody is a humanized antibody having the same CDRs as the antibody shown in Figure 2.

31. The antibody of Claim 22 wherein said antibody is a chimeric antibody that includes the CDRs shown in Figure 2.

32. The antibody of Claim 22 wherein said antibody is a humanized antibody identical to the humanized antibody shown in Figure 3.

33. The antibody of Claim 22 wherein said antibody is a humanized antibody having the same CDRs as the antibody shown in Figure 3.

34. The antibody of Claim 22 wherein said antibody is a chimeric antibody that includes the CDRs shown in Figure 3.

35. The antibody of Claim 22 wherein said antibody is a humanized antibody identical to the humanized antibody shown in Figure 4.

36. The antibody of Claim 22 wherein said antibody is a humanized antibody having the same CDRs as the antibody shown in Figure 4.

37. The antibody of Claim 22 wherein said antibody is a chimeric antibody that includes the same CDRs as the antibody shown in Figure 4.

38. A composition, comprising:

(a) the antibody of any one of Claims 22-37; and

(b) an acceptable pharmaceutical carrier.

39. A process for inducing tolerance to an antigen in a patient, comprising:

administering to said patient an effective amount of the antibody of any one of Claims 22-37.

40. A process for inhibiting an immune response in a patient comprising:

administering to said patient an effective amount of the antibody of any one of Claims 22-37.

41. A process for inhibiting the rejection of a graft in a human patient, comprising:

administering to said patient the antibody of any one of Claims 22-37, wherein said antibody is administered in an amount effective to inhibit rejection of said graft.

42. The process of Claim 41 wherein said graft is an organ.

43. A use of the antibody of any one of Claims 22-37 in the manufacture of a medicament for inducing tolerance to an antigen in a patient.

44. A use of the antibody of any one of Claims 22-37 in the manufacture of a medicament for inhibiting an immune response in a patient.

45. A use of the antibody of any one of Claims 22-37 in the manufacture of a medicament for inhibiting the rejection of a graft in a human patient.

46. The use of Claim 45 wherein said graft is an organ.

47. A process for screening for a compound for use in inducing tolerance, comprising:

(a) stimulating and causing T cells to proliferate in the presence of a compound to be tested for its ability to induce tolerance; and

(b) determining the presence of cells that are both CD4 and CD25 positive to determine whether said compound reduced the production of said cells that are both CD4 and CD25 positive with the reduction of such cells indicating that said compound is capable of inducing tolerance.

48. The process of Claim 47 and further performing a secondary MLR in the presence of cells produced in step (a) and determining the presence of at least one of (x) $CD4^+$ $CD25^+$ cells and (y) at least one of IL-2, IL-4 and IL-12, with reduction of at least one of (x) or (y) indicating that said compound is capable of inducing tolerance.

49. The process of Claim 48 wherein in the secondary MLR, reduction of $CD4^+$ $CD25^+$ cells is determined.

FIGURE 1A
TRX1 Light Chain

```
ATG GAG ACA GAC ACA ATC CTG CTA TGG GTG CTG CTG CTC TGG GTT CCA GGC TCC ACT GGT GAC ATT GTG ATG ACC CAA TCT CCA GAT TCT TTG
 M   E   T   D   T   I   L   L   W   V   L   L   L   W   V   P   G   S   T   G   D   I   V   M   T   Q   S   P   D   S   L
<----------------------------------Leader----------------------------------------> <-------------------------FR1----------------

GCT GTG TCT CTA GGT GAG AGG GCC ACC ATC AAC TGC AAG GCC AGC CAA AGT GTT GAT TAT GAT GGT GAT AGT TAT ATG AAC TGG TAT CAA CAG
 A   V   S   L   G   E   R   A   T   I   N   C   K   A   S   Q   S   V   D   Y   D   G   D   S   Y   M   N   W   Y   Q   Q
-----------------------------------------------><-------------------------CDR1----------------------------> <--------------

AAA CCA GGA CAG CCA CCC AAA CTC CTC ATC TAT GTT GCA TCC AAT CTA GAG TCT GGG GTC CCA GAC AGG TTT AGT GGC AGT GGG TCT GGG ACA
 K   P   G   Q   P   P   K   L   L   I   Y   V   A   S   N   L   E   S   G   V   P   D   R   F   S   G   S   G   S   G   T
------------------FR2---------------------> <-----------CDR2----------> <---------------------------FR3-------------------

GAC TTC ACC CTC ACC ATC AGT TCT CTG CAG GCG GAG GAT GTT GCA GTC TAT TAC TGT CAG CAA AGT CTT CAG GAC CCT CCG ACG TTC GGT GGA
 D   F   T   L   T   I   S   S   L   Q   A   E   D   V   A   V   Y   Y   C   Q   Q   S   L   Q   D   P   P   T   F   G   G
-------------------------------------------------------------> <---------------CDR3-------------> <----------

GGT ACC AAG GTG GAA ATC AAA CGA ACT GTG GCT GCA CCA TCT GTC TTC ATC TTC CCG CCA TCT GAT GAG CAG TTG AAA TCT GGA ACT GCC TCT
 G   T   K   V   E   I   K   R   T   V   A   A   P   S   V   F   I   F   P   P   S   D   E   Q   L   K   S   G   T   A   S
------------FR4-----------> <-----------------------------------------Constant----------------------------------------

GTT GTG TGC CTG CTG AAT AAC TTC TAT CCC AGA GAG GCC AAA GTA CAG TGG AAG GTG GAT AAC GCC CTC CAA TCG GGT AAC TCC CAG GAG AGT
 V   V   C   L   L   N   N   F   Y   P   R   E   A   K   V   Q   W   K   V   D   N   A   L   Q   S   G   N   S   Q   E   S
-------------------------------------------------------------------------------------------------------------------------

GTC ACA GAG CAG GAC AGC AAG GAC AGC ACC TAC AGC CTC AGC AGC ACC CTG ACG CTG AGC AAA GCA GAC TAC GAG AAA CAC AAA GTC TAC GCC
 V   T   E   Q   D   S   K   D   S   T   Y   S   L   S   S   T   L   T   L   S   K   A   D   Y   E   K   H   K   V   Y   A
-------------------------------------------------------------------------------------------------------------------------

TGC GAA GTC ACC CAT CAG GGC CTG AGC TCG CCC GTC ACA AAG AGC TTC AAC AGG GGA GAG TGT TAG
 C   E   V   T   H   Q   G   L   S   S   P   V   T   K   S   F   N   R   G   E   C   *
---------------------------------------------------------------------------------------->
```

FIGURE 1B
TRX1 Light Chain Nucleic Acid Sequence

ATGGAGACAGACACAATCCTGCTATGGGTGCTGCTGCTCTGGGTTCCAGGCTCCACTGGTGACAT
TGTGATGACCCAATCTCCAGATTCTTTGGCTGTGTCTCTAGGTGAGAGGGCCACCATCAACTGCAAG
GCCAGCCAAAGTGTTGATTATGATGGTGATAGTTATATGAACTGGTATCAACAGAAACCAGGACAG
CCACCCAAACTCCTCATCTATGTTGCATCCAATCTAGAGTCTGGGGTCCCAGACAGGTTTAGTGG
CAGTGGGTCTGGGACAGACTTCACCCTCACCATCAGTTCTCTGCAGGCGGAGGATGTTGCAGTCT
ATTACTGTCAGCAAAGTCTTCAGGACCCTCCGACGTTCGGTGGAGGTACCAAGGTGGAAATCAAA
CGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACT
GCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGAT
AACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTA
CAGCCTCAGCACACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCG
AAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

FIGURE 1C
TRX1 Light Chain Amino Acid Sequence with CDRs Highlighted

With leader sequence:

METDTILLWVLLLWVPGSTGDIVMTQSPDSLAVSLGERATINC**KASQSVDYDGDSYMN**WYQQKPG
QPPKLLIY**VASNLES**GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**QQSLQDPPT**FGGGTKVEIKR
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Without leader sequence:

DIVMTQSPDSLAVSLGERATINC**KASQSVDYDGDSYMN**WYQQKPGQPPKLLIY**VASNLES**GVPDR
FSGSGSGTDFTLTISSLQAEDVAVYYC**QQSLQDPPT**FGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGT
ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV
THQGLSSPVTKSFNRGEC

FIGURE 1D
TRX1 Heavy Chain

```
ATG GAA TGG ATC TGG ATC TTT CTC CTC ATC CTG TCA GGA ACT CGA GGT GTC CAG TCC CAG GTT CAG CTG GTG CAG TCT GGA GCT GAA GTG AAG
 M   E   W   I   W   I   F   L   L   I   L   S   G   T   R   G   V   Q   S   Q   V   Q   L   V   Q   S   G   A   E   V   K
<----------------------------Leader---------------------------------------> <--------------------FR1---------------------

AAG CCT GGG GCT TCA GTG AAG GTG TCC TGT AAG GCT TCT GGA TAC ACA TTC ACT GCC TAT GTT ATA AGC TGG GTG AGG CAG GCA CCT GGA CAG
 K   P   G   A   S   V   K   V   S   C   K   A   S   G   Y   T   F   T   A   Y   V   I   S   W   V   R   Q   A   P   G   Q
-----------------------------------------------------------------------> <------CDR1-------> <-----------FR2---------------

GGC CTT GAG TGG ATG GGA GAG ATT TAT CCT GGA AGC GGT AGT AGT TAT TAT AAT GAG AAG TTC AAG GGC AGG GTC ACA ATG ACT AGA GAC ACA
 G   L   E   W   M   G   E   I   Y   P   G   S   G   S   S   Y   Y   N   E   K   F   K   G   R   V   T   M   T   R   D   T
---------------------> <-------------------------------CDR2-------------------------------> <-----------------------------

TCC ACC AGC ACA GTC TAC ATG GAA CTC AGC AGC CTG AGG TCT GAG GAC ACT GCG GTC TAT TAC TGT GCA AGA TCC GGG GAC GGC AGT CGG TTT
 S   T   S   T   V   Y   M   E   L   S   S   L   R   S   E   D   T   A   V   Y   Y   C   A   R   S   G   D   G   S   R   F
-------------------------------------FR3-----------------------------------------------------> <-------------CDR3---------

GTT TAC TGG GGC CAA GGG ACA CTA GTC ACA GTC TCC TCA GCC TCC ACC AAG GGC CCA TCG GTC TTC CCC CTG GCA CCC TCC TCC AAG AGC ACC
 V   Y   W   G   Q   G   T   L   V   T   V   S   S   A   S   T   K   G   P   S   V   F   P   L   A   P   S   S   K   S   T
------> <------------------FR4--------------------> <---------------------------Constant---------------------------------

TCT GGG GGC ACA GCG GCC CTG GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA GGC GCC CTG ACC AGC GGC
 S   G   G   T   A   A   L   G   C   L   V   K   D   Y   F   P   E   P   V   T   V   S   W   N   S   G   A   L   T   S   G
-----------------------------------------------------------------------------------------------------------------------


GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA CTC TAC TCC CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC AGC TTG GGC ACC CAG ACC
 V   H   T   F   P   A   V   L   Q   S   S   G   L   Y   S   L   S   S   V   V   T   V   P   S   S   S   L   G   T   Q   T
-----------------------------------------------------------------------------------------------------------------------


TAC ATC TGC AAC GTG AAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AAA GTT GAG CCC AAA TCT TGT GAC AAA ACT CAC ACA TGC CCA CCG
 Y   I   C   N   V   N   H   K   P   S   N   T   K   V   D   K   K   V   E   P   K   S   C   D   K   T   H   T   C   P   P
-----------------------------------------------------------------------------------------------------------------------


TGC CCA GCA CCT GAA CTC GCG GGG GCA CCG TCA GTC TTC CTC TTC CCC CCA AAA CCC AAG GAC ACC CTC ATG ATC TCC CGG ACC CCT GAG GTC
 C   P   A   P   E   L   A   G   A   P   S   V   F   L   F   P   P   K   P   K   D   T   L   M   I   S   R   T   P   E   V
-----------------------------------------------------------------------------------------------------------------------


ACA TGC GTG GTG GTG GAC GTG AGC CAC GAA GAC CCT GAG GTC AAG TTC AAC TGG TAC GTG GAC GGC GTG GAG GTG CAT AAT GCC AAG ACA AAG
 T   C   V   V   V   D   V   S   H   E   D   P   E   V   K   F   N   W   Y   V   D   G   V   E   V   H   N   A   K   T   K
-----------------------------------------------------------------------------------------------------------------------


CCG CGG GAG GAG CAG TAC AAC AGC ACG TAC CGT GTG GTC AGC GTC CTC ACC GTC CTG CAC CAG GAC TGG CTG AAT GGC AAG GAG TAC AAG TGC
 P   R   E   E   Q   Y   N   S   T   Y   R   V   V   S   V   L   T   V   L   H   Q   D   W   L   N   G   K   E   Y   K   C
-----------------------------------------------------------------------------------------------------------------------


AAG GTC TCC AAC AAA GCC CTC CCA GCC CCC ATC GAG AAA ACC ATC TCC AAA GCC AAA GGG CAG CCC CGA GAA CCA CAG GTG TAC ACC CTG CCC
 K   V   S   N   K   A   L   P   A   P   I   E   K   T   I   S   K   A   K   G   Q   P   R   E   P   Q   V   Y   T   L   P
-----------------------------------------------------------------------------------------------------------------------


CCA TCC CGG GAT GAG CTG ACC AAG AAC CAG GTC AGC CTG ACC TGC CTG GTC AAA GGC TTC TAT CCC AGC GAC ATC GCC GTG GAG TGG GAG AGC
 P   S   R   D   E   L   T   K   N   Q   V   S   L   T   C   L   V   K   G   F   Y   P   S   D   I   A   V   E   W   E   S
-----------------------------------------------------------------------------------------------------------------------


AAT GGG CAG CCG GAG AAC AAC TAC AAG ACC ACG CCT CCC GTG CTG GAC TCC GAC GGC TCC TTC TTC CTC TAC AGC AAG CTC ACC GTG GAC AAG
 N   G   Q   P   E   N   N   Y   K   T   T   P   P   V   L   D   S   D   G   S   F   F   L   Y   S   K   L   T   V   D   K
-----------------------------------------------------------------------------------------------------------------------


AGC AGG TGG CAG CAG GGG AAC GTC TTC TCA TGC TCC GTG ATG CAT GAG GCT CTG CAC AAC CAC TAC ACG CAG AAG AGC CTC TCC CTG TCT CCG
 S   R   W   Q   Q   G   N   V   F   S   C   S   V   M   H   E   A   L   H   N   H   Y   T   Q   K   S   L   S   L   S   P
-----------------------------------------------------------------------------------------------------------------------


GGT AAA TGA
 G   K   *
---------->
```

FIGURE 1E

TRX1 Heavy Chain Nucleic Acid Sequence

ATGGAATGGATCTGGATCTTTCTCCTCATCCTGTCAGGAACTCGAGGTGTCCAGTCC
CAGGTTCAGCTGGTGCAGTCTGGAGCTGAAGTGAAGAAGCCTGGGGCTTCAGTGA
AGGTGTCCTGTAAGGCTTCTGGATACACATTCACTGCCTATGTTATAAGCTGGGTGA
GGCAGGCACCTGGACAGGGCCTTGAGTGGATGGGAGAGATTTATCCTGGAAGCGG
TAGTAGTTATTATAATGAGAAGTTCAAGGGCAGGGTCACAATGACTAGAGACACATC
CACCAGCACAGTCTACATGGAACTCAGCAGCCTGAGGTCTGAGGACACTGCGGTCT
ATTACTGTGCAAGATCCGGGGACGGCAGTCGGTTTGTTTACTGGGGCCAAGGGACA
CTAGTCACAGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACC
CTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGAC
TACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCG
TGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTG
GTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCA
CAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAA
CTCACACATGCCCACCGTGCCCAGCACCTGAACTCGCGGGGGCACCGTCAGTCTT
CCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCA
CATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTA
CGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTAC
AACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGA
ATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAG
AAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCC
CCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAA
GGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGA
ACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTAC
AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCT
CCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCT
CCGGGTAAATGA

FIGURE 1F
TRX1 Heavy Chain Amino Acid Sequence with CDRs Highlighted

With leader sequence:

MEWIWIFLLILSGTRGVQSQVQLVQSGAEVKKPGASVKVSCKASGYTFT**AYVIS**WVRQAPGQGLEW
MG**EIYPGSGSSYYNEKFKG**RVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR**SGDGSRFVY**WGQG
TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG
LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKP
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ
ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Without leader sequence:

QVQLVQSGAEVKKPGASVKVSCKASGYTFT**AYVIS**WVRQAPGQGLEWMG**EIYPGSGSSYYNEKF**
KGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR**SGDGSRFVY**WGQGTLVTVSSASTKGPSVFPLA
PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT
CNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL
SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

FIGURE 2A

TRX1 Light Chain

```
ATG GAG ACA GAC ACA ATC CTG CTA TGG GTG CTG CTG CTC TGG GTT CCA GGC TCC ACT GGT GAC ATT GTG ATG ACC CAA TCT CCA GAT TCT TTG
 M   E   T   D   T   I   L   L   W   V   L   L   L   W   V   P   G   S   T   G   D   I   V   M   T   Q   S   P   D   S   L
<----------------------------Leader----------------------------------------> <-----------------------FR1----------------

GCT GTG TCT CTA GGT GAG AGG GCC ACC ATC AAC TGC AAG GCC AGC CAA AGT GTT GAT TAT GAT GGT GAT AGT TAT ATG AAC TGG TAT CAA CAG
 A   V   S   L   G   E   R   A   T   I   N   C   K   A   S   Q   S   V   D   Y   D   G   D   S   Y   M   N   W   Y   Q   Q
-----------------------------------------------><-------------------------CDR1----------------------------> <-------------

AAA CCA GGA CAG CCA CCC AAA CTC CTC ATC TAT GTT GCA TCC AAT CTA GAG TCT GGG GTC CCA GAC AGG TTT AGT GGC AGT GGG TCT GGG ACA
 K   P   G   Q   P   P   K   L   L   I   Y   V   A   S   N   L   E   S   G   V   P   D   R   F   S   G   S   G   S   G   T
-------------------FR2--------------------> <-----------CDR2----------> <---------------------------FR3--------------------

GAC TTC ACC CTC ACC ATC AGT TCT CTG CAG GCG GAG GAT GTT GCA GTC TAT TAC TGT CAG CAA AGT CTT CAG GAC CCT CCG ACG TTC GGT GGA
 D   F   T   L   T   I   S   S   L   Q   A   E   D   V   A   V   Y   Y   C   Q   Q   S   L   Q   D   P   P   T   F   G   G
-----------------------------------------------------------------------> <---------------CDR3-------------> <----------

GGT ACC AAG GTG GAA ATC AAA CGA ACT GTG GCT GCA CTA TCT GTC TTC ATC TTC CCG CCA TCT GAT GAG CAG TTG AAA TCT GGA ACT GCC TCT
 G   T   K   V   E   I   K   R   T   V   A   A   L   S   V   F   I   F   P   P   S   D   E   Q   L   K   S   G   T   A   S
------------FR4-----------> <-----------------------------------------Constant---------------------------------------

GTT GTG TGC CTG CTG AAT AAC TTC TAT CCC AGA GAG GCC AAA GTA CAG TGG AAG GTG GAT AAC GCC CTC CAA TCG GGT AAC TCC CAG GAG AGT
 V   V   C   L   L   N   N   F   Y   P   R   E   A   K   V   Q   W   K   V   D   N   A   L   Q   S   G   N   S   Q   E   S
-----------------------------------------------------------------------------------------------------------------------

GTC ACA GAG CAG GAC AGC AAG GAC AGC ACC TAC AGC CTC AGC AGC ACC CTG ACG CTG AGC AAA GCA GAC TAC GAG AAA CAC AAA GTC TAC GCC
 V   T   E   Q   D   S   K   D   S   T   Y   S   L   S   S   T   L   T   L   S   K   A   D   Y   E   K   H   K   V   Y   A
-----------------------------------------------------------------------------------------------------------------------

TGC GAA GTC ACC CAT CAG GGC CTG AGC TCG CCC GTC ACA AAG AGC TTC AAC AGG GGA GAG TGT TAG
 C   E   V   T   H   Q   G   L   S   S   P   V   T   K   S   F   N   R   G   E   C   *
-------------------------------------------------------------------------------------->
```

FIGURE 2B

TRX1 Light Chain Nucleic Acid Sequence

ATGGAGACAGACACAATCCTGCTATGGGTGCTGCTGCTCTGGGTTCC
AGGCTCCACTGGTGACATTGTGATGACCCAATCTCCAGATTCTTTGGC
TGTGTCTCTAGGTGAGAGGGCCACCATCAACTGCAAGGCCAGCCAAA
GTGTTGATTATGATGGTGATAGTTATATGAACTGGTATCAACAGAAAC
CAGGACAGCCACCCAAACTCCTCATCTATGTTGCATCCAATCTAGAGT
CTGGGGTCCCAGACAGGTTTAGTGGCAGTGGGTCTGGGACAGACTTC
ACCCTCACCATCAGTTCTCTGCAGGCGGAGGATGTTGCAGTCTATTAC
TGTCAGCAAAGTCTTCAGGACCCTCCGACGTTCGGTGGAGGTACCAA
GGTGGAAATCAAACGAACTGTGGCTGCACTATCTGTCTTCATCTTCCC
GCCATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTGTGCCT
GCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGG
ATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAG
GACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAG
CAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCC
ATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAG
TGTTAG

FIGURE 2C

TRX1 Light Chain Amino Acid Sequence with CDRs Highlighted

With leader sequence:

METDTILLWVLLLWVPGSTGDIVMTQSPDSLAVSLGERATINC**KASQSVDYDGDSYMN**WYQQKP
GQPPKLLIY**VASNLES**GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**QQSLQDPPT**FGGGTKVEI
KRTVAALSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS
TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Without leader sequence:

DIVMTQSPDSLAVSLGERATINC**KASQSVDYDGDSYMN**WYQQKPGQPPKLLIY**VASNLES**GVPDR
FSGSGSGTDFTLTISSLQAEDVAVYYC**QQSLQDPPT**FGGGTKVEIKRTVAALSVFIFPPSDEQLKSG
TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY
ACEVTHQGLSSPVTKSFNRGEC

FIGURE 2D

TRX1 Heavy Chain (aglycosyl)

```
ATG GAA TGG ATC TGG ATC TTT CTC CTC ATC CTG TCA GGA ACT CGA GGT GTC CAG TCC CAG GTT CAG CTG GTG CAG TCT GGA GCT GAA GTG AAG
 M   E   W   I   W   I   F   L   L   I   L   S   G   T   R   G   V   Q   S   Q   V   Q   L   V   Q   S   G   A   E   V   K
<------------------------------Leader-------------------------------------> <--------------------FR1----------------------

AAG CCT GGG GCT TCA GTG AAG GTG TCC TGT AAG GCT TCT GGA TAC ACA TTC ACT GCC TAT GTT ATA AGC TGG GTG AGG CAG GCA CCT GGA CAG
 K   P   G   A   S   V   K   V   S   C   K   A   S   G   Y   T   F   T   A   Y   V   I   S   W   V   R   Q   A   P   G   Q
-----------------------------------------------------------------------------> <------CDR1-------> <-------------FR2--------------

GGC CTT GAG TGG ATG GGA GAG ATT TAT CCT GGA AGC GGT AGT AGT TAT TAT AAT GAG AAG TTC AAG GGC AGG GTC ACA ATG ACT AGA GAC ACA
 G   L   E   W   M   G   E   I   Y   P   G   S   G   S   S   Y   Y   N   E   K   F   K   G   R   V   T   M   T   R   D   T
----------------------> <------------------------------CDR2-------------------------------> <-------------------------------

TCC ACC AGC ACA GTC TAC ATG GAA CTC AGC AGC CTG AGG TCT GAG GAC ACT GCG GTC TAT TAC TGT GCA AGA TCC GGG GAC GGC AGT CGG TTT
 S   T   S   T   V   Y   M   E   L   S   S   L   R   S   E   D   T   A   V   Y   Y   C   A   R   S   G   D   G   S   R   F
-------------------------------------FR3-----------------------------------------------> <-------------CDR3---------

GTT TAC TGG GGC CAA GGG ACA CTA GTC ACA GTC TCC TCA GCC TCC ACC AAG GGC CCA TCG GTC TTC CCC CTG GCA CCC TCC TCC AAG AGC ACC
 V   Y   W   G   Q   G   T   L   V   T   V   S   S   A   S   T   K   G   P   S   V   F   P   L   A   P   S   S   K   S   T
------> <------------------FR4--------------------> <----------------------------Constant---------------------------------

TCT GGG GGC ACA GCG GCC CTG GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA GGC GCC CTG ACC AGC GGC
 S   G   G   T   A   A   L   G   C   L   V   K   D   Y   F   P   E   P   V   T   V   S   W   N   S   G   A   L   T   S   G
-------------------------------------------------------------------------------------------------------------------------

GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA CTC TAC TCC CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC AGC TTG GGC ACC CAG ACC
 V   H   T   F   P   A   V   L   Q   S   S   G   L   Y   S   L   S   S   V   V   T   V   P   S   S   S   L   G   T   Q   T
-------------------------------------------------------------------------------------------------------------------------

TAC ATC TGC AAC GTG AAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AAA GTT GAG CCC AAA TCT TGT GAC AAA ACT CAC ACA TGC CCA CCG
 Y   I   C   N   V   N   H   K   P   S   N   T   K   V   D   K   K   V   E   P   K   S   C   D   K   T   H   T   C   P   P
-------------------------------------------------------------------------------------------------------------------------

TGC CCA GCA CCT GAA CTC CTG GGG GGA CCG TCA GTC TTC CTC TTC CCC CCA AAA CCC AAG GAC ACC CTC ATG ATC TCC CGG ACC CCT GAG GTC
 C   P   A   P   E   L   L   G   G   P   S   V   F   L   F   P   P   K   P   K   D   T   L   M   I   S   R   T   P   E   V
-------------------------------------------------------------------------------------------------------------------------

ACA TGC GTG GTG GTG GAC GTG AGC CAC GAA GAC CCT GAG GTC AAG TTC AAC TGG TAC GTG GAC GGC GTG GAG GTG CAT AAT GCC AAG ACA AAG
 T   C   V   V   V   D   V   S   H   E   D   P   E   V   K   F   N   W   Y   V   D   G   V   E   V   H   N   A   K   T   K
-------------------------------------------------------------------------------------------------------------------------

CCG CGG GAG GAG CAG TAC GCC AGC ACG TAC CGT GTG GTC AGC GTC CTC ACC GTC CTG CAC CAG GAC TGG CTG AAT GGC AAG GAG TAC AAG TGC
 P   R   E   E   Q   Y   A   S   T   Y   R   V   V   S   V   L   T   V   L   H   Q   D   W   L   N   G   K   E   Y   K   C
-------------------------------------------------------------------------------------------------------------------------

AAG GTC TCC AAC AAA GCC CTC CCA GCC CCC ATC GAG AAA ACC ATC TCC AAA GCC AAA GGG CAG CCC CGA GAA CCA CAG GTG TAC ACC CTG CCC
 K   V   S   N   K   A   L   P   A   P   I   E   K   T   I   S   K   A   K   G   Q   P   R   E   P   Q   V   Y   T   L   P
-------------------------------------------------------------------------------------------------------------------------

CCA TCC CGG GAT GAG CTG ACC AAG AAC CAG GTC AGC CTG ACC TGC CTG GTC AAA GGC TTC TAT CCC AGC GAC ATC GCC GTG GAG TGG GAG AGC
 P   S   R   D   E   L   T   K   N   Q   V   S   L   T   C   L   V   K   G   F   Y   P   S   D   I   A   V   E   W   E   S
-------------------------------------------------------------------------------------------------------------------------

AAT GGG CAG CCG GAG AAC AAC TAC AAG ACC ACG CCT CCC GTG CTG GAC TCC GAC GGC TCC TTC TTC CTC TAC AGC AAG CTC ACC GTG GAC AAG
 N   G   Q   P   E   N   N   Y   K   T   T   P   P   V   L   D   S   D   G   S   F   F   L   Y   S   K   L   T   V   D   K
-------------------------------------------------------------------------------------------------------------------------

AGC AGG TGG CAG CAG GGG AAC GTC TTC TCA TGC TCC GTG ATG CAT GAG GCT CTG CAC AAC CAC TAC ACG CAG AAG AGC CTC TCC CTG TCT CCG
 S   R   W   Q   Q   G   N   V   F   S   C   S   V   M   H   E   A   L   H   N   H   Y   T   Q   K   S   L   S   L   S   P
-------------------------------------------------------------------------------------------------------------------------

GGT AAA TGA
 G   K   *
---------->
```

FIGURE 2E

TRX1 aglycosyl mut Heavy Chain Nucleic Acid Sequence

ATGGAATGGATCTGGATCTTTCTCCTCATCCTGTCAGGAACTCGAGGTGTCCAGTCCCAG
GTTCAGCTGGTGCAGTCTGGAGCTGAAGTGAAGAAGCCTGGGGCTTCAGTGAAGGTGTC
CTGTAAGGCTTCTGGATACACATTCACTGCCTATGTTATAAGCTGGGTGAGGCAGGCACC
TGGACAGGGCCTTGAGTGGATGGGAGAGATTTATCCTGGAAGCGGTAGTAGTTATTATAA
TGAGAAGTTCAAGGGCAGGGTCACAATGACTAGAGACACATCCACCAGCACAGTCTACAT
GGAACTCAGCAGCCTGAGGTCTGAGGACACTGCGGTCTATTACTGTGCAAGATCCGGGG
ACGGCAGTCGGTTTGTTTACTGGGGCCAAGGGACACTAGTCACAGTCTCCTCAGCCTCCA
CCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACA
GCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGA
ACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGA
CTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTA
CATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCA
AATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGA
CCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCT
GAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTG
GTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTAC
GCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGG
CAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCA
TCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGG
GATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAG
CGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACG
CCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAA
GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACA
ACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

FIGURE 2F

TRX1 Heavy Chain aglycosyl mut Amino Acid Sequence with CDRs Highlighted

With leader sequence:

ME**W**IWIFLLILSGTRGVQSQVQLVQSGAEVKKPGASVKVSCKASGYTFT**AYVIS**WVRQAPGQGLE
WMG**EIYPGSGSSYYNEKFKG**RVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR**SGDGSRFVY**WG
QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVL
TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF
YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK

Without leader sequence:

QVQLVQSGAEVKKPGASVKVSCKASGYTFT**AYVIS**WVRQAPGQGLEWMG**EIYPGSGSSYYNEK**
FKGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR**SGDGSRFVY**WGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC
VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

FIGURE 3A
TRX1 Light Chain

```
ATG GAG ACA GAC ACA ATC CTG CTA TGG GTG CTG CTG CTC TGG GTT CCA GGC TCC ACT GGT GAC ATT GTG ATG ACC CAA TCT CCA GAT TCT TTG
 M   E   T   D   T   I   L   L   W   V   L   L   L   W   V   P   G   S   T   G   D   I   V   M   T   Q   S   P   D   S   L
<----------------------------Leader---------------------------------------> <----------------------FR1---------------

GCT GTG TCT CTA GGT GAG AGG GCC ACC ATC AAC TGC AAG GCC AGC CAA AGT GTT GAT TAT GAT GGT GAT AGT TAT ATG AAC TGG TAT CAA CAG
 A   V   S   L   G   E   R   A   T   I   N   C   K   A   S   Q   S   V   D   Y   D   G   D   S   Y   M   N   W   Y   Q   Q
----------------------------------------------><-----------------------CDR1----------------------------> <-------------

AAA CCA GGA CAG CCA CCC AAA CTC CTC ATC TAT GTT GCA TCC AAT CTA GAG TCT GGG GTC CCA GAC AGG TTT AGT GGC AGT GGG TCT GGG ACA
 K   P   G   Q   P   P   K   L   L   I   Y   V   A   S   N   L   E   S   G   V   P   D   R   F   S   G   S   G   S   G   T
------------------FR2--------------------> <-----------CDR2----------> <----------------------------FR3-------------------

GAC TTC ACC CTC ACC ATC AGT TCT CTG CAG GCG GAG GAT GTT GCA GTC TAT TAC TGT CAG CAA AGT CTT CAG GAC CCT CCG ACG TTC GGT GGA
 D   F   T   L   T   I   S   S   L   Q   A   E   D   V   A   V   Y   Y   C   Q   Q   S   L   Q   D   P   P   T   F   G   G
------------------------------------------------------------> <---------------CDR3-------------> <----------

GGT ACC AAG GTG GAA ATC AAA CGA ACT GTG GCT GCA CTA TCT GTC TTC ATC TTC CCG CCA TCT GAT GAG CAG TTG AAA TCT GGA ACT GCC TCT
 G   T   K   V   E   I   K   R   T   V   A   A   L   S   V   F   I   F   P   P   S   D   E   Q   L   K   S   G   T   A   S
------------FR4-----------> <-----------------------------------------Constant---------------------------------------

GTT GTG TGC CTG CTG AAT AAC TTC TAT CCC AGA GAG GCC AAA GTA CAG TGG AAG GTG GAT AAC GCC CTC CAA TCG GGT AAC TCC CAG GAG AGT
 V   V   C   L   L   N   N   F   Y   P   R   E   A   K   V   Q   W   K   V   D   N   A   L   Q   S   G   N   S   Q   E   S
-----------------------------------------------------------------------------------------------------------------------

GTC ACA GAG CAG GAC AGC AAG GAC AGC ACC TAC AGC CTC AGC AGC ACC CTG ACG CTG AGC AAA GCA GAC TAC GAG AAA CAC AAA GTC TAC GCC
 V   T   E   Q   D   S   K   D   S   T   Y   S   L   S   S   T   L   T   L   S   K   A   D   Y   E   K   H   K   V   Y   A
-----------------------------------------------------------------------------------------------------------------------

TGC GAA GTC ACC CAT CAG GGC CTG AGC TCG CCC GTC ACA AAG AGC TTC AAC AGG GGA GAG TGT TAG
 C   E   V   T   H   Q   G   L   S   S   P   V   T   K   S   F   N   R   G   E   C   *
-------------------------------------------------------------------------------------->
```

FIGURE 3B
TRX1 Light Chain Nucleic Acid Sequence

ATGGAGACAGACACAATCCTGCTATGGGTGCTGCTGCTCTGGGTTCCAGGCTCCACTGGTGACAT
TGTGATGACCCAATCTCCAGATTCTTTGGCTGTGTCTCTAGGTGAGAGGGCCACCATCAACTGCAAG
GCCAGCCAAAGTGTTGATTATGATGGTGATAGTTATATGAACTGGTATCAACAGAAACCAGGACAG
CCACCCAAACTCCTCATCTATGTTGCATCCAATCTAGAGTCTGGGGTCCCAGACAGGTTTAGTGG
CAGTGGGTCTGGGACAGACTTCACCCTCACCATCAGTTCTCTGCAGGCGGAGGATGTTGCAGTCT
ATTACTGTCAGCAAAGTCTTCAGGACCCTCCGACGTTCGGTGGAGGTACCAAGGTGGAAATCAAA
CGAACTGTGGCTGCACTATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACT
GCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATA
CGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAG
CTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTC
CCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

FIGURE 3C
TRX1 Light Chain Amino Acid Sequence with CDRs Highlighted

With leader sequence:

METDTILLWVLLLWVPGSTGDIVMTQSPDSLAVSLGERATINC**KASQSVDYDGDSYMN**WYQQKPG
QPPKLLIY**VASNLES**GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**QQSLQDPPT**FGGGTKVEIKR
TVAALSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Without leader sequence:

DIVMTQSPDSLAVSLGERATINC**KASQSVDYDGDSYMN**WYQQKPGQPPKLLIY**VASNLES**GVPDR
FSGSGSGTDFTLTISSLQAEDVAVYYC**QQSLQDPPT**FGGGTKVEIKRTVAALSVFIFPPSDEQLKSGT
ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV
THQGLSSPVTKSFNRGEC

FIGURE 3D
TRX1 Heavy Chain

```
ATG GAA TGG ATC TGG ATC TTT CTC CTC ATC CTG TCA GGA ACT CGA GGT GTC CAG TCC CAG GTT CAG CTG GTG CAG TCT GGA GCT GAA GTG AAG
 M   E   W   I   W   I   F   L   L   I   L   S   G   T   R   G   V   Q   S   Q   V   Q   L   V   Q   S   G   A   E   V   K
<----------------------------Leader----------------------------------------> <--------------------FR1----------------------

AAG CCT GGG GCT TCA GTG AAG GTG TCC TGT AAG GCT TCT GGA TAC ACA TTC ACT GCC TAT GTT ATA AGC TGG GTG AGG CAG GCA CCT GGA CAG
 K   P   G   A   S   V   K   V   S   C   K   A   S   G   Y   T   F   T   A   Y   V   I   S   W   V   R   Q   A   P   G   Q
-------------------------------------------------------------> <------CDR1-------> <------------FR2---------------

GGC CTT GAG TGG ATG GGA GAG ATT TAT CCT GGA AGC GGT AGT AGT TAT TAT AAT GAG AAG TTC AAG GGC AGG GTC ACA ATG ACT AGA GAC ACA
 G   L   E   W   M   G   E   I   Y   P   G   S   G   S   S   Y   Y   N   E   K   F   K   G   R   V   T   M   T   R   D   T
----------------------> <-------------------------------CDR2-------------------------------> <-------------------------------

TCC ACC AGC ACA GTC TAC ATG GAA CTC AGC AGC CTG AGG TCT GAG GAC ACT GCG GTC TAT TAC TGT GCA AGA TCC GGG GAC GGC AGT CGG TTT
 S   T   S   T   V   Y   M   E   L   S   S   L   R   S   E   D   T   A   V   Y   Y   C   A   R   S   G   D   G   S   R   F
-----------------------------------FR3-----------------------------------------------------> <-------------CDR3---------

GTT TAC TGG GGC CAA GGG ACA CTA GTC ACA GTC TCC TCA GCC TCC ACC AAG GGC CCA TCG GTC TTC CCC CTG GCA CCC TCC TCC AAG AGC ACC
 V   Y   W   G   Q   G   T   L   V   T   V   S   S   A   S   T   K   G   P   S   V   F   P   L   A   P   S   S   K   S   T
------> <-----------------FR4--------------------> <---------------------------Constant---------------------------------

TCT GGG GGC ACA GCG GCC CTG GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA GGC GCC CTG ACC AGC GGC
 S   G   G   T   A   A   L   G   C   L   V   K   D   Y   F   P   E   P   V   T   V   S   W   N   S   G   A   L   T   S   G
-----------------------------------------------------------------------------------------------------------------------


GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA CTC TAC TCC CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC AGC TTG GGC ACC CAG ACC
 V   H   T   F   P   A   V   L   Q   S   S   G   L   Y   S   L   S   S   V   V   T   V   P   S   S   S   L   G   T   Q   T
-----------------------------------------------------------------------------------------------------------------------


TAC ATC TGC AAC GTG AAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AAA GTT GAG CCC AAA TCT TGT GAC AAA ACT CAC ACA TGC CCA CCG
 Y   I   C   N   V   N   H   K   P   S   N   T   K   V   D   K   K   V   E   P   K   S   C   D   K   T   H   T   C   P   P
-----------------------------------------------------------------------------------------------------------------------


TGC CCA GCA CCT GAA CTC GCG GGG GCA CCG TCA GTC TTC CTC TTC CCC CCA AAA CCC AAG GAC ACC CTC ATG ATC TCC CGG ACC CCT GAG GTC
 C   P   A   P   E   L   A   G   A   P   S   V   F   L   F   P   P   K   P   K   D   T   L   M   I   S   R   T   P   E   V
-----------------------------------------------------------------------------------------------------------------------


ACA TGC GTG GTG GTG GAC GTG AGC CAC GAA GAC CCT GAG GTC AAG TTC AAC TGG TAC GTG GAC GGC GTG GAG GTG CAT AAT GCC AAG ACA AAG
 T   C   V   V   V   D   V   S   H   E   D   P   E   V   K   F   N   W   Y   V   D   G   V   E   V   H   N   A   K   T   K
-----------------------------------------------------------------------------------------------------------------------


CCG CGG GAG GAG CAG TAC AAC AGC ACG TAC CGT GTG GTC AGC GTC CTC ACC GTC CTG CAC CAG GAC TGG CTG AAT GGC AAG GAG TAC AAG TGC
 P   R   E   E   Q   Y   N   S   T   Y   R   V   V   S   V   L   T   V   L   H   Q   D   W   L   N   G   K   E   Y   K   C
-----------------------------------------------------------------------------------------------------------------------


AAG GTC TCC AAC AAA GCC CTC CCA GCC CCC ATC GAG AAA ACC ATC TCC AAA GCC AAA GGG CAG CCC CGA GAA CCA CAG GTG TAC ACC CTG CCC
 K   V   S   N   K   A   L   P   A   P   I   E   K   T   I   S   K   A   K   G   Q   P   R   E   P   Q   V   Y   T   L   P
-----------------------------------------------------------------------------------------------------------------------


CCA TCC CGG GAT GAG CTG ACC AAG AAC CAG GTC AGC CTG ACC TGC CTG GTC AAA GGC TTC TAT CCC AGC GAC ATC GCC GTG GAG TGG GAG AGC
 P   S   R   D   E   L   T   K   N   Q   V   S   L   T   C   L   V   K   G   F   Y   P   S   D   I   A   V   E   W   E   S
-----------------------------------------------------------------------------------------------------------------------


AAT GGG CAG CCG GAG AAC AAC TAC AAG ACC ACG CCT CCC GTG CTG GAC TCC GAC GGC TCC TTC TTC CTC TAC AGC AAG CTC ACC GTG GAC AAG
 N   G   Q   P   E   N   N   Y   K   T   T   P   P   V   L   D   S   D   G   S   F   F   L   Y   S   K   L   T   V   D   K
-----------------------------------------------------------------------------------------------------------------------


AGC AGG TGG CAG CAG GGG AAC GTC TTC TCA TGC TCC GTG ATG CAT GAG GCT CTG CAC AAC CAC TAC ACG CAG AAG AGC CTC TCC CTG TCT CCG
 S   R   W   Q   Q   G   N   V   F   S   C   S   V   M   H   E   A   L   H   N   H   Y   T   Q   K   S   L   S   L   S   P
-----------------------------------------------------------------------------------------------------------------------


GGT AAA TGA
 G   K   *
---------->
```

FIGURE 3E

TRX1 Heavy Chain Nucleic Acid Sequence

ATGGAATGGATCTGGATCTTTCTCCTCATCCTGTCAGGAACTCGAGGTGTCCAGTCC
CAGGTTCAGCTGGTGCAGTCTGGAGCTGAAGTGAAGAAGCCTGGGGCTTCAGTGA
AGGTGTCCTGTAAGGCTTCTGGATACACATTCACTGCCTATGTTATAAGCTGGGTGA
GGCAGGCACCTGGACAGGGCCTTGAGTGGATGGGAGAGATTTATCCTGGAAGCGG
TAGTAGTTATTATAATGAGAAGTTCAAGGGCAGGGTCACAATGACTAGAGACACATC
CACCAGCACAGTCTACATGGAACTCAGCAGCCTGAGGTCTGAGGACACTGCGGTCT
ATTACTGTGCAAGATCCGGGGACGGCAGTCGGTTTGTTTACTGGGGCCAAGGGACA
CTAGTCACAGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACC
CTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGAC
TACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCG
TGCACACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTG
GTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCA
CAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAA
CTCACACATGCCCACCGTGCCCAGCACCTGAACTCGCGGGGGCACCGTCAGTCTT
CCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCA
CATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTA
CGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTAC
AACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGA
ATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAG
AAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCC
CCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAA
GGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGA
ACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTAC
AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCT
CCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCT
CCGGGTAAATGA

FIGURE 3F
TRX1 Heavy Chain Amino Acid Sequence with CDRs Highlighted

With leader sequence:

MEWIWIFLLILSGTRGVQSQVQLVQSGAEVKKPGASVKVSCKASGYTFT**AYVIS**WVRQAPGQGLEW
MG**EIYPGSGSSYYNEKFKG**RVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR**SGDGSRFVY**WGQG
TLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG
LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKP
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQ
ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Without leader sequence:

QVQLVQSGAEVKKPGASVKVSCKASGYTFT**AYVIS**WVRQAPGQGLEWMG**EIYPGSGSSYYNEKF**
KGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR**SGDGSRFVY**WGQGTLVTVSSASTKGPSVFPLA
PSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT
CNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELAGAPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL
SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

FIGURE 4A
TRX1 Light Chain

```
ATG GAG ACA GAC ACA ATC CTG CTA TGG GTG CTG CTG CTC TGG GTT CCA GGC TCC ACT GGT GAC ATT GTG ATG ACC CAA TCT CCA GAT TCT TTG
 M   E   T   D   T   I   L   L   W   V   L   L   L   W   V   P   G   S   T   G   D   I   V   M   T   Q   S   P   D   S   L
<----------------------------Leader----------------------------------------> <----------------------FR1---------------

GCT GTG TCT CTA GGT GAG AGG GCC ACC ATC AAC TGC AAG GCC AGC CAA AGT GTT GAT TAT GAT GGT GAT AGT TAT ATG AAC TGG TAT CAA CAG
 A   V   S   L   G   E   R   A   T   I   N   C   K   A   S   Q   S   V   D   Y   D   G   D   S   Y   M   N   W   Y   Q   Q
-----------------------------------------><-----------------------CDR1----------------------------> <-------------

AAA CCA GGA CAG CCA CCC AAA CTC CTC ATC TAT GTT GCA TCC AAT CTA GAG TCT GGG GTC CCA GAC AGG TTT AGT GGC AGT GGG TCT GGG ACA
 K   P   G   Q   P   P   K   L   L   I   Y   V   A   S   N   L   E   S   G   V   P   D   R   F   S   G   S   G   S   G   T
------------------FR2--------------------> <-----------CDR2----------> <---------------------------FR3-------------------

GAC TTC ACC CTC ACC ATC AGT TCT CTG CAG GCG GAG GAT GTT GCA GTC TAT TAC TGT CAG CAA AGT CTT CAG GAC CCT CCG ACG TTC GGT GGA
 D   F   T   L   T   I   S   S   L   Q   A   E   D   V   A   V   Y   Y   C   Q   Q   S   L   Q   D   P   P   T   F   G   G
-----------------------------------------------------------------------> <----------------CDR3------------> <----------

GGT ACC AAG GTG GAA ATC AAA CGA ACT GTG GCT GCA CCA TCT GTC TTC ATC TTC CCG CCA TCT GAT GAG CAG TTG AAA TCT GGA ACT GCC TCT
 G   T   K   V   E   I   K   R   T   V   A   A   P   S   V   F   I   F   P   P   S   D   E   Q   L   K   S   G   T   A   S
------------FR4-----------> <-------------------------------------Constant---------------------------------------

GTT GTG TGC CTG CTG AAT AAC TTC TAT CCC AGA GAG GCC AAA GTA CAG TGG AAG GTG GAT AAC GCC CTC CAA TCG GGT AAC TCC CAG GAG AGT
 V   V   C   L   L   N   N   F   Y   P   R   E   A   K   V   Q   W   K   V   D   N   A   L   Q   S   G   N   S   Q   E   S
-----------------------------------------------------------------------------------------------------------------------

GTC ACA GAG CAG GAC AGC AAG GAC AGC ACC TAC AGC CTC AGC AGC ACC CTG ACG CTG AGC AAA GCA GAC TAC GAG AAA CAC AAA GTC TAC GCC
 V   T   E   Q   D   S   K   D   S   T   Y   S   L   S   S   T   L   T   L   S   K   A   D   Y   E   K   H   K   V   Y   A
-----------------------------------------------------------------------------------------------------------------------

TGC GAA GTC ACC CAT CAG GGC CTG AGC TCG CCC GTC ACA AAG AGC TTC AAC AGG GGA GAG TGT TAG
 C   E   V   T   H   Q   G   L   S   S   P   V   T   K   S   F   N   R   G   E   C   *
-------------------------------------------------------------------------------------->
```

FIGURE 4B
TRX1 Light Chain Nucleic Acid Sequence

ATGGAGACAGACACAATCCTGCTATGGGTGCTGCTGCTCTGGGTTCCAGGCTCCACTGGTGACAT
TGTGATGACCCAATCTCCAGATTCTTTGGCTGTGTCTCTAGGTGAGAGGGCCACCATCAACTGCAAG
GCCAGCCAAAGTGTTGATTATGATGGTGATAGTTATATGAACTGGTATCAACAGAAACCAGGACAG
CCACCCAAACTCCTCATCTATGTTGCATCCAATCTAGAGTCTGGGGTCCCAGACAGGTTTAGTGG
CAGTGGGTCTGGGACAGACTTCACCCTCACCATCAGTTCTCTGCAGGCGGAGGATGTTGCAGTCT
ATTACTGTCAGCAAAGTCTTCAGGACCCTCCGACGTTCGGTGGAGGTACCAAGGTGGAAATCAAA
CGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACT
GCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGAT
AACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTA
CAGCCTCAGCACACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCG
AAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAG

FIGURE 4C
TRX1 Light Chain Amino Acid Sequence with CDRs Highlighted

With leader sequence:

METDTILLWVLLLWVPGSTGDIVMTQSPDSLAVSLGERATINC**KASQSVDYDGDSYMN**WYQQKPG
QPPKLLIY**VASNLES**GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**QQSLQDPPT**FGGGTKVEIKR
TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Without leader sequence:

DIVMTQSPDSLAVSLGERATINC**KASQSVDYDGDSYMN**WYQQKPGQPPKLLIY**VASNLES**GVPDR
FSGSGSGTDFTLTISSLQAEDVAVYYC**QQSLQDPPT**FGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGT
ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV
THQGLSSPVTKSFNRGEC

FIGURE 4D

TRX1 Heavy Chain (aglycosyl)

```
ATG GAA TGG ATC TGG ATC TTT CTC CTC ATC CTG TCA GGA ACT CGA GGT GTC CAG TCC CAG GTT CAG CTG GTG CAG TCT GGA GCT GAA GTG
 M   E   W   I   W   I   F   L   L   I   L   S   G   T   R   G   V   Q   S   Q   V   Q   L   V   Q   S   G   A   E   V
<----------------------------------Leader----------------------------------> <--------------------FR1------------------

AAG CCT GGG GCT TCA GTG AAG GTG TCC TGT AAG GCT TCT GGA TAC ACA TTC ACT GCC TAT GTT ATA AGC TGG GTG AGG CAG GCA CCT GGA
 K   P   G   A   S   V   K   V   S   C   K   A   S   G   Y   T   F   T   A   Y   V   I   S   W   V   R   Q   A   P   G
----------------------------------------------------------------> <------CDR1-------> <------------FR2-----------

GGC CTT GAG TGG ATG GGA GAG ATT TAT CCT GGA AGC GGT AGT AGT TAT TAT AAT GAG AAG TTC AAG GGC AGG GTC ACA ATG ACT AGA GAC
 G   L   E   W   M   G   E   I   Y   P   G   S   G   S   S   Y   Y   N   E   K   F   K   G   R   V   T   M   T   R   D
----------------------> <------------------------------CDR2-------------------------------> <-------------------------

TCC ACC AGC ACA GTC TAC ATG GAA CTC AGC AGC CTG AGG TCT GAG GAC ACT GCG GTC TAT TAC TGT GCA AGA TCC GGG GAC GGC AGT CGG
 S   T   S   T   V   Y   M   E   L   S   S   L   R   S   E   D   T   A   V   Y   Y   C   A   R   S   G   D   G   S   R
-----------------------------------FR3-----------------------------------------------------> <-------------CDR3-----

GTT TAC TGG GGC CAA GGG ACA CTA GTC ACA GTC TCC TCA GCC TCC ACC AAG GGC CCA TCG GTC TTC CCC CTG GCA CCC TCC TCC AAG AGC
 V   Y   W   G   Q   G   T   L   V   T   V   S   S   A   S   T   K   G   P   S   V   F   P   L   A   P   S   S   K   S
------> <------------------FR4--------------------> <---------------------------Constant---------------------------

TCT GGG GGC ACA GCG GCC CTG GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA GGC GCC CTG ACC AGC
 S   G   G   T   A   A   L   G   C   L   V   K   D   Y   F   P   E   P   V   T   V   S   W   N   S   G   A   L   T   S
-----------------------------------------------------------------------------------------------------------------------

GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA CTC TAC TCC CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC AGC TTG GGC ACC CAG
 V   H   T   F   P   A   V   L   Q   S   S   G   L   Y   S   L   S   S   V   V   T   V   P   S   S   S   L   G   T   Q
-----------------------------------------------------------------------------------------------------------------------

TAC ATC TGC AAC GTG AAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AAA GTT GAG CCC AAA TCT TGT GAC AAA ACT CAC ACA TGC CCA
 Y   I   C   N   V   N   H   K   P   S   N   T   K   V   D   K   K   V   E   P   K   S   C   D   K   T   H   T   C   P
-----------------------------------------------------------------------------------------------------------------------

TGC CCA GCA CCT GAA CTC CTG GGG GGA CCG TCA GTC TTC CTC TTC CCC CCA AAA CCC AAG GAC ACC CTC ATG ATC TCC CGG ACC CCT GAG
 C   P   A   P   E   L   L   G   G   P   S   V   F   L   F   P   P   K   P   K   D   T   L   M   I   S   R   T   P   E
-----------------------------------------------------------------------------------------------------------------------

ACA TGC GTG GTG GTG GAC GTG AGC CAC GAA GAC CCT GAG GTC AAG TTC AAC TGG TAC GTG GAC GGC GTG GAG GTG CAT AAT GCC AAG ACA
 T   C   V   V   V   D   V   S   H   E   D   P   E   V   K   F   N   W   Y   V   D   G   V   E   V   H   N   A   K   T
-----------------------------------------------------------------------------------------------------------------------

CCG CGG GAG GAG CAG TAC GCC AGC ACG TAC CGT GTG GTC AGC GTC CTC ACC GTC CTG CAC CAG GAC TGG CTG AAT GGC AAG GAG TAC AAG
 P   R   E   E   Q   Y   A   S   T   Y   R   V   V   S   V   L   T   V   L   H   Q   D   W   L   N   G   K   E   Y   K
-----------------------------------------------------------------------------------------------------------------------

AAG GTC TCC AAC AAA GCC CTC CCA GCC CCC ATC GAG AAA ACC ATC TCC AAA GCC AAA GGG CAG CCC CGA GAA CCA CAG GTG TAC ACC CTG
 K   V   S   N   K   A   L   P   A   P   I   E   K   T   I   S   K   A   K   G   Q   P   R   E   P   Q   V   Y   T   L
-----------------------------------------------------------------------------------------------------------------------

CCA TCC CGG GAT GAG CTG ACC AAG AAC CAG GTC AGC CTG ACC TGC CTG GTC AAA GGC TTC TAT CCC AGC GAC ATC GCC GTG GAG TGG GAG
 P   S   R   D   E   L   T   K   N   Q   V   S   L   T   C   L   V   K   G   F   Y   P   S   D   I   A   V   E   W   E
-----------------------------------------------------------------------------------------------------------------------

AAT GGG CAG CCG GAG AAC AAC TAC AAG ACC ACG CCT CCC GTG CTG GAC TCC GAC GGC TCC TTC TTC CTC TAC AGC AAG CTC ACC GTG GAC
 N   G   Q   P   E   N   N   Y   K   T   T   P   P   V   L   D   S   D   G   S   F   F   L   Y   S   K   L   T   V   D
-----------------------------------------------------------------------------------------------------------------------

AGC AGG TGG CAG CAG GGG AAC GTC TTC TCA TGC TCC GTG ATG CAT GAG GCT CTG CAC AAC CAC TAC ACG CAG AAG AGC CTC TCC CTG TCT
 S   R   W   Q   Q   G   N   V   F   S   C   S   V   M   H   E   A   L   H   N   H   Y   T   Q   K   S   L   S   L   S
-----------------------------------------------------------------------------------------------------------------------

GGT AAA TGA
 G   K   *
---------->
```

FIGURE 4E

TRX1 aglycosyl mut Heavy Chain Nucleic Acid Sequence

ATGGAATGGATCTGGATCTTTCTCCTCATCCTGTCAGGAACTCGAGGTGTCCAGTCCCAG
GTTCAGCTGGTGCAGTCTGGAGCTGAAGTGAAGAAGCCTGGGGCTTCAGTGAAGGTGTC
CTGTAAGGCTTCTGGATACACATTCACTGCCTATGTTATAAGCTGGGTGAGGCAGGCACC
TGGACAGGGCCTTGAGTGGATGGGAGAGATTTATCCTGGAAGCGGTAGTAGTTATTATAA
TGAGAAGTTCAAGGGCAGGGTCACAATGACTAGAGACACATCCACCAGCACAGTCTACAT
GGAACTCAGCAGCCTGAGGTCTGAGGACACTGCGGTCTATTACTGTGCAAGATCCGGGG
ACGGCAGTCGGTTTGTTTACTGGGGCCAAGGGACACTAGTCACAGTCTCCTCAGCCTCC
ACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCAC
AGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGG
AACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCAGG
ACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCT
ACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCC
AAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGG
ACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCC
TGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACT
GGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTA
CGCCAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATG
GCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACC
ATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCG
GGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCA
GCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCAC
GCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACA
AGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCAC
AACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGA

FIGURE 4F

TRX1 Heavy Chain aglycosyl mut Amino Acid Sequence with CDRs Highlighted

With leader sequence:

ME**W**IWIFLLILSGTRGVQSQVQLVQSGAEVKKPGASVKVSCKASGYTFT**AYVIS**WVRQAPGQGLE
WMG**EIYPGSGSSYYNEKFKG**RVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR**SGDGSRFVY**WG
QGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVL
TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF
YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK

Without leader sequence:

QVQLVQSGAEVKKPGASVKVSCKASGYTFT**AYVIS**WVRQAPGQGLEWMG**EIYPGSGSSYYNEK**
FKGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR**SGDGSRFVY**WGQGTLVTVSSASTKGPSVFP
LAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG
TQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC
VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVS
NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

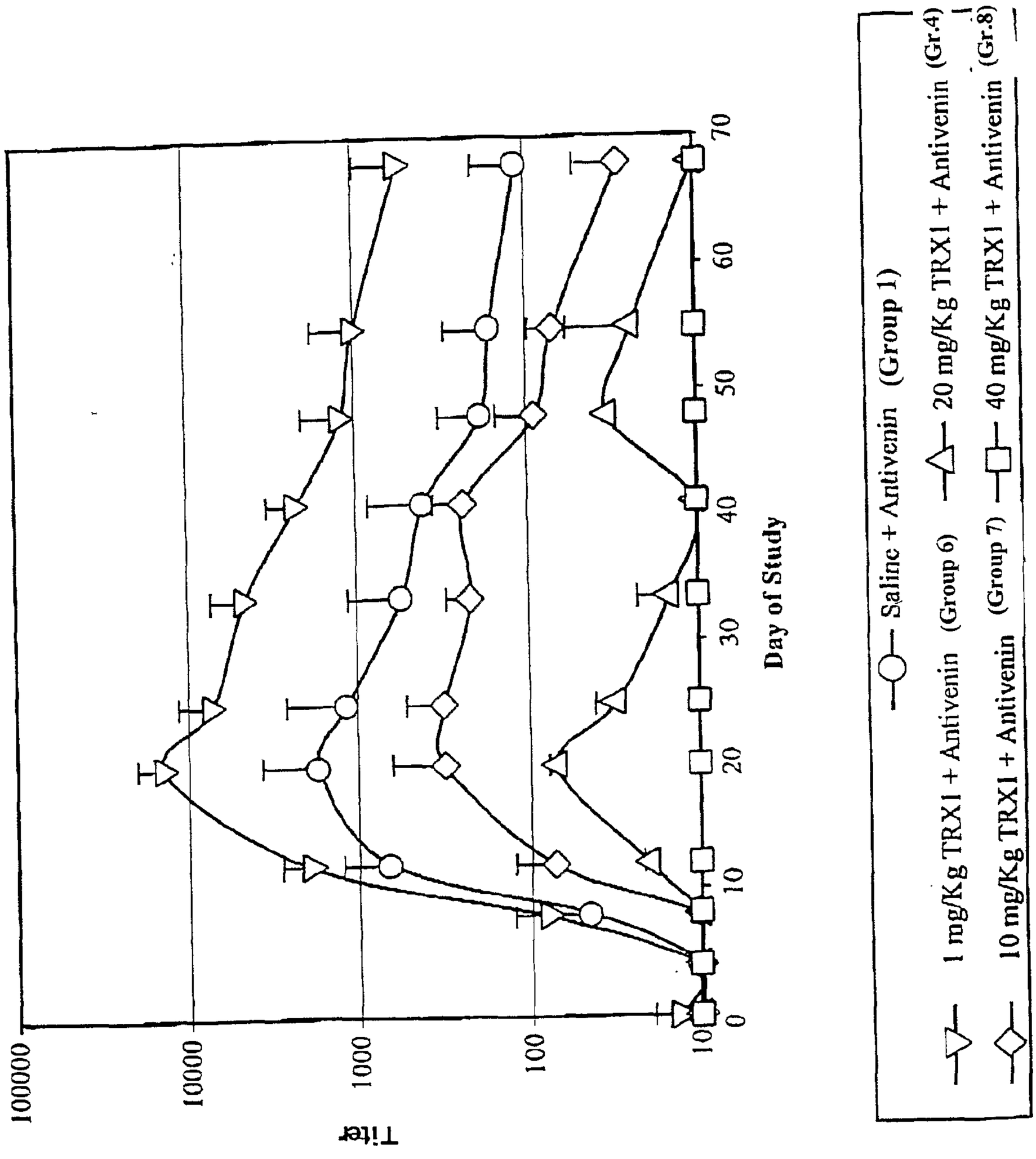

Immune Response to Antivenin, Tolerization Phase, All Groups
Titer
100000
10000
1000
100
10
0
10
20
30
40
50
60
70
Day of Study
Saline + Antivenin (Group 1)
1 mg/Kg TRX1 + Antivenin (Group 6)
10 mg/Kg TRX1 + Antivenin (Group 7)
20 mg/Kg TRX1 + Antivenin (Gr.4)
40 mg/Kg TRX1 + Antivenin (Gr.8)

Figure 5

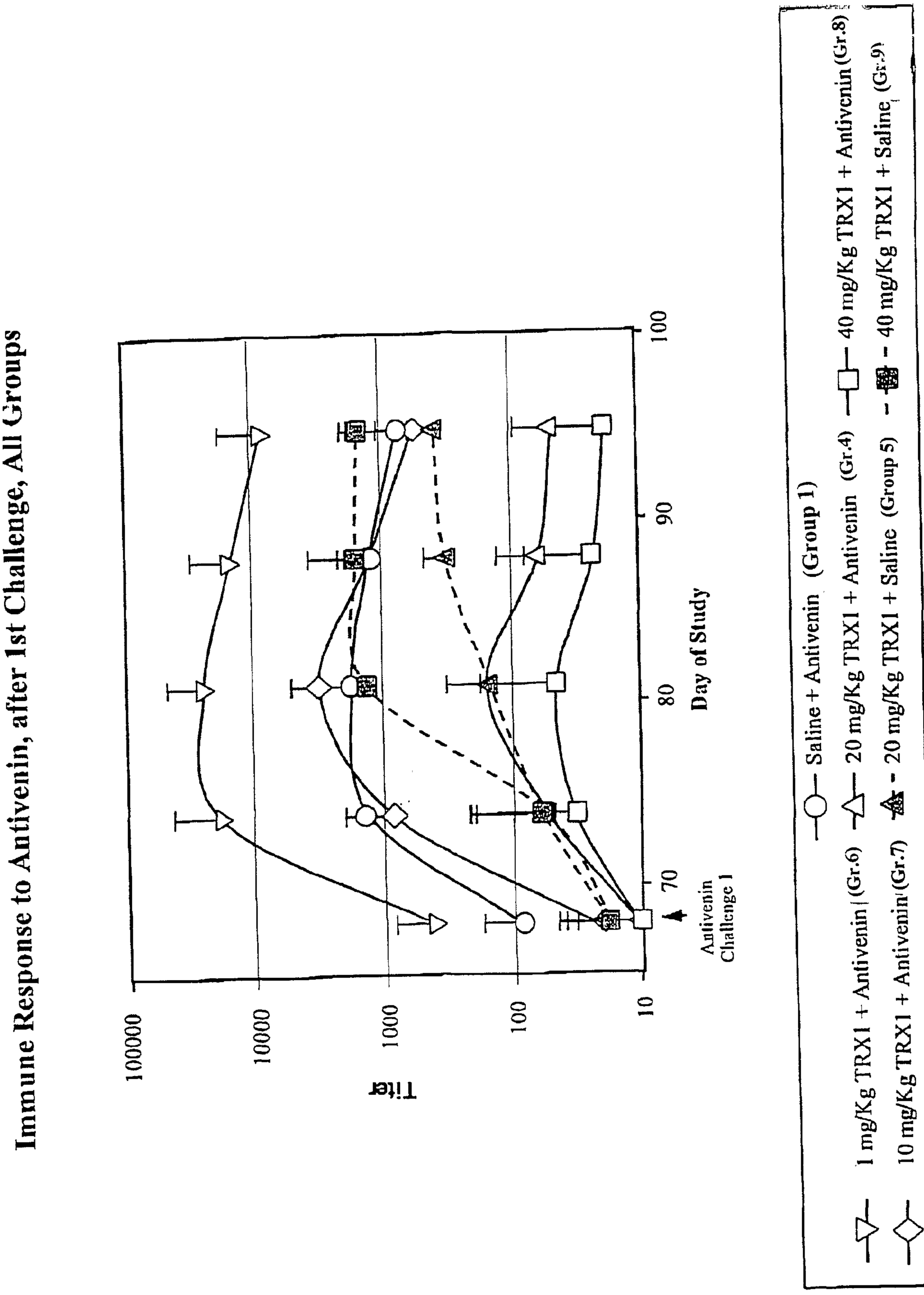

Immune Response to Antivenin, after 1st Challenge, All Groups
Titer
100000
10000
1000
100
10
70
80
90
100
Antivenin Challenge 1
Day of Study
Saline + Antivenin (Group 1)
1 mg/Kg TRX1 + Antivenin (Gr.6)
10 mg/Kg TRX1 + Antivenin (Gr.7)
20 mg/Kg TRX1 + Antivenin (Gr.8)
40 mg/Kg TRX1 + Antivenin (Gr.4)
20 mg/Kg TRX1 + Saline (Group 5)
40 mg/Kg TRX1 + Saline (Gr.9)

Figure 6

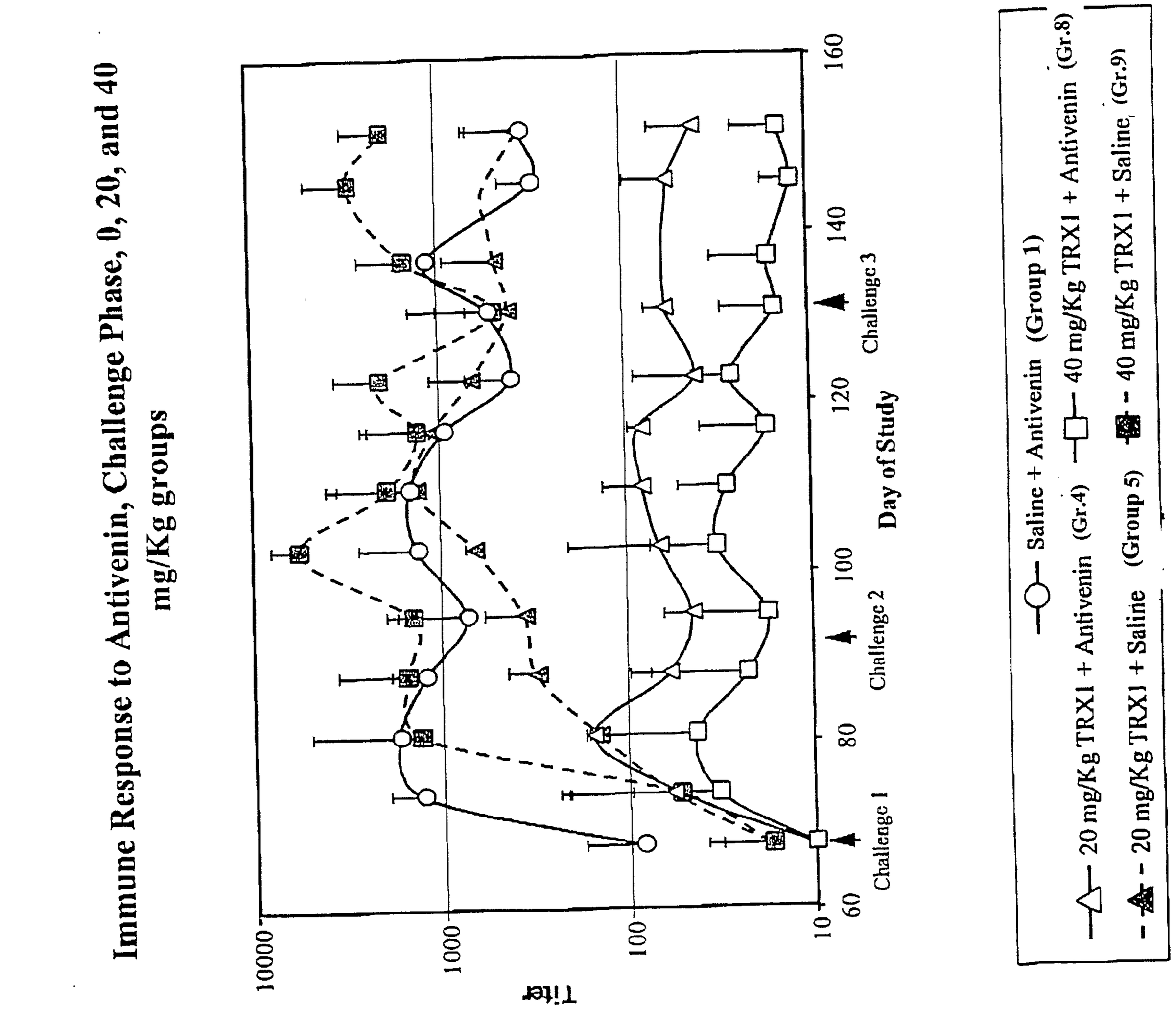
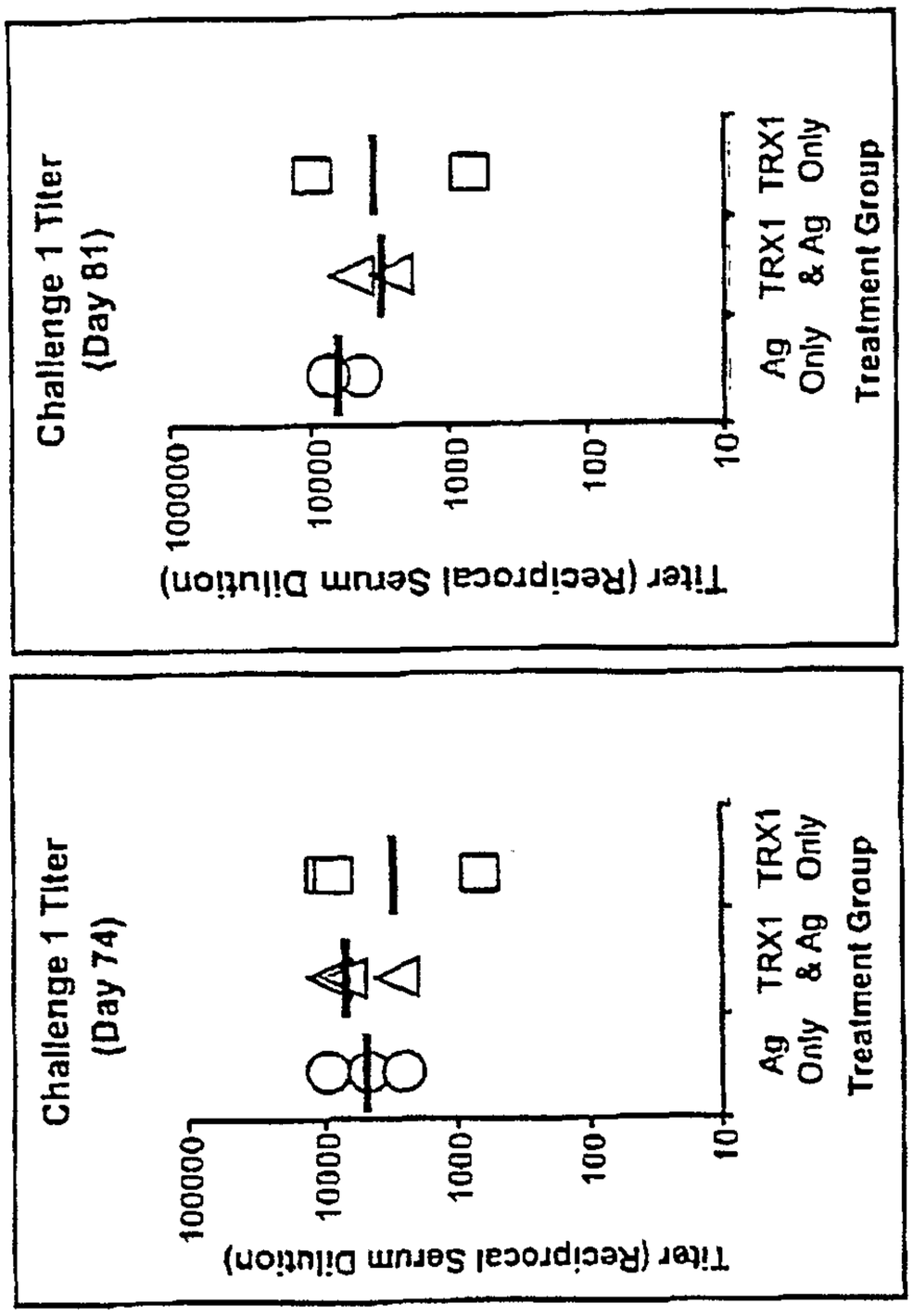
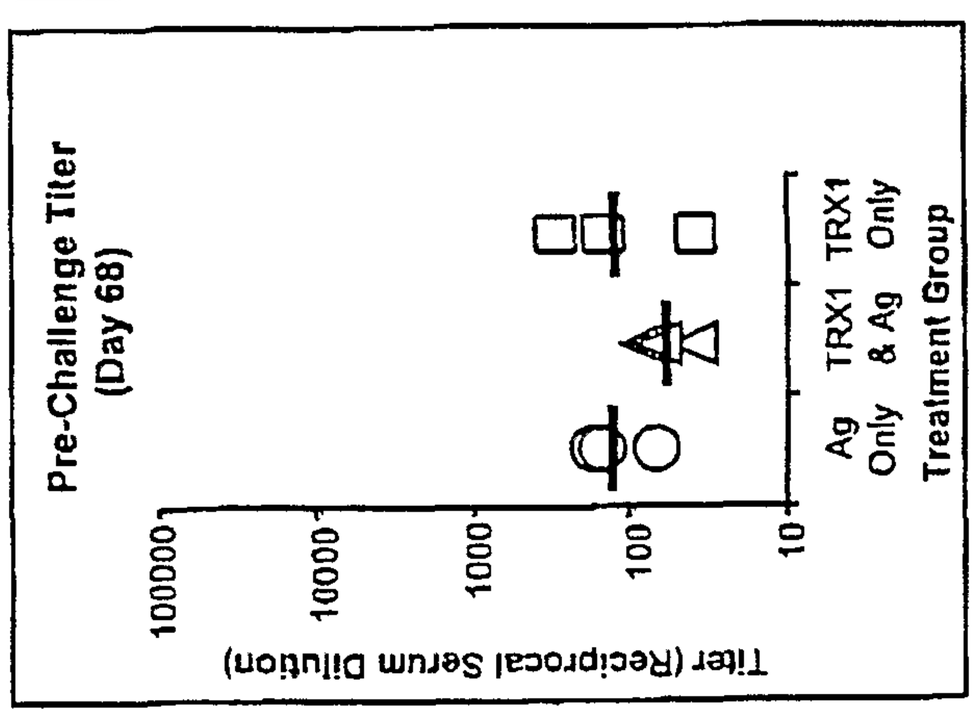

Immune Response to Antivenin, Challenge Phase, 0, 20, and 40 mg/Kg groups
Titer
10000
1000
100
10
60
80
100
120
140
160
Challenge 1
Challenge 2
Challenge 3
Day of Study
Saline + Antivenin (Group 1)
20 mg/Kg TRX1 + Antivenin (Gr.4)
40 mg/Kg TRX1 + Antivenin (Gr.8)
20 mg/Kg TRX1 + Saline (Group 5)
40 mg/Kg TRX1 + Saline (Gr.9)

Figure 7

Immune response to Sheep Red Blood Cells, Challenge 1, 20 mg/Kg Group





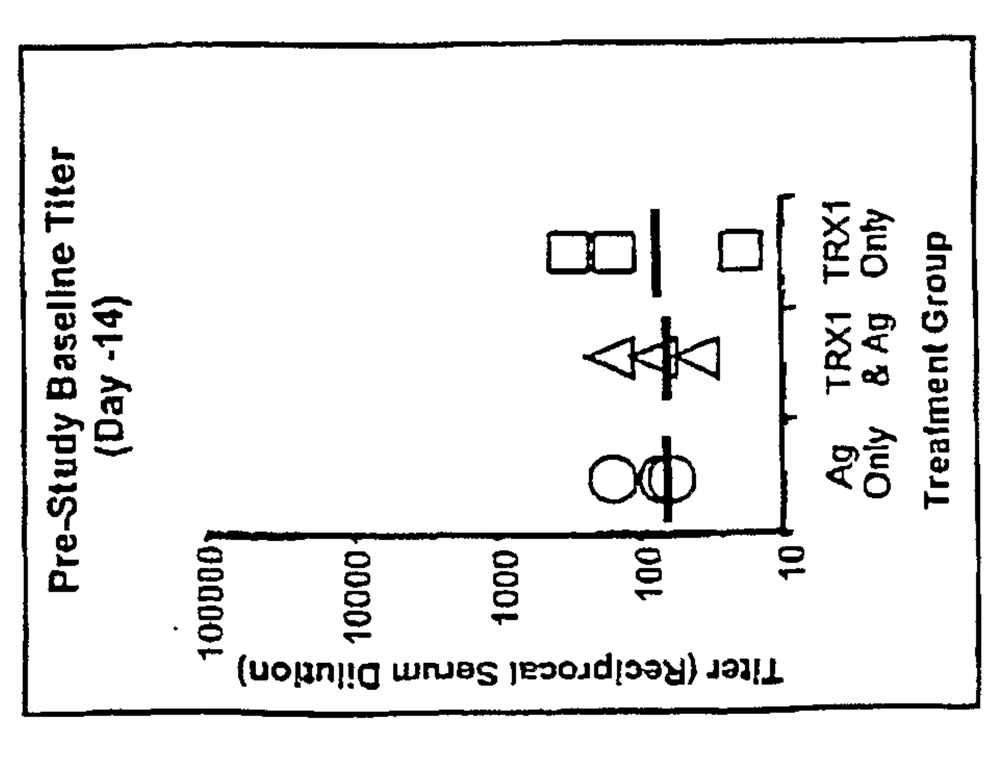


Figure 8