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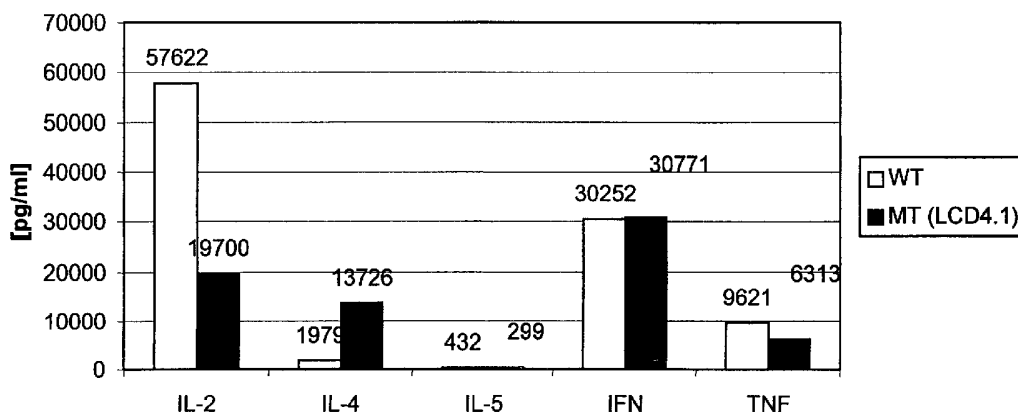
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(54) Title: MANIPULATION OF CYTOKINE LEVELS USING CD83 GENE PRODUCTS



(57) Abstract: The invention provides methods for modulating cytokine levels, GM-CSF levels and the immune system using CD83 nucleic acids, CD83 polypeptides, anti-CD83 antibodies and factors that influence CD83 activity or expression. The invention also provides mice having a mutant CD83 gene and mice having a transgenic CD83 gene, which are useful for defining the role of CD83 in the immune system and for identifying compounds that can modulate CD83 and the immune system.

MANIPULATION OF CYTOKINE LEVELS
USING CD83 GENE PRODUCTS

5 This application is related to U.S. Application Ser. No. 60/331,958 filed November 21, 2001.

FIELD OF THE INVENTION

10 The invention relates to an altered CD83 gene product, and methods of modulating cytokine levels by modulating the expression of mutant and wild type CD83 gene products produced in a mammal. The invention also relates to the regulation of T cell and dendritic cell activity and conditions and treatments related thereto.

15 **BACKGROUND OF THE INVENTION**

 CD83 is a 45 kilodalton glycoprotein that is predominantly expressed on the surface of dendritic cells and other cells of the immune system. Structural analysis of the predicted amino acid sequence of CD83 indicates that it is a member of the immunoglobulin superfamily. *See*, Zhou et al., J. Immunol. 149:735 (1992)). U.S. Patent 5,316,920 and WO 95/29236 disclose further information about CD83. While such information suggests that CD83 plays a role in the immune system, that role is undefined, and the interrelationship of CD83 with cellular factors remains unclear.

25 Moreover, treatment of many diseases could benefit from more effective methods for increasing or decreasing the immune response. Hence, further information about how to modulate the immune system by using factors such as CD83 are needed.

SUMMARY OF THE INVENTION

30 The invention provides a method of modulating cytokine levels by modulating the activity or expression of the CD83 gene products. According to the invention, cytokine levels can be modulated in a mammal or in mammalian

cells that are involved in the immune response, for example, antigen presenting cells or T cells.

The invention therefore provides a method of modulating cytokine production in a mammal or in an immune cell by modulating the activity or expression of a CD83 polypeptide. According to the invention, the production of a cytokine such as interleukin-2, interleukin-4, or interleukin-10 can be modulated by modulating the activity or expression of a CD83 polypeptide. In some embodiments, an antibody is used that can modulate the activity or expression of a CD83 polypeptide. For example, the antibody can be administered to the mammal or the immune cell can be contacted with the antibody. In some embodiments, the immune cells are T cells or antigen presenting cells. In other embodiments, the immune cells are CD4+ T cells.

The invention also provides a method of modulating granulocyte macrophage colony stimulating factor production in a mammal or in an immune cell by modulating the activity or expression of CD83 polypeptides. In some embodiments, an antibody is used that can modulate the activity or expression of a CD83 polypeptide. For example, the antibody can be administered to the mammal or the immune cell can be contacted with the antibody. In some embodiments, the immune cells are T cells or antigen presenting cells. In other embodiments, the immune cells are CD4+ T cells.

The invention also provides a method of modulating tumor necrosis factor production in a mammal or in a mammalian cell by modulating the activity or expression of CD83 polypeptides. In some embodiments, an antibody is used that can modulate the activity or expression of a CD83 polypeptide. For example, the antibody can be administered to the mammal or the mammalian cell can be contacted with the antibody. In some embodiments, the immune cells are T cells or antigen presenting cells. In other embodiments, the immune cells are CD4+ T cells.

The invention further provides a method of inhibiting proliferation of a human peripheral blood mononuclear cell by modulating the activity or expression of CD83 polypeptides. In some embodiments, an antibody is used that can modulate the activity or expression of a CD83 polypeptide. For

example, the antibody can be administered to the mammal or the human peripheral blood mononuclear cell can be contacted with the antibody.

The invention also provides an antibody that can bind to a CD83 polypeptide comprising SEQ ID NO:4, SEQ ID NO:8 or SEQ ID NO:9, wherein
5 activated CD4⁺ T-cells produce lower levels of interleukin-4 when the T-cells are contacted with the antibody. The invention further provides an antibody that can bind to a CD83 polypeptide comprising SEQ ID NO:4, SEQ ID NO:8 or SEQ ID NO:9, wherein CD4⁺ T-cells proliferation is decreased when the T-cells are contacted with the antibody. Such an antibody can have an amino acid
10 sequence that includes SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ
15 ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64. Nucleic acids encoding such an antibody can have, for example,
20 a sequence that includes SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:59, SEQ ID NO:61, SEQ ID NO:63 or SEQ ID NO:65.

The invention also provides a method for decreasing the activity of a CD83 gene product, comprising contacting the CD83 gene product with an
25 antibody that comprises SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38,
30 SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID

NO:62 or SEQ ID NO:64. The activity of a CD83 gene product can be decreased in a mammal or in a cell that is involved in an immune response, for example, a T cell.

The invention further provides a method for decreasing the translation of a CD83 gene product in a mammalian cell, comprising contacting the mammalian cell with a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

In another embodiment, the invention provides a method for decreasing the translation of a CD83 gene product in a mammal, comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

The invention further provides a method for decreasing proliferation of CD4+ T-cells in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9. The antibody can have a sequence comprising SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

The invention also provides a method for decreasing interleukin-2 levels and increasing interleukin-4 levels in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9. The antibody can have a sequence comprising SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID

NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

The invention further provides a method for decreasing interleukin-2 levels and increasing interleukin-4 levels in a mammal comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10. In some embodiments the interleukin-2 levels are decreased and the interleukin-4 levels are increased to treat an autoimmune disease. In other embodiments, the interleukin-2 levels are decreased and the interleukin-4 levels are increased to stimulate production of Th2-associated cytokines in transplant recipients, for example, to prolong survival of transplanted tissues.

The invention also provides a method for increasing interleukin-10 levels in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9. The antibody can have a sequence comprising SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

The invention further provides a method for increasing interleukin-10 levels in a mammal comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10. In some embodiments, the interleukin-

10 levels are increased to treat neoplastic disease. In other embodiments, the interleukin-10 levels are increased to treat a tumor.

The invention also provides a method for increasing interleukin-2 levels in a mammal comprising administering to the mammal a functional CD83 polypeptide that comprises SEQ ID NO:9.

The invention further provides a method for increasing interleukin-2 levels in a mammal comprising: (a) transforming a T cell from the mammal with a nucleic acid encoding a functional CD83 polypeptide operably linked to a promoter functional in a mammalian cell, to generate a transformed T cell; (b) administering the transformed T cell to the mammal to provide increased levels of interleukin-2. In some embodiments, the CD83 polypeptide has a sequence that comprises SEQ ID NO:9 or the nucleic acid has a sequence that comprises SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10. Such methods for increasing interleukin-2 levels can be used to treat an allergy or an infectious disease.

The invention also provides a method for increasing granulocyte macrophage colony stimulating factor levels in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9.

Such an antibody can have a sequence comprising SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

The invention further provides a method for increasing granulocyte macrophage colony stimulating factor levels in a mammal comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic

acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

The invention also provides a method for increasing tumor necrosis factor levels at a selected site in a mammal comprising administering to the site a functional CD83 polypeptide. In another embodiment, the invention provides a method for increasing tumor necrosis factor levels in a selected mammalian cell comprising transforming the cell with a nucleic acid encoding a functional CD83 polypeptide. The CD83 polypeptide employed can, for example, have a sequence comprising SEQ ID NO:9.

Mammals and birds may be treated by the methods and compositions described and claimed herein. Such mammals and birds include humans, dogs, cats, and livestock, for example, horses, cattle, sheep, goats, chickens, turkeys and the like.

The invention further provides a mutant mouse that can serve as an animal model of diminished T cell activation or altered cytokine levels. The mutant mouse has an altered CD83 gene that produces a larger gene product, having SEQ ID NO:4 or containing SEQ ID NO:8. Also provided are methods of using the mutant mouse model to study the effects of cytokines on the immune system, inflammation, the function and regulation of CD83, T cell and dendritic cell activity, the immune response and conditions and treatments related thereto. Hence, the invention further provides a mutant mouse whose somatic and germ cells comprise a mutant CD83 gene encoding a polypeptide comprising SEQ ID NO:4 or SEQ ID NO:8, wherein expression of the mutant CD83 gene reduces CD4+T cell activation. The mutant CD83 gene can, for example, comprise SEQ ID NO:3.

The invention further provides a method of identifying a compound that can modulate CD4+T cell activation comprising administering a test compound to a mouse having a mutant or wild type transgenic CD83 gene and observing whether CD4+ T cell activation is decreased or increased. The somatic and/or germ cells of the mutant mouse can comprise a mutant CD83 gene encoding a polypeptide comprising SEQ ID NO:4 or SEQ ID NO:8. Alternatively, the somatic and/or germ cells of the mouse can contain a wild type CD83 gene, for example, SEQ ID NO:1 or SEQ ID NO:9.

The invention also provides a mutant CD83 gene encoding a polypeptide comprising SEQ ID NO:4 or SEQ ID NO:8. The invention further provides a mutant CD83 gene comprising nucleotide sequence SEQ ID NO:3.

5 DESCRIPTION OF THE FIGURES

Figure 1 provides flow cytometry data for G3 animals. As shown, reduced numbers of CD4⁺ T cells are seen in two animals from Pedigree 9, mouse 9.4.1 and mouse 9.4.9. All other animals analyzed on that day exhibit normal numbers of CD4⁺ T cells.

10 Figure 2 provides a graph of flow cytometry data for G3 animals. Each diamond symbol represents an individual animal. As shown, multiple animals from the N2 generation exhibit a reduced percentage of CD4⁺ T cells.

Figure 3 provides the nucleotide sequence of wild type mouse CD83 (SEQ ID NO:1). The ATG start codon and the TGA stop codon are underlined.

15 Figure 4A-B provides the nucleotide sequence of the mutant CD83 gene (SEQ ID NO:3) of the invention derived from the mutant LCD4.1 animal. The ATG start codon, the mutation and the TGA stop codon are underlined.

Figure 5 provides the amino acid sequence for wild type (top, SEQ ID NO:2) and mutant (bottom, SEQ ID NO:4) CD83 coding regions. The additional C-terminal sequences arising because of the CD83 mutation are underlined.

20 Figure 6A illustrates that dendritic cells from wild type (◆, WT DC) and mutant (■, mutant DC) mice are capable of the allogeneic activation of CD4⁺ T cells. CD4⁺ T cells were stimulated with 10,000, 1000 or 100 dendritic cells for 5 days and proliferation measured by incorporation of tritiated thymidine.

25 Figure 6B illustrates that CD4⁺ T cells from mutant mice (■, mutant CD4) fail to respond to allogeneic stimulation with BALBc dendritic cells, although wild type animals (◆, WT CD4⁺) respond normally. CD4⁺ T cells were stimulated with 10,000, 1000 or 100 dendritic cells for 5 days and proliferation measured by incorporation of tritiated thymidine.

30 Figure 7 provides a bar graph illustrating IL-2, IL-4, IL-5, TNF α , and IFN γ production from wild type CD4⁺ T cells (white bar) or CD83 mutant CD4⁺ T cells (dark bar) that had been stimulated with 1 μ g/ml of anti-CD3 antibodies

and 0.2 $\mu\text{g/ml}$ of anti-CD28 antibodies for 72 hours. As illustrated, IL-2 levels are lower, and IL-4 levels are higher in the CD83 mutant T cells.

Figure 8 provides a bar graph illustrating IL-10 production from wild type CD4+ T cells (white bar) or CD83 mutant CD4+ T cells (dark bar) that had been stimulated with 0.1 $\mu\text{g/ml}$ of anti-CD28 antibodies and 1 to 10 $\mu\text{g/ml}$ of anti-CD3 antibodies for 72 hours. As illustrated, IL-10 levels are higher in the CD83 mutant T cells.

Figure 9 provides a bar graph illustrating GM-CSF production from wild type CD4+ T cells (white bar) or CD83 mutant CD4+ T cells (dark bar) that had been stimulated with anti-CD3 and anti-CD28 antibodies. As illustrated, GM-CSF production is higher in the CD83 mutant cells than in wild type cells.

Figure 10A provides a bar graph illustrating IL-4 mRNA levels from wild type CD4+ T cells (white bar) or CD83 mutant CD4+ T cells (dark bar) that had been stimulated with anti-CD3 and anti-CD28 antibodies. As illustrated, the IL-4 mRNA levels are higher in the CD83 mutant cells.

Figure 10B provides a bar graph illustrating IL-10 mRNA levels from wild type CD4+ T cells (white bar) or CD83 mutant CD4+ T cells (dark bar) that had been stimulated with anti-CD3 and anti-CD28 antibodies. As illustrated, the IL-10 mRNA levels are higher in the CD83 mutant cells.

Figure 11 provides a graph illustrating that various preparations of anti-CD83 antibodies inhibit IL-4 production in anti-CD3 and anti-CD28 antibody stimulated T cells. The amount of IL-4 produced by T cells in pg/ml is plotted versus the concentration of different anti-CD83 antibody preparations, including the 20B08 ($\blacklozenge$) anti-CD83 preparation, the 20D04 ($\blacksquare$) anti-CD83 preparation, the 14C12 ($\blacktriangle$) anti-CD83 preparation and the 11G05 (X) anti-CD83 antibody preparation.

Figure 12 provides a graph illustrating that various preparations of anti-CD83 antibodies inhibit T cell proliferation. The graph plots the incorporation of radioactive thymidine in cpms, which was used as an indicator of the amount of T cell proliferation, versus the concentration of the different anti-CD83 antibody preparations, including the 20D04 ($\blacklozenge$) anti-CD83 preparation, the 11G05 ($\blacksquare$) anti-CD83 antibody preparation, the 14C12 ($\blacktriangle$) anti-CD83 preparation and the 6G05 anti-CD83 preparation (X).

Figure 13 provides a graph illustrating that transgenic mice that over-express wild type CD83 have increased T cell proliferation. The graph plots the incorporation of radioactive thymidine in cpms, which was used as an indicator of the amount of T cell proliferation, versus the concentration of OVA peptide.

- 5 The transgenic mice utilized had a T-cell receptor specific for chicken ovalbumin (OVA) 323-339 peptide that can activate T-cells. When mixed with either transgenic or wild type dendritic cells in the presence of OVA peptide, transgenic CD4+ T cells had increased T-cell proliferation. However, transgenic dendritic cells could not substantially increase wild type CD4+ T cell proliferation.
- 10 Transgenic CD83 CD4+ T cells mixed with wild type dendritic cells (◆); transgenic CD83 CD4+ T cells mixed with transgenic dendritic cells (■); wild type CD4+ T cells mixed with transgenic dendritic cells (▲); and wild type CD4+ T cells mixed with wild type dendritic cells (X).

- Figure 14 provides a schematic diagram of the structural elements included in the mouse CD83 protein used for generating antibodies.
- 15

Figure 15 provides a graph of ELISA data illustrating the titer obtained for different isolates of polyclonal anti-CD83 anti-sera. The first (◆), second (■) and third (▲) isolates had similar titers, though the titer of the second isolate (■) was somewhat higher.

- 20 Figure 16 illustrates that proliferation of PHA-activated human PBMCs was inhibited by antibodies raised against the external region of the mouse CD83 protein (◆). Pre-immune serum (■) had little effect on the proliferation of human PBMCs.

- Figure 17A provides a sequence alignment of anti-CD83 heavy chain variable regions isolated by the invention. Sequences for isolates 20B08H (SEQ ID NO:52), 6G05H (SEQ ID NO:53), 20D04H (SEQ ID NO:54), 11G05 (SEQ ID NO:66) and 14C12 (SEQ ID NO:67) are provided. The CDR regions are highlighted in bold.
- 25

- Figure 17B provides a sequence alignment of anti-CD83 light chain variable regions isolated by the invention. Sequences for isolates 20B08H (SEQ ID NO:55), 6G05H (SEQ ID NO:56), 20D04H (SEQ ID NO:57), 11G05 (SEQ ID NO:68) and 14C12 (SEQ ID NO:69) are provided. The CDR regions are highlighted in bold.
- 30

DETAILED DESCRIPTION OF THE INVENTION

The invention provides methods for modulating the immune system by using CD83 proteins, CD83 nucleic acids and factors that modulate CD83 activity or expression.

According to the invention, loss or reduction of CD83 activity *in vivo* results in altered cytokine levels, for example, lower interleukin-2 levels, increased interleukin-4 levels, increased GM-CSF levels and increased interleukin-10 levels. Loss or reduction of CD83 activity *in vivo* can also result in decreased numbers of T cells.

Moreover, the invention also relates to increased CD83 activity *in vivo* that can result in altered cytokine levels, for example, higher interleukin-2 levels, decreased interleukin-4 levels, decreased GM-CSF levels and decreased interleukin-10 levels. Increased CD83 expression or activity *in vitro* and *in vivo* can also result in increased activation and increased numbers of T cells.

The effects of CD83 on the immune system, on GM-CSF and on cytokine levels were analyzed by using mutant and transgenic mice. The mutant mouse has an altered CD83 gene that expresses altered (defective) CD83 gene product. The transgenic mouse overexpresses CD83 gene products. Accordingly, the invention provides mammals such as mice that have a mutant or wild type CD83 gene. These mice are useful for identifying the role that CD83 plays in the immune response. These mutant and transgenic animals are useful for identifying factors for manipulating cytokine levels and T cell activation by testing whether those factors and compositions can modulate, inhibit or replace the activity of CD83 *in vivo*.

CD83

CD83 is a lymphocyte and dendritic cell activation antigen that is expressed by activated lymphocytes and dendritic cells. CD83 is also a single-chain cell-surface glycoprotein with a molecular weight of about 45,000 that is believed to be a member of the Ig superfamily. The structure predicted from the CD83 amino acid sequence indicates that CD83 is a membrane glycoprotein with a single extracellular Ig-like domain, a transmembrane domain and cytoplasmic

domain of approximately forty amino acids. The mature CD83 protein has about 186 amino acids and is composed of a single extracellular V type immunoglobulin (Ig)-like domain, a transmembrane domain and a thirty nine amino acid cytoplasmic domain. Northern blot analysis has revealed that CD83 is translated from three mRNA transcripts of about 1.7, 2.0 and 2.5 kb that are expressed by lymphoblastoid cell lines. It is likely that CD83 undergoes extensive post-translational processing because CD83 is expressed as a single chain molecule, but the determined molecular weight is twice the predicted size of the core protein. *See* U.S. Patent 5,766,570.

10 An example of a human CD83 gene product that can be used in the invention is provided below (SEQ ID NO:9):

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1 MSRGLQLLLL SCAYSLAPAT PEVKVACSED VDLPTAPWD
41 PQVPYTVSWV KLEGGEERM ETPQEDHLRG QHYHQKGQNG
81 SFDAPNERPY SLKIRNTTSC NSGTyrCTLQ DPDGQRNLSG
15 121 KVILRVTGCP AQRKEETFKK YRAEIVLLLA LVIFYLTLII
161 FTCKFARLQS IFPDFSKAGM ERAFLPVTSP NKHLGLVTPH
201 KTELV

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Such a CD83 gene product can be encoded by a number of different nucleic acids. One example of a human CD83 nucleic acid is provided below (SEQ ID NO:10).

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1 CCTGGCGCAG CCGCAGCAGC GACGCGAGCG AACTCGGCCG
41 GGCCCGGGCG CGCGGGGGCG GGACGCGCAC GCGGCGAGGG
81 CGGCGGGTGA GCCGGGGGCG GGGACGGGGG CGGGACGGGG
25 121 GCGAAGGGGG CGGGGACGGG GCGCGCCGCC GGCCTAACGG
161 GATTAGGAGG GCGCGCCACC CGCTTCCGCT GCCCGCCGGG
201 GAATCCCCCG GGTGGCGCCC AGGGAAGTTC CCGAACGGGC
241 GGGCATAAAA GGGCAGCCGC GCCGGCGCCC CACAGCTCTG
281 CAGCTCGTGG CAGCGGCGCA GCGCTCCAGC CATGTTCGCGC
30 321 GGCCTCCAGC TTCTGCTCCT GAGCTGCGCC TACAGCCTGG
361 CTCCCGCGAC GCCGGAGGTG AAGGTGGCTT GCTCCGAAGA
401 TGTGGACTTG CCCTGCACCG CCCCCTGGGA TCCGCAGGTT
441 CCCTACACGG TCTCCTGGGT CAAGTTATTG GAGGGTGGTG
481 AAGAGAGGAT GGAGACACCC CAGGAAGACC ACCTCAGGGG
35 521 ACAGCACTAT CATCAGAAGG GGCAAAATGG TTCTTTCGAC

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561 GCCCCCAATG AAAGGCCCTA TTCCCTGAAG ATCCGAAACA
 601 CTACCAGCTG CAACTCGGGG ACATACAGGT GCACTCTGCA
 641 GGACCCGGAT GGGCAGAGAA ACCTAAGTGG CAAGGTGATC
 681 TTGAGAGTGA CAGGATGCCC TGCACAGCGT AAAGAAGAGA
 5 721 CTTTTAAGAA ATACAGAGCG GAGATTGTCC TGCTGCTGGC
 761 TCTGGTTATT TTCTACTTAA CACTCATCAT TTCTACTTGT
 801 AAGTTTGCAC GGCTACAGAG TATCTTCCCA GATTTTTCTA
 841 AAGCTGGCAT GGAACGAGCT TTTCTCCCAG TTACCTCCCC
 881 AAATAAGCAT TTAGGGCTAG TGACTCCTCA CAAGACAGAA
 10 921 CTGGTATGAG CAGGATTTCT GCAGGTTCTT CTTCTGAAG
 961 CTGAGGCTCA GGGGTGTGCC TGTCTGTTAC ACTGGAGGAG
 1001 AGAAGAATGA GCCTACGCTG AAGATGGCAT CCTGTGAAGT
 1041 CCTTCACCTC ACTGAAAACA TCTGGAAGGG GATCCCACCC
 1081 CATTTTCTGT GGGCAGGCCT CGAAAACCAT CACATGACCA
 15 1121 CATAGCATGA GGCCACTGCT GCTTCTCCAT GGCCACCTTT
 1161 TCAGCGATGT ATGCAGCTAT CTGGTCAACC TCCTGGACAT
 1201 TTTTTCAGTC ATATAAAAGC TATGGTGAGA TGCAGCTGGA
 1241 AAAGGGTCTT GGGAAATATG AATGCCCCCA GCTGGCCCGT
 1281 GACAGACTCC TGAGGACAGC TGTCTCTTTC TGCATCTTGG
 20 1321 GGACATCTCT TTGAATTTTC TGTGTTTTGC TGTACCAGCC
 1361 CAGATGTTTT ACGTCTGGGA GAAATTGACA GATCAAGCTG
 1401 TGAGACAGTG GGAAATATTT AGCAAATAAT TTCCTGGTGT
 1441 GAAGGTCCTG CTATTACTAA GGAGTAATCT GTGTACAAAG
 1481 AAATAACAAG TCGATGAACT ATTCCCCAGC AGGGTCTTTT
 25 1521 CATCTGGGAA AGACATCCAT AAAGAAGCAA TAAAGAAGAG
 1561 TGCCACATTT ATTTTTATAT CTATATGTAC TTGTCAAAGA
 1601 AGGTTTGTGT TTTTCTGCTT TTGAAATCTG TATCTGTAGT
 1641 GAGATAGCAT TGTGAACTGA CAGGCAGCCT GGACATAGAG
 1681 AGGGAGAAGA AGTCAGAGAG GGTGACAAGA TAGAGAGCTA
 30 1721 TTTAATGGCC GGCTGGAAAT GCTGGGCTGA CGGTGCAGTC
 1761 TGGGTGCTCG CCCACTTGTC CCACTATCTG GGTGCATGAT
 1801 CTTGAGCAAG TTCCTTCTGG TGTCTGCTTT CTCCATTGTA
 1841 AACCACAAGG CTGTTGCATG GGCTAATGAA GATCATATAC
 1881 GTGAAAATTA TTTGAAAACA TATAAAGCAC TATACAGATT
 35 1921 CGAAACTCCA TTGAGTCATT ATCCTTGCTA TGATGATGGT
 1961 GTTTTGGGGA TGAGAGGGTG CTATCCATTT CTCATGTTTT

2001 CCATTGTTTG AAACAAAGAA GGTTACCAAG AAGCCTTTCC
 2041 TGTAGCCTTC TGTAGGAATT CTTTTGGGGA AGTGAGGAAG
 2081 CCAGGTCCAC GGTCTGTTCT TGAAGCAGTA GCCTAACACA
 2121 CTCCAAGATA TGGACACACG GGAGCCGCTG GCAGAAGGGA
 5 2161 CTTACGAAG TGTTCATGG ATGTTTTAGC CATTGTTGGC
 2201 TTTCCCTTAT CAAACTTGGG CCCTTCCCTT CTTGGTTTCC
 2241 AAAGGCATTT ATTGCTGAGT TATATGTTCA CTGTCCCCCT
 2281 AATATTAGGG AGTAAACGG ATACCAAGTT GATTTAGTGT
 2321 TTTTACCTCT GTCTTGGCTT TCATGTTATT AAACGTATGC
 10 2361 ATGTGAAGAA GGGTGTTTTT CTGTTTTATA TTCAACTCAT
 2401 AAGACTTTGG GATAGGAAAA ATGAGTAATG GTTACTAGGC
 2441 TTAATACCTG GGTGATTACA TAATCTGTAC AACGAACCCC
 2481 CATGATGTAA GTTTACCTAT GTAACAAACC TGCACCTATA
 2521 CCCATGAACT TAAAATGAAA GTTAAAAATA AAAAACATAT
 15 2561 ACAAATAAAA AAAA

A sequence of a wild type mouse CD83 gene that can be used in the invention is provided herein as SEQ ID NO:1. SEQ ID NO:1 is provided below with the ATG start codon and the TGA stop codon identified by underlining.

20

1 GCGCTCCAGC CGCATGTCGC AAGGCCTCCA GCTCCTGTTT
 41 CTAGGCTGCG CCTGCAGCCT GGCACCCGCG ATGGCGATGC
 81 GGGAGGTGAC GGTGGCTTGC TCCGAGACCG CCGACTTGCC
 121 TTGCACAGCG CCCTGGGACC CGCAGCTCTC CTATGCAGTG
 25 161 TCCTGGGCCA AGGTCTCCGA GAGTGGCACT GAGAGTGTGG
 201 AGCTCCCGGA GAGCAAGCAA AACAGCTCCT TCGAGGCCCC
 241 CAGGAGAAGG GCCTATTCCC TGACGATCCA AAACACTACC
 281 ATCTGCAGCT CGGGCACCTA CAGGTGTGCC CTGCAGGAGC
 321 TCGGAGGGCA GCGCAACTTG AGCGGCACCG TGGTTCTGAA
 30 361 GGTGACAGGA TGCCCCAAGG AAGCTACAGA GTCAACTTTC
 401 AGGAAGTACA GGGCAGAAGC TGTGTTGCTC TTCTCTCTGG
 441 TTGTTTTCTA CCTGACACTC ATCATTTTCA CCTGCAAATT
 481 TGCACGACTA CAAAGCATTT TCCCAGATAT TTCTAAACCT
 521 GGTACGGAAC AAGCTTTTCT TCCAGTCACC TCCCCAAGCA
 35 561 AACATTTGGG GCCAGTGACC CTTCCTAAGA CAGAAACGGT
 601 ATGAGTAGGA TCTCCACTGG TTTTACAAA GCCAAGGGCA

641 CATCAGATCA GTGTGCCTGA ATGCCACCCG GACAAGAGAA
 681 GAATGAGCTC CATCCTCAGA TGGCAACCTT TCTTTGAAGT
 721 CCTTCACCTG ACAGTGGGCT CCACACTACT CCCTGACACA
 761 GGGTCTTGAG CACCATCATA TGATCACGAA GCATGGAGTA
 5 801 TCACCGCTTC TCTGTGGCTG TCAGCTTAAT GTTTCATGTG
 841 GCTATCTGGT CAACCTCGTG AGTGCTTTTC AGTCATCTAC
 881 AAGCTATGGT GAGATGCAGG TGAAGCAGGG TCATGGGAAA
 921 TTTGAACACT CTGAGCTGGC CCTGTGACAG ACTCCTGAGG
 961 ACAGCTGTCC TCTCCTACAT CTGGGATACA TCTCTTTGAA
 10 1001 TTTGTCCTGT TTCGTTGCAC CAGCCCAGAT GTCTCACATC
 1041 TGGCGGAAAT TGACAGGCCA AGCTGTGAGC CAGTGGGAAA
 1081 TATTTAGCAA ATAATTTCCC AGTGCGAAGG TCCTGCTATT
 1121 AGTAAGGAGT ATTATGTGTA CATAGAAATG AGAGGTCAGT
 1161 GAACTATTCC CCAGCAGGGC CTTTTCATCT GGAAAAGACA
 15 1201 TCCACAAAAG CAGCAATACA GAGGGATGCC ACATTTATTT
 1241 TTTTAATCTT CATGTACTTG TCAAAGAAGA ATTTTTCATG
 1281 TTTTTTCAAA GAAGTGTGTT TCTTTCCTTT TTTAAATAT
 1321 GAAGGTCTAG TTACATAGCA TTGCTAGCTG ACAAGCAGCC
 1361 TGAGAGAAGA TGGAGAATGT TCCTCAAAAT AGGGACAGCA
 20 1401 AGCTAGAAGC ACTGTACAGT GCCCTGCTGG GAAGGGCAGA
 1441 CAATGGACTG AGAAACCAGA AGTCTGGCCA CAAGATTGTC
 1481 TGTATGATTC TGGACGAGTC ACTTGTGGTT TCACTCTCT
 1521 GGTTAGTAAA CCAGATAGTT TAGTCTGGGT TGAATACAAT
 1561 GGATGTGAAG TTGCTTGGGG AAAGCTGAAT GTAGTGAATA
 25 1601 CATTGGCAAC TCTACTGGGC TGTTACCTTG TTGATATCCT
 1641 AGAGTTCTGG AGCTGAGCGA ATGCCTGTCA TATCTCAGCT
 1681 TGCCCATCAA TCCAAACACA GGAGGCTACA AAAAGGACAT
 1721 GAGCATGGTC TTCTGTGTGA ACTCCTCCTG AGAAACGTGG
 1761 AGACTGGCTC AGCGCTTTGC GCTTGAAGGA CTAATCACAA
 30 1801 GTTCTTGAAG ATATGGACCT AGGGGAGCTA TTGCGCCACG
 1841 ACAGGAGGAA GTTCTCAGAT GTTGCAATTGA TGTAACATTG
 1881 TTGCATTTCT TTAATGAGCT GGGCTCCTTC CTCATTTGCT
 1921 TCCCAAAGAG ATTTTGTCCC ACTAATGGTG TGCCCATCAC
 1961 CCACACTATG AAAGTAAAAG GGATGCTGAG CAGATACAGC
 35 2001 GTGCTTACCT CTCAGCCATG ACTTTCATGC TATTAAAAGA
 2041 ATGCATGTGA A

Nucleic acids having SEQ ID NO:1 encode a mouse polypeptide having SEQ ID NO:2, provided below.

5 1 MSQGLQLLFL GCACSLAPAM AMRETVACS ETADLPCTAP
 41 WDPQLSYAVS WAKVSESGTE SVELPESKQN SSFEAPRRRA
 81 YSLTIQNTTI CSSGTYRCAL QELGGQRNLS GTVVLKVTGC
 121 PKEATESTFR KYRAEAVLLF SLVVFYLTLL IFTCKFARLQ
 161 SIFPDISKPG TEQAFLPVTS PSKHLGPVTL PKTETV

10

According to the invention, loss or reduction of CD83 activity *in vivo* results in altered cytokine levels, for example, lower interleukin-2 levels, increased interleukin-4 levels, increased GM-CSF levels and increased interleukin-10 levels. Loss or reduction of CD83 activity *in vivo* can also result
 15 in decreased numbers of T cells.

Moreover, increased CD83 activity *in vivo* can also result in altered cytokine levels, for example, higher interleukin-2 levels, decreased interleukin-4 levels, decreased GM-CSF levels and decreased interleukin-10 levels. Increased CD83 expression or activity *in vivo* can also result in increased activation or
 20 increased numbers of T cells.

The effect of CD83 on cytokine levels was ascertained through use of a mutant mouse that encodes a mutant CD83. Such a mutant mouse has a CD83 gene encoding SEQ ID NO:4, with added C-terminal sequences provided by SEQ ID NO:8. In contrast to these wild type CD83 nucleic acids and
 25 polypeptides, the mutant CD83 gene of the invention has SEQ ID NO:3. SEQ ID NO:3 is provided below with the ATG start codon, the mutation, and the TGA stop codon are identified by underlining.

 1 GCGCTCCAGC CGCATGTCGC AAGGCCTCCA GCTCCTGTTT
 41 CTAGGCTGCG CCTGCAGCCT GGCACCCGCG ATGGCGATGC
 30 81 GGGAGGTGAC GGTGGCTTGC TCCGAGACCG CCGACTTGCC
 121 TTGCACAGCG CCCTGGGACC CGCAGCTCTC CTATGCAGTG
 161 TCCTGGGCCA AGGTCTCCGA GAGTGGCACT GAGAGTGTGG
 201 AGCTCCCGGA GAGCAAGCAA AACAGCTCCT TCGAGGCCCC
 241 CAGGAGAAGG GCCTATTCCC TGACGATCCA AAACACTACC

281 ATCTGCAGCT CGGGCACCTA CAGGTGTGCC CTGCAGGAGC
 321 TCGGAGGGCA GCGCAACTTG AGCGGCACCG TGGTTCTGAA
 361 GGTGACAGGA TGCCCCAAGG AAGCTACAGA GTCAACTTTTC
 401 AGGAAGTACA GGGCAGAAGC TGTGTTGCTC TTCTCTCTGG
 5 441 TTGTTTTCTA CCTGACACTC ATCATTTTCA CCTGCAAATT
 481 TGCACGACTA CAAAGCATTT TCCCAGATAT TTCTAAACCT
 521 GGTACGGAAC AAGCTTTTCT TCCAGTCACC TCCCCAAGCA
 561 AACATTTGGG GCCAGTGACC CTTCTTAAGA CAGAAACGGT
 601 AAGAGTAGGA TCTCCACTGG TTTTACAAA GCCAAGGGCA
 10 641 CATCAGATCA GTGTGCCTGA ATGCCACCCG GACAAGAGAA
 681 GAATGAGCTC CATCCTCAGA TGGCAACCTT TCTTTGAAGT
 721 CCTTCACCTG ACAGTGGGCT CCACACTACT CCCTGACACA
 761 GGGTCTTGAG CACCATCATA TGATCACGAA GCATGGAGTA
 801 TCACCGCTTC TCTGTGGCTG TCAGCTTAAT GTTTCATGTG
 15 841 GCTATCTGGT CAACCTCGTG AGTGCTTTTC AGTCATCTAC
 881 AAGCTATGGT GAGATGCAGG TGAAGCAGGG TCATGGGAAA
 921 TTTGAACACT CTGAGCTGGC CCTGTGACAG ACTCCTGAGG
 961 ACAGCTGTCC TCTCCTACAT CTGGGATACA TCTCTTTGAA
 1001 TTTGTCCTGT TTCGTTGCAC CAGCCCAGAT GTCTCACATC
 20 1041 TGGCGGAAAT TGACAGGCCA AGCTGTGAGC CAGTGGGAAA
 1081 TATTTAGCAA ATAATTTCCC AGTGCGAAGG TCCTGCTATT
 1121 AGTAAGGAGT ATTATGTGTA CATAGAAATG AGAGGTCAGT
 1161 GAACTATTCC CCAGCAGGGC CTTTTCATCT GGAAAAGACA
 1201 TCCACAAAAG CAGCAATACA GAGGGATGCC ACATTTATTT
 25 1241 TTTTAATCTT CATGTACTTG TCAAAGAAGA ATTTTTCATG
 1281 TTTTTTCAAA GAAGTGTGTT TCTTTCCTTT TTTAAATAT
 1321 GAAGGTCTAG TTACATAGCA TTGCTAGCTG ACAAGCAGCC
 1361 TGAGAGAAGA TGGAGAATGT TCCTCAAAAT AGGGACAGCA
 1401 AGCTAGAAGC ACTGTACAGT GCCCTGCTGG GAAGGGCAGA
 30 1441 CAATGGACTG AGAAACCAGA AGTCTGGCCA CAAGATTGTC
 1481 TGTATGATTC TGGACGAGTC ACTTGTGGTT TTCACTCTCT
 1521 GGTTAGTAAA CCAGATAGTT TAGTCTGGGT TGAATACAAT
 1561 GGATGTGAAG TTGCTTGGGG AAAGCTGAAT GTAGTGAATA
 1601 CATTGGCAAC TCTACTGGGC TGTTACCTTG TTGATATCCT
 35 1641 AGAGTTCTGG AGCTGAGCGA ATGCCTGTCA TATCTCAGCT
 1681 TGCCCATCAA TCCAAACACA GGAGGCTACA AAAAGGACAT

1721 GAGCATGGTC TTCTGTGTGA ACTCCTCCTG AGAAACGTGG
 1761 AGACTGGCTC AGCGCTTTGC GCTTGAAGGA CTAATCACAA
 1801 GTTCTTGAAG ATATGGACCT AGGGGAGCTA TTGCGCCACG
 1841 ACAGGAGGAA GTTCTCAGAT GTTGCATTGA TGTAACATTG
 5 1881 TTGCATTTCT TTAATGAGCT GGGCTCCTTC CTCATTGCT
 1921 TCCCAAAGAG ATTTTGTCCC ACTAATGGTG TGCCCATCAC
 1961 CCACACTATG AAAGTAAAAG GGATGCTGAG CAGATACAGC
 2001 GTGCTTACCT CTCAGCCATG ACTTTCATGC TATTAAAAGA
 2041 ATGCATGTGA A

10

The change from a thymidine in SEQ ID NO:1 to an adenine in SEQ ID NO:3 at the indicated position (602) leads to read-through translation because the stop codon at positions 602-604 in SEQ ID NO:1 is changed to a codon that encodes an arginine. Accordingly, mutant CD83 nucleic acids having SEQ ID NO:3
 15 encode an elongated polypeptide having SEQ ID NO:4, provided below, where the extra amino acids are underlined.

1 MSQGLQLLFL GCACSLAPAM AMREVTVACS ETADLPCTAP
 41 WDPQLSYAVS WAKVSESGTE SVELPESKQN SSFEAPRRRA
 20 81 YSLTIQNTTI CSSGTYRCAL QELGGQRNLS GTVVLLKVTGC
 121 PKEATESTFR KYRAEAVLLF SLVVFYLTLL IFTCKFARLQ
 161 SIFPDISKPG TEQAFLPVTS PSKHLGPVTL PKTETVRVGS
 201 PLVFTKPAH QISVPECHPD KRMSSILRW QPFFEVLHLT
 241 VGSTLLPDTG S

25

In another embodiment, the invention provides mutant CD83 nucleic acids that include SEQ ID NO:5.

1 ATGTCGCAAG GCCTCCAGCT CCTGTTTCTA GGCTGCGCCT
 30 41 GCAGCCTGGC ACCCGCGATG GCGATGCGGG AGGTGACGGT
 81 GGCTTGCTCC GAGACCGCCG ACTTGCCTTG CACAGCGCCC
 121 TGGGACCCGC AGCTCTCCTA TGCAGTGTCC TGGGCCAAGG
 161 TCTCCGAGAG TGGCACTGAG AGTGTGGAGC TCCCGGAGAG
 201 CAAGCAAAAC AGCTCCTTCG AGGCCCCCAG GAGAAGGGCC
 35 241 TATTCCCTGA CGATCCAAAA CACTACCATC TGCAGCTCGG

281 GCACCTACAG GTGTGCCCTG CAGGAGCTCG GAGGGCAGCG
 321 CAACTTGAGC GGCACCGTGG TTCTGAAGGT GACAGGATGC
 361 CCCAAGGAAG CTACAGAGTC AACTTTCAGG AAGTACAGGG
 401 CAGAAGCTGT GTTGCTCTTC TCTCTGGTTG TTTTCTACCT
 5 441 GACACTCATC ATTTTCACCT GCAAATTTGC ACGACTACAA
 481 AGCATTTTCC CAGATATTTT TAAACCTGGT ACGGAACAAG
 521 CTTTTCTTCC AGTCACCTCC CCAAGCAAAC ATTTGGGGCC
 561 AGTGACCCTT CCTAAGACAG AAACGGTAAG AGTAGGATCT
 601 CCACTGGTTT TTACAAAGCC AAGGGCACAT CAGATCAGTG
 10 641 TGCCTGAATG CCACCCGGAC AAGAGAAGAA TGAGCTCCAT
 681 CCTCAGATGG CAACCTTTCT TTGAAGTCCT TCACCTGACA
 721 GTGGGCTCCA CACTACTCCC TGACACAGGG TCTTGA

Nucleic acids having SEQ ID NO:5 also encode a polypeptide having SEQ ID
 15 NO:4.

In another embodiment, the invention provides mutant CD83 nucleic
 acids that include SEQ ID NO:7.

1 AGAGTAGGAT CTCCACTGGT TTTTACAAAG CCAAGGGCAC
 20 41 ATCAGATCAG TGTGCCTGAA TGCCACCCGG ACAAGAGAAG
 81 AATGAGCTCC ATCCTCAGAT GGCAACCTTT CTTTGAAGTC
 121 CTTACCTGA CAGTGGGCTC CACACTACTC CCTGACACAG
 161 GGTCTTGA

25 The invention also provides a mutant CD83 containing SEQ ID NO:8,
 provided below.

1 RVGSPLVFTK PRAHQISVPE CHPDKRRMSS ILRWQPFPEV
 41 LHLTVGSTLL PDTGS

30 SEQ ID NO:8 contains read through sequences that are not present in the wild
 type CD83 polypeptide but are present in the mutant CD83 gene product
 provided by the invention.

CD83 Modulation of Cytokine Levels

The invention also provides compositions and methods for increasing interleukin-4 levels, increasing GM-CSF levels, increasing interleukin-10 levels and decreasing interleukin-2 levels in a mammal. Such compositions and methods generally operate by decreasing the expression or function of CD83 gene products in the mammal. Interleukin-4 promotes the differentiation of Th2 cells while decreasing the differentiation of precursor cells into Th1 cells. Th2 cells are involved in helping B lymphocytes and in stimulating production of IgG1 and IgE antibodies. Enhancement of Th2 formation may be useful, for example, in autoimmune diseases and in organ transplantation.

Alternatively, the invention provides compositions and methods for decreasing interleukin-4 levels, decreasing interleukin-10 levels and increasing interleukin-2 levels in a mammal. Such compositions and methods generally increase the expression or function of CD83 gene products in the mammal. Interleukin-2 promotes the differentiation of Th1 cells and decreases the differentiation of Th-2 cells. Th1 cells are, for example, involved in inducing autoimmune and delayed type hypersensitivity responses. Inhibition of Th2 formation may be useful in treating allergic diseases, malignancies and infectious diseases.

CD4+T helper cells are not a homogeneous population but can be divided on the basis of cytokine secretion into at least two subsets termed T helper type 1 (Th1) and T helper type 2 (Th2) (see e.g., Mosmann, T. R. et al. (1986) J. Immunol. 136:2348-2357; Paul, W. E. and Seder, R. A. (1994) Cell 76:241-251; Seder, R. A. and Paul, W. E. (1994) Ann. Rev. Immunol. 12:635-673). Th1 cells secrete interleukin-2 (IL-2) and interferon- γ (IFN- γ) while Th2 cells produce interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-10 (IL-10) and interleukin-13 (IL-13). Both subsets produce cytokines such as tumor necrosis factor (TNF) and granulocyte/macrophage-colony stimulating factor (GM-CSF).

In addition to their different pattern of cytokine expression, Th1 and Th2 cells are thought to have differing functional activities. For example, Th1 cells are involved in inducing delayed type hypersensitivity responses, whereas Th2 cells are involved in providing efficient "help" to B lymphocytes and stimulating production of IgG1 and IgE antibodies.

The ratio of Th1 to Th2 cells is highly relevant to the outcome of a wide array of immunologically-mediated clinical diseases including autoimmune, allergic and infectious diseases. For example, in experimental leishmania infections in mice, animals that are resistant to infection mount predominantly a Th1 response, whereas animals that are susceptible to progressive infection mount predominantly a Th2 response (Heinzel, F. P., et al. (1989) *J. Exp. Med.* 169:59-72; Locksley, R. M. and Scott, P. (1992) *Immunoparasitology Today* 1:A58-A61). In murine schistosomiasis, a Th1 to Th2 switch is observed coincident with the release of eggs into the tissues by female parasites and is associated with a worsening of the disease condition (Pearce, E. J., et al. (1991) *J. Exp. Med.* 173:159-166; Grzych, J-M., et al. (1991) *J. Immunol* 141:1322-1327; Kullberg, M. C., et al. (1992) *J. Immunol.* 148:3264-3270).

Many human diseases, including chronic infections (such as with human immunodeficiency virus (HIV) and tuberculosis) and certain metastatic carcinomas, also are characterized by a Th1 to Th2 switch (see e.g., Shearer, G. M. and Clerici, M. (1992) *Prog. Chem. Immunol.* 54:21-43; Clerici, M and Shearer, G. M. (1993) *Immunology Today* 14:107-111; Yamamura, M., et al. (1993) *J Clin. Invest.* 91:1005-1010; Pisa, P., et al. (1992) *Proc. Natl. Acad. Sci. USA* 89:7708-7712; Fauci, A. S. (1988) *Science* 239:617-623).

Certain autoimmune diseases have been shown to be associated with a predominant Th1 response. For example, patients with rheumatoid arthritis have predominantly Th1 cells in synovial tissue (Simon, A. K., et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:8562-8566) and experimental autoimmune encephalomyelitis (EAE) can be induced by autoreactive Th1 cells (Kuchroo, V. K., et al. (1993) *J. Immunol.* 151:4371-4381).

The ability to alter or manipulate ratios of Th1 and Th2 subsets requires an understanding of the mechanisms by which the differentiation of CD4 T helper precursor cells (Thp), which secrete only IL-2, choose to become Th1 or Th2 effector cells. It is clear that the cytokines themselves are potent Th cell inducers and form an autoregulatory loop (see e.g., Paul, W. E. and Seder, R. A. (1994) *Cell* 76:241-251; Seder, R. A. and Paul, W. E. (1994) *Ann. Rev. Immunol.* 12:635-673). Thus, IL4 promotes the differentiation of Th2 cells while

preventing the differentiation of precursors into Th1 cells, while IL-12 and IFN- γ have the opposite effect.

According to the invention, one way to alter Th1:Th2 ratios is to increase or decrease the level of selected cytokines by using CD83. Direct administration
5 of cytokines or antibodies to cytokines has been shown to have an effect on certain diseases mediated by either Th1 or Th2 cells. For example, administration of recombinant IL-4 or antibodies to IL-12 ameliorate EAE, a Th1-driven autoimmune disease (see Racke; M. K. et al. (1994) J. Exp. Med. 180:1961-1966; and Leonard, J. P. et al. (1995) J. Exp. Med. 181:381-386),
10 while anti-IL-4 antibodies can ameliorate the Th2-mediated parasitic disease, *Leishmania major* (Sadick, M. D. et al. (1990) J. Exp. Med. 171:115-127).

Numerous disease conditions are associated with either a predominant Th1-type response or a predominant Th2-type response and the individuals suffering from such disease conditions could benefit from treatment with the
15 CD83 related compositions and methods of the invention. Application of the immunomodulatory methods of the invention to such diseases is described in further detail below.

Allergies

20 Allergies are mediated through IgE antibodies whose production is regulated by the activity of Th2 cells and the cytokines produced thereby. In allergic reactions, IL-4 is produced by Th2 cells, which further stimulates production of IgE antibodies and activation of cells that mediate allergic reactions, i.e., mast cells and basophils. IL-4 also plays an important role in
25 eosinophil mediated inflammatory reactions.

Accordingly, the stimulation of CD83 production by use of the compositions and methods of the invention can be used to inhibit the production of Th2-associated cytokines, for example IL-4, in allergic patients as a means to down-regulate production of pathogenic IgE antibodies. A stimulatory agent
30 may be directly administered to the subject mammal. Alternatively, the CD83 stimulatory agent (e.g. CD83 expression cassette) can be administered to cells (e.g., Thp cells or Th2 cells) that may be obtained from the subject and those modified cells can be readministered to the subject mammal. Moreover, in

certain situations it may be beneficial to co-administer the allergen together with the stimulatory agent either to the subject or to cells treated with the stimulatory agent. Such co-administration can inhibit (e.g., desensitize) the allergen-specific response. The treatment may be further enhanced by administering Th1-
5 promoting agents, such as the cytokine IL-12 or antibodies to Th2-associated cytokines (e.g., anti-IL-4 antibodies), to the allergic subject in amounts sufficient to further stimulate a Th1-type response.

Cancer

10 The invention also relates to CD83-related methods for increasing interleukin-10 (IL-10) levels to reduce the spread of neoplastic diseases and/or prevent neoplastic diseases and the growth of a tumor. According to the invention, decreased CD83 activity can dramatically increase the levels of IL-10 in the body and such increased interleukin-10 can be used to treat neoplastic
15 diseases. Hence, the invention provides a method for preventing or treating tumors in a mammal, which involves diminishing CD83 expression or activity in the mammal. In various embodiments, the tumor is IL-2-dependent, a plasmacytoma, or a leukemia, including a lymphocytic leukemia such as a B cell lymphocytic leukemia.

20 The invention also provides methods for increasing T cell activation or T cell proliferation by increasing CD83 activity or expression. Such methods can also be used to prevent or treat tumors in a mammal.

Infectious Diseases

25 The expression of Th2-promoting cytokines also has been reported to increase during a variety of infectious diseases. For example, HIV infection, tuberculosis, leishmaniasis, schistosomiasis, filarial nematode infection, intestinal nematode infection and other such infectious diseases are associated with a Th1 to Th2 shift in the immune response. See e.g., Shearer, G. M. and Clerici, M. (1992) Prog. Chem. Immunol. 54:2143; Clerici, M and Shearer, G.
30 M. (1993) Immunology Today 14:107-111; Fauci, A. S. (1988) Science 239:617-623; Locksley, R. M. and Scott, P. (1992) Immunoparasitology Today 1:A58-A61; Pearce, E. J., et al. (1991) J. Exp. Med. 173:159-166; Grzych, J-M., et al.

(1991) J. Immunol. 141:1322-1327; Kullberg, M. C., et al. (1992) J. Immunol. 148:3264-3270; Bancroft, A. J., et al. (1993) J. Immunol 150:1395-1402; Pearlman, E., et al. (1993) Infect. Immun. 61:1105-1112; Else, K. J., et al. (1994) J. Exp. Med. 179:347-351.

5 Accordingly, the stimulatory CD83-related compositions and methods of the invention can be used to inhibit the production of Th2-cells in subjects with infectious diseases to promote an ongoing Th1 response in the patients and to ameliorate the course of the infection. The treatment may be further enhanced by administering other Th1-promoting agents, such as the cytokine IL-12 or
10 antibodies to Th2-associated cytokines (e.g., anti-IL-4 antibodies), to the recipient in amounts sufficient to further stimulate a Th 1-type response.

Hence, for example, infections of the following microbial organisms can be treated by the methods of the invention: *Aeromonas* spp., *Bacillus* spp., *Bacteroides* spp., *Campylobacter* spp., *Clostridium* spp., *Enterobacter* spp.,
15 *Enterococcus* spp., *Escherichia* spp., *Gastrospirillum* sp., *Helicobacter* spp., *Klebsiella* spp., *Salmonella* spp., *Shigella* spp., *Staphylococcus* spp., *Pseudomonas* spp., *Vibrio* spp., *Yersinia* spp., and the like. Infections that can be treated by the methods of the invention include those associated with staph infections (*Staphylococcus aureus*), typhus (*Salmonella typhi*), food poisoning
20 (*Escherichia coli*, such as O157:H7), bacillary dysentery (*Shigella dysenteriae*), pneumonia (*Pseudomonas aeruginosa* and/or *Pseudomonas cepacia*), cholera (*Vivrio cholerae*), ulcers (*Helicobacter pylori*) and others. *E. coli* serotype O157:H7 has been implicated in the pathogenesis of diarrhea, hemorrhagic colitis, hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic
25 purpura (TTP). The methods of the invention are also active against drug-resistant and multiply-drug resistant strains of bacteria, for example, multiply-resistant strains of *Staphylococcus aureus* and vancomycin-resistant strains of *Enterococcus faecium* and *Enterococcus faecalis*.

The methods of the invention are also effective against viruses. The term
30 "virus" refers to DNA and RNA viruses, viroids, and prions. Viruses include both enveloped and non-enveloped viruses, for example, hepatitis A virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus (HIV), poxviruses, herpes viruses, adenoviruses, papovaviruses, parvoviruses,

- reoviruses, orbiviruses, picornaviruses, rotaviruses, alphaviruses, rubiviruses, influenza virus type A and B, flaviviruses, coronaviruses, paramyxoviruses, morbilliviruses, pneumoviruses, rhabdoviruses, lyssaviruses, orthomyxoviruses, bunyaviruses, phleboviruses, nairoviruses, hepadnaviruses, arenaviruses,
- 5 retroviruses, enteroviruses, rhinoviruses and the filovirus.

Autoimmune Diseases

- The CD83-related compositions and methods of the invention can be used in the treatment of autoimmune diseases that are associated with a Th2-type
- 10 dysfunction. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against "self tissues" and that promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Modulation of T helper-type responses can have an effect on the course of the autoimmune disease. For example, in experimental allergic
- 15 encephalomyelitis, stimulation of a Th2-type response by administration of IL-4 at the time of the induction of the disease diminishes the intensity of the autoimmune disease (Paul, W. E., et al. (1994) Cell 76:241-251). Furthermore, recovery of the animals from the disease has been shown to be associated with an increase in a Th2-type response as evidenced by an increase of Th2-specific
- 20 cytokines (Koury, S. J., et al. (1992) J Exp. Med. 176:1355-1364). Moreover, T cells that can suppress EAE secrete Th2-specific cytokines (Chen, C., et al. (1994) Immunity 1:147-154). Since stimulation of a Th2-type response in experimental allergic encephalomyelitis has a protective effect against the disease, stimulation of a Th2 response in subjects with multiple sclerosis (for
- 25 which EAE is a model) is likely to be beneficial therapeutically.

- Similarly, stimulation of a Th2-type response in type I diabetes in mice provides a protective effect against the disease. Indeed, treatment of NOD mice with IL-4 (which promotes a Th2 response) prevents or delays onset of type I diabetes that normally develops in these mice (Rapoport, M. J., et al. (1993) J.
- 30 Exp. Med. 178:87-99). Thus, inhibition of CD83 production can stimulate IL-4 production and/or a Th2 response in a subject suffering from or susceptible to diabetes may ameliorate the effects of the disease or inhibit the onset of the disease.

Yet another autoimmune disease in which stimulation of a Th2-type response may be beneficial is rheumatoid arthritis (RA). Studies have shown that patients with rheumatoid arthritis have predominantly Th1 cells in synovial tissue (Simon, A. K., et al., (1994) Proc. Natl. Acad. Sci. USA 91:8562-8566).

- 5 By stimulating a Th2 response in a subject with rheumatoid arthritis, the detrimental Th1 response can be concomitantly down-modulated to thereby ameliorate the effects of the disease.

Accordingly, the CD83-related compositions and methods of the invention can be used to stimulate production of Th2-associated cytokines in
10 subjects suffering from, or susceptible to, an autoimmune disease in which a Th2-type response is beneficial to the course of the disease. Such compositions and methods would modulate CD83 activity. In some embodiments, the compositions would decrease CD83 activity and thereby increase the level of certain cytokines, for example, IL-4 levels are increased when CD83 activity is
15 diminished. The treatment may be further enhanced by administering other Th2-promoting agents, such as IL-4 itself or antibodies to Th1-associated cytokines, to the subject in amounts sufficient to further stimulate a Th2-type response. The treatment may be further enhanced by administering a Th1-promoting cytokine (e.g., IFN- γ) to the subject in amounts sufficient to further stimulate a Th1-type
20 response.

The efficacy of CD83-related for treating autoimmune diseases can be tested in the animal models provided herein or other models of human diseases (e.g., EAE as a model of multiple sclerosis and the NOD mice as a model for diabetes). Such animal models include the mrl/lpr/lpr mouse as a model for lupus
25 erythematosus, murine collagen-induced arthritis as a model for rheumatoid arthritis, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856). A CD83-modulatory (i.e., stimulatory or inhibitory) agent of the invention is administered to test animals and the course of the disease in the test animals is then monitored by the
30 standard methods for the particular model being used. Effectiveness of the modulatory agent is evidenced by amelioration of the disease condition in animals treated with the agent as compared to untreated animals (or animals treated with a control agent).

Non-limiting examples of autoimmune diseases and disorders having an autoimmune component that may be treated according to the invention include diabetes mellitus, arthritis (including rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, psoriatic arthritis), multiple sclerosis, myasthenia gravis, systemic lupus erythematosus, autoimmune thyroiditis, dermatitis (including atopic dermatitis and eczematous dermatitis), psoriasis, Sjogren's Syndrome, including keratoconjunctivitis sicca secondary to Sjogren's Syndrome, alopecia areata, allergic responses due to arthropod bite reactions, Crohn's disease, aphthous ulcer, iritis, conjunctivitis, keratoconjunctivitis, ulcerative colitis, asthma, allergic asthma, cutaneous lupus erythematosus, scleroderma, vaginitis, proctitis, drug eruptions, leprosy reversal reactions, erythema nodosum leprosum, autoimmune uveitis, allergic encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, polychondritis, Wegener's granulomatosis, chronic active hepatitis, Stevens-Johnson syndrome, idiopathic sprue, lichen planus, Crohn's disease, Graves ophthalmopathy, sarcoidosis, primary biliary cirrhosis, uveitis posterior, and interstitial lung fibrosis.

20 *Transplantation*

While graft rejection or graft acceptance may not be attributable exclusively to the action of a particular T cell subset (i.e., Th1 or Th2 cells) in the graft recipient, studies have implicated a predominant Th2 response in prolonged graft survival and a predominant Th1 response in graft rejection (for a discussion see Dallman, M. J. (1995) *Curr. Opin. Immunol.* 7:632-638; Takeuchi, T. et al. (1992) *Transplantation* 53:1281-1291; Tzakis, A. G. et al. (1994) *J. Pediatr. Surg.* 29:754-756; Thai, N. L. et al. (1995) *Transplantation* 59:274-281. Additionally, adoptive transfer of cells having a Th2 cytokine phenotype prolongs skin graft survival (Maeda, H. et al. (1994) *Int. Immunol.* 6:855-862) and reduces graft-versus-host disease (Fowler, D. H. et al. (1994) *Blood* 84:3540-3549; Fowler, D. H. et al. (1994) *Prog. Clin. Biol. Res.* 389:533-540). Furthermore, administration of IL-4, which promotes Th2 differentiation, prolongs cardiac allograft survival (Levy, A. E. and Alexander, J. W. (1995)

Transplantation 60:405-406), whereas administration of IL-12 in combination with anti-IL-10 antibodies, which promotes Th1 differentiation, enhances skin allograft rejection (Gorczynski, R. M. et al. (1995) Transplantation 60:1337-1341).

5 As provided herein, loss of CD83 function increases interleukin-4 production, which in turn promotes the differentiation of Th2 cells and depresses the differentiation of precursor cells into Th1 cells. Accordingly, methods of the invention that involve decreasing CD83 function can be used to stimulate production of Th2-associated cytokines in transplant recipients to prolong
10 survival of the graft. These methods can be used both in solid organ transplantation and in bone marrow transplantation (e.g., to inhibit graft-versus-host disease). These methods can involve either direct administration of a CD83 inhibitory agent to the transplant recipient or ex vivo treatment of cells obtained from the subject (e.g., Thp, Th1 cells, B cells, non-lymphoid cells) with an
15 inhibitory agent followed by readministration of the cells to the subject. The treatment may be further enhanced by administering other Th2-promoting agents, such as IL-4 itself or antibodies to Th1-associated cytokines, to the recipient in amounts sufficient to further stimulate a Th2-type response.

20 **Additional Methods of Using CD83**

In addition to the foregoing disease situations, the modulatory methods of the invention also are useful for other purposes.

For example, inhibition of CD83 activity or function gives rise to increased granulocyte macrophage-colony stimulating factor (GM-CSF).
25 Granulocyte macrophage colony stimulating factor is a hematopoietic growth factor that promotes the proliferation and differentiation of hematopoietic progenitor cells. GM-CSF is approved for treatment of patients requiring increased proliferation of white blood cells. Data indicates that GM-CSF is also useful as a vaccine adjuvant Morrissey, et al., J. Immunology 139, 1113-1119
30 (1987). GM-CSF can also be used to treat patients prone to infection such as those undergoing high risk bowel surgery, trauma victims and individuals with HIV.

Accordingly, the invention provides a method of increasing the levels of

GM-CSF in a mammal or in a mammalian cell by administering an agent that modulates or inhibits CD83 activity or expression.

The invention also provides a method of decreasing the levels of GM-CSF in a mammal or in a mammalian cell by administering an agent that
5 modulates or stimulates CD83 activity or expression.

Moreover, in other embodiments the CD83 inhibitory methods of the invention can be used to stimulate production of IL-4 or IL-10 in vitro for commercial production of these cytokines. For example, CD4+ T cells with a null or other mutation in the CD83 gene can be cultured and then stimulated to
10 produce cytokines, for example, by use of anti-CD3 and/or anti-CD28 antibodies to activate the mutant CD4+ T cells. Significant amounts of IL-4 and IL-10 can then be isolated from the culture media. Alternatively, CD4+ T cells can be contacted with the CD83 inhibitory agent in vitro to stimulate IL-4 or IL-10 production and the IL-4 or IL-10 can be recovered from the culture supernatant.
15 The isolated IL-4 and/or IL-10 can be further purified if necessary, and packaged for commercial use.

The methods of the invention can be adapted to vaccinations to promote either a Th1 or a Th2 response to an antigen of interest in a subject. That is, CD83 or CD83 modulators of the invention can serve as adjuvants to direct an
20 immune response to a vaccine either to a Th1 response or a Th2 response. For example, to stimulate an antibody response to an antigen of interest (i.e., for vaccination purposes), the antigen and a CD83 inhibitory agent of the invention can be coadministered to a subject to promote a Th2 response to the antigen in the subject, since Th2 responses provide efficient B cell help and promote IgG1
25 production.

Alternatively, to promote a cellular immune response to an antigen of interest, the antigen and a CD83 stimulating agent of the invention can be coadministered to a subject to promote a Th1 response to the antigen in a subject, since Th1 responses favor the development of cell-mediated immune
30 responses (e.g., delayed hypersensitivity responses).

The antigen of interest and the modulatory agent can be formulated together into a single pharmaceutical composition or in separate compositions.

Thus, in some embodiments, the antigen of interest and the modulatory agent are administered simultaneously to the subject. Alternatively, in certain situations it may be desirable to administer the antigen first and then the modulatory agent or vice versa. For example, in the case of an antigen that naturally evokes a Th1 response, it may be beneficial to first administer the antigen alone to stimulate a Th1 response and then administer a CD83 inhibitory agent, alone or together with a boost of antigen, to shift the immune response to a Th2 response.

According to the invention, any agent that can modulate CD83 to increase or decrease cytokine levels, increase or decrease T cell levels or produce any other CD83-related response can be used in the compositions and methods of the invention. In some embodiments, anti-CD83 antibodies of the invention are used to either activate or inhibit CD83 activity. Activation or inhibition by such antibodies can depend on the epitope to which the antibody binds. Hence, antibodies may play a role in boosting or depressing CD83 activity. These CD83 modulatory agents, including anti-CD83 antibodies, are described in more detail below.

Stimulating or Inhibiting CD83

According to the invention, any agent that can stimulate CD83 to perform its natural functions can be used in the compositions and methods of the invention as a CD83 stimulatory agent. Indicators that CD83 activity is stimulated include increased IL-2 cytokine levels, increased T cell levels, and increased TNF levels relative to unstimulated levels in wild type CD83 cells. Examples of CD83 stimulatory agents include, for example, the CD83 gene product itself, certain anti-CD83 antibodies, CD83-encoding nucleic acids (DNA or RNA), factors that promote CD83 transcription or translation, organic molecules, peptides and the like.

Also, according to the invention, any agent that can inhibit CD83 from performing its natural functions can be used in the compositions and methods of the invention as a CD83 inhibitory agent. Indicators that CD83 activity is inhibited include increased IL-4 cytokine levels, increased IL-10 levels, decreased IL-2

production, decreased T cell levels, and decreased TNF levels relative to uninhibited levels in wild type CD83 cells.

Examples of CD83 inhibitors include anti-CD83 antibodies, CD83 anti-sense nucleic acids (e.g. nucleic acids that can hybridize to CD83 nucleic acids),
5 organic compounds, peptides and agents that can mutate an endogenous CD83 gene. In some embodiments, the CD83 stimulatory or inhibitory agents are proteins, for example, CD83 gene products, anti-CD83 antibody preparations, CD83 inhibitors, peptides and protein factors that can promote CD83 transcription or translation. In other embodiments, the CD83 stimulatory or
10 inhibitory agents are peptides or organic molecules. Such proteins, organic molecules and organic molecules can be prepared and/or purified as described herein or by methods available in the art, and administered as provided herein.

In other embodiments, the CD83 stimulatory or inhibitory agents can be nucleic acids including recombinant expression vectors or expression cassettes
15 encoding CD83 gene products, CD83 transcription factors, CD83 anti-sense nucleic acid, intracellular antibodies capable of binding to CD83 or dominant negative CD83 inhibitors. Such nucleic acids can be operably linked to a promoter that is functional in a mammalian cell, and then introduced into cells of the subject mammal using methods known in the art for introducing nucleic acid
20 (e.g., DNA) into cells.

The "promoter functional in a mammalian cell" or "mammalian promoter" is capable of directing transcription of a polypeptide coding sequence operably linked to the promoter. The promoter should generally be active in T cells and antigen presenting cells and may be obtained from a gene that is
25 expressed in T cells or antigen presenting cells. However, it need not be a T cell-specific or an antigen presenting cell specific-promoter. Instead, the promoter may be selected from any mammalian or viral promoter that can function in a T cell. Hence the promoter may be an actin promoter, an immunoglobulin promoter, a heat-shock promoter, or a viral promoter obtained
30 from the genome of viruses such as adenoviruses, retroviruses, lentiviruses, herpes viruses, including but not limited to, polyoma virus, fowlpox virus, adenovirus 2, bovine papilloma virus, avian sarcoma virus, cytomegalovirus (CMV), hepatitis-B virus, Simian Virus 40 (SV40), Epstein Barr virus (EBV),

feline immunodeficiency virus (FIV), and SV40 , or are respiratory syncytial viral promoters (RSV) or long terminal repeats (LTRs) of a retrovirus, i.e., a Moloney Murine Leukemia Virus (MoMuLV) (Cepko et al. (1984) Cell 37:1053-1062). The promoter functional in a mammalian cell can be inducible or
5 constitutive.

Any cloning procedure used by one of skill in the art can be employed to make the expression vectors or expression that comprise a promoter operably linked to a CD83 nucleic acid, CD83 transcription factor or a nucleic acid encoding an anti-CD83 antibody. See, e.g., Sambrook et al., Molecular Cloning,
10 A Laboratory Manual, Cold Spring Harbor Laboratory, N.Y., 1989; Sambrook et al., Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, N.Y., 2001.

After constructing an expression vector or an expression cassette encoding CD83 gene products, CD83 transcription factors, CD83 anti-sense
15 nucleic acid, intracellular antibodies capable of binding to CD83 or dominant negative CD83 inhibitors, mammalian cells can be transformed with the vector or cassette. Examples of such methods include:

Direct Injection: Naked DNA can be introduced into cells in vivo by directly injecting the DNA into the cells (see e.g., Acsadi et al. (1991) Nature
20 332:815-818; Wolff et al. (1990) Science 247:1465-1468). For example, a delivery apparatus (e.g., a "gene gun") for injecting DNA into cells in vivo can be used. Such an apparatus is commercially available (e.g., from BioRad).

Receptor-Mediated DNA Uptake: Naked DNA can also be introduced into cells in vivo by complexing the DNA to a cation, such as polylysine, which
25 is coupled to a ligand for a cell-surface receptor (see for example Wu, G. and Wu, C. H. (1988) J. Biol. Chem. 263:14621; Wilson et al. (1992) J. Biol. Chem. 267:963-967; and U.S. Pat. No. 5,166,320). Binding of the DNA-ligand complex to the receptor facilitates uptake of the DNA by receptor-mediated endocytosis. A DNA-ligand complex linked to adenovirus capsids that naturally
30 disrupt endosomes, thereby releasing material into the cytoplasm can be used to avoid degradation of the complex by intracellular lysosomes (see for example Curiel et al. (1991) Proc. Natl. Acad. Sci. USA 88:8850; Cristiano et al. (1993) Proc. Natl. Acad. Sci. USA 90:2122-2126).

Retroviruses: Defective retroviruses are well characterized for use in gene transfer for gene therapy purposes (for a review see Miller, A. D. (1990) Blood 76:271). A recombinant retrovirus can be constructed having nucleotide sequences of interest incorporated into the retroviral genome. Additionally, portions of the retroviral genome can be removed to render the retrovirus replication defective. The replication defective retrovirus is then packaged into virions that can be used to infect a target cell through the use of a helper virus by standard techniques. Protocols for producing recombinant retroviruses and for infecting cells in vitro or in vivo with such viruses can be found in Current Protocols in Molecular Biology, Ausubel, F. M. et al. (eds.) Greene Publishing Associates, (1989), Sections 9.10-9.14 and other standard laboratory manuals. Examples of suitable retroviruses include pLJ, pZIP, pWE and pEM which are available to those skilled in the art. Examples of suitable packaging virus lines include Ψ Crip, Ψ Cre, Ψ 2 and Ψ Am. Retroviruses have been used to introduce a variety of genes into many different cell types, including epithelial cells, endothelial cells, lymphocytes, myoblasts, hepatocytes, bone marrow cells, in vitro and/or in vivo (see for example Eglitis, et al. (1985) Science 230:1395-1398; Danos and Mulligan (1988) Proc. Natl. Acad. Sci. USA 85:6460-6464; Wilson et al. (1988) Proc. Natl. Acad. Sci. USA 85:3014-3018; Armentano et al. (1990) Proc. Natl. Acad. Sci. USA 87:6141-6145; Huber et al. (1991) Proc. Natl. Acad. Sci. USA 88:8039-8043; Ferry et al. (1991) Proc. Natl. Acad. Sci. USA 88:8377-8381; Chowdhury et al. (1991) Science 254:1802-1805; van Beusechem et al. (1992) Proc. Natl. Acad. Sci. USA 89:7640-7644; Kay et al. (1992) Human Gene Therapy 3:641-647; Dai et al. (1992) Proc. Natl. Acad. Sci. USA 89:10892-10895; Hwu et al. (1993) J. Immunol. 150:4104-4115; U.S. Pat. Nos. 4,868,116; 4,980,286; PCT Application WO 89/07136; PCT Application WO 89/02468; PCT Application WO 89/05345; and PCT Application WO 92/07573). Retroviral vectors require target cell division in order for the retroviral genome (and foreign nucleic acid inserted into it) to be integrated into the host genome to stably introduce nucleic acid into the cell. Thus, it may be necessary to stimulate replication of the target cell.

Adenoviruses: The genome of an adenovirus can be manipulated such that it encodes and expresses a gene product of interest but is inactivated in terms

of its ability to replicate in a normal lytic viral life cycle. See, for example, Berkner et al. (1988) *BioTechniques* 6:616; Rosenfeld et al. (1991) *Science* 252:431-434; and Rosenfeld et al. (1992) *Cell* 68:143-155. Suitable adenoviral vectors derived from the adenovirus strain Ad type 5 d1324 or other strains of adenovirus (e.g., Ad2, Ad3, Ad7 etc.) are available to those skilled in the art. Recombinant adenoviruses are advantageous in that they do not require dividing cells to be effective gene delivery vehicles and can be used to infect a wide variety of cell types, including airway epithelium (Rosenfeld et al. (1992) cited supra), endothelial cells (Lemarchand et al. (1992) *Proc. Natl. Acad. Sci. USA* 89:6482-6486), hepatocytes (Herz and Gerard (1993) *Proc. Natl. Acad. Sci. USA* 90:2812-2816) and muscle cells (Quantin et al. (1992) *Proc. Natl. Acad. Sci. USA* 89:2581-2584). Additionally, introduced adenoviral DNA (and foreign DNA contained therein) is not integrated into the genome of a host cell but remains episomal, thereby avoiding potential problems that can occur as a result of insertional mutagenesis in situations where introduced DNA becomes integrated into the host genome (e.g., retroviral DNA). Moreover, the carrying capacity of the adenoviral genome for foreign DNA is large (up to 8 kilobases) relative to other gene delivery vectors (Berkner et al. cited supra; Haj-Ahmand and Graham (1986) *J. Virol.* 57:267). Most replication-defective adenoviral vectors currently in use are deleted for all or parts of the viral E1 and E3 genes but retain as much as 80% of the adenoviral genetic material.

Adeno-Associated Viruses: Adeno-associated virus (AAV) is a naturally occurring defective virus that requires another virus, such as an adenovirus or a herpes virus, as a helper virus for efficient replication and a productive life cycle. (For a review see Muzyczka et al. *Curr. Topics in Micro. and Immunol.* (1992) 158:97-129). It is also one of the few viruses that may integrate its DNA into non-dividing cells, and exhibits a high frequency of stable integration (see for example Flotte et al. (1992) *Am. J. Respir. Cell. Mol. Biol.* 7:349-356; Samulski et al. (1989) *J. Virol.* 63:3822-3828; and McLaughlin et al. (1989) *J. Virol.* 62:1963-1973). Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate. Space for exogenous DNA is limited to about 4.5 kb. An AAV vector such as that described in Tratschin et al. (1985) *Mol. Cell. Biol.* 5:3251-3260 can be used to introduce DNA into cells. A variety of nucleic

acids have been introduced into different cell types using AAV vectors (see for example Hermonat et al. (1984) Proc. Natl. Acad. Sci. USA 81:6466-6470; Tratschin et al. (1985) Mol. Cell. Biol. 4:2072-2081; Wondisford et al. (1988) Mol. Endocrinol. 2:32-39; Tratschin et al. (1984) J Virol. 51:611-619; and Flotte
5 et al. (1993) J. Biol. Chem. 268:3781-3790).

Transformed mammalian cells can then be identified and administered to the mammal from whence they came to permit expression of a CD83 gene product, CD83 transcription factor, CD83 anti-sense nucleic acid, intracellular antibody capable of binding to CD83 proteins, or dominant negative CD83
10 inhibitors. The efficacy of a particular expression vector system and method of introducing nucleic acid into a cell can be assessed by standard approaches routinely used in the art. For example, DNA introduced into a cell can be detected by a filter hybridization technique (e.g., Southern blotting). RNA produced by transcription of an introduced DNA can be detected, for example,
15 by Northern blotting, RNase protection or reverse transcriptase-polymerase chain reaction (RT-PCR). The CD83 gene product can be detected by an appropriate assay, for example, by immunological detection of a produced CD83 protein, such as with a CD83-specific antibody.

20 **CD83 Antibodies**

The invention provides antibody preparations directed against the mutant and wild type CD83 polypeptides of the invention, for example, against a polypeptide having SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:7, SEQ ID NO:8 or SEQ ID NO:9. Other antibodies of interest can bind to the cytoplasmic tail of
25 CD83.

In one embodiment, the invention provides antibodies that block the function of CD83 polypeptides. Such antibodies may be used as CD83 inhibitory agents in the methods of the invention as described herein. In another embodiment, the antibodies of the invention can activate CD83 activity. Such
30 activating antibodies may be used as CD83 stimulatory agents.

All antibody molecules belong to a family of plasma proteins called immunoglobulins, whose basic building block, the immunoglobulin fold or domain, is used in various forms in many molecules of the immune system and

other biological recognition systems. A typical immunoglobulin has four polypeptide chains, containing an antigen binding region known as a variable region and a non-varying region known as the constant region.

Native antibodies and immunoglobulins are usually heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies between the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (VH) followed by a number of constant domains. Each light chain has a variable domain at one end (VL) and a constant domain at its other end. The constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light and heavy chain variable domains (Clothia et al., J. Mol. Biol. 186, 651-66, 1985); Novotny and Haber, Proc. Natl. Acad. Sci. USA 82, 4592-4596 (1985).

Depending on the amino acid sequences of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are at least five (5) major classes of immunoglobulins: IgA, IgD, IgE, IgG and IgM, and several of these may be further divided into subclasses (isotypes), e.g. IgG-1, IgG-2, IgG-3 and IgG-4; IgA-1 and IgA-2. The heavy chains constant domains that correspond to the different classes of immunoglobulins are called alpha (α), delta (δ), epsilon (ϵ), gamma (γ) and mu (μ), respectively. The light chains of antibodies can be assigned to one of two clearly distinct types, called kappa (κ) and lambda (λ), based on the amino sequences of their constant domain. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

The term "variable" in the context of variable domain of antibodies, refers to the fact that certain portions of the variable domains differ extensively in sequence among antibodies. The variable domains are for binding and determine the specificity of each particular antibody for its particular antigen. However, the variability is not evenly distributed through the variable domains

of antibodies. It is concentrated in three segments called complementarity determining regions (CDRs) also known as hypervariable regions both in the light chain and the heavy chain variable domains.

5 The more highly conserved portions of variable domains are called the framework (FR). The variable domains of native heavy and light chains each comprise four FR regions, largely adopting a β -sheet configuration, connected by three CDRs, which form loops connecting, and in some cases forming part of, the β -sheet structure. The CDRs in each chain are held together in close proximity by the FR regions and, with the CDRs from the other chain, contribute
10 to the formation of the antigen binding site of antibodies. The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector function, such as participation of the antibody in antibody-dependent cellular toxicity.

An antibody that is contemplated for use in the present invention thus can
15 be in any of a variety of forms, including a whole immunoglobulin, an antibody fragment such as Fv, Fab, and similar fragments, a single chain antibody that includes the variable domain complementarity determining regions (CDR), and the like forms, all of which fall under the broad term "antibody," as used herein. The present invention contemplates the use of any specificity of an antibody,
20 polyclonal or monoclonal, and is not limited to antibodies that recognize and immunoreact with a specific antigen. In preferred embodiments, in the context of both the therapeutic and screening methods described below, an antibody or fragment thereof is used that is immunospecific for an antigen or epitope of the invention.

25 The term "antibody fragment" refers to a portion of a full-length antibody, generally the antigen binding or variable region. Examples of antibody fragments include Fab, Fab', F(ab')₂ and Fv fragments. Papain digestion of antibodies produces two identical antigen binding fragments, called the Fab fragment, each with a single antigen binding site, and a residual "Fc" fragment, so-called for its ability to crystallize readily. Pepsin treatment yields an F(ab')₂
30 fragment that has two antigen binding fragments, which are capable of cross-linking antigen, and a residual other fragment (which is termed pFc'). Additional fragments can include diabodies, linear antibodies, single-chain antibody

molecules, and multispecific antibodies formed from antibody fragments. As used herein, "functional fragment" with respect to antibodies, refers to Fv, F(ab) and F(ab')₂ fragments.

Antibody fragments retain some ability to selectively bind with its antigen or receptor and are defined as follows:

(1) Fab is the fragment that contains a monovalent antigen-binding fragment of an antibody molecule. A Fab fragment can be produced by digestion of whole antibody with the enzyme papain to yield an intact light chain and a portion of one heavy chain.

(2) Fab' is the fragment of an antibody molecule can be obtained by treating whole antibody with pepsin, followed by reduction, to yield an intact light chain and a portion of the heavy chain. Two Fab' fragments are obtained per antibody molecule. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxyl terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region.

(3) (Fab')₂ is the fragment of an antibody that can be obtained by treating whole antibody with the enzyme pepsin without subsequent reduction. F(ab')₂ is a dimer of two Fab' fragments held together by two disulfide bonds.

(4) Fv is the minimum antibody fragment that contains a complete antigen recognition and binding site. This region consists of a dimer of one heavy and one light chain variable domain in a tight, non-covalent association (V_H-V_L dimer). It is in this configuration that the three CDRs of each variable domain interact to define an antigen binding site on the surface of the V_H-V_L dimer. Collectively, the six CDRs confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

(5) Single chain antibody ("SCA"), defined as a genetically engineered molecule containing the variable region of the light chain, the variable region of the heavy chain, linked by a suitable polypeptide linker as a genetically fused single chain molecule. Such single chain antibodies are also referred to as "single-chain Fv" or "sFv" antibody fragments. Generally, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L

domains that enables the sFv to form the desired structure for antigen binding. For a review of sFv see Pluckthun in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenberg and Moore eds. Springer-Verlag, N.Y., pp. 269-315 (1994).

5 The term "diabodies" refers to a small antibody fragments with two antigen-binding sites, which fragments comprise a heavy chain variable domain (VH) connected to a light chain variable domain (VL) in the same polypeptide chain (VH-VL). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the
10 complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161, and Hollinger et al., *Proc. Natl. Acad. Sci. USA* 90: 6444-6448 (1993).

 The preparation of polyclonal antibodies is well-known to those skilled in the art. See, for example, Green, et al., *Production of Polyclonal Antisera*, in:
15 Immunochemical Protocols (Manson, ed.), pages 1-5 (Humana Press); Coligan, et al., *Production of Polyclonal Antisera in Rabbits, Rats Mice and Hamsters*, in: Current Protocols in Immunology, section 2.4.1 (1992), which are hereby incorporated by reference.

 The preparation of monoclonal antibodies likewise is conventional. See,
20 for example, Kohler & Milstein, *Nature*, 256:495 (1975); Coligan, et al., sections 2.5.1-2.6.7; and Harlow, et al., in: Antibodies: A Laboratory Manual, page 726 (Cold Spring Harbor Pub. (1988)), which are hereby incorporated by reference. Methods of *in vitro* and *in vivo* manipulation of monoclonal antibodies are also available to those skilled in the art. For example, the monoclonal antibodies to
25 be used in accordance with the present invention may be made by the hybridoma method first described by Kohler and Milstein, *Nature* 256, 495 (1975), or may be made by recombinant methods, e.g., as described in U.S. Patent No. 4,816,567. The monoclonal antibodies for use with the present invention may also be isolated from antibody libraries using the techniques described in
30 Clackson et al. *Nature* 352: 624-628 (1991), as well as in Marks et al., *J. Mol. Biol.* 222: 581-597 (1991).

 Monoclonal antibodies can be isolated and purified from hybridoma cultures by a variety of well-established techniques. Such isolation techniques

include affinity chromatography with Protein-A Sepharose, size-exclusion chromatography, and ion-exchange chromatography. See, e.g., Coligan, et al., sections 2.7.1-2.7.12 and sections 2.9.1-2.9.3; Barnes, et al., Purification of Immunoglobulin G (IgG), in: Methods in Molecular Biology, Vol. 10, pages 79-104 (Humana Press (1992)).

Another method for generating antibodies involves a Selected Lymphocyte Antibody Method (SLAM). The SLAM technology permits the generation, isolation and manipulation of monoclonal antibodies without the process of hybridoma generation. The methodology principally involves the growth of antibody forming cells, the physical selection of specifically selected antibody forming cells, the isolation of the genes encoding the antibody and the subsequent cloning and expression of those genes.

More specifically, an animal (rabbit, mouse, rat, other) is immunized with a source of specific antigen. This immunization may consist of purified protein, in either native or recombinant form, peptides, DNA encoding the protein of interest or cells expressing the protein of interest. After a suitable period, during which antibodies can be detected in the serum of the animal (usually weeks to months), blood (or other tissue) from the animal is harvested. Lymphocytes are isolated from the blood and cultured under specific conditions to generate antibody-forming cells, with antibody being secreted into the culture medium. These cells are detected by any of several means (complement mediated lysis of antigen-bearing cells, fluorescence detection or other) and then isolated using micromanipulation technology. The individual antibody forming cells are then processed for eventual single cell PCR to obtain the expressed Heavy and Light chain genes that encode the specific antibody. Once obtained and sequenced, these genes are cloned into an appropriate expression vector and recombinant, monoclonal antibody produced in a heterologous cell system. These antibodies are then purified via standard methodologies such as the use of protein A affinity columns. These types of methods are further described in Babcook, et al., Proc. Natl. Acad. Sci. (USA) **93**: 7843-7848 (1996); U.S. Patent No. 5,627,052; and PCT WO 92/02551 by Schrader.

Another method involves humanizing a monoclonal antibody by recombinant means to generate antibodies containing human specific and

recognizable sequences. See, for review, Holmes, et al., J. Immunol., 158:2192-2201 (1997) and Vaswani, et al., Annals Allergy, Asthma & Immunol., 81:105-115 (1998). The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional polyclonal antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the antibody is obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method.

The monoclonal antibodies herein specifically include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Pat. No. 4,816,567); Morrison et al. Proc. Natl. Acad. Sci. 81, 6851-6855 (1984).

Methods of making antibody fragments are also known in the art (see for example, Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, New York, (1988), incorporated herein by reference). Antibody fragments of the present invention can be prepared by proteolytic hydrolysis of the antibody or by expression in *E. coli* of DNA encoding the fragment. Antibody fragments can be obtained by pepsin or papain digestion of whole antibodies conventional methods. For example, antibody fragments can be produced by enzymatic cleavage of antibodies with pepsin to provide a 5S

fragment denoted F(ab')₂. This fragment can be further cleaved using a thiol reducing agent, and optionally a blocking group for the sulfhydryl groups resulting from cleavage of disulfide linkages, to produce 3.5S Fab= monovalent fragments. Alternatively, an enzymatic cleavage using pepsin produces two
5 monovalent Fab' fragments and an Fc fragment directly. These methods are described, for example, in U.S. Patents No. 4,036,945 and No. 4,331,647, and references contained therein. These patents are hereby incorporated in their entireties by reference.

Other methods of cleaving antibodies, such as separation of heavy chains
10 to form monovalent light-heavy chain fragments, further cleavage of fragments, or other enzymatic, chemical, or genetic techniques may also be used, so long as the fragments bind to the antigen that is recognized by the intact antibody. For example, Fv fragments comprise an association of V_H and V_L chains. This association may be noncovalent or the variable chains can be linked by an
15 intermolecular disulfide bond or cross-linked by chemicals such as glutaraldehyde. Preferably, the Fv fragments comprise V_H and V_L chains connected by a peptide linker. These single-chain antigen binding proteins (sFv) are prepared by constructing a structural gene comprising DNA sequences encoding the V_H and V_L domains connected by an oligonucleotide. The
20 structural gene is inserted into an expression vector, which is subsequently introduced into a host cell such as *E. coli*. The recombinant host cells synthesize a single polypeptide chain with a linker peptide bridging the two V domains. Methods for producing sFvs are described, for example, by Whitlow, et al., Methods: a Companion to Methods in Enzymology, Vol. 2, page 97 (1991);
25 Bird, et al., Science 242:423-426 (1988); Ladner, et al, US Patent No. 4,946,778; and Pack, et al., Bio/Technology 11:1271-77 (1993).

Another form of an antibody fragment is a peptide coding for a single complementarity-determining region (CDR). CDR peptides ("minimal recognition units") can be obtained by constructing genes encoding the CDR of
30 an antibody of interest. Such genes are prepared, for example, by using the polymerase chain reaction to synthesize the variable region from RNA of antibody-producing cells. See, for example, Larrick, et al., Methods: a Companion to Methods in Enzymology, Vol. 2, page 106 (1991).

The invention further contemplates human and humanized forms of non-human (e.g. murine) antibodies. Such humanized antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')₂ or other antigen-binding subsequences of antibodies) that contain
5 minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a nonhuman species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity.

10 In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences. These modifications are made to further refine and optimize antibody performance. In general, humanized
15 antibodies can comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the Fv regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an
20 immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see: Jones et al., Nature 321, 522-525 (1986); Reichmann et al., Nature 332, 323-329 (1988); Presta, Curr. Op. Struct. Biol. 2, 593-596 (1992); Holmes, et al., J. Immunol., 158:2192-2201 (1997) and Vaswani, et al., Annals Allergy, Asthma & Immunol., 81:105-115 (1998).

25 The invention also provides methods of mutating antibodies to optimize their affinity, selectivity, binding strength or other desirable property. A mutant antibody refers to an amino acid sequence variant of an antibody. In general, one or more of the amino acid residues in the mutant antibody is different from what is present in the reference antibody. Such mutant antibodies necessarily have less
30 than 100% sequence identity or similarity with the reference amino acid sequence. In general, mutant antibodies have at least 75% amino acid sequence identity or similarity with the amino acid sequence of either the heavy or light chain variable domain of the reference antibody. Preferably, mutant antibodies

have at least 80%, more preferably at least 85%, even more preferably at least 90%, and most preferably at least 95% amino acid sequence identity or similarity with the amino acid sequence of either the heavy or light chain variable domain of the reference antibody.

5 The antibodies of the invention are isolated antibodies. An isolated antibody is one that has been identified and separated and/or recovered from a component of the environment in which it was produced. Contaminant components of its production environment are materials that would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes,
10 hormones, and other proteinaceous or nonproteinaceous solutes. The term "isolated antibody" also includes antibodies within recombinant cells because at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

15 If desired, the antibodies of the invention can be purified by any available procedure. For example, the antibodies can be affinity purified by binding an antibody preparation to a solid support to which the antigen used to raise the antibodies is bound. After washing off contaminants, the antibody can be eluted by known procedures. Those of skill in the art will know of various techniques
20 common in the immunology arts for purification and/or concentration of polyclonal antibodies, as well as monoclonal antibodies (see for example, Coligan, et al., Unit 9, Current Protocols in Immunology, Wiley Interscience, 1991, incorporated by reference).

 In preferred embodiments, the antibody will be purified as measurable by
25 at least three different methods: 1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight; 2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequentator; or 3) to homogeneity by SDS-PAGE under reducing or non-reducing conditions using
30 Coomassie blue or, preferably, silver stain.

 The invention also provides antibodies that can bind to CD83 polypeptides. Sequences of complementarity determining regions (CDRs) or hypervariable regions from light and heavy chains of these anti-CD83 antibodies

are provided. For example, a heavy chain variable region having a CDR1 sequence of SYDMT (SEQ ID NO:23), SYDMS (SEQ ID NO:24), DYDLS (SEQ ID NO:25) or SYDMS (SEQ ID NO:26) can be used in an antibody or other binding moiety to bind to CD83 gene products. In other embodiments, a heavy chain variable region having a CDR2 sequence of YASGSTYY (SEQ ID NO:27), SSSGTTY (SEQ ID NO:28), YASGSTYY (SEQ ID NO:29), AIDGNPYY (SEQ ID NO:30) or STAYNSHY (SEQ ID NO:31) can be used in an antibody or other binding moiety to bind to CD83 gene products. In further embodiments of the invention, a heavy chain variable region having a CDR3 sequence of EHAGYSGDTGH (SEQ ID NO:32), EGAGVSMT (SEQ ID NO:33), EDAGFSNA (SEQ ID NO:34), GAGD (SEQ ID NO:35) or GGSWLD (SEQ ID NO:36) can be used in an antibody or other binding moiety to bind to CD83 gene products.

Moreover, a light chain variable region having a CDR1 sequence of RCAYD (SEQ ID NO:37), RCADV (SEQ ID NO:38), or RCALV (SEQ ID NO:39) can be used in an antibody or other binding moiety to bind to CD83 gene products. In other embodiments, a light chain variable region having a CDR2 sequence of QSISTY (SEQ ID NO:40), QSVSSY (SEQ ID NO:41), ESISNY (SEQ ID NO:42), KNVYNNNW (SEQ ID NO:43), or QSVYDNDE (SEQ ID NO:43) can be used in an antibody or other binding moiety to bind to CD83 gene products. In further embodiments, a light chain variable region having a CDR3 sequence of QQGYTHSNVDNV (SEQ ID NO:44), QQGYSISDIDNA (SEQ ID NO:45), QCTSGGKFISDGAA (SEQ ID NO:46), AGDYSSSSDNG (SEQ ID NO:47), or QATHYSSDWLTY (SEQ ID NO:48) can be used in an antibody or other binding moiety to bind to CD83 gene products.

Light and heavy chains that can bind CD83 polypeptides are also provided by the invention. For example, in one embodiment, the invention provides a 20D04 light chain that can bind to CD83 polypeptides. The amino acid sequence for this 20D04 light chain is provided below (SEQ ID NO:11).

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30      1 MDMRAPTQLL  GLLLLWLPGA  RCADVMTQT  PASVSAAVGG
      41 TVTINCQASE  SISNYLSWYQ  QKPGQPPKLL  IYRTSTLASG
      81 VSSRFKSGS  GTEYTLTISG  VQCDDVATYY  CQCTSGGKFI
     121 SDGAAFGGGT  EVVVKGDPVA  PTVLLFPPSS  DEVATGTVTI
     161 VCVANKYFPD  VTVTWEVDGT  TQTTGIENSK  TPQNSADCTY

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201 NLSSTLTLLTS TQYNHKEYT CKVTQGTTSV VQSFSRKNC

A nucleic acid sequence for this 20D04 anti-CD83 light chain is provided below (SEQ ID NO:12).

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5      1 ATGGACATGA GGGCCCCCAC TCAGCTGCTG GGGCTCCTGC
      41 TGCTCTGGCT CCCAGGTGCC AGATGTGCCG ATGTCGTGAT
      81 GACCCAGACT CCAGCCTCCG TGTCTGCAGC TGTGGGAGGC
     121 ACAGTCACCA TCAATTGCCA GGCCAGTGAA AGCATTAGCA
     161 ACTACTTATC CTGGTATCAG CAGAAACCAG GGCAGCCTCC
10    201 CAAGCTCCTG ATCTACAGGA CATCCACTCT GGCATCTGGG
     241 GTCTCATCGC GGTTCAAAGG CAGTGGATCT GGGACAGAGT
     281 ACACTCTCAC CATCAGCGGC GTGCAGTGTG ACGATGTTGC
     321 CACTTACTAC TGTCAATGCA CTTCTGGTGG GAAGTTCATT
     361 AGTGATGGTG CTGCTTTCGG CGGAGGGACC GAGGTGGTGG
15    401 TCAAAGGTGA TCCAGTTGCA CCTACTGTCC TCCTCTTCCC
     441 ACCATCTAGC GATGAGGTGG CAACTGGAAC AGTCACCATC
     481 GTGTGTGTGG CGAATAAATA CTTTCCCGAT GTCACCGTCA
     521 CCTGGGAGGT GGATGGCACC ACCCAAACAA CTGGCATCGA
     561 GAACAGTAAA ACACCGCAGA ATTCTGCAGA TTGTACCTAC
20    601 AACCTCAGCA GCACTCTGAC ACTGACCAGC ACACAGTACA
     641 ACAGCCACAA AGAGTACACC TGCAAGGTGA CCCAGGGCAC
     681 GACCTCAGTC GTCCAGAGCT TCAGTAGGAA GAACTGTTAA

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25 In another embodiment, the invention provides a 20D04 heavy chain that can bind to CD83 polypeptides. The amino acid sequence for this 20D04 heavy chain is provided below (SEQ ID NO:13).

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      1 METGLRWLLL VAVLKGVCQ SVEESGGRLV TPGTPLTLTC
30    41 TVSGFSLSNN AINWVRQAPG KGLEWIGYIW SGGLTYIANW
      81 AEGRFTISK TTTVDLKM TS PTIEDTATYF CARGINNSAL
     121 WPGTTLVTVS SGQPKAPSVF PLAPCCGDTP SSTVTLGCLV
     161 KGYLPEPVTV TWNSGTLTNG VRTFPSVRQS SGLYSLSSVV
     201 SVTSSSQPVT CNVAHPATNT KVDKTVAPST CSKPTCPPPE
35    241 LLGGPSVFIF PPKPKDTLMI SRTPEVTCVV VDV SQDDPEV
     281 QFTWYINNEQ VRTARPLRE QQFNSTIRVV STLPIAHQDW
     321 LRGKEFKCKV HNKALPAPIE KTISKARGQP LEPKVYTMGP
     361 PREELSSRSV SLTCMINGFY PSDISVEWEK NGKAEDNYKT
     401 TPAVLDS DGS YFLYNKLSVP TSEWQRGDVF TCSVMHEALH
40    441 NHYTQKSISR SPGK

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A nucleic acid sequence for this 20D04 anti-CD83 heavy chain is provided below (SEQ ID NO:14).

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      1 ATGGAGACAG GCCTGCGCTG GCTTCTCCTG GTCGCTGTGC
5     41 TCAAAGGTGT CCAGTGTCTAG TCGGTGGAGG AGTCCGGGGG
      81 TCGCCTGGTC ACGCCTGGGA CACCCCTGAC ACTCACCTGC
     121 ACCGTCTCTG GATTCTCCCT CAGTAACAAT GCAATAAACT
     161 GGGTCCGCCA GGCTCCAGGG AAGGGGCTAG AGTGGATCGG
     201 ATACATTTGG AGTGGTGGGC TTACATACTA CGCGAACTGG
10    241 GCGGAAGGCC GATTCAACCAT CTCCAAAACC TCGACTACGG
     281 TGGATCTGAA GATGACCAGT CCGACAATCG AGGACACGGC
     321 CACCTATTTT TGTGCCAGAG GGATTAATAA CTCCGCTTTG
     361 TGGGGCCCAG GCACCCCTGGT CACCGTCTCC TCAGGGCAAC
     401 CTAAGGCTCC ATCAGTCTTC CCACTGGCCC CCTGCTGCGG
15    441 GGACACACCC TCTAGCACGG TGACCTTGGG CTGCCTGGTC
     481 AAAGGCTACC TCCCGGAGCC AGTGACCGTG ACCTGGAACT
     521 CGGGCACCC T CACCAATGGG GTACGCACCT TCCCGTCCGT
     561 CCGGCAGTCC TCAGGCCTCT ACTCGCTGAG CAGCGTGGTG
     601 AGCGTGACCT CAAGCAGCCA GCCCGTCACC TGCAACGTGG
20    641 CCCACCCAGC CACCAACACC AAAGTGGACA AGACCGTTGC
     681 GCCCTCGACA TGCAGCAAGC CCACGTGCCC ACCCCCTGAA
     721 CTCCTGGGGG GACCGTCTGT CTTTCATCTTC CCCCCAAAAC
     761 CCAAGGACAC CCTCATGATC TCACGCACCC CCGAGGTCAC
     801 ATGCGTGGTG GTGGACGTGA GCCAGGATGA CCCCAGAGTG
25    841 CAGTTCACAT GGTACATAAA CAACGAGCAG GTGCGCACCG
     881 CCCGGCCGCC GCTACGGGAG CAGCAGTTCA ACAGCACGAT
     921 CCGCGTGGTC AGCACCCCTCC CCATCGCGCA CCAGGACTGG
     961 CTGAGGGGCA AGGAGTTCAA GTGCAAAGTC CACAACAAGG
    1001 CACTCCCGGC CCCCATCGAG AAAACCATCT CCAAAGCCAG
30    1041 AGGGCAGCCC CTGGAGCCGA AGGTCTACAC CATGGGCCCT
     1081 CCCC GGAGG AGCTGAGCAG CAGGTCGGTC AGCCTGACCT
     1121 GCATGATCAA CGGCTTCTAC CTTTCCGACA TCTCGGTGGA
     1161 GTGGGAGAAG AACGGGAAGG CAGAGGACAA CTACAAGACC
     1201 ACGCCGGCCG TGCTGGACAG CGACGGCTCC TACTTCCTCT
35    1241 ACAACAAGCT CTCAGTGCCC ACGAGTGAGT GGCAGCGGGG
     1281 CGACGTCTTC ACCTGCTCCG TGATGCACGA GGCTTGCAC

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1321 AACCACTACA CGCAGAAGTC CATCTCCCGC TCTCCGGGTA
1361 AA

In another embodiment, the invention provides a 11G05 light chain that
5 can bind to CD83 polypeptides. The amino acid sequence for this 11G05 light
chain is provided below (SEQ ID NO:15).

1 MDTRAPTQLL GLLLLLWLPGA RCADVVMQT PASVSAAVGG
41 TVTINCQSSK NVYNNNWLSW FQQKPGQPPK LLIYYASTLA
10 81 SGVPSRFRGS GSGTQFTLTI SDVQCDDAAT YYCAGDYSSS
121 SDNGFGGGTE VVVKGDPVAP TVLLFPPSSD EVATGTVTIV
161 CVANKYFPDV TVTWEVDGTT QTTGIENSKT PQNSADCTYN
201 LSSTLTLTST QYNSHKEYTC KVTQGTTSVV QFSRKNK

15 A nucleic acid sequence for this 11G05 anti-CD83 light chain is provided
below (SEQ ID NO:16).

1 ATGGACACCA GGGCCCCAC TCAGCTGCTG GGGCTCCTGC
41 TGCTCTGGCT CCCAGGTGCC AGATGTGCCG ACGTCGTGAT
81 GACCCAGACT CCAGCCTCCG TGTCTGCAGC TGTGGGAGGC
20 121 ACAGTCACCA TCAATTGCCA GTCCAGTAAG AATGTTTATA
161 ATAACAATG GTTATCCTGG TTTGAGCAGA AACCAGGGCA
201 GCCTCCCAAG CTCCTGATCT ATTATGCATC CACTCTGGCA
241 TCTGGGGTCC CATCGCGGT CAGAGGCAGT GGATCTGGGA
281 CACAGTTCAC TCTACCAT T AGCGACGTGC AGTGTGACGA
25 321 TGCTGCCACT TACTACTGTG CAGGCGATTA TAGTAGTAGT
361 AGTGATAATG GTTTCGGCGG AGGGACCGAG GTGGTGGTCA
401 AAGGTGATCC AGTTGCACCT ACTGTCTCTCC TCTTCCCACC
441 ATCTAGCGAT GAGGTGGCAA CTGGAACAGT CACCATCGTG
481 TGTGTGGCGA ATAAATACTT TCCCGATGTC ACCGTCACCT
30 521 GGGAGGTGGA TGGCACCACC CAAACAATG GCATCGAGAA
561 CAGTAAAACA CCGCAGAATT CTGCAGATTG TACCTACAAC
601 CTCAGCAGCA CTCTGACACT GACCAGCACA CAGTACAACA
641 GCCACAAAGA GTACACCTGC AAGGTGACCC AGGGCACGAC
681 CTCAGTCGTC CAGAGCTTCA GTAGGAAGAA CTGTTAA
35

In another embodiment, the invention provides a 11G05 heavy chain that
can bind to CD83 polypeptides. The amino acid sequence for this 11G05 heavy
chain is provided below (SEQ ID NO:17).

40 1 METGLRWLLL VAVLKGVCQ SVEESGGRLV TPGTPLTLTC
41 TVSGFTISDY DLSWVRQAPG EGLKYIGFIA IDGNPYATW

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      81 AKGRFTISK TTTVDLKITA PTTEDTATYF CARGAGDLWG
    121 PGTLVTVSSG QPKAPSVFPL APCCGDTFSS TVTLGCLVKG
    161 YLPEPVTVTW NSGTLTNGVR TFPSVRQSSG LYSLSVVSV
    201 TSSSQPVTCN VAHPATNTKV DKTVPSTCS KPTCPPELL
5    241 GGPSVFIFPP KPKDTLMISR TPEVTCVVVD VSQDDPEVQF
    281 TWYINNEQVR TARPPLREQQ FNSTIRVVST LPIAHQDWLR
    321 GKEFKCKVHN KALPAPIEKT ISKARGQPLE PKVYTMGPPR
    361 EELSSRSVSL TCMINGFYPS DISVEWEKNG KAEDNYKTTT
    401 AVLDSGYSYF LYNKLSVPTS EWQRGDVFTC SVMHEALHNNH
10   441 YTQKSISRSP GK

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A nucleic acid sequence for this 11G05 anti-CD83 heavy chain is provided below (SEQ ID NO:18).

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15      1 ATGGAGACAG GCCTGCGCTG GCTTCTCCTG GTCGCTGTGC
      41 TCAAAGGTGT CCAGTGTCAG TCGGTGGAGG AGTCCGGGGG
      81 TCGCCTGGTC ACGCCTGGGA CACCCTGAC ACTCACCTGC
    121 ACAGTCTCTG GATTACCAT CAGTGACTAC GACTTGAGCT
    161 GGGTCCGCCA GGCTCCAGGG GAGGGGCTGA AATACATCGG
20   201 ATTCATTGCT ATTGATGGTA ACCCATACTA CGCGACCTGG
      241 GCAAAAGGCC GATTACCAT CTCCAAAACC TCGACCACGG
      281 TGGATCTGAA AATCACCGCT CCGACAACCG AAGACACGGC
      321 CACGTATTTT TGTGCCAGAG GGGCAGGGGA CCTCTGGGGC
      361 CCAGGGACCC TCGTCACCGT CTCTTCAGGG CAACCTAAGG
25   401 CTCCATCAGT CTTCCCCTG GCCCCCTGCT GCGGGGACAC
      441 ACCCTCTAGC ACGGTGACCT TGGGCTGCCT GGTCAAAGGC
      481 TACCTCCCGG AGCCAGTGAC CGTGACCTGG AACTCGGGCA
      521 CCCTCACCAA TGGGGTACGC ACCTTCCCCT CCGTCCGGCA
      561 GTCCTCAGGC CTCTACTCGC TGAGCAGCGT GGTGAGCGTG
30   601 ACCTCAAGCA GCCAGCCCCT CACCTGCAAC GTGGCCCCACC
      641 CAGCCACCAA CACCAAAGTG GACAAGACCG TTGCGCCCTC
      681 GACATGCAGC AAGCCCACGT GCCCACCCTC TGAACCTCTG
      721 GGGGGACCGT CTGTCTTCAT CTTCCCCCA AAACCCAAGG
      761 ACACCCTCAT GATCTCACGC ACCCCGAGG TCACATGCGT
35   801 GGTGGTGGAC GTGAGCCAGG ATGACCCCGA GGTGCAGTTC
      841 ACATGGTACA TAAACAACGA GCAGGTGCGC ACCGCCCGGC

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881 CGCCGCTACG GGAGCAGCAG TTCAACAGCA CGATCCGCGT
 921 GGTTCAGCACC CTCCCCATCG CGCACCAGGA CTGGCTGAGG
 961 GGCAAGGAGT TCAAGTGCAA AGTCCACAAC AAGGCACTCC
 1001 CGGCCCCCAT CGAGAAAACC ATCTCCAAAG CCAGAGGGCA
 5 1041 GCCCCTGGAG CCGAAGGTCT ACACCATGGG CCCTCCCCGG
 1081 GAGGAGCTGA GCAGCAGGTC GGTTCAGCCTG ACCTGCATGA
 1120 TCAACGGCTT CTACCCTTCC GACATCTCGG TGGAGTGGGA
 1161 GAAGAACGGG AAGGCAGAGG ACAACTACAA GACCACGCCG
 1201 GCCGTGCTGG ACAGCGACGG CTCCTACTTC CTCTACAACA
 10 1241 AGCTCTCAGT GCCCAGCAGT GAGTGGCAGC GGGGCGACGT
 1281 CTTACCTGTC TCCGTGATGC ACGAGGCCTT GCACAACCAC
 1321 TACACGCAGA AGTCCATCTC CCGCTCTCCG GGTAAA

In another embodiment, the invention provides a 14C12 light chain that
 15 can bind to CD83 polypeptides. The amino acid sequence for this 14C12 light
 chain is provided below (SEQ ID NO:19).

1 MDXRAPTQLL GLLLLWLPGA RCALVMTQTP ASVSAAVGGT
 41 VTINCQSSQS VYDNDELSWY QQKPGQPPKL LIYLASKLAS
 20 81 GVPSRFBKSG SGTQFALTIS GVQCDDAATY YCQATHYSSD
 121 WYLTFGGGTE VVVKGDPVAP TVLLFPSSD EVATGTVTIV
 161 CVANKYFPDV TVTWEVDGTT QTTGIENSKT PQNSADCTYN
 201 LSSTLTLTST QYNSHKEYTC KVTQGTTSVV QSF SRKNC

25 A nucleic acid sequence for this 14C12 anti-CD83 light chain is provided
 below (SEQ ID NO:20).

1 ATGGACATRA GGGCCCCCAC TCAGCTGCTG GGGCTCCTGC
 41 TGCTCTGGCT CCCAGGTGCC AGATGTGCCC TTGTGATGAC
 30 81 CCAGACTCCA GCCTCCGTGT CTGCAGCTGT GGGAGGCACA
 121 GTCACCATCA ATTGCCAGTC CAGTCAGAGT GTTTATGATA
 161 ACGACGAATT ATCCTGGTAT CAGCAGAAAC CAGGGCAGCC
 201 TCCCAAGCTC CTGATCTATC TGGCATCCAA GTTGGCATCT
 241 GGGGTCCCAT CCCGATTCAA AGGCAGTGGA TCTGGGACAC
 35 281 AGTTCGCTCT CACCATCAGC GGCGTGCAGT GTGACGATGC
 321 TGCCACTTAC TACTGTCAAG CCACTCATTA TAGTAGTGAT
 361 TGGTATCTTA CTTTCGGCGG AGGGACCGAG GTGGTGGTCA
 401 AAGGTGATCC AGTTGCACCT ACTGTCTTCC TCTTCCCACC
 441 ATCTAGCGAT GAGGTGGCAA CTGGAACAGT CACCATCGTG
 40 481 TGTGTGGCGA ATAAATACTT TCCCGATGTC ACCGTCACCT
 521 GGGAGGTGGA TGGCACCACC CAAACAACCTG GCATCGAGAA
 561 CAGTAAAACA CCGCAGAATT CTGCAGATTG TACCTACAAC

601 CTCAGCAGCA CTCTGACACT GACCAGCACA CAGTACAACA
 641 GCCACAAAGA GTACACCTGC AAGGTGACCC AGGGCACGAC
 681 CTCAGTCGTC CAGAGCTTCA GTAGGAAGAA CTGTTAA

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In another embodiment, the invention provides a 14C12 heavy chain that can bind to CD83 polypeptides. The amino acid sequence for this 14C12 heavy chain is provided below (SEQ ID NO:21).

1 METGLRWLLL VAVLKGVHCQ SVEESGGRLV TPGTPLTLTC
 10 41 TASGFSRSSY DMSWVRQAPG KGLEWVGVIS TAYNSHYASW
 81 AKGRFTISRT STTVDLKMTS LTTEDTATYF CARGGSWLDL
 121 WGQGTLLVTVS SGQPKAPSVF PLAPCCGDTF SSTVTLGCLV
 161 KGYLPEPVTV TWNSGTLTNG VRTFPSVRQS SGLYSLSSVV
 201 SVTSSSQPVT CNVAHPATNT KVDKTVAPST CSKPTCPPPE
 15 241 LLGGPSVFIF PPKPKDTLMI SRTPEVTCVV VDVSQDDPEV
 281 QFTWYINNEQ VRTARPPLE QQFNSTIRVV STLPIAHQDW
 321 LRGKEFKCKV HNKALPAPIE KTISKARGQP LEPKVYTMGP
 361 PREELSSRSV SLTCMINGFY PSDISVEWEK NGKAEDNYKT
 401 TPAVLDSGDS YFLYNKLSVP TSEWQRGDVF TCSVMHEALH
 20 441 NHYTQKSISR SPGK

A nucleic acid sequence for this 14C12 anti-CD83 heavy chain is provided below (SEQ ID NO:22).

25 1 ATGGAGACAG GCCTGCGCTG GCTTCTCCTG GTCGCTGTGC
 41 TCAAAGGTGT CCACTGTCAG TCGGTGGAGG AGTCCGGGGG
 81 TCGCCTGGTC ACGCCTGGGA CACCCCTGAC ACTCACCTGC
 121 ACAGCCTCTG GATTCTCCCG CAGCAGCTAC GACATGAGCT
 161 GGGTCCGCCA GGCTCCAGGG AAGGGGCTGG AATGGGTCTG
 30 201 AGTCATTAGT ACTGCTTATA ACTCACACTA CGCGAGCTGG
 241 GCAAAAGGCC GATTCACCAT CTCCAGAACC TCGACCACGG
 281 TGGATCTGAA AATGACCAGT CTGACAACCG AAGACACGGC
 321 CACCTATTTC TGTGCCAGAG GGGGTAGTTG GTTGGATCTC
 361 TGGGGCCAGG GCACCCTGGT CACCGTCTCC TCAGGGCAAC
 35 401 CTAAGGCTCC ATCAGTCTTC CCACTGGCCC CCTGCTGCGG
 441 GGACACACCC TCTAGCACGG TGACCTTGGG CTGCCTGGTC
 481 AAAGGCTACC TCCCGGAGCC AGTGACCGTG ACCTGGAAC

521 CGGGCACCTT CACCAATGGG GTACGCACCT TCCCGTCCGT
 561 CCGGCAGTCC TCAGGCCTCT ACTCGCTGAG CAGCGTGGTG
 601 AGCGTGACCT CAAGCAGCCA GCCCGTCACC TGCAACGTGG
 641 CCCACCCAGC CACCAACACC AAAGTGGACA AGACCGTTGC
 5 681 GCCCTCGACA TGCAGCAAGC CCACGTGCCC ACCCCCTGAA
 721 CTCCTGGGGG GACCGTCTGT CTTTCATCTTC CCCCCAAAAC
 761 CCAAGGACAC CCTCATGATC TCACGCACCC CCGAGGTCAC
 801 ATGCGTGGTG GTGGACGTGA GCCAGGATGA CCCCAGAGTG
 841 CAGTTCACAT GGTACATAAA CAACGAGCAG GTGCGCACCG
 10 881 CCCGGCCGCC GCTACGGGAG CAGCAGTTCA ACAGCACGAT
 921 CCGCGTGGTC AGCACCTCTC CCATCGCGCA CCAGGACTGG
 961 CTGAGGGGCA AGGAGTTCAA GTGCAAAGTC CACAACAAGG
 1001 CACTCCCGGC CCCCATCGAG AAAACCATCT CCAAAGCCAG
 1041 AGGGCAGCCC CTGGAGCCGA AGGTCTACAC CATGGGCCCT
 15 1081 CCCCAGGAGG AGCTGAGCAG CAGGTCGGTC AGCCTGACCT
 1121 GCATGATCAA CGGCTTCTAC CCTTCCGACA TCTCGGTGGA
 1161 GTGGGAGAAG AACGGGAAGG CAGAGGACAA CTACAAGACC
 1200 ACGCCGCGCG TGCTGGACAG CGACGGCTCC TACTTCCTCT
 1241 ACAACAAGCT CTCAGTGCCC ACGAGTGAGT GGCAGCGGGG
 20 1281 CGACGTCTTC ACCTGCTCCG TGATGCACGA GGCCTTGAC
 1321 AACCCTACTA CGCAGAAGTC CATCTCCCGC TCTCCGGGTA
 1361 AA

In another embodiment, the invention provides a M83 020B08L light
 25 chain that can bind to CD83 polypeptides. The amino acid sequence for this
 M83 020B08L light chain is provided below (SEQ ID NO:58).

1 MDMRAPTQLL GLLLLWLPGA RCAYDMTQTP ASVEVAVGGT
 41 VTIKCQASQS ISTYLDWYQQ KPGQPPKLLI YDASDLASGV
 30 81 PSRFKSGSGS TQFTLTISDL ECADAATYYC QQGYTHSNVD
 121 NVFGGGTEVV VKGDPVAPTV LLFPPSSDEV ATGTVTIVCV
 161 ANKYFPDVTV TWEVDGTTQT TGIENSKTPQ NSADCTYNLS
 201 STLTLTSTQY NSHKEYTCKV TQGTTSVVQS FSRKNC

35 A nucleic acid sequence for this M83 020B08L anti-CD83 light chain is
 provided below (SEQ ID NO:59).

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      1 ATGGACATGA GGGCCCCCAC TCAGCTGCTG GGGCTCCTGC
     41 TGCTCTGGCT CCCAGGTGCC AGATGTGCC T ATGATATGAC
     81 CCAGACTCCA GCCTCTGTGG AGGTAGCTGT GGGAGGCACA
5    121 GTCACCATCA AGTGCCAGGC CAGTCAGAGC ATTAGTACCT
    161 ACTTAGACTG GTATCAGCAG AAACCAGGGC AGCCTCCCAA
    201 GCTCCTGATC TATGATGCAT CCGATCTGGC ATCTGGGGTC
    241 CCATCGCGGT TCAAAGGCAG TGGATCTGGG ACACAGTTCA
    281 CTCTCACCAT CAGCGACCTG GAGTGTGCCG ATGCTGCCAC
10   321 TTACTACTGT CAACAGGGTT ATACACATAG TAATGTTGAT
    361 AATGTTTTTCG GCGGAGGGAC CGAGGTGGTG GTCAAAGGTG
    401 ATCCAGTTGC ACCTACTGTC CTCCTCTTCC CACCATCTAG
    441 CGATGAGGTG GCAACTGGAA CAGTCACCAT CGTGTGTGTG
    481 GCGAATAAAT ACTTTCCCGA TGTCAACGTC ACCTGGGAGG
15   521 TGGATGGCAC CACCCAAACA ACTGGCATCG AGAACAGTAA
    561 AACACCGCAG AATTCTGCAG ATTGTACCTA CAACCTCAGC
    601 AGCACTCTGA CACTGACCAG CACACAGTAC AACAGCCACA
    641 AAGAGTACAC CTGCAAGGTG ACCCAGGGCA CGACCTCAGT
    681 CGTCCAGAGC TTCAGTAGGA AGAACTGTTA A
20

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In another embodiment, the invention provides a M83 020B08H heavy chain that can bind to CD83 polypeptides. The amino acid sequence for this M83 020B08H heavy chain is provided below (SEQ ID NO:60).

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25     1 METGLRWLLL VAVLKGVQCQ SVEESGGRLV TPGTPLTLTC
     41 TVSGFSLSSY DMTWVRQAPG KGLEWIGIYY ASGTTYANW
     81 AKGRFTISK TSTVDLKVTS PTIGDTATYF CAREGAGVSM
    121 TLWGPGLVT VSSGQPKAPS VFPLAPCCGD TPSSTVTLGC
    161 LVKGYLPEPV TVTWNSGTLT NGVRTFPSVR QSSGLYSLSS
30   201 VVSVTSSSQP VTCNVAHPAT NTKVDKTVAP STCSKPTCPP
    241 PELLGGPSVF IFPPKPKDTL MISRTPEVTC VVVDVSQDDP
    281 EVQFTWYINN EQVRTARPPL REQQFNSTIR VVSTLPIAHQ
    321 DWLRGKEFKC KVHNKALPAP IEKTISKARG QPLEPKVYTM
    361 GPPREELSSR SVSLTCMING FYPSDISVEW EKNGKAEDNY
35   401 KTTPAVLDS GSYFLYNKLS VPTSEWQRGD VFTCSVMHEA
    441 LHNHYTQKSI SRSPGK

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A nucleic acid sequence for this M83 020B08H anti-CD83 heavy chain is provided below (SEQ ID NO:61).

```

40     1 ATGGAGACAG GCCTGCGCTG GCTTCTCCTG GTCGCTGTGC
     41 TCAAAGGTGT CCAGTGTCAG TCGGTGGAGG AGTCCGGGGG
     81 TCGCCTGGTC ACGCCTGGGA CACCCCTGAC ACTCACCTGC
    121 ACAGTCTCTG GATTCTCCCT CAGCAGCTAC GACATGACCT
    161 GGGTCCGCCA GGCTCCAGGG AAGGGGCTGG AATGGATCGG
45   201 AATCATTTAT GCTAGTGGTA CCACATACTA CGCGAACTGG
    241 GCGAAAGGCC GATTCAACCAT CTCCAAAACC TCGACCACGG
    281 TGGATCTGAA AGTCACCAGT CCGACAATCG GGGACACGGC
    321 CACCTATTTT TGTGCCAGAG AGGGGGCTGG TGTTAGTATG
    361 ACCTTGTGGG GCCCAGGCAC CCTGGTCACC GTCTCCTCAG
50   401 GGCAACCTAA GGCTCCATCA GTCTTCCCAC TGGCCCCCTG

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    441 CTGCGGGGAC ACACCCTCTA GCACGGTGAC CTTGGGCTGC
    481 CTGGTCAAAG GCTACCTCCC GGAGCCAGTG ACCGTGACCT
    521 GGAATCGGG CACCCTCACC AATGGGGTAC GCACCTTCCC
    561 GTCCGTCCGG CAGTCCTCAG GCCTCTACTC GCTGAGCAGC
5   601 GTGGTGAGCG TGACCTCAAG CAGCCAGCCC GTCACCTGCA
    641 ACGTGGCCCA CCCAGCCACC AACACCAAAG TGGACAAGAC
    681 CGTTGCGCCC TCGACATGCA GCAAGCCCAC GTGCCCACCC
    721 CCTGAACTCC TGGGGGGACC GTCTGTCTTC ATCTTCCCCC
    761 CAAAACCCAA GGACACCCTC ATGATCTCAC GCACCCCCGA
10  801 GGTCACATGC GTGGTGGTGG ACGTGAGCCA GGATGACCCC
    841 GAGGTGCAGT TCACATGGTA CATAAACAAAC GAGCAGGTGC
    881 GCACCGCCCG GCCGCCGCTA CGGGAGCAGC AGTTCAACAG
    921 CACGATCCGC GTGGTCAGCA CCCTCCCCAT CGCGCACCAG
    961 GACTGGCTGA GGGGCAAGGA GTTCAAGTGC AAAGTCCACA
15 1001 ACAAGGCACT CCCGGCCCCC ATCGAGAAAA CCATCTCCAA
    1041 AGCCAGAGGG CAGCCCCTGG AGCCGAAGGT CTACACCATG
    1081 GGGCCCTCCC GGGAGGAGCT GAGCAGCAGG TCGGTCAGCC
    1121 TGACCTGCAT GATCAACGGC TTCTACCCTT CCGACATCTC
    1161 GGTGGAGTGG GAGAAGAACG GGAAGGCAGA GGACAACACT
20 1201 AAGACCACGC CGGCCGTGCT GGACAGCGAC GGCTCCTACT
    1241 TCCTCTACAA CAAGCTCTCA GTGCCACGA GTGAGTGGCA
    1281 GCGGGGCGAC GTCTTCACCT GCTCCGTGAT GCACGAGGCC
    1321 TTGCACAACC ACTACACGCA GAAGTCCATC TCCCGCTCTC
    1361 CGGGTAAA
25

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In another embodiment, the invention provides a M83 006G05L light chain that can bind to CD83 polypeptides. The amino acid sequence for this M83 006G05L light chain is provided below (SEQ ID NO:62).

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30 1 MDMRAPTQLL GLLLLWLPGA RCAYDMTQTP ASVEVAVGGT
    41 VAIKCQASQS VSSYLAWYQQ KPGQPPKPLI YEASMLAAGV
    81 SSRFKGSGSG TDFTLTISDL ECDDAATYYC QQGYSISDID
    121 NAFGGGTEVV VKGDPVAPTV LLFPPSSDEV ATGTVTIVCV
    161 ANKYFPDVTV TWEVDGTTQT TGIENSKTPQ NSADCTYNLS
35 201 STLTLTSTQY NSHKEYTCKV TQGTTSVVQS FSRKNC

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A nucleic acid sequence for M83 006G05L anti-CD83 light chain is provided below (SEQ ID NO:63).

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40 1 ATGGACATGA GGGCCCCCAC TCAACTGCTG GGGCTCCTGC
    41 TGCTCTGGCT CCCAGGTGCC AGATGTGCCT ATGATATGAC
    81 CCAGACTCCA GCCTCTGTGG AGGTAGCTGT GGGAGGCACA
    121 GTCGCCATCA AGTGCCAGGC CAGTCAGAGC GTTAGTAGTT
    161 ACTTAGCCTG GTATCAGCAG AAACCAGGGC AGCCTCCCAA
    201 GCCCCTGATC TACGAAGCAT CCATGCTGGC GGCTGGGGTC
45 241 TCATCGCGGT TCAAAGGCAG TGGATCTGGG ACAGACTTCA
    281 CTCTCACCAT CAGCGACCTG GAGTGTGACG ATGCTGCCAC

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321 TTACTATTGT CAACAGGGTT ATTCTATCAG TGATATTGAT
361 AATGCTTTTCG GCGGAGGGAC CGAGGTGGTG GTCAAAGGTG
401 ATCCAGTTGC ACCTACTGTC CTCCTCTTCC CACCATCTAG
441 CGATGAGGTG GCAACTGGAA CAGTCACCAT CGTGTGTGTG
5 481 GCGAATAAAT ACTTTCCTCGA TGTCACCGTC ACCTGGGAGG
521 TGGATGGCAC CACCCAAACA ACTGGCATCG AGAACAGTAA
561 AACACCGCAG AATTCTGCAG ATTGTACCTA CAACCTCAGC
601 AGCACTCTGA CACTGACCAG CACACAGTAC AACAGCCACA
641 AAGAGTACAC CTGCAAGGTG ACCCAGGGCA CGACCTCAGT
10 681 CGTCCAGAGC TTCAGTAGGA AGAACTGTTA A

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In another embodiment, the invention provides a M83 006G05L heavy chain that can bind to CD83 polypeptides. The amino acid sequence for this M83 006G05L heavy chain is provided below (SEQ ID NO:64).

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1 METGLRWLLL VAVLKGVCQ SVEESGGRLV SPGTPLTLTC
41 TASGFSLSY DMSWVRQAPG KGLEYGIIIS SSGSTYYASW
81 AKGRFTISK STTVDLVTS LTTEDTATYF CSREHAGYSY
121 DTGHLWPGT LVTVSSGQPK APSVFPLAPC CGDTPSSSTVT
20 161 LGCLVKGYLP EPVTVTWNSG TLTVNGVTRFP SVRQSSGLYS
201 LSSVSVTS SQPVTNVAH PATNTKVDKT VAPSTCSKPT
241 CPPPELLGGP SVFIFPPKPK DTLNISRTPE VTCVVVDVSQ
281 DDPEVQFTWY INNEQVTRAR PPLREQQFNS TIRVVSTLPI
321 AHQDWLRGKE FKCKVHNKAL PAPIEKTISK ARGQPLEPKV
25 361 YTMGPPREEL SSRSVSLTCM INGFYPSDIS VEWEKNGKAE
401 DNYKTTPAVL DSDGSYFLYN KLSVPTSEWQ RGDVFTCSVM
441 HEALHNHYTQ KSISRSPGK

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A nucleic acid sequence for this M83 006G05L anti-CD83 heavy chain is provided below (SEQ ID NO:65).

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1 ATGGAGACAG GCCTGCGCTG GCTTCTCCTG GTCGCTGTGC
41 TCAAAGGTGT CCAGTGTCAG TCGGTGGAGG AGTCCGGGGG
81 TCGCCTGGTC TCGCCTGGGA CACCCCTGAC ACTCACCTGC
121 ACAGCCTCTG GATTCTCCCT CAGTAGCTAC GACATGAGCT
35 161 GGGTCCGCCA GGCTCCAGGG AAGGGGCTGG AATACATCGG
201 AATCATTAGT AGTAGTGTA GCACATACTA CGCGAGCTGG
241 GCGAAAGGCC GATTCAACCAT CTCCAAAACC TCGACCACGG
281 TGGATCTGGA AGTGACCACT CTGACAACCG AGGACACGGC
321 CACCTATTTT TGTAGTAGAG AACATGCTGG TTATAGTGGT
40 361 GATACGGGTC ACTTGTGGGG CCCAGGCACC CTGGTCACCG
401 TCTCCTCGGG GCAACCTAAG GCTCCATCAG TCTTCCCCT
441 GGCCCCCTGC TCGGGGACA CACCCTCTAG CACGGTGACC
481 TTGGGCTGCC TGGTCAAAGG CTACCTCCCG GAGCCAGTGA
521 CCGTGACCTG GAACTCGGGC ACCCTACCA ATGGGGTACG
45 561 CACCTTCCCG TCCGTCCGGC AGTCCTCAGG CCTCTACTCG
601 CTGAGCAGC TGGTGAGCGT GACCTCAAGC AGCCAGCCCG
641 TCACCTGCAA CGTGGCCAC CCAGCCACCA ACACCAAAGT
681 GGACAAGACC GTTGCGCCCT CGACATGCAG CAAGCCCACG
721 TGCCACCCCC CTGAACCTCT GGGGGGACCG TCTGTCTTCA

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      761 TCTTCCCCC AAAACCCAAG GACACCCTCA TGATCTCACG
      801 CACCCCCGAG GTCACATGCG TGGTGGTGGA CGTGAGCCAG
      841 GATGACCCCG AGGTGCAGTT CACATGGTAC ATAAACAACG
      881 AGCAGGTGCG CACCGCCCGG CCGCCGCTAC GGGAGCAGCA
5      921 GTTCAACAGC ACGATCCGCG TGGTCAGCAC CCTCCCCATC
      961 GCGCACCAGG ACTGGCTGAG GGGCAAGGAG TTCAAGTGCA
     1001 AAGTCCACAA CAAGGCACTC CCGGCCCCCA TCGAGAAAAC
     1041 CATCTCCAAA GCCAGAGGGC AGCCCCTGGA GCCGAAGGTC
     1081 TACACCATGG GCCCTCCCCG GGAGGAGCTG AGCAGCAGGT
10     1121 CGGTCAGCCT GACCTGCATG ATCAACGGCT TCTACCCCTC
     1162 CGACATCTCG GTGGAGTGGG AGAAGAACGG GAAGGCAGAG
     1201 GACAACTACA AGACCACGCC GGCCGTGCTG GACAGCGACG
     1241 GCTCCTACTT CCTCTACAAC AAGCTCTCAG TGCCCACGAG
     1281 TGAGTGGCAG CGGGGCGACG TCTTCACCTG CTCCGTGATG
15     1321 CACGAGGCCT TGCACAACCA CTACACGCAG AAGTCCATCT
     1361 CCCGCTCTCC GGGTAAA

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Anti-sense Nucleic Acids

20 Anti-sense nucleic acids can be used to inhibit the function of CD83. In general, the function of CD83 RNA is inhibited, for example, by administering to a mammal a nucleic acid that can inhibit the functioning of CD83 RNA. Nucleic acids that can inhibit the function of a CD83RNA can be generated from coding and non-coding regions of the CD83 gene. However, nucleic acids that

25 can inhibit the function of a CD83 RNA are often selected to be complementary to CD83 nucleic acids that are naturally expressed in the mammalian cell to be treated with the methods of the invention. In some embodiments, the nucleic acids that can inhibit CD83 RNA functions are complementary to CD83 sequences found near the 5' end of the CD83 coding region. For example,

30 nucleic acids that can inhibit the function of a CD83 RNA can be complementary to the 5' region of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:10.

A nucleic acid that can inhibit the functioning of a CD83 RNA need not be 100% complementary to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ

35 ID NO:10. Instead, some variability the sequence of the nucleic acid that can inhibit the functioning of a CD83 RNA is permitted. For example, a nucleic acid that can inhibit the functioning of a CD83 RNA from a human can be complementary to a nucleic acid encoding either a human or a mouse CD83 gene product.

Moreover, nucleic acids that can hybridize under moderately or highly stringent hybridization conditions to a nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:10 are sufficiently complementary to inhibit the functioning of a CD83 RNA and can be utilized in the methods of the invention.

"Stringent hybridization conditions" and "stringent hybridization wash conditions" in the context of nucleic acid hybridization are somewhat sequence dependent, and may differ depending upon the environmental conditions of the nucleic acid. For example, longer sequences tend to hybridize specifically at higher temperatures. An extensive guide to the hybridization of nucleic acids is found in Tijssen, Laboratory Techniques in Biochemistry and Molecular biology- Hybridization with Nucleic Acid Probes, page 1, chapter 2 "Overview of principles of hybridization and the strategy of nucleic acid probe assays" Elsevier, New York (1993). See also, J. Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, N.Y., pp 9.31-9.58 (1989); J. Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, N.Y. (3rd ed. 2001).

Generally, highly stringent hybridization and wash conditions are selected to be about 5°C lower than the thermal melting point (T_m) for the specific double-stranded sequence at a defined ionic strength and pH. For example, under "highly stringent conditions" or "highly stringent hybridization conditions" a nucleic acid will hybridize to its complement to a detectably greater degree than to other sequences (e.g., at least 2- fold over background). By controlling the stringency of the hybridization and/or washing conditions nucleic acids that are 100% complementary can be hybridized.

For DNA-DNA hybrids, the T_m can be approximated from the equation of Meinkoth and Wahl Anal. Biochem. 138:267-284 (1984):

$$T_m = 81.5^{\circ}\text{C} + 16.6 (\log M) + 0.41 (\%GC) - 0.61 (\% \text{ form}) - 500/L$$

where M is the molarity of monovalent cations, %GC is the percentage of guanosine and cytosine nucleotides in the DNA, % form is the percentage of formamide in the hybridization solution, and L is the length of the hybrid in base pairs. The T_m is the temperature (under defined ionic strength and pH) at which

50% of a complementary target sequence hybridizes to a perfectly matched probe.

Very stringent conditions are selected to be equal to the T_m for a particular probe.

5 Alternatively, stringency conditions can be adjusted to allow some mismatching in sequences so that lower degrees of similarity can hybridize. Typically, stringent conditions will be those in which the salt concentration is less than about 1.5 M Na ion, typically about 0.01 to 1.0 M Na ion concentration (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for
10 short probes (e.g., 10 to 50 nucleotides) and at least about 60°C for long probes (e.g., greater than 50 nucleotides). Stringent conditions may also be achieved with the addition of destabilizing agents such as formamide.

Exemplary low stringency conditions include hybridization with a buffer solution of 30 to 35% formamide, 1 M NaCl, 1% SDS (sodium dodecyl
15 sulphate) at 37°C, and a wash in 1X to 2X SSC (20X SSC = 3.0 M NaCl and 0.3 M trisodium citrate) at 50 to 55°C. Exemplary moderate stringency conditions include hybridization in 40 to 45% formamide, 1.0 M NaCl, 1% SDS at 37°C, and a wash in 0.5X to 1X SSC at 55 to 60°C. Exemplary high stringency conditions include hybridization in 50% formamide, 1 M NaCl, 1% SDS at
20 37°C, and a wash in 0.1X SSC at 60 to 65°C.

The degree of complementarity or sequence identity of hybrids obtained during hybridization is typically a function of post-hybridization washes, the critical factors being the ionic strength and temperature of the final wash solution. The type and length of hybridizing nucleic acids also affects whether
25 hybridization will occur and whether any hybrids formed will be stable under a given set of hybridization and wash conditions.

An example of stringent hybridization conditions for hybridization of complementary nucleic acids that have more than 100 complementary residues on a filter in a Southern or Northern blot is 50% formamide with 1 mg of heparin
30 at 42°C, with the hybridization being carried out overnight. An example of highly stringent conditions is 0.15 M NaCl at 72°C for about 15 minutes. An example of stringent wash conditions is a 0.2x SSC wash at 65°C for 15 minutes (see also, Sambrook, *infra*). Often, a high stringency wash is preceded by a low

stringency wash to remove background probe signal. An example of medium stringency for a duplex of, e.g., more than 100 nucleotides, is 1x SSC at 45°C for 15 minutes. An example low stringency wash for a duplex of, e.g., more than 100 nucleotides, is 4-6x SSC at 40°C for 15 minutes. For short probes (e.g.,
5 about 10 to 50 nucleotides), stringent conditions typically involve salt concentrations of less than about 1.0M Na ion, typically about 0.01 to 1.0 M Na ion concentration (or other salts) at pH 7.0 to 8.3, and the temperature is typically at least about 30°C.

Stringent conditions can also be achieved with the addition of
10 destabilizing agents such as formamide. In general, a signal to noise ratio of 2x (or higher) than that observed for an unrelated probe in the particular hybridization assay indicates detection of a specific hybridization. Nucleic acids that do not hybridize to each other under stringent conditions are still substantially identical if the proteins that they encode are substantially identical.
15 This occurs, e.g., when a copy of a nucleic acid is created using the maximum codon degeneracy permitted by the genetic code.

The following are examples of sets of hybridization/wash conditions that may be used to detect and isolate homologous nucleic acids that are substantially identical to reference nucleic acids of the present invention: a reference
20 nucleotide sequence preferably hybridizes to the reference nucleotide sequence in 7% sodium dodecyl sulfate (SDS), 0.5 M NaPO₄, 1 mM EDTA at 50°C with washing in 2X SSC, 0.1% SDS at 50°C, more desirably in 7% sodium dodecyl sulfate (SDS), 0.5 M NaPO₄, 1 mM EDTA at 50°C with washing in 1X SSC, 0.1% SDS at 50°C, more desirably still in 7% sodium dodecyl sulfate (SDS), 0.5
25 M NaPO₄, 1 mM EDTA at 50°C with washing in 0.5X SSC, 0.1% SDS at 50°C, preferably in 7% sodium dodecyl sulfate (SDS), 0.5 M NaPO₄, 1 mM EDTA at 50°C with washing in 0.1X SSC, 0.1% SDS at 50°C, more preferably in 7% sodium dodecyl sulfate (SDS), 0.5 M NaPO₄, 1 mM EDTA at 50°C with washing in 0.1X SSC, 0.1% SDS at 65°C.

30 In general, T_m is reduced by about 1°C for each 1% of mismatching. Thus, T_m, hybridization, and/or wash conditions can be adjusted to hybridize to sequences of the desired sequence identity. For example, if sequences with >90% identity are sought, the T_m can be decreased 10°C. Generally, stringent

conditions are selected to be about 5°C lower than the thermal melting point (T_m) for the specific sequence and its complement at a defined ionic strength and pH. However, severely stringent conditions can utilize a hybridization and/or wash at 1, 2, 3, or 4°C lower than the thermal melting point (T_m); moderately stringent
5 conditions can utilize a hybridization and/or wash at 6, 7, 8, 9, or 10°C lower than the thermal melting point (T_m); low stringency conditions can utilize a hybridization and/or wash at 11, 12, 13, 14, 15, or 20°C lower than the thermal melting point (T_m).

If the desired degree of mismatching results in a T_m of less than 45°C (aqueous solution) or 32°C (formamide solution), it is preferred to increase the
10 SSC concentration so that a higher temperature can be used. An extensive guide to the hybridization of nucleic acids is found in Tijssen (1993) *Laboratory Techniques in Biochemistry and Molecular Biology-Hybridization with Nucleic Acid Probes*, Part 1, Chapter 2 (Elsevier, New York); and Ausubel et al., eds.
15 (1995) *Current Protocols in Molecular Biology*, Chapter 2 (Greene Publishing and Wiley - Interscience, New York). See Sambrook et al. (1989) *Molecular Cloning: A Laboratory Manual* (2d ed., Cold Spring Harbor Laboratory Press, Plainview, New York). Using these references and the teachings herein on the relationship between T_m , mismatch, and hybridization and wash conditions,
20 those of ordinary skill can generate variants of the present homocysteine S-methyltransferase nucleic acids.

Precise complementarity is therefore not required for successful duplex formation between a nucleic acid that can inhibit a CD83 RNA and the complementary coding sequence of a CD83 RNA. Inhibitory nucleic acid
25 molecules that comprise, for example, 2, 3, 4, or 5 or more stretches of contiguous nucleotides that are precisely complementary to a CD83 coding sequence, each separated by a stretch of contiguous nucleotides that are not complementary to adjacent CD83 coding sequences, can inhibit the function of CD83 RNA. In general, each stretch of contiguous nucleotides is at least 4, 5, 6,
30 7, or 8 or more nucleotides in length. Non-complementary intervening sequences are preferably 1, 2, 3, or 4 nucleotides in length. One skilled in the art can easily use the calculated melting point of an anti-sense nucleic acid hybridized to a sense nucleic acid to determine the degree of mismatching that

will be tolerated between a particular anti-sense nucleic acid and a particular CD83 RNA.

Nucleic acids that complementary a CD83 RNA can be administered to a mammal or to directly to the site of the inappropriate immune system activity.

5 Alternatively, nucleic acids that are complementary to a CD83 RNA can generated by transcription from an expression cassette that has been administered to a mammal. For example, a complementary RNA can be transcribed from a CD83 nucleic acid that has been inserted into an expression cassette in the 3' to 5' orientation, that is, opposite to the usual orientation employed to generate
10 sense RNA transcripts. Hence, to generate a complementary RNA that can inhibit the function of an endogenous CD83 RNA, the promoter would be positioned to transcribe from a 3' site towards the 5' end of the CD83 coding region.

In some embodiments an RNA that can inhibit the function of an
15 endogenous CD83 RNA is an anti-sense oligonucleotide. The anti-sense oligonucleotide is complementary to at least a portion of the coding sequence of a gene comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:10. Such anti-sense oligonucleotides are generally at least six nucleotides in length, but can be about 8, 12, 15, 20, 25, 30, 35, 40, 45, or 50 nucleotides long.
20 Longer oligonucleotides can also be used. CD83 anti-sense oligonucleotides can be provided in a DNA construct and introduced into cells whose division is to be decreased, for example, into CD4+ T cells, Th-1 cells, Th-2 cells or lymphocyte precursor cells.

Anti-sense oligonucleotides can be composed of deoxyribonucleotides,
25 ribonucleotides, or a combination of both. Oligonucleotides can be synthesized endogenously from transgenic expression cassettes or vectors as described herein. Alternatively, such oligonucleotides can be synthesized manually or by an automated synthesizer, by covalently linking the 5' end of one nucleotide with the 3' end of another nucleotide with non-phosphodiester internucleotide
30 linkages such alkylphosphonates, phosphorothioates, phosphorodithioates, alkylphosphonothioates, alkylphosphonates, phosphoramidates, phosphate esters, carbamates, acetamidate, carboxymethyl esters, carbonates, and phosphate

triesters. See Brown, 1994, *Meth. Mol. Biol.* 20:1-8; Sonveaux, 1994, *Meth. Mol. Biol.* 26:1-72; Uhlmann et al., 1990, *Chem. Rev.* 90:543-583.

CD83 anti-sense oligonucleotides can be modified without affecting their ability to hybridize to a CD83 RNA. These modifications can be internal or at
5 one or both ends of the anti-sense molecule. For example, internucleoside phosphate linkages can be modified by adding peptidyl, cholesteryl or diamine moieties with varying numbers of carbon residues between these moieties and the terminal ribose. Modified bases and/or sugars, such as arabinose instead of
10 the 5' phosphate group are substituted, can also be employed in a modified anti-sense oligonucleotide. These modified oligonucleotides can be prepared by methods available in the art. Agrawal et al., 1992, *Trends Biotechnol.* 10:152-158; Uhlmann et al., 1990, *Chem. Rev.* 90:543-584; Uhlmann et al., 1987, *Tetrahedron. Lett.* 215:3539-3542.

15 In one embodiment of the invention, expression of a CD83 gene is decreased using a ribozyme. A ribozyme is an RNA molecule with catalytic activity. See, e.g., Cech, 1987, *Science* 236: 1532-1539; Cech, 1990, *Ann. Rev. Biochem.* 59:543-568; Cech, 1992, *Curr. Opin. Struct. Biol.* 2: 605-609; Couture and Stinchcomb, 1996, *Trends Genet.* 12: 510-515. Ribozymes can be used to
20 inhibit gene function by cleaving an RNA sequence, as is known in the art (see, e.g., Haseloff et al., U.S. Pat. No. 5,641,673).

CD83 nucleic acids complementary to SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5 or SEQ ID NO:10 can be used to generate ribozymes that will specifically bind to mRNA transcribed from a CD83 gene. Methods of
25 designing and constructing ribozymes that can cleave other RNA molecules in trans in a highly sequence specific manner have been developed and described in the art (see Haseloff et al. (1988), *Nature* 334:585-591). For example, the cleavage activity of ribozymes can be targeted to specific RNAs by engineering a discrete "hybridization" region into the ribozyme. The hybridization region
30 contains a sequence complementary to the target RNA and thus specifically hybridizes with the target (see, for example, Gerlach et al., EP 321,201). The target sequence can be a segment of about 10, 12, 15, 20, or 50 contiguous nucleotides selected from a nucleotide sequence shown in SEQ ID NO:1, SEQ

ID NO:3, SEQ ID NO:5 or SEQ ID NO:10. Longer complementary sequences can be used to increase the affinity of the hybridization sequence for the target. The hybridizing and cleavage regions of the ribozyme can be integrally related; thus, upon hybridizing to the target RNA through the complementary regions, the
5 catalytic region of the ribozyme can cleave the target.

Other CD83 Modulating Molecules

A wide variety of molecules may be used to modulate CD83 activity or function. Such molecules can also be used to modulate the immune system
10 independent of CD83. Compositions and methods for modulating CD83 activity or expression can include these molecules as well as other components. Representative examples that are discussed in more detail below include transcription factors, RNA-binding factors, organic molecules, or peptides.

15 RNA-Binding Factors:

One class of molecules that can be used to modulate cytokine levels or GM-CSF levels by way of the CD83 gene is the RNA binding factors. Such factors include those described in PCT/EP01/14820 and other sources.

For example, the HuR protein (Genbank accession number U38175) has
20 the ability to specifically bind to CD83 RNA at AU-rich elements or sites. Such AU-rich elements comprise sequences such as AUUUA (SEQ ID NO:49), AUUUUA (SEQ ID NO:50) and AUUUUUA (SEQ ID NO:51). Binding by such HuR proteins to CD83 mRNA is thought to increase the stability, transport and translation of CD83 mRNA, and thereby increase the expression of CD83
25 polypeptides. Hence, CD83 expression may be increase by administering HuR proteins or nucleic acids to a mammal.

Conversely, CD83 expression may be decreased by administering factors that block HuR binding to CD83 mRNA. Factors that block HuR binding include proteins or nucleic acids that can bind to the AU-rich elements normally
30 bound by HuR, for example, nucleic acids or anti-sense nucleic acids that are complementary to AU-rich elements.

Organic Molecules:

Numerous organic molecules may be used to modulate the immune system. These compounds include any compound that can interact with a component of the immune system. Such compounds may interact directly with CD83, indirectly with
5 CD83 or with some other polypeptide, cell or factor that plays a role in the function of the immune system. In some embodiments, the organic molecule can bind to a CD83 polypeptide or a CD83 nucleic acid.

Organic molecules can be tested or assayed for their ability to modulate CD83 activity, CD83 function or for their ability to modulate components of the
10 immune system. For example, within one embodiment of the invention suitable organic molecules may be selected either from a chemical library, wherein chemicals are assayed individually, or from combinatorial chemical libraries where multiple compounds are assayed at once, then deconvoluted to determine and isolate the most active compounds.

Representative examples of such combinatorial chemical libraries include
15 those described by Agrafiotis et al., "System and method of automatically generating chemical compounds with desired properties," U.S. Patent No. 5,463,564; Armstrong, R.W., "Synthesis of combinatorial arrays of organic compounds through the use of multiple component combinatorial array syntheses,"
20 WO 95/02566; Baldwin, J.J. et al., "Sulfonamide derivatives and their use," WO 95/24186; Baldwin, J.J. et al., "Combinatorial dihydrobenzopyran library," WO 95/30642; Brenner, S., "New kit for preparing combinatorial libraries," WO 95/16918; Chenera, B. et al., "Preparation of library of resin-bound aromatic carbocyclic compounds," WO 95/16712; Ellman, J.A., "Solid phase and
25 combinatorial synthesis of benzodiazepine compounds on a solid support," U.S. Patent No. 5,288,514; Felder, E. et al., "Novel combinatorial compound libraries," WO 95/16209; Lerner, R. et al., "Encoded combinatorial chemical libraries," WO 93/20242; Pavia, M.R. et al., "A method for preparing and selecting pharmaceutically useful non-peptide compounds from a structurally diverse
30 universal library," WO 95/04277; Summerton, J.E. and D.D. Weller, "Morpholino-subunit combinatorial library and method," U.S. Patent No. 5,506,337; Holmes, C., "Methods for the Solid Phase Synthesis of Thiazolidinones, Metathiazanones, and Derivatives thereof," WO 96/00148; Phillips, G.B. and G.P. Wei, "Solid-phase

- Synthesis of Benzimidazoles," *Tet. Letters* 37:4887-90, 1996; Ruhland, B. et al., "Solid-supported Combinatorial Synthesis of Structurally Diverse β -Lactams," *J. Amer. Chem. Soc.* 111:253-4, 1996; Look, G.C. et al., "The Identification of Cyclooxygenase-1 Inhibitors from 4-Thiazolidinone Combinatorial Libraries," *Bioorg and Med. Chem. Letters* 6:707-12, 1996.

Peptides:

Peptide molecules that modulate the immune system may be obtained through the screening of combinatorial peptide libraries. Such libraries may either be prepared by one of skill in the art (*see e.g.*, U.S. Patent Nos. 4,528,266 and 4,359,535, and Patent Cooperation Treaty Publication Nos. WO 92/15679, WO 92/15677, WO 90/07862, WO 90/02809, or purchased from commercially available sources (*e.g.*, New England Biolabs Ph.D.TM Phage Display Peptide Library Kit).

15

Methods of Using the CD83 Mutant Mouse

In one embodiment, the invention provides a method for identifying ligands, receptors, therapeutic drugs and other molecules that can modulate the phenotype of the mutant CD83 in vivo. This method involves administering a test compound to the mutant CD83 mouse of the invention and observing whether the compound causes a change in the phenotype of the mutant mouse. Changes in phenotype that are of interest include increases or decreases in T cells (especially CD4⁺ T cells), increases or decreases in GM-CSF, IL-2, IL-4 or IL-10 cytokine production, increases or decreases in inflammation, increases or decreases in dendritic cell function and other T cell responses known to one of skill in the art.

Test compounds can be screened in vitro to ascertain whether they interact directly with CD83. In vitro screening can, for example, identify whether a test compound or molecule can bind to the cytoplasmic tail or the membrane-associated portions of CD83. Such information, combined with observation of the in vivo phenotype before and after administration of the test compound provides further insight into the function of CD83 and provides

targets for manipulation T cell activation and other functions modulated by CD83.

The invention is not limited to identification of molecules that directly associate with CD83. The in vivo screening methods provided herein can, also
5 identify test compounds that have an indirect effect on CD83, or that partially or completely replace a function of CD83.

Increases or decreases in T cell numbers can be observed in blood samples or in samples obtained from thymus, spleen or lymph node tissues. In order to observe the activation of T cells and/or the interaction of T cells and
10 dendritic cells, dendritic cells can be pulsed with antigens ex vivo and then injected into mice to prime CD4+ T cells in draining lymphoid organs. *See* Inaba et al., J. Exp. Med. 172: 631-640, 1990; Liu, et al., J. Exp. Med. 177: 1299-1307, 1993; Sornasse et al., J. Exp. Med. 175: 15-21, 1992. Antigens can also be deposited intramuscularly and dendritic cells from the corresponding
15 afferent lymphatics can carry that antigen in a form stimulatory for T cells. Bujdoso et al., J. Exp. Med. 170: 1285-1302, 1989. According to the invention, factors stimulating the interaction of dendritic cells with T cells in vivo can be identified by administering antigens in this manner and then observing how T cell respond, e.g. by observing whether T cell activation occurs.

20 Increases or decreases in cytokine levels can be observed by methods provided herein or by other methods available in the art.

Compositions

The CD83 polypeptides and antibodies of the invention, including their
25 salts, are administered so as to achieve a reduction in at least one symptom associated with an infection, indication or disease.

To achieve the desired effect(s), the polypeptide or antibody, a variant thereof or a combination thereof, may be administered as single or divided dosages, for example, of at least about 0.01 mg/kg to about 500 to 750 mg/kg, of
30 at least about 0.01 mg/kg to about 300 to 500 mg/kg, at least about 0.1 mg/kg to about 100 to 300 mg/kg or at least about 1 mg/kg to about 50 to 100 mg/kg of body weight, although other dosages may provide beneficial results. The amount administered will vary depending on various factors including, but not limited to,

the polypeptide or antibody chosen, the disease, the weight, the physical condition, the health, the age of the mammal, whether prevention or treatment is to be achieved, and if the polypeptide or antibody is chemically modified. Such factors can be readily determined by the clinician employing animal models or
5 other test systems that are available in the art.

Administration of the therapeutic agents in accordance with the present invention may be in a single dose, in multiple doses, in a continuous or intermittent manner, depending, for example, upon the recipient's physiological condition, whether the purpose of the administration is therapeutic or
10 prophylactic, and other factors known to skilled practitioners. The administration of the CD83 polypeptides and antibodies of the invention may be essentially continuous over a preselected period of time or may be in a series of spaced doses. Both local and systemic administration is contemplated.

To prepare the composition, CD83 polypeptides and antibodies are
15 synthesized or otherwise obtained, purified as necessary or desired and then lyophilized and stabilized. The polypeptide or antibody can then be adjusted to the appropriate concentration, and optionally combined with other agents. The absolute weight of a given polypeptide or antibody included in a unit dose can vary widely. For example, about 0.01 to about 2 g, or about 0.1 to about 500 mg,
20 of at least one polypeptide or antibody of the invention, or a plurality of CD83 polypeptides and antibodies specific for a particular cell type can be administered. Alternatively, the unit dosage can vary from about 0.01 g to about 50 g, from about 0.01 g to about 35 g, from about 0.1 g to about 25 g, from about 0.5 g to about 12 g, from about 0.5 g to about 8 g, from about 0.5 g to about 4 g,
25 or from about 0.5 g to about 2 g.

Daily doses of the CD83 polypeptides or antibodies of the invention can vary as well. Such daily doses can range, for example, from about 0.1 g/day to about 50 g/day, from about 0.1 g/day to about 25 g/day, from about 0.1 g/day to about 12 g/day, from about 0.5 g/day to about 8 g/day, from about 0.5 g/day to about 4 g/day, and from about 0.5 g/day to about 2 g/day.
30

Thus, one or more suitable unit dosage forms comprising the therapeutic CD83 polypeptides or antibodies of the invention can be administered by a variety of routes including oral, parenteral (including subcutaneous, intravenous,

intramuscular and intraperitoneal), rectal, dermal, transdermal, intrathoracic, intrapulmonary and intranasal (respiratory) routes. The therapeutic CD83 polypeptides or antibodies may also be formulated for sustained release (for example, using microencapsulation, see WO 94/ 07529, and U.S. Patent
5 No.4,962,091). The formulations may, where appropriate, be conveniently presented in discrete unit dosage forms and may be prepared by any of the methods well known to the pharmaceutical arts. Such methods may include the step of mixing the therapeutic agent with liquid carriers, solid matrices, semi-solid carriers, finely divided solid carriers or combinations thereof, and then, if
10 necessary, introducing or shaping the product into the desired delivery system.

When the therapeutic CD83 polypeptides or antibodies of the invention are prepared for oral administration, they are generally combined with a pharmaceutically acceptable carrier, diluent or excipient to form a pharmaceutical formulation, or unit dosage form. For oral administration, the
15 CD83 polypeptides or antibodies may be present as a powder, a granular formulation, a solution, a suspension, an emulsion or in a natural or synthetic polymer or resin for ingestion of the active ingredients from a chewing gum. The active CD83 polypeptides or antibodies may also be presented as a bolus, electuary or paste. Orally administered therapeutic CD83 polypeptides or
20 antibodies of the invention can also be formulated for sustained release, e.g., the CD83 polypeptides or antibodies can be coated, micro-encapsulated, or otherwise placed within a sustained delivery device. The total active ingredients in such formulations comprise from 0.1 to 99.9% by weight of the formulation.

By "pharmaceutically acceptable" it is meant a carrier, diluent, excipient,
25 and/or salt that is compatible with the other ingredients of the formulation, and not deleterious to the recipient thereof.

Pharmaceutical formulations containing the therapeutic CD83 polypeptides or antibodies of the invention can be prepared by procedures known in the art using well-known and readily available ingredients. For example, the
30 polypeptide or antibody can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, solutions, suspensions, powders, aerosols and the like. Examples of excipients, diluents, and carriers that are suitable for such formulations include buffers, as well as fillers and extenders

such as starch, cellulose, sugars, mannitol, and silicic derivatives. Binding agents can also be included such as carboxymethyl cellulose, hydroxymethylcellulose, hydroxypropyl methylcellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl-pyrrolidone. Moisturizing agents
5 can be included such as glycerol, disintegrating agents such as calcium carbonate and sodium bicarbonate. Agents for retarding dissolution can also be included such as paraffin. Resorption accelerators such as quaternary ammonium compounds can also be included. Surface active agents such as cetyl alcohol and glycerol monostearate can be included. Adsorptive carriers such as kaolin and
10 bentonite can be added. Lubricants such as talc, calcium and magnesium stearate, and solid polyethyl glycols can also be included. Preservatives may also be added. The compositions of the invention can also contain thickening agents such as cellulose and/or cellulose derivatives. They may also contain gums such as xanthan, guar or carbo gum or gum arabic, or alternatively
15 polyethylene glycols, bentones and montmorillonites, and the like.

For example, tablets or caplets containing the CD83 polypeptides or antibodies of the invention can include buffering agents such as calcium carbonate, magnesium oxide and magnesium carbonate. Caplets and tablets can also include inactive ingredients such as cellulose, pregelatinized starch, silicon
20 dioxide, hydroxy propyl methyl cellulose, magnesium stearate, microcrystalline cellulose, starch, talc, titanium dioxide, benzoic acid, citric acid, corn starch, mineral oil, polypropylene glycol, sodium phosphate, zinc stearate, and the like. Hard or soft gelatin capsules containing at least one polypeptide or antibody of the invention can contain inactive ingredients such as gelatin, microcrystalline
25 cellulose, sodium lauryl sulfate, starch, talc, and titanium dioxide, and the like, as well as liquid vehicles such as polyethylene glycols (PEGs) and vegetable oil. Moreover, enteric-coated caplets or tablets containing one or more CD83 polypeptides or antibodies of the invention are designed to resist disintegration in the stomach and dissolve in the more neutral to alkaline environment of the
30 duodenum.

The therapeutic CD83 polypeptides or antibodies of the invention can also be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for instance by intramuscular,

subcutaneous, intraperitoneal or intravenous routes. The pharmaceutical formulations of the therapeutic CD83 polypeptides or antibodies of the invention can also take the form of an aqueous or anhydrous solution or dispersion, or alternatively the form of an emulsion or suspension or salve.

5 Thus, the therapeutic CD83 polypeptides or antibodies may be formulated for parenteral administration (e.g., by injection, for example, bolus injection or continuous infusion) and may be presented in unit dose form in ampules, pre-filled syringes, small volume infusion containers or in multi-dose containers. As noted above, preservatives can be added to help maintain the
10 shelve life of the dosage form. The active CD83 polypeptides or antibodies and other ingredients may form suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active CD83 polypeptides or antibodies and other ingredients may be in powder form, obtained by aseptic
15 isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

 These formulations can contain pharmaceutically acceptable carriers, vehicles and adjuvants that are well known in the art. It is possible, for example, to prepare solutions using one or more organic solvent(s) that is/are acceptable
20 from the physiological standpoint, chosen, in addition to water, from solvents such as acetone, ethanol, isopropyl alcohol, glycol ethers such as the products sold under the name "Dowanol," polyglycols and polyethylene glycols, C₁-C₄ alkyl esters of short-chain acids, ethyl or isopropyl lactate, fatty acid triglycerides such as the products marketed under the name "Miglyol," isopropyl myristate,
25 animal, mineral and vegetable oils and polysiloxanes.

 It is possible to add, if necessary, an adjuvant chosen from antioxidants, surfactants, other preservatives, film-forming, keratolytic or comedolytic agents, perfumes, flavorings and colorings. Antioxidants such as t-butylhydroquinone, butylated hydroxyanisole, butylated hydroxytoluene and α -tocopherol and its
30 derivatives can be added.

 Also contemplated are combination products that include one or more CD83 polypeptides or antibodies of the present invention and one or more other anti-microbial agents. For example, a variety of antibiotics can be included in the

pharmaceutical compositions of the invention, such as aminoglycosides (e.g., streptomycin, gentamicin, sisomicin, tobramycin and amikacin), ansamycins (e.g. rifamycin), antimycotics (e.g. polyenes and benzofuran derivatives), β -lactams (e.g. penicillins and cephalosporins), chloramphenicol (including thiamphenol
5 and azidamphenicol), linosamides (lincomycin, clindamycin), macrolides (erythromycin, oleandomycin, spiramycin), polymyxins, bacitracins, tyrothycin, capreomycin, vancomycin, tetracyclines (including oxytetracycline, minocycline, doxycycline), phosphomycin and fusidic acid.

Additionally, the CD83 polypeptides or antibodies are well suited to
10 formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active polypeptide or antibody, for example, in a particular part of the intestinal or respiratory tract, possibly over a period of time. Coatings, envelopes, and protective matrices may be made, for example, from polymeric substances, such as polylactide-glycolates, liposomes,
15 microemulsions, microparticles, nanoparticles, or waxes. These coatings, envelopes, and protective matrices are useful to coat indwelling devices, e.g., stents, catheters, peritoneal dialysis tubing, draining devices and the like.

For topical administration, the therapeutic agents may be formulated as is known in the art for direct application to a target area. Forms chiefly
20 conditioned for topical application take the form, for example, of creams, milks, gels, dispersion or microemulsions, lotions thickened to a greater or lesser extent, impregnated pads, ointments or sticks, aerosol formulations (e.g., sprays or foams), soaps, detergents, lotions or cakes of soap. Other conventional forms for this purpose include wound dressings, coated bandages or other polymer
25 coverings, ointments, creams, lotions, pastes, jellies, sprays, and aerosols. Thus, the therapeutic CD83 polypeptides or antibodies of the invention can be delivered via patches or bandages for dermal administration. Alternatively, the polypeptide or antibody can be formulated to be part of an adhesive polymer, such as polyacrylate or acrylate/vinyl acetate copolymer. For long-term
30 applications it might be desirable to use microporous and/or breathable backing laminates, so hydration or maceration of the skin can be minimized. The backing layer can be any appropriate thickness that will provide the desired

protective and support functions. A suitable thickness will generally be from about 10 to about 200 microns.

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents.

5 Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. The active CD83 polypeptides or antibodies can also be delivered via iontophoresis, e.g., as disclosed in U.S. Patent Nos. 4,140,122; 4,383,529; or 4,051,842. The percent
10 by weight of a therapeutic agent of the invention present in a topical formulation will depend on various factors, but generally will be from 0.01% to 95% of the total weight of the formulation, and typically 0.1-85% by weight.

Drops, such as eye drops or nose drops, may be formulated with one or more of the therapeutic CD83 polypeptides or antibodies in an aqueous or non-
15 aqueous base also comprising one or more dispersing agents, solubilizing agents or suspending agents. Liquid sprays are conveniently delivered from pressurized packs. Drops can be delivered via a simple eye dropper-capped bottle, or via a plastic bottle adapted to deliver liquid contents dropwise, via a specially shaped closure.

20 The therapeutic polypeptide or antibody may further be formulated for topical administration in the mouth or throat. For example, the active ingredients may be formulated as a lozenge further comprising a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the composition in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes
25 comprising the composition of the present invention in a suitable liquid carrier.

The pharmaceutical formulations of the present invention may include, as optional ingredients, pharmaceutically acceptable carriers, diluents, solubilizing or emulsifying agents, and salts of the type that are available in the art. Examples of such substances include normal saline solutions such as
30 physiologically buffered saline solutions and water. Specific non-limiting examples of the carriers and/or diluents that are useful in the pharmaceutical formulations of the present invention include water and physiologically

acceptable buffered saline solutions such as phosphate buffered saline solutions pH 7.0-8.0.

The CD83 polypeptides or antibodies of the invention can also be administered to the respiratory tract. Thus, the present invention also provides
5 aerosol pharmaceutical formulations and dosage forms for use in the methods of the invention. In general, such dosage forms comprise an amount of at least one of the agents of the invention effective to treat or prevent the clinical symptoms of a specific infection, indication or disease. Any statistically significant attenuation of one or more symptoms of an infection, indication or disease that
10 has been treated pursuant to the method of the present invention is considered to be a treatment of such infection, indication or disease within the scope of the invention.

Alternatively, for administration by inhalation or insufflation, the composition may take the form of a dry powder, for example, a powder mix of
15 the therapeutic agent and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges, or, e.g., gelatin or blister packs from which the powder may be administered with the aid of an inhalator, insufflator, or a metered-dose inhaler (see, for example, the pressurized metered dose inhaler (MDI) and the
20 dry powder inhaler disclosed in Newinan, S. P. in Aerosols and the Lung, Clarke, S. W. and Davia, D. eds., pp. 197-224, Butterworths, London, England, 1984).

Therapeutic CD83 polypeptides or antibodies of the present invention can also be administered in an aqueous solution when administered in an aerosol or inhaled form. Thus, other aerosol pharmaceutical formulations may comprise,
25 for example, a physiologically acceptable buffered saline solution containing between about 0.1 mg/ml and about 100 mg/ml of one or more of the CD83 polypeptides or antibodies of the present invention specific for the indication or disease to be treated. Dry aerosol in the form of finely divided solid polypeptide or antibody or nucleic acid particles that are not dissolved or suspended in a
30 liquid are also useful in the practice of the present invention. CD83 polypeptides or antibodies of the present invention may be formulated as dusting powders and comprise finely divided particles having an average particle size of between about 1 and 5 μm , alternatively between 2 and 3 μm . Finely divided particles

may be prepared by pulverization and screen filtration using techniques well known in the art. The particles may be administered by inhaling a predetermined quantity of the finely divided material, which can be in the form of a powder. It will be appreciated that the unit content of active ingredient or ingredients
5 contained in an individual aerosol dose of each dosage form need not in itself constitute an effective amount for treating the particular infection, indication or disease since the necessary effective amount can be reached by administration of a plurality of dosage units. Moreover, the effective amount may be achieved using less than the dose in the dosage form, either individually, or in a series of
10 administrations.

For administration to the upper (nasal) or lower respiratory tract by inhalation, the therapeutic CD83 polypeptides or antibodies of the invention are conveniently delivered from a nebulizer or a pressurized pack or other convenient means of delivering an aerosol spray. Pressurized packs may
15 comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Nebulizers include, but are not limited to, those described in U.S. Patent Nos. 4,624,251;
20 3,703,173; 3,561,444; and 4,635,627. Aerosol delivery systems of the type disclosed herein are available from numerous commercial sources including Fisons Corporation (Bedford, Mass.), Schering Corp. (Kenilworth, NJ) and American Pharmoseal Co., (Valencia, CA). For intra-nasal administration, the therapeutic agent may also be administered via nose drops, a liquid spray, such
25 as via a plastic bottle atomizer or metered-dose inhaler. Typical of atomizers are the Mistometer (Wintrop) and the Medihaler (Riker).

Furthermore, the active ingredients may also be used in combination with other therapeutic agents, for example, pain relievers, anti-inflammatory agents, antihistamines, bronchodilators and the like, whether for the conditions
30 described or some other condition.

The present invention further pertains to a packaged pharmaceutical composition for controlling microbial infections such as a kit or other container. The kit or container holds a therapeutically effective amount of a pharmaceutical

composition for controlling microbial infections and instructions for using the pharmaceutical composition for control of the microbial infection. The pharmaceutical composition includes at least one polypeptide or antibody of the present invention, in a therapeutically effective amount such that the selected
5 disease or immunological condition is controlled.

The invention will be further described by reference to the following detailed examples, which are given for illustration of the invention, and are not intended to be limiting thereof.

10 **EXAMPLE 1: Mouse Mutation and Characterization**

Mutant Generation

Male C57BL6 mice received 3 weekly injections of N-ethyl-N-nitrosourea (ENU) at a concentration of 100mg/kg. N-Ethyl-N-nitrosourea was quantified prior to injection by spectrophotometry. Mice that regained fertility
15 after a minimum period of 12 weeks were then used to generate pedigree founder G1 animals. G1 male mice were crossed to C57BL6J females and their female progeny (G2 animals) crossed back to their fathers to generate G3 animals for screening.

G3 mice were weaned at 3 weeks of age. Each animal then underwent a
20 series of screens designed to assess a number of parameters, including immune function, inflammatory response and bone development. In the initial screen, conducted at 6 weeks of age, 150-200ul of whole blood was collected by retro-orbital bleed into heparinized tubes. Cells were pelleted and red blood cells lysed. Samples were then stained with antibodies to cell surface markers
25 expressed on distinct lymphoid and myeloid sub-populations. These samples were analyzed by flow-cytometry.

Mutant Identification

A group of 27 G3 mice from 2 different pedigrees, pedigree 9 and
30 pedigree 57 (i.e. derived from 2 distinct G1 fathers) were analyzed in this screen. Two animals from pedigree 9 were identified as having a reduced (>2 standard deviation from normal) percentage of CD4+ T cells in peripheral blood (Figure 1). Both animals were descended from the same G1 and shared the same

mother. All other animals screened on that day had a normal percentage of CD4⁺ T cells. The number of phenodeviants identified (2 from a litter of 9 animals) was suggestive of a trait controlled by a single gene and inherited in a Mendelian fashion.

- 5 A second litter generated from Pedigree 9 bred to G2 daughter #4 exhibited an identical phenotype with reduced numbers of CD4⁺ T cells, further suggesting that the trait had a genetic basis. The phenotype was designated LCD4.1 (Low CD4 Mutant # 1) and was used for mapping experiments.

10 **Mutation Mapping**

- In order to map the LCD4.1 mutant phenotype, affected G3 male mice (presumptive homozygous for the mutation) were bred to female animals from the C3HeB/FeJ strain to generate F1 progeny. These F1 females (presumptively heterozygous for the mutation) were then mated back to their affected father to
15 generate N2 progeny.

- Blood was collected from N2 animals and flow cytometric analysis was performed to identify CD4⁺ T cells. For a phenotype controlled by a single gene, breeding homozygous fathers to heterozygous daughters should yield 50% normal N2 animals and 50% affected N2 animals. This ratio of normal to
20 affected animals was observed in the N2 generation: Multiple N2 animals exhibited a reduced percentage of CD4⁺ T cells, indicating that the phenotype was heritable (Figure 2).

- DNA samples were prepared from samples of tail tissue collected from these N2 mice and used for a genome scan, using a collection of assembled
25 markers, and performed on the ABI 3100 DNA analyzer. Initial genetic linkage was seen to the tip of chromosome 13, where the closest microsatellite marker was D13Mit139 with a LOD score of 8.2. By calculating upper and lower confidence limits, the mutant gene was located between 13.4 and 29.6 cM on chromosome 13. Through additional genotyping, this region was reduced to an
30 11 cM interval on chromosome 13. No significant linkage to other chromosomal regions was seen.

Mutation Identification

A candidate gene, CD83, was identified for gene-testing based upon its reported position within the interval. CD83 has previously been used as a marker of dendritic cell activation, suggesting that it might play a role in
5 dendritic cell function and hence in regulating T cell development and function.

Sequence analysis of the mutant DNA revealed a mutation in the stop codon of CD83. All affected animals were homozygous for this mutation while non-affected animals carried one wild-type allele and one mutant allele (Figure 3 and Figure 4). The mutation destroyed the stop codon and resulted in the
10 addition of a unique 55 amino acid tail to the C-terminus of CD83 (Figure 5).

Additional Functional Data

A reduction in CD4+ T cells was seen in peripheral blood, spleen tissues and lymph nodes from homozygous LCD4.1 mice. Although there was a
15 reduced number of CD4+ T cells in the thymus there is no overt block in the developmental process and there was no alteration in B cell development in the bone marrow. Histological evaluation of thymus, spleen and lymph nodes from affected mice revealed no gross alteration in tissue architecture.

Dendritic cells can be differentiated from bone marrow of wild type mice
20 by culture in GM-CSF. These cells can be characterized by the surface expression of dendritic cell markers, including CD86 and CD11c. Both LCD4.1 affected and normal animals were capable of giving rise to CD86+CD11c+ cells under these culture conditions. LCD4.1 mutant mice thus were capable of generating dendritic cells under in vitro culture conditions. These data suggest
25 that the phenotype seen in LCD4.1 mice is not due to a failure of dendritic cells to develop but rather may reflect a defect in function.

To track dendritic cells the sensitizing agent FITC was applied to the dorsal surface of the ears of LCD4.1 affected and wild-type mice. FITC was picked up by dendritic cells that then migrated to the draining auricular lymph
30 nodes, where the presence of the FITC label on the dendritic cell surface permitted detection by flow-cytometry. FITC labeled cells expressing CD86 were detected in equal proportions in draining lymph node from normal and affected LCD4.1 mice. These data indicate that LCD4.1 mutant animals are

capable of generating dendritic cells in vivo and that these cells are able to pick up antigen in the ear and travel to the draining lymph node.

5 **EXAMPLE 2: CD83 and CD4+ T Cell Function**

Materials and Methods

Spleens were removed from wild type and mutant mice and digested with collagenase to liberate dendritic cells. Spleens were stained for surface expression of CD4 (helper T cells) and CD11c (dendritic cells). Cells expressing
10 these markers were purified by fluorescence activated cell sorting (FACS sorting). CD11c and CD4+ positive cells were also purified from an allogeneic mouse strain, BALBc.

Mixed lymphocyte cultures were set up using purified cell populations. Dendritic cells from BALBc animals were used to stimulate CD4+ T cells from
15 wild type and mutant mice. In a reciprocal experiment dendritic cells prepared from wild type and mutant mice were used to stimulate BALBc CD4+ T cells. After 5 days in culture proliferative responses were measured by incorporation of tritiated thymidine.

Dendritic cells from wild type and mutant mice were both capable of
20 activating allogeneic T cells, suggesting that dendritic cell function was unimpaired in the mutant animal (Figure 6a). In contrast CD4+ T cells from mutant animals exhibited a diminished response after 5 days of stimulation (Figure 6b).

These data suggest that the mutation in the CD83 gene has minimal effect
25 on dendritic cells intrinsic function but rather has a profound effect upon T cell activity. The CD4+ T cell therefore may have a novel requirement for CD83 functionality on T cells during allogeneic activation. CD83 may be influencing the extent of CD4+ T cell activation or altering the duration of the CD4+ T cell proliferative response. The therapeutic manipulation of CD83 may thus
30 represent a mechanism for the specific regulation of T cell function in the treatment of T cell mediated diseases, including autoimmune disorders. Antibodies capable of blocking CD83 function may be used as therapeutics in

the treatment of immune diseases whilst the activation of CD83 may have utility in enhancing immune responses in cancer and other circumstances.

Conclusion

5 Although CD83 has been described as a marker of dendritic cell activation there is little data as to its function in vivo. The mutation provided by the invention destabilizes or inactivates the protein and leads to impaired surface expression. As a consequence, CD4⁺ T cell function is impaired although the development of dendritic cells is not inhibited and mutant dendritic cells retain
10 functionality. This results in the impaired development of CD4⁺ T cells. This impaired ability to activate T cells is also seen in a slight decrease in contact sensitivity responses in LCD4.1 mutant mice.

15 **EXAMPLE 3: Mutant CD83 Have Different Cytokine Levels than Wild Type Mice**

This Example demonstrates that CD4⁺ T-cells from CD83 mutant animals express higher levels of IL-4 and lower levels of IL-2 compared to CD4⁺ T-cells from CD83 wild type animals.

20

Methods for cell activation and cytokine measurements:

Spleens cells from 6-8-week-old homozygous CD83 wild type or CD83 mutant (LCD4.1) mice were used to isolate CD4⁺ T-cells by positive selection using magnetic beads (Miltenyi Biotec). A 96 round bottom plate was coated
25 with 50µL per well of a solution containing either 1 or 10 µg/mL of anti-CD3 and 0.1 or 0.2 µg/mL of anti-CD28 antibodies (both from Pharmingen) in PBS overnight. This plate was then washed using 150 µL of PBS three times. To this pre-coated plate, 20,000 CD4⁺ T-cells (either wild type or CD83 mutant) were added in a 200 µL final volume of RPMI containing 10% FBS, 55 µM β-
30 mercaptoethanol and antibiotics. The plates were then incubated in a CO₂ incubator at 37 °C for 44 to 72 hours. For determination of cytokine levels, supernatants were harvested and cytokines were measured using either a Cytometric Bead Array system (Pharmingen) or ELISA (R&D). For RNA

measurements, the cells were harvested and RNA was isolated using Tri reagent (Sigma). IL-10 and IL-4 mRNA levels were measured by reverse transcription and TaqMan (Applied Biosystems) analysis.

5 **Results:**

Figure 7 shows the IL-2, IL-4, IL-5, TNF α and IFN γ levels produced by either wild type or CD83 mutant CD4⁺ T-cells. Purified cells were incubated as described above in the presence of 1 μ g/mL of anti-CD3 and 0.2 μ g/mL of anti-CD28 antibodies for 72 hours. The supernatants were then simultaneously
10 analyzed for production of IL-2, IL-4, IL-5, TNF α and IFN γ using the cytometric bead array system from Pharmingen.

Figure 7 demonstrates that CD4⁺ T-cells from CD83 mutant animals expressed higher levels of IL-4 and lower levels of IL-2 compared to CD4⁺ T-cells from CD83 wild type animals. Other cytokines and a new set of
15 stimulation assays were analyzed including the production levels of IL-10 and GM-CSF by these cells (Figures 8 and 9). In both cases, cells from mutant animals produce larger amounts of IL-10 and GM-CSF than did wild type animals. Figure 10 shows that mRNA levels for both IL-4 and IL-10 were increased in cells from activated mutant CD83, CD4⁺ T-cells compared with
20 cells from wild type animals.

EXAMPLE 4: Anti-CD83 Antibodies May Mimic the Effects of the CD83 Mutation

25 **Methods for antibody testing:**

For modulation of cytokine production by anti-CD83 antibodies, CD4⁺ T-cells were isolated and activated as mentioned above in the presence of increasing concentrations of anti-CD83 antibodies. For proliferation assays, CD4⁺ T-cells were isolated from an OT2tg [transgenic mice with a T-cell
30 receptor specific for chicken ovalbumin (OVA) 323-339 peptide]. Dendritic cells were isolated from a C57BL6 mouse by a negative selection using B220 magnetic beads (Miltenyi Biotec) followed by positive selection using CD11-c magnetic beads (Miltenyi Biotec). Five thousand CD4⁺ T-cells were then mixed

with five thousand dendritic cells in a 96 well plate in the presences of 1 μ M OVA peptide using RPMI (55 μ M BME, 10%FBS plus antibiotics) in a final 200uL volume. These cells were then incubated for 48 to 72 hours in a CO₂ incubator at 37°C and pulsed using [³H] thymidine for 8 hours. Cells were then
5 harvested and [³H] thymidine incorporation was quantified using a top counter.

Results:

In some assays, anti-CD83 antibodies decreased production of IL-4 by activated CD4⁺ T-cells in a dose dependent manner. Different antibody
10 preparations did provide somewhat different degrees of inhibition of IL-4 production (Figure 11). Accordingly, the epitope and/or degree of affinity of the antibodies for the CD83 antigen may influence whether or not IL-4 production is significantly inhibited.

The effects of anti CD83 antibodies on proliferation of a peptide specific
15 T-cell proliferation assay using the OT2 T-cell receptor (TCR) transgenic system were also observed. CD4⁺ T-cells derived from these TCR transgenic animals express high levels of a T-cell receptor specific for chicken ovalbumin (OVA) 323-339 peptide and thus have high levels of proliferation when mixed with antigen presenting cells (dendritic cells were used) in the presence of the OVA
20 peptide. In such assays, anti-CD83 antibodies were able to decrease proliferation of CD4⁺ T-cells in this system (Figure 12). However, different antibody preparations had somewhat different effects on the proliferation of CD4⁺ T-cells. Accordingly, the CD83 epitope and/or degree of affinity of the antibodies for the CD83 antigen may influence whether or not CD4⁺ T-cell proliferation is
25 significantly inhibited.

EXAMPLE 5: Increased T-Cell Proliferation by Transgenic Expression of CD83

30 This Example illustrates that over expression of CD83 in transgenic mice leads to increased T-cell proliferation.

Materials and Methods

A 34.3 kb fragment of normal mouse genomic DNA, including the ~18 kb coding region of the CD83 gene, as well as ~10.6 kb of upstream flanking sequences and ~5.7 kb of downstream sequences was microinjected into normal mouse one-cell embryos. Four individual founder animals were generated. Transgenic mice were then crossed to a male OT2tg mouse. Male offspring carrying both the CD83 and OT2 transgene were used to analyze peptide specific T-cell proliferation.

For proliferation assays, CD4⁺ T-cells and dendritic cells were isolated from either OT2tg [transgenic mice with a T-cell receptor specific for chicken ovalbumin (OVA) 323-339 peptide] CD83 wild type or from OT2tg CD83 transgenic mice as described above (Example 4). Five thousand OT2tg CD4⁺ T-cells from either wild type or CD83 transgenic animals were then mixed with five thousand wild type dendritic cells or five thousand CD83 transgenic dendritic cells in a 96 well plate in the presence of increasing concentrations of OVA peptide using RPMI (55 μ M BME, 10%FBS plus antibiotics) in a final 200uL volume. These cells were then incubated for 48 to 72 hours in a CO₂ incubator at 37C and pulsed using [³H] thymidine for 8 hours. Cells were then harvested and [³H] thymidine incorporation was quantified using a top counter.

Results:

OT2tg CD4⁺ T-cells derived from CD83 transgenic mice proliferated at higher rates than the same cell population derived from a CD83 wild type animal (Figure 13). This increased proliferation was seen at all the concentrations of OVA peptide tested. Whereas OT2tg CD4⁺ T-cells derived from CD83 transgenic animals exhibited increased proliferation, dendritic cells from CD83 transgenic animals did not exhibit a substantial increase in proliferation. Therefore, it appears that transgenic expression in the CD4⁺ T-cell, and not in dendritic cells is what led to the increased proliferation of CD4⁺ T-cells.

**EXAMPLE 6: Inhibition of proliferation of PHA activated human PBMCs
by protein A purified rabbit anti mouse CD83 polyclonal sera.**

This Example shows that antibodies raised against the mouse CD83 protein can inhibit proliferation of human peripheral blood mononuclear cells.

5

Materials and Methods

Rabbit polyclonal sera was raised against mouse CD83 protein by immunizing rabbits using a mouse CD83 external domain protein fused to a rabbit Ig domain (Figure 14). Pre-immune sera and anti-mouse polyclonal sera were then purified using a protein A column (Pharmacia Biotech) as described by the manufacturer, then dialyzed against PBS and stored at 4° C. To monitor the recognition of mouse CD83 protein by the polyclonal sera, which was obtained at different dates post immunization, a titer was obtained using an antigen specific ELISA (Figure 15). As illustrated by Figure 15, a good polyclonal response was obtained against the mouse CD83 protein.

Human peripheral blood mononuclear cells (PBMCs) were isolated using a Ficoll gradient (Ficoll Paque Plus, Pharmacia) and washed with PBS buffer. For activation and proliferation studies, five thousand cells were incubated in 200 μ L of media (RPMI, 10%FBS, antibiotics) and 5ug/mL of *Phaseolus vulgaris* leucoagglutinin (PHA) in the presence or absence of increasing concentrations of Protein A purified pre-immune sera or with similarly purified anti-CD83 polyclonal antibodies. After 48 hours at 37°C in a CO₂ incubator the cells were pulsed with [³H] thymidine for ~8 hours and harvested. Thymidine incorporation into the PBMCs was measured using a top counter for analysis.

25

Results

Figure 16 illustrates that proliferation of PHA-activated human PBMCs was inhibited by antibodies raised against the external region of the mouse CD83 protein. Proliferation of PHA-activated human PBMCs was not affected by addition of increasing concentrations of protein A purified rabbit pre-immune sera. When increasing concentrations of protein A purified rabbit polyclonal sera raised against the mouse CD83 protein was added, a concentration dependent decrease in proliferation was observed.

30

These data indicate that antibodies raised against the mouse protein are able to cross-react with the human protein. Moreover, antibodies raised against the mouse protein are able to inhibit proliferation of PHA-activated human PBMCs.

- 5 All publications, patents and patent applications are incorporated herein by reference. While in the foregoing specification this invention has been described in relation to certain preferred embodiments thereof, and many details have been set forth for purposes of illustration, it will be apparent to those skilled in the art that the invention is susceptible to additional embodiments and that
- 10 certain of the details described herein may be varied considerably without departing from the basic principles of the invention.

WHAT IS CLAIMED

1. A method of modulating cytokine production in a mammal by modulating the activity or expression of a CD83 polypeptide.
- 5 2. A method of modulating cytokine production in a mammal by administering to the mammal an antibody that can modulate the activity or expression of a CD83 polypeptide.
3. A method of modulating cytokine production by a T cell by modulating
10 the activity or expression of a CD83 polypeptide in the T cell.
4. A method of modulating cytokine production by a T cell by contacting the T cell with an antibody that can modulate the activity or expression of a CD83 polypeptide.
15
5. A method of modulating a CD4+ T cell by modulating the activity or expression of a CD83 polypeptide in the T cell.
6. A method of modulating a CD4+ T cell by contacting the T cell with an
20 antibody that can modulate the activity or expression of a CD83 polypeptide.
7. A method of modulating granulocyte macrophage colony stimulating factor production in a mammal by modulating the activity or expression of CD83 polypeptides.
25
8. A method of modulating granulocyte macrophage colony stimulating factor production in a mammal by administering to the mammal an antibody that can modulate the activity or expression of CD83 polypeptides.
- 30 9. A method of modulating granulocyte macrophage colony stimulating factor production by a T cell by modulating the activity or expression of a CD83 polypeptide in the T cell.

10. A method of modulating granulocyte macrophage colony stimulating factor production by a T cell by contacting the T cell with an antibody that can modulate the activity or expression of a CD83 polypeptide.
- 5 11. A method of tumor necrosis factor production in a mammal by modulating the activity or expression of CD83 polypeptides.
12. A method of modulating tumor necrosis factor production in a mammal by administering to the mammal an antibody that can modulate the activity or
10 expression of CD83 polypeptides.
13. A method of inhibiting proliferation of a human peripheral blood mononuclear cell by modulating the activity or expression of CD83 polypeptides.
- 15 14. A method of inhibiting proliferation of a human peripheral blood mononuclear cell in a mammal by administering to the mammal an antibody that can modulate the activity or expression of CD83 polypeptides.
15. An antibody that can bind to a CD83 polypeptide comprising SEQ ID
20 NO:4, SEQ ID NO:8 or SEQ ID NO:9, wherein activated CD4⁺ T-cells produce lower levels of interleukin-4 when said T-cells are contacted with the antibody.
16. An antibody that can bind to a CD83 polypeptide comprising SEQ ID NO:4, SEQ ID NO:8 or SEQ ID NO:9, wherein CD4⁺ T-cells proliferation is
25 decreased when said T-cells are contacted with the antibody.
17. An antibody comprising SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28,
30 SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID

NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

- 5 18. A nucleic acid encoding an antibody comprising SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

15

19. The nucleic acid of claim 18, wherein the nucleic acid comprises nucleotide sequence SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:59, SEQ ID NO:61, SEQ ID NO:63 or SEQ ID NO:65.

20

20. A method for decreasing the activity of a CD83 gene product, comprising contacting the CD83 gene product with an antibody that comprises SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

30

21. A method for decreasing the activity of a CD83 gene product in a mammal, comprising administering to the mammal an antibody that comprises SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

22. A method for decreasing the translation of a CD83 gene product in a mammalian cell, comprising contacting the mammalian cell with a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

23. A method for decreasing the translation of a CD83 gene product in a mammal, comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

24. A method for decreasing proliferation of CD4⁺ T-cells in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9.

25. The method of claim 24, wherein the antibody comprises SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ

ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

5

26. A method for decreasing interleukin-2 levels and increasing interleukin-4 levels in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9.

10

27. The method of claim 26, wherein the antibody SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

20

28. A method for decreasing interleukin-2 levels and increasing interleukin-4 levels in a mammal comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.

25

29. The method of claim 26 or 28, wherein the interleukin-2 levels are decreased and the interleukin-4 levels are increased to treat an autoimmune disease.

30

30. The method of claim 29, wherein the autoimmune disease is diabetes mellitus, arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, psoriatic arthritis, multiple sclerosis, myasthenia gravis, systemic

- lupus erythematosus, autoimmune thyroiditis, dermatitis, atopic dermatitis, eczematous dermatitis, psoriasis, Sjogren's Syndrome, keratoconjunctivitis sicca secondary to Sjogren's Syndrome, alopecia areata, allergic responses due to arthropod bite reactions, Crohn's disease, aphthous ulcer, iritis, conjunctivitis,
- 5 keratoconjunctivitis, ulcerative colitis, asthma, allergic asthma, cutaneous lupus erythematosus, scleroderma, vaginitis, proctitis, drug eruptions, leprosy reversal reactions, erythema nodosum leprosum, autoimmune uveitis, allergic encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss, aplastic anemia, pure red cell
- 10 anemia, idiopathic thrombocytopenia, polychondritis, Wegener's granulomatosis, chronic active hepatitis, Stevens-Johnson syndrome, idiopathic sprue, lichen planus, Crohn's disease, Graves ophthalmopathy, sarcoidosis, primary biliary cirrhosis, uveitis posterior, or interstitial lung fibrosis.
- 15 31. The method of claim 26 or 28, wherein the interleukin-2 levels are decreased and the interleukin-4 levels are increased to stimulate production of Th2-associated cytokines in transplant recipients.
- 20 32. The method of claim 31, wherein the Th2-associated cytokines prolong survival of transplanted tissue.
33. The method of claim 32, wherein the transplanted tissue is skin, cardiac or bone marrow.
- 25 34. The method of claim 26 or 28, wherein the mammal is a human.
- 30 35. A method for increasing interleukin-10 levels in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9.
36. The method of claim 35, wherein the antibody comprises SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ

ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31,
SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID
NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ
ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45,
5 SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID
NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ
ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.

37. A method for increasing interleukin-10 levels in a mammal comprising
10 administering to the mammal a nucleic acid complementary to a CD83 nucleic
acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID
NO:10.

38. The method of claim 35 or 37, wherein the interleukin-10 levels are
15 increased to treat neoplastic disease.

39. The method of claim 35 or 37, wherein the interleukin-10 levels are
increased to treat a tumor.

20 40. A method for increasing interleukin-2 levels in a mammal comprising
administering to the mammal a functional CD83 polypeptide that comprises SEQ
ID NO:9.

41. A method for increasing interleukin-2 levels in a mammal comprising:
25 (a) transforming a T cell from the mammal with a nucleic acid
encoding a functional CD83 polypeptide operably linked to a
promoter functional in a mammalian cell, to generate a
transformed T cell;
(b) administering the transformed T cell to the mammal to provide
30 increased levels of interleukin-2.

42. The method of claim 41, wherein the CD83 polypeptide comprises SEQ
ID NO:9.

43. The method of claim 41, wherein the nucleic acid comprises SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.
- 5 44. The method of claim 41, wherein the mammal is a human.
45. The method of claim 41, wherein the interleukin-2 levels are increased to treat an allergy or an infectious disease.
- 10 46. The method of claim 45, wherein the infectious disease is related to HIV infection, tuberculosis, leishmaniasis, schistosomiasis, filarial nematode infection, or intestinal nematode infection.
47. The method of claim 45, wherein the infectious disease is related to
15 infection by *Aeromonas* spp., *Bacillus* spp., *Bacteroides* spp., *Campylobacter* spp., *Clostridium* spp., *Enterobacter* spp., *Enterococcus* spp., *Escherichia* spp., *Gastrospirillum* sp., *Helicobacter* spp., *Klebsiella* spp., *Salmonella* spp., *Shigella* spp., *Staphylococcus* spp., *Pseudomonas* spp., *Vibrio* spp., or *Yersinia* spp.
- 20 48. The method of claim 45, wherein the infectious disease is related to staph infection, typhus, food poisoning, bacillary dysentery, pneumonia, cholera, an ulcer, diarrhea, hemorrhagic colitis, hemolytic uremic syndrome, or thrombotic thrombocytopenic purpura.
- 25 49. The method of claim 45, wherein the infectious disease is related to infection by *Staphylococcus aureus*, *Salmonella typhi*, *Escherichia coli*, *Escherichia coli* O157:H7, *Shigella dysenteriae*, *Pseudomonas aeruginosa*, *Pseudomonas cepacia*, *Vibrio cholerae*, *Helicobacter pylori*, a multiply-resistant strain of *Staphylococcus aureus*, a vancomycin-resistant strain of *Enterococcus*
30 *faecium*, or a vancomycin-resistant strain of *Enterococcus faecalis*.
50. The method of claim 45, wherein the infectious disease is related to infection by a virus.

51. The method of claim 50, wherein the virus is a hepatitis A virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus, poxvirus, herpes virus, adenovirus, papovavirus, parvovirus, reovirus, orbivirus, picornavirus, rotavirus, alphavirus, rubivirus, influenza virus type A, influenza virus type B, flavivirus, coronavirus, paramyxovirus, morbillivirus, pneumovirus, rhabdovirus, lyssavirus, orthomyxovirus, bunyavirus, phlebovirus, nairovirus, hepadnavirus, arenavirus, retrovirus, enterovirus, rhinovirus or filovirus.
52. A method for increasing granulocyte macrophage colony stimulating factor levels in a mammal comprising administering to the mammal an antibody that can bind to a CD83 gene product, wherein the CD83 gene product comprises SEQ ID NO:2 or SEQ ID NO:9.
53. The method of claim 52, wherein the antibody comprises SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:60, SEQ ID NO:62 or SEQ ID NO:64.
54. A method for increasing granulocyte macrophage colony stimulating factor levels in a mammal comprising administering to the mammal a nucleic acid complementary to a CD83 nucleic acid comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, or SEQ ID NO:10.
55. A method for increasing tumor necrosis factor levels at a selected site in a mammal comprising administering to the site a functional CD83 polypeptide.

56. A method for increasing tumor necrosis factor levels in a selected mammalian cell comprising transforming the cell with a nucleic acid encoding a functional CD83 polypeptide.
- 5 57. The method of claim 55 or 56, wherein the mammal is human and the CD83 polypeptide comprises SEQ ID NO:9.
58. A method of identifying a compound that can modulate CD4+T cell activation comprising administering a test compound to a mutant mouse and
10 observing whether CD4+ T cells become activated, wherein the somatic and germ cells of the mutant mouse comprise a mutant CD83 gene encoding a polypeptide comprising SEQ ID NO:4 or SEQ ID NO:8.
59. A mutant CD83 gene encoding a polypeptide comprising SEQ ID NO:4
15 or SEQ ID NO:8.
60. The mutant CD83 gene of claim 63 comprising nucleotide sequence SEQ ID NO:3.
- 20 61. A mutant mouse whose somatic and germ cells comprise a mutant CD83 gene encoding a polypeptide comprising SEQ ID NO:4 or SEQ ID NO:8, wherein expression of said mutant CD83 gene reduces CD4+T cell activation.
62. The mutant mouse of claim 61, wherein the mutant CD83 gene comprises
25 SEQ ID NO:3.

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	Mom	G3 ID	% CD4+
Pedigree 57	G2 # 1	57.1.1	22
		57.1.2	26
		57.1.3	24
	G2 # 4	57.4.1	15
		57.4.2	18
	G2 # 5	57.5.1	21
		57.5.2	19
		57.5.3	24
		57.5.4	22
		57.5.5	19
		57.5.6	17
Pedigree 9	G2 # 4	9.4.1	6
		9.4.2	20
		9.4.3	16
		9.4.4	12
		9.4.5	20
		9.4.6	15
		9.4.7	24
		9.4.8	27
		9.4.9	5
	G2 # 5	9.5.1	18
		9.5.2	20
		9.5.3	22
		9.5.4	20
		9.5.5	22
		9.5.6	20
		9.5.7	23

average	19.1
stdev	5.2
= + 2SD	29.6
= -2SD	8.7

FIG. 1

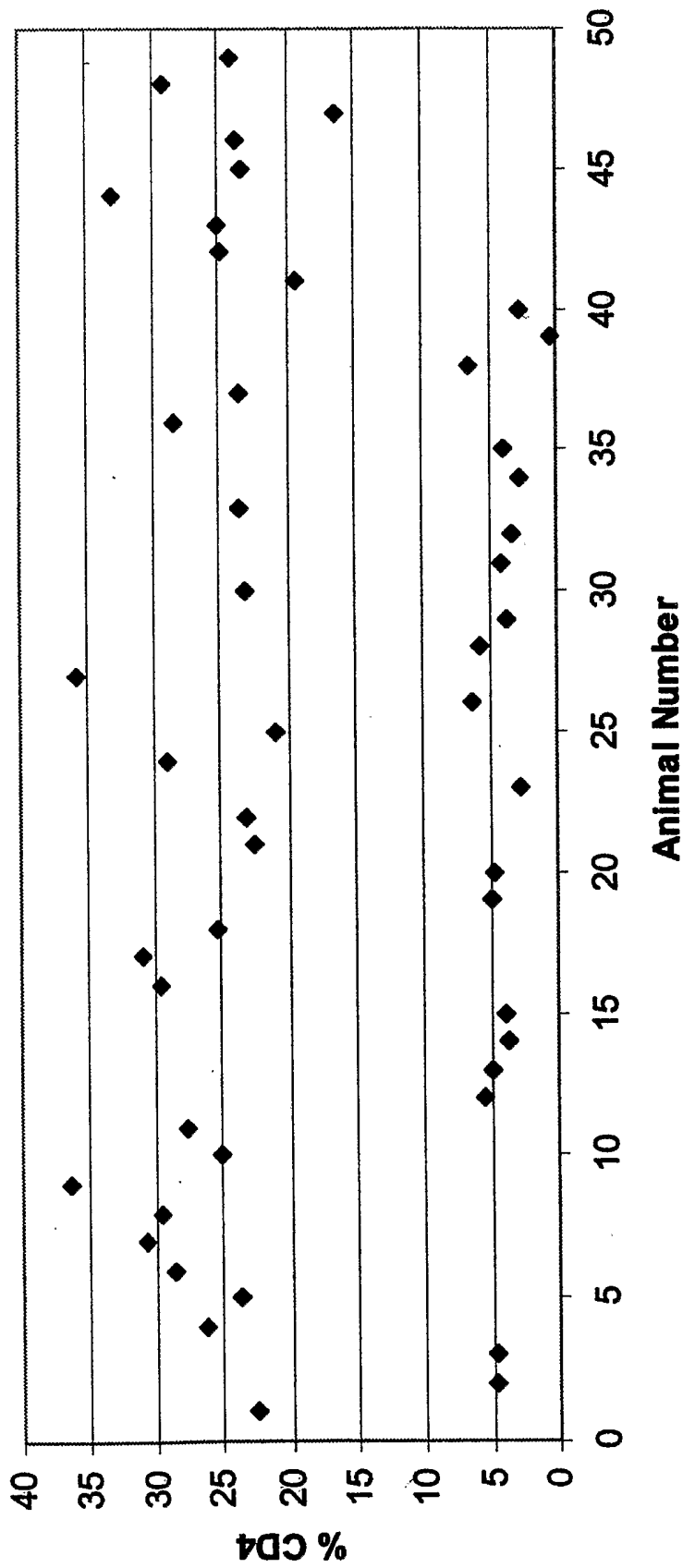


FIG. 2

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```

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101    TCCGAGACCG CCGACTTGCC TTGCACAGCG CCCTGGGACC CGCAGCTCTC
151    CTATGCAGTG TCCTGGGCCA AGGTCTCCGA GAGTGGCACT GAGAGTGTGG
201    AGCTCCCGGA GAGCAAGCAA AACAGCTCCT TCGAGGCCCC CAGGAGAAGG
251    GCCTATTCCC TGACGATCCA AAACACTACC ATCTGCAGCT CGGGCACCTA
301    CAGGTGTGCC CTGCAGGAGC TCGGAGGGCA GCGCAACTTG AGCGGCACCG
351    TGGTTCTGAA GGTGACAGGA TGCCCCAAGG AAGCTACAGA GTCAACTTTC
401    AGGAAGTACA GGGCAGAAGC TGTGTTGCTC TTCTCTCTGG TTGTTTTCTA
451    CCTGACACTC ATCATTTTCA CCTGCAAATT TGCACGACTA CAAAGCATTT
501    TCCCAGATAT TTCTAAACCT GGTACGGAAC AAGCTTTTCT TCCAGTCACC
551    TCCCCAAGCA AACATTTGGG GCCAGTGACC CTTCTAAGA CAGAAACGGT
601    ATGAG TAGGA TCTCCACTGG TTTTACAAA GCCAAGGGCA CATCAGATCA
651    GTGTGCCTGA ATGCCACCCG GACAAGAGAA GAATGAGCTC CATCCTCAGA
701    TGGCAACCTT TCTTTGAAGT CCTTCACCTG ACAGTGGGCT CCACACTACT
751    CCCTGACACA GGGTCTTGAG CACCATCATA TGATCACGAA GCATGGAGTA
801    TCACCGCTTC TCTGTGGCTG TCAGCTTAAT GTTTCATGTG GCTATCTGGT
851    CAACCTCGTG AGTGCTTTTC AGTCATCTAC AAGCTATGGT GAGATGCAGG
901    TGAAGCAGGG TCATGGGAAA TTTGAACACT CTGAGCTGGC CCTGTGACAG
951    ACTCCTGAGG ACAGCTGTCC TCTCCTACAT CTGGGATACA TCTCTTTGAA
1001   TTTGTCCTGT TTCGTTCAC CAGCCCAGAT GTCTCACATC TGGCGGAAAT
1051   TGACAGGCCA AGCTGTGAGC CAGTGGGAAA TATTTAGCAA ATAATTTCCC
1101   AGTGCGAAGG TCCTGCTATT AGTAAGGAGT ATTATGTGTA CATAGAAATG
1151   AGAGGTCAGT GAACTATTCC CCAGCAGGGC CTTTTCATCT GGAAAAGACA
1201   TCCACAAAAG CAGCAATACA GAGGGATGCC ACATTTATTT TTTTAATCTT
1251   CATGTACTTG TCAAAGAAGA ATTTTTCATG TTTTTCAAA GAAGTGTGTT
1301   TCTTTCCTTT TTTAAAATAT GAAGGTCTAG TTACATAGCA TTGCTAGCTG
1351   ACAAGCAGCC TGAGAGAAGA TGGAGAATGT TCCTCAAAT AGGGACAGCA
1401   AGCTAGAAGC ACTGTACAGT GCCCTGCTGG GAAGGGCAGA CAATGGACTG
1451   AGAAACCAGA AGTCTGGCCA CAAGATTGTC TGTATGATTC TGGACGAGTC
1501   ACTTGTGGTT TTTACTCTCT GGTTAGTAAA CCAGATAGTT TAGTCTGGGT
1551   TGAATACAAT GGATGTGAAG TTGCTTGGGG AAAGCTGAAT GTAGTGAATA
1601   CATTGGCAAC TCTACTGGGC TGTTACCTTG TTGATATCCT AGAGTTCTGG
1651   AGCTGAGCGA ATGCCTGTCA TATCTCAGCT TGCCCATCAA TCCAAACACA
1701   GGAGGCTACA AAAAGGACAT GAGCATGGTC TTCTGTGTGA ACTCCTCCTG
1751   AGAAACGTGG AGACTGGCTC AGCGCTTTGC GCTTGAAGGA CTAATCACAA
1801   GTTCTTGAAG ATATGGACCT AGGGGAGCTA TTGCGCCACG ACAGGAGGAA
1851   GTTCTCAGAT GTTGCATTGA TGTAACATTG TTGCATTTCT TTAATGAGCT
1901   GGGCTCCTTC CTCATTTGCT TCCCAAAGAG ATTTTGTCCC ACTAATGGTG
1951   TGCCCATCAC CCACACTATG AAAGTAAAAG GGATGCTGAG CAGATACAGC
2001   GTGCTTACCT CTCAGCCATG ACTTTCATGC TATTAAAAGA ATGCATGTGA
2051   A

```

FIG. 3

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1 GCGCTCCAGC CGCATGTCGC AAGGCCTCCA GTCCTGTTT CTAGGCTGCG
51 CCTGCAGCCT GGCACCCGCG ATGGCGATGC GGGAGGTGAC GGTGGCTTGC
101 TCCGAGACCG CCGACTTGCC TTGCACAGCG CCCTGGGACC CGCAGCTCTC
151 CTATGCAGTG TCCTGGGCCA AGGTCTCCGA GAGTGGCACT GAGAGTGTGG
201 AGCTCCCGGA GAGCAAGCAA AACAGCTCCT TCGAGGCCCC CAGGAGAAGG
251 GCCTATTCCC TGACGATCCA AAACACTACC ATCTGCAGCT CGGGCACCTA
301 CAGGTGTGCC CTGCAGGAGC TCGGAGGGCA GCGCAACTTG AGCGGCACCG
351 TGGTTCTGAA GGTGACAGGA TGCCCCAAGG AAGCTACAGA GTCAACTTTC
401 AGGAAGTACA GGGCAGAAGC TGTGTTGCTC TTCTCTCTGG TTGTTTTCTA
451 CCTGACACTC ATCATTTTCA CCTGCAAATT TGCACGACTA CAAAGCATTT
501 TCCCAGATAT TTCTAAACCT GGTACGGAAC AAGCTTTTCT TCCAGTCACC
551 TCCCCAAGCA AACATTTGGG GCCAGTGACC CTTCTAAGA CAGAAACGGT
601 AAGAGTAGGA TCTCCACTGG TTTTACAAA GCCAAGGGCA CATCAGATCA
651 GTGTGCCTGA ATGCCACCCG GACAAGAGAA GAATGAGCTC CATCCTCAGA
701 TGGCAACCTT TCTTTGAAGT CCTTCACCTG ACAGTGGGCT CCACACTACT
751 CCCTGACACA GGGTCTTGAG CACCATCATA TGATCACGAA GCATGGAGTA
801 TCACCGCTTC TCTGTGGCTG TCAGCTTAAT GTTTCATGTG GCTATCTGGT
851 CAACCTCGTG AGTGCTTTTC AGTCATCTAC AAGCTATGGT GAGATGCAGG
901 TGAAGCAGGG TCATGGGAAA TTTGAACACT CTGAGCTGGC CCTGTGACAG
951 ACTCCTGAGG ACAGCTGTCC TCTCCTACAT CTGGGATACA TCTCTTTGAA
1001 TTTGTCCTGT TTCGTTGCAC CAGCCCAGAT GTCTCACATC TGGCGGAAAT
1051 TGACAGGCCA AGCTGTGAGC CAGTGGGAAA TATTTAGCAA ATAATTTCCC
1101 AGTGCGAAGG TCCTGCTATT AGTAAGGAGT ATTATGTGTA CATAGAAATG
1151 AGAGGTCAGT GAACTATTCC CCAGCAGGGC CTTTTCATCT GGAAAAGACA
1201 TCCACAAAAG CAGCAATACA GAGGGATGCC ACATTTATTT TTTTAATCTT
1251 CATGTACTTG TCAAAGAAGA ATTTTTCATG TTTTTTCAAA GAAGTGTGTT

FIG. 4A

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1301 TCTTTCCTTT TTTAAAATAT GAAGGTCTAG TTACATAGCA TTGCTAGCTG
1351 ACAAGCAGCC TGAGAGAAGA TGGAGAATGT TCCTCAAAT AGGGACAGCA
1401 AGCTAGAAGC ACTGTACAGT GCCCTGCTGG GAAGGGCAGA CAATGGACTG
1451 AGAAACCAGA AGTCTGGCCA CAAGATTGTC TGTATGATTC TGGACGAGTC
1501 ACTTGTGGTT TTTACTCTCT GGTTAGTAAA CCAGATAGTT TAGTCTGGGT
1551 TGAATACAAT GGATGTGAAG TTGCTTGGGG AAAGCTGAAT GTAGTGAATA
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1651 AGCTGAGCGA ATGCCTGTCA TATCTCAGCT TGCCCATCAA TCCAAACACA
1701 GGAGGCTACA AAAAGGACAT GAGCATGGTC TTCTGTGTGA ACTCCTCCTG
1751 AGAAACGTGG AGACTGGCTC AGCGCTTTGC GCTTGAAGGA CTAATCACAA
1801 GTTCTTGAAG ATATGGACCT AGGGGAGCTA TTGCGCCACG ACAGGAGGAA
1851 GTTCTCAGAT GTTGCATTGA TGTAACATTG TTGCATTTCT TTAATGAGCT
1901 GGGCTCCTTC CTCATTTGCT TCCCAAAGAG ATTTTGTCCC ACTAATGGTG
1951 TGCCCATCAC CCACACTATG AAAGTAAAAG GGATGCTGAG CAGATACAGC
2001 GTGCTTACCT CTCAGCCATG ACTTTCATGC TATTAAAAGA ATGCATGTGA
2051 A

FIG. 4B

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Wild Type Amino Acid Sequence for CD83 protein [Mus musculus]

MSQGLQLLFL GCACSLAPAM AMREVTVACS ETADLPCTAP WDPQLSYAVS
WAKVSESGTE SVELPESKQN SSFEAPRRRA YSLTIQNTTI CSSGTYRCAL
QELGGQRNLS GTVVLKVTGC PKEATESTFR KYRAEAVLLF SLVVFYLTLI
IFTCKFARLQ SIFPDISKPG TEQAFLPVT SPSKHLGPVTL PKTETV

Mutant CD83 Amino Acid Sequence: novel tail underlined, in bold.

MSQGLQLLFL GCACSLAPAM AMREVTVACS ETADLPCTAP WDPQLSYAVS
WAKVSESGTE SVELPESKQN SSFEAPRRRA YSLTIQNTTI CSSGTYRCAL
QELGGQRNLS GTVVLKVTGC PKEATESTFR KYRAEAVLLF SLVVFYLTLI
IFTCKFARLQ SIFPDISKPG TEQAFLPVT SPSKHLGPVTL PKTETV**RVGS**
PLVFTKPRAH QISVPECHPD KRMSSILRW OPFFEVLHLT VGSTLLPDTG

S

FIG. 5

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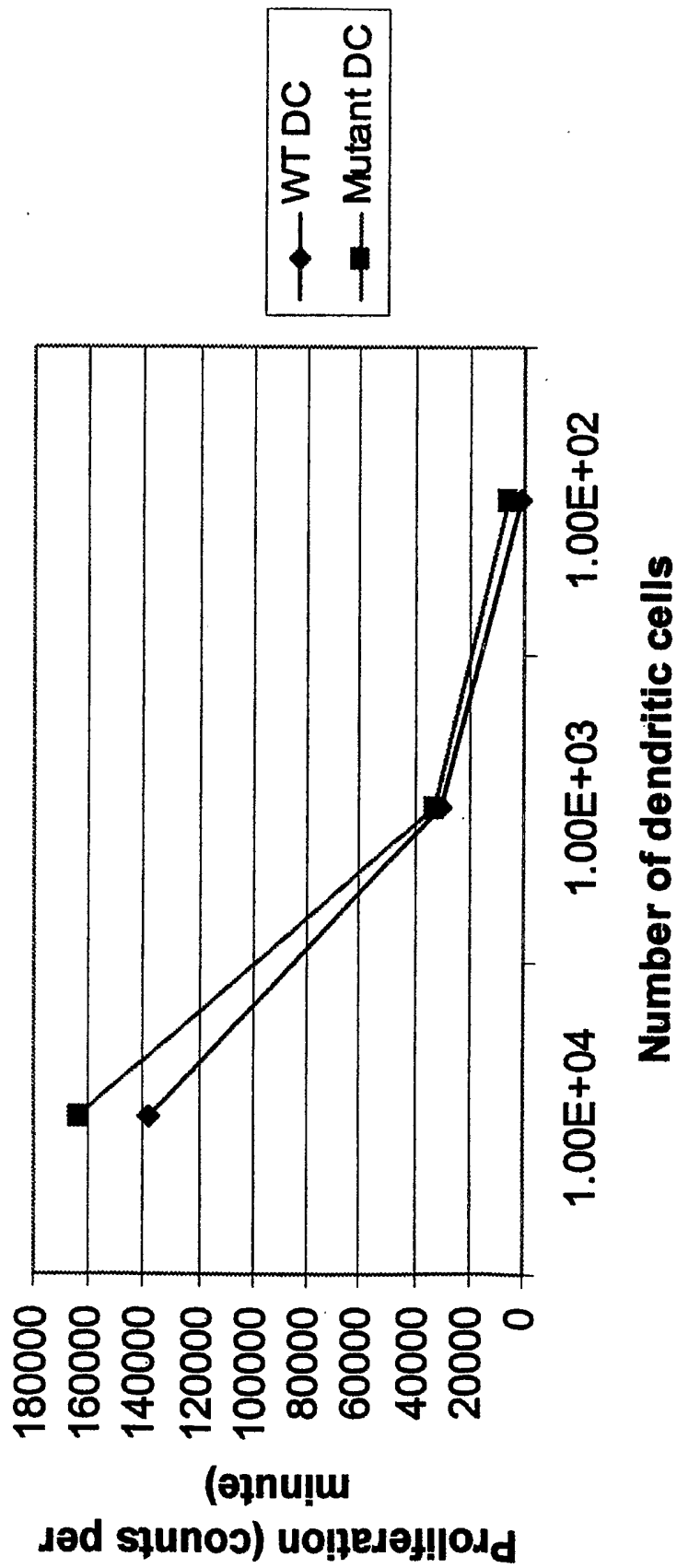


FIG. 6A

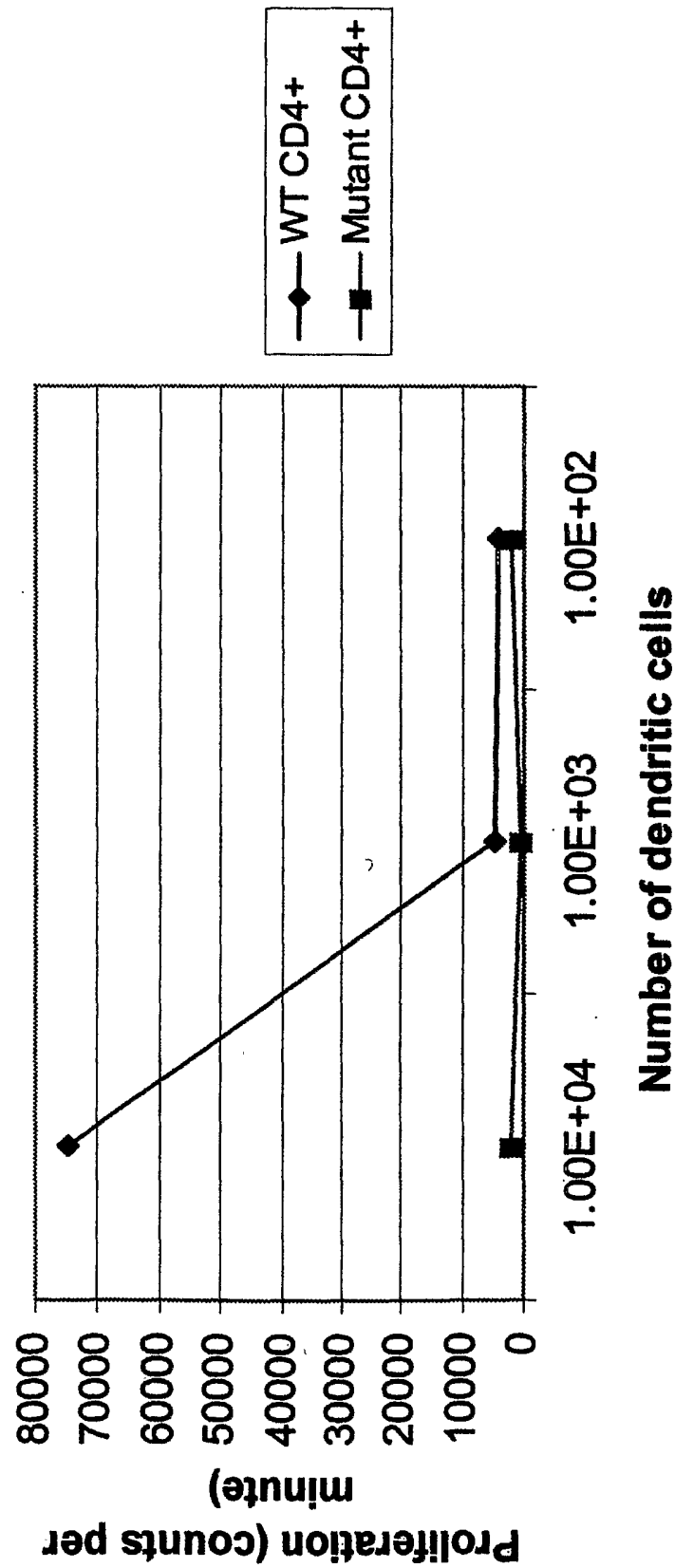


FIG. 6B

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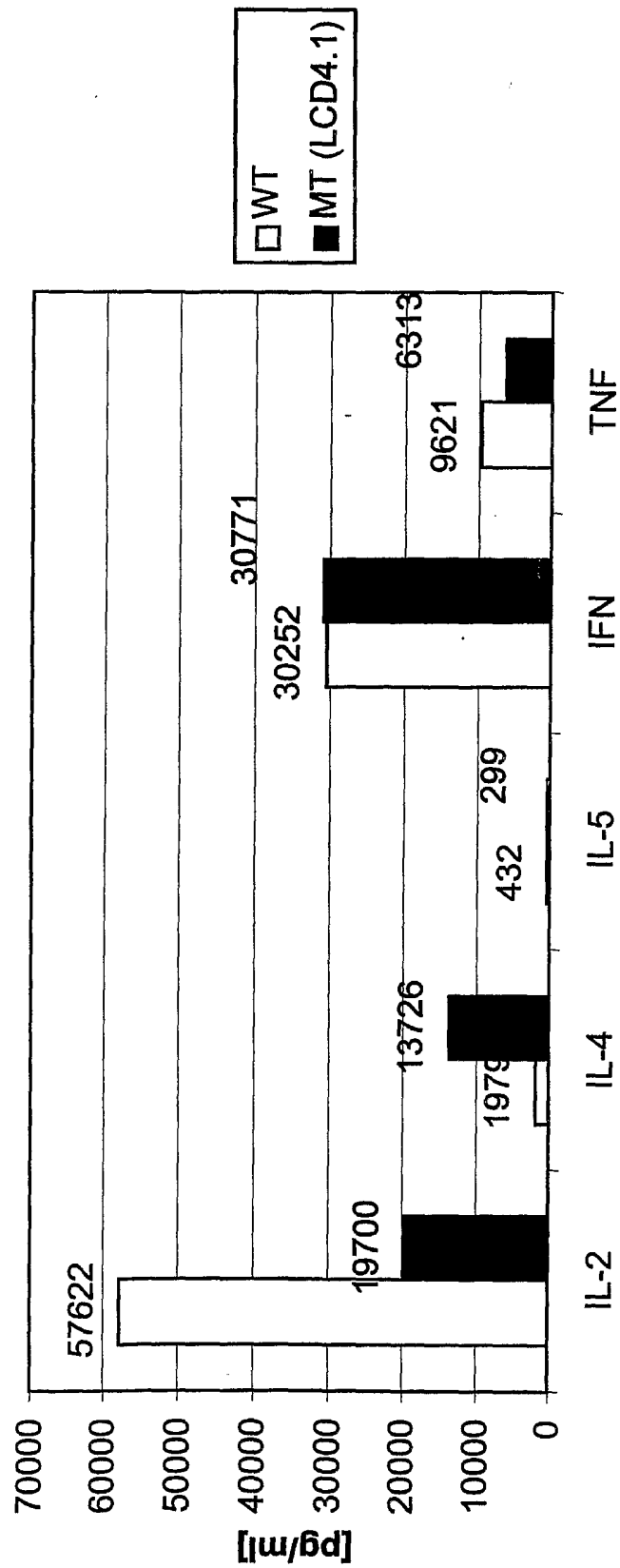


FIG. 7

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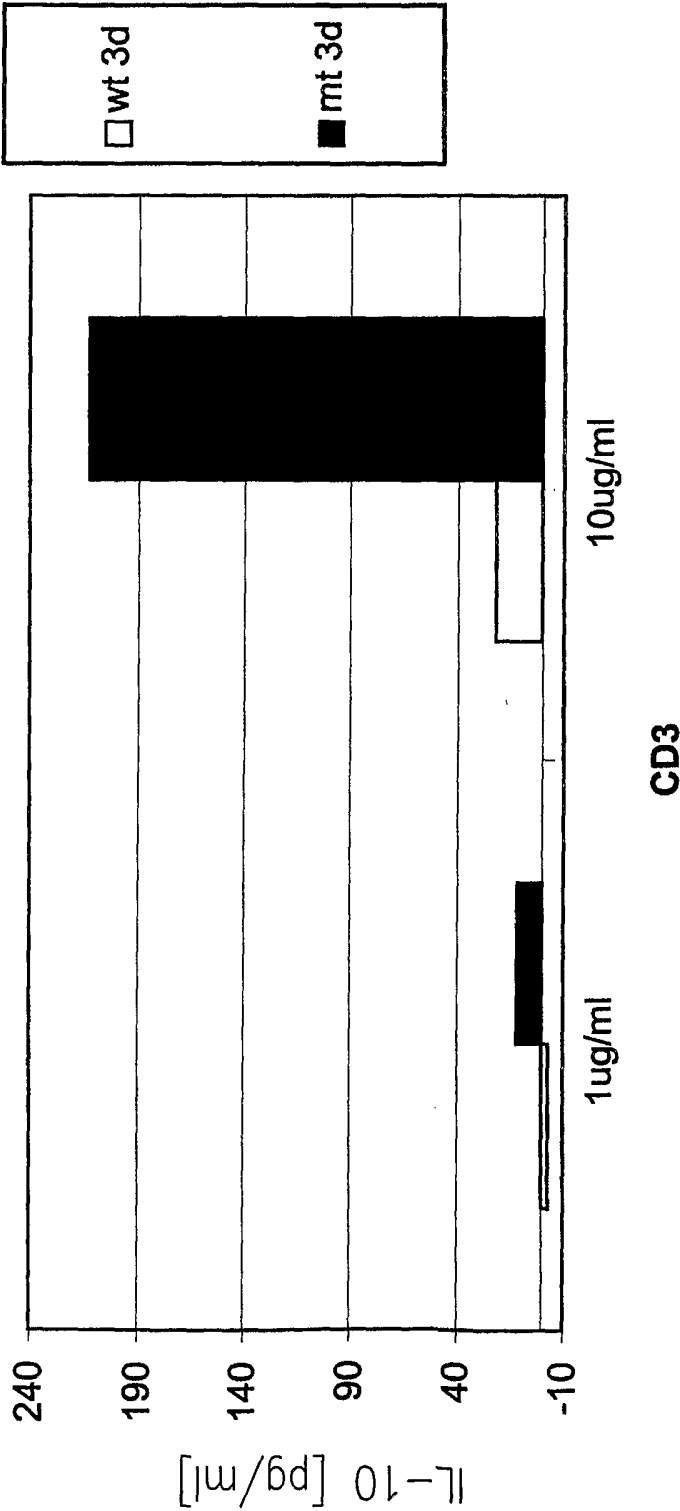


FIG. 8

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FIG. 9

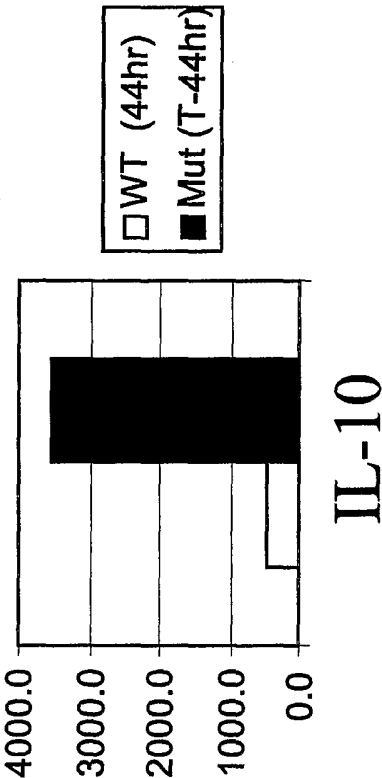


FIG. 10B

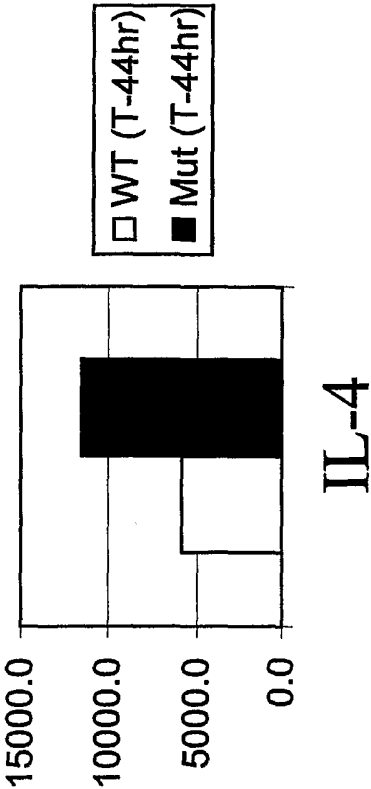


FIG. 10A

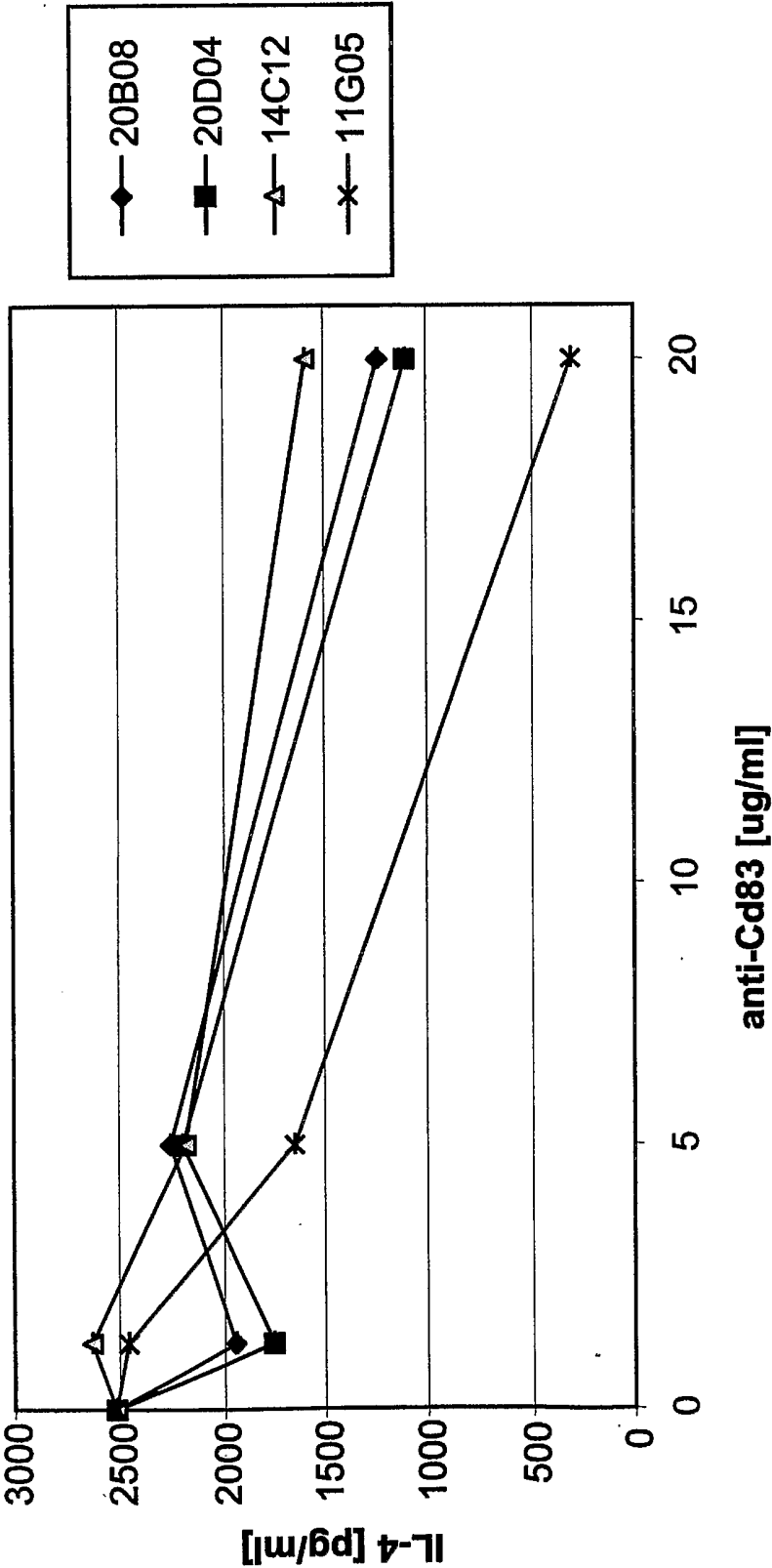


FIG. 11

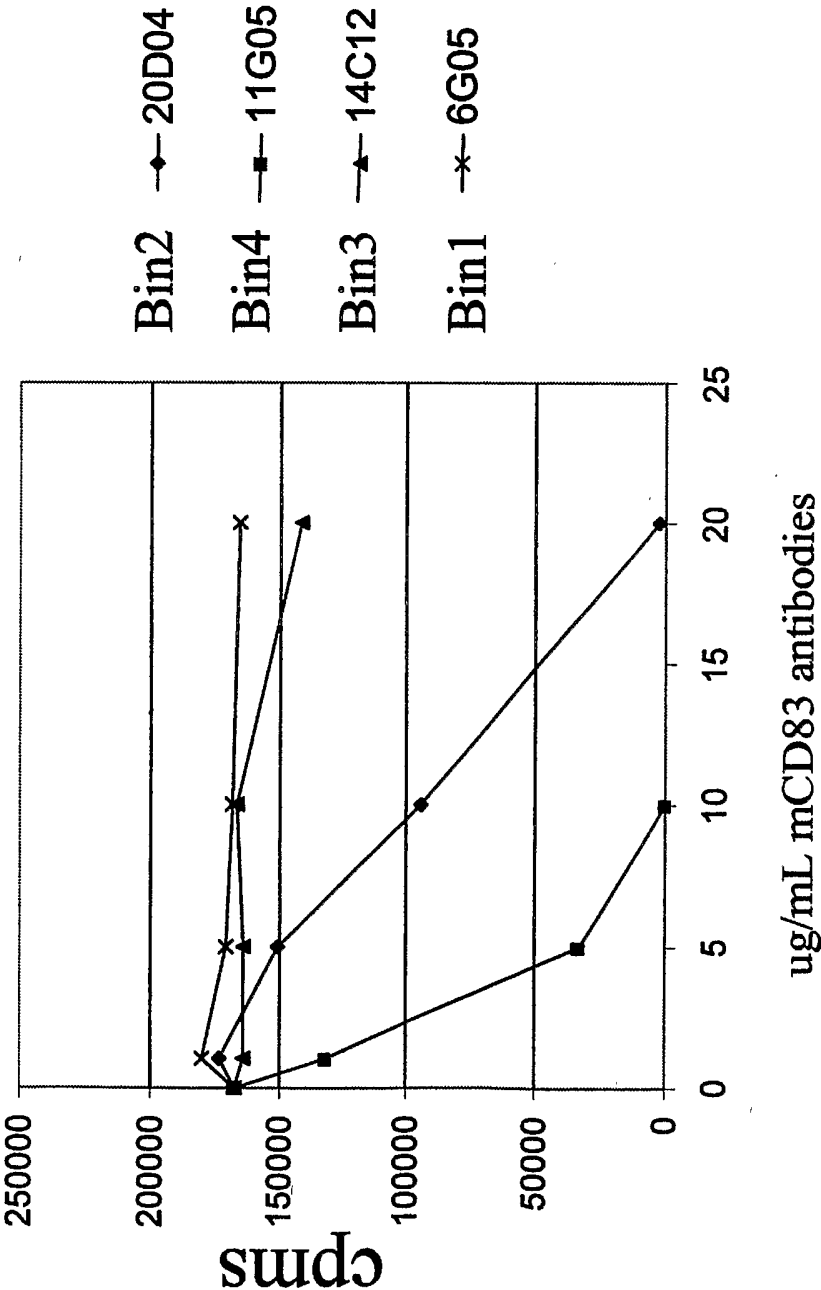


FIG. 12

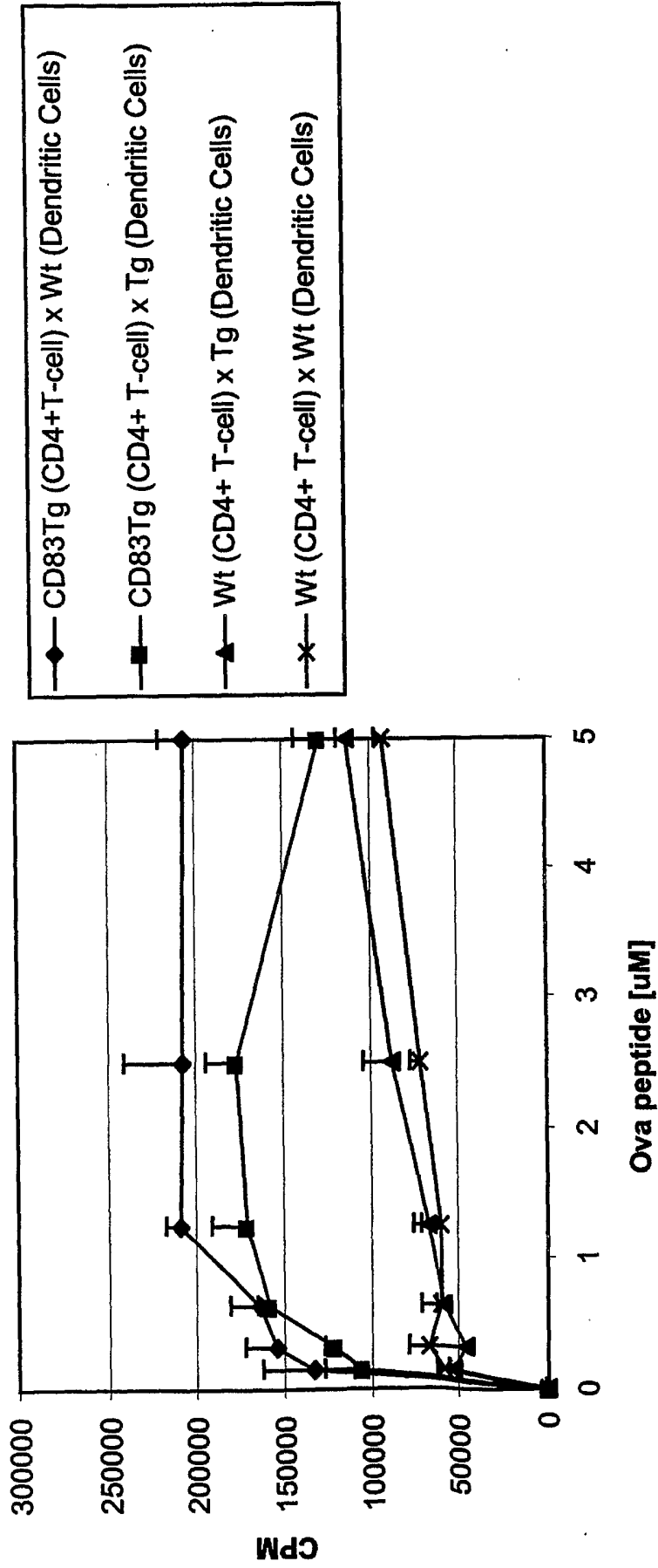


FIG. 13

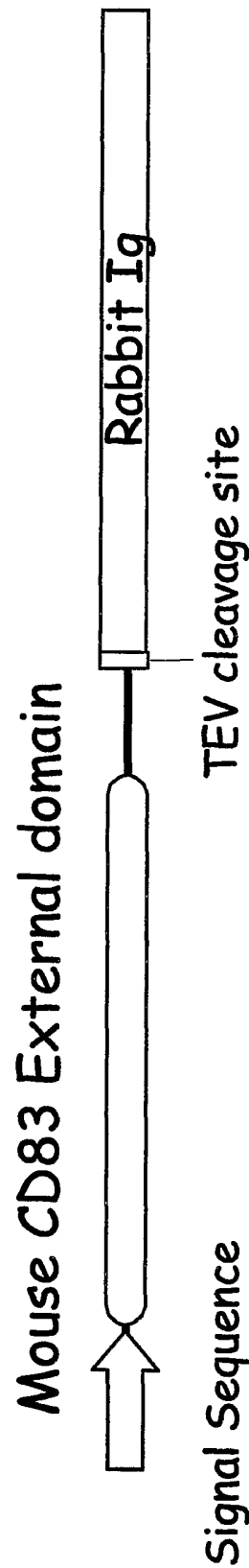


FIG. 14

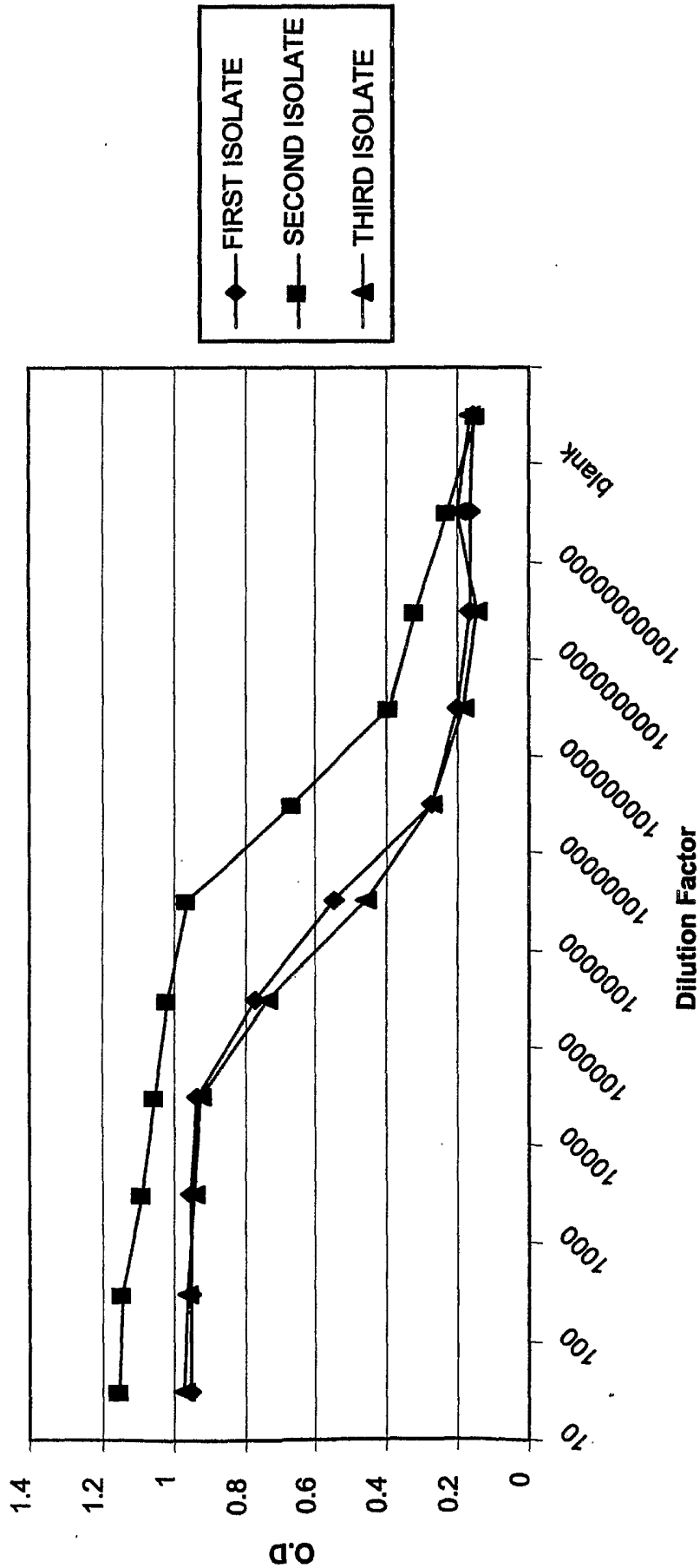


FIG. 15

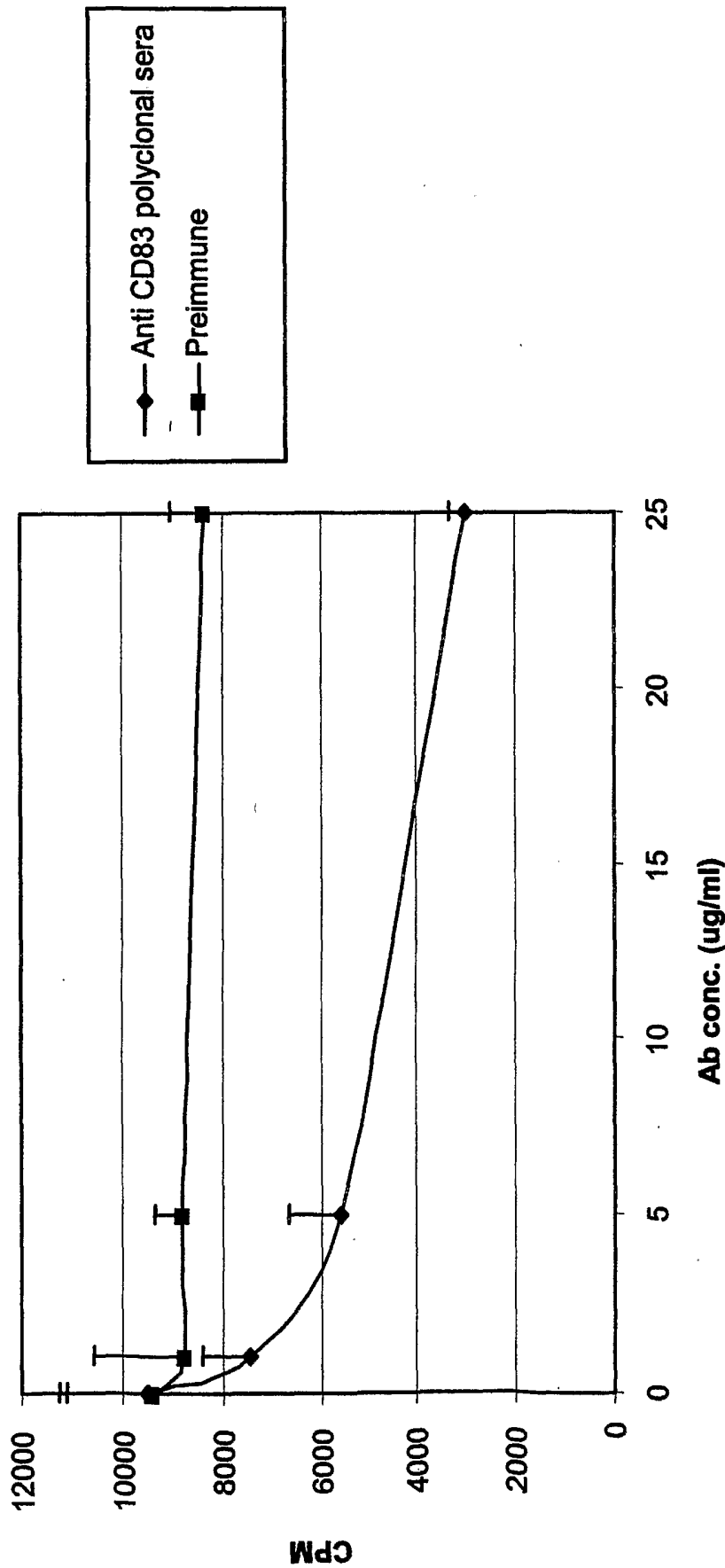


FIG. 16

	CDR1	CDR2
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6G05H	METGLRWLLLVAVLKGVCQCQSVESGGRLVSPGTPLTLTCTASGFSLSYD	MSWVRQAPGKLEYIGIISSS-
20D04H	METGLRWLLLVAVLKGVCQCQSVESGGRLVTPGTPLTLTCTVSGFSLSSYD	MSWVRQAPGKLEWIGIITYAS-
11G05	METGLRWLLLVAVLKGVCQCQSVESGGRLVTPGTPLTLTCTVSGFTISDYD	LSWVRQAPGEGIKYIGFIAID-
14C12	METGLRWLLLVAVLKGVHCQSVESGGRLVTPGTPLTLTCTASGFSRSYD	MSWVRQAPGKLEWVGVIESTA-
	CDR3	
20B08H	GSTYYASWAKGRFTISKSTTTVDLEVTSLTTEDTATYFCSREHAGYSGDTGHL	WGPGTLTVTVSSGQPKAPSVF
6G05H	GTTYANWAKGRFTISKSTTTVDLKVTSPTIGDTATYFCAREGAGVSMT---	LWPGTLTVTVSSGQPKAPSVF
20D04H	GSTYYASWAKGRVAISKSTTTVDLKITSPPTEDTATYFCAREDAGFSNA---	LWPGTLTVTVSSGQPKAPSVF
11G05	GNPYYATWAKGRFTISKSTTTVDLKITAPTTEDTATYFCARGAGD-----	LWPGTLTVTVSSGQPKAPSVF
14C12	YNSHYASWAKGRFTISRTSTTTVDLKMTSLTTEDTATYFCARGGSWLD-----	LWQGTLTVTVSSGQPKAPSVF
20B08H	PLAPCCGDTTPSS	
6G05H	PLAPCCGDTTPSS	
20D04H	PLAPCCGDTTPSS	
11G05	PLAPCCGDTTPSS	
14C12	PLAPCCGDTTPSS	

FIG. 17A

FIG. 17B

SEQUENCE LISTING

<110> Appleby, MW
5 Proll, S
Paeper, B
Staehling-Hampton, K

<120> MANIPULATION OF CYTOKINE LEVELS USING CD83 GENE PRODUCTS

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<150> US 60/331,958
<151> 2001-11-21

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Ala Asp Leu Pro Cys Thr Ala Pro Trp Asp Pro Gln Leu Ser Tyr Ala
           35           40           45
30Val Ser Trp Ala Lys Val Ser Glu Ser Gly Thr Glu Ser Val Glu Leu
           50           55           60
Pro Glu Ser Lys Gln Asn Ser Ser Phe Glu Ala Pro Arg Arg Arg Ala
           65           70           75           80
Tyr Ser Leu Thr Ile Gln Asn Thr Thr Ile Cys Ser Ser Gly Thr Tyr
35           85           90           95
Arg Cys Ala Leu Gln Glu Leu Gly Gly Gln Arg Asn Leu Ser Gly Thr
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Val Val Leu Lys Val Thr Gly Cys Pro Lys Glu Ala Thr Glu Ser Thr
           115          120          125
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15<223> Mutant CD83 sequence

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	caggagaagg	gcctattccc	tgacgatcca	aaacactacc	atctgcagct	cgggcacctc	300
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35	cagcccagat	gtctcacatc	tggcggaaat	tgacaggcca	agctgtgagc	cagtgggaaa	1080
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	catagaaatg	agaggtcagt	gaactattcc	ccagcagggc	cttttcatct	ggaaaagaca	1200
	tccacaaaag	cagcaataca	gagggatgcc	acatttattt	ttttaatctt	catgtacttg	1260
	tcaaagaaga	atttttcatg	ttttttcaaa	gaagtgtggt	tctttccttt	tttaaaatat	1320
40	gaaggtctag	ttacatagca	ttgctagctg	acaagcagcc	tgagagaaga	tggagaatgt	1380
	tcctcaaaat	agggacagca	agctagaagc	actgtacagt	gccctgctgg	gaagggcaga	1440
	caatggactg	agaaaccaga	agtctggcca	caagattgtc	tgtatgattc	tggacgaatc	1500

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acttgtggtt ttcactctct ggtagtaaa ccagatagtt tagtctgggt tgaatacaat 1560
ggatgtgaag ttgcttgagg aaagctgaat gtagtgaata cattggcaac tctactgggc 1620
tgttaccttg ttgatatcct agagttcttg agctgagcga atgcctgtca tatctcagct 1680
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tcccaaagag attttgtccc actaatggtg tgcccatcac ccacactatg aaagtaaaag 1980
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<210> 4

<211> 251

<212> PRT

15<213> Artificial Sequence

<220>

<223> Mutant CD83 sequence

20<400> 4

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Met Ser Gln Gly Leu Gln Leu Leu Phe Leu Gly Cys Ala Cys Ser Leu
  1             5             10             15
Ala Pro Ala Met Ala Met Arg Glu Val Thr Val Ala Cys Ser Glu Thr
      20             25             30
25Ala Asp Leu Pro Cys Thr Ala Pro Trp Asp Pro Gln Leu Ser Tyr Ala
      35             40             45
Val Ser Trp Ala Lys Val Ser Glu Ser Gly Thr Glu Ser Val Glu Leu
      50             55             60
Pro Glu Ser Lys Gln Asn Ser Ser Phe Glu Ala Pro Arg Arg Arg Ala
3065             70             75             80
Tyr Ser Leu Thr Ile Gln Asn Thr Thr Ile Cys Ser Ser Gly Thr Tyr
      85             90             95
Arg Cys Ala Leu Gln Glu Leu Gly Gly Gln Arg Asn Leu Ser Gly Thr
      100            105            110
35Val Val Leu Lys Val Thr Gly Cys Pro Lys Glu Ala Thr Glu Ser Thr
      115            120            125
Phe Arg Lys Tyr Arg Ala Glu Ala Val Leu Leu Phe Ser Leu Val Val
      130            135            140
Phe Tyr Leu Thr Leu Ile Ile Phe Thr Cys Lys Phe Ala Arg Leu Gln
40145            150            155            160
Ser Ile Phe Pro Asp Ile Ser Lys Pro Gly Thr Glu Gln Ala Phe Leu
      165            170            175

```

5

Pro Val Thr Ser Pro Ser Lys His Leu Gly Pro Val Thr Leu Pro Lys
 180 185 190
 Thr Glu Thr Val Arg Val Gly Ser Pro Leu Val Phe Thr Lys Pro Arg
 195 200 205
 5Ala His Gln Ile Ser Val Pro Glu Cys His Pro Asp Lys Arg Arg Met
 210 215 220
 Ser Ser Ile Leu Arg Trp Gln Pro Phe Phe Glu Val Leu His Leu Thr
 225 230 235 240
 Val Gly Ser Thr Leu Leu Pro Asp Thr Gly Ser
 10 245 250

<210> 5

<211> 756

<212> DNA

15<213> Artificial Sequence

<220>

<223> Mutant CD83 sequence

20<400> 5

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 tgggacccgc agctctccta tgcagtgtcc tgggccaagg tctccgagag tggcactgag 180
 agtgtggagc tcccggagag caagcaaaac agtccttcg agggccccag gagaagggcc 240
 25tattccctga cgatccaaaa cactaccatc tgcagctcgg gcacctacag gtgtgcctg 300
 caggagctcg gagggcagcg caacttgagc ggcaccgtgg ttctgaagggt gacaggatgc 360
 cccaaggaag ctacagagtc aactttcagg aagtacaggg cagaagctgt gttgctcttc 420
 tctctggttg ttttctacct gacactcatc attttcacct gcaaatttgc acgactacaa 480
 agcattttcc cagatatttc taaacctggg acggaacaag cttttcttcc agtcacctcc 540
 30ccaagcaaac atttggggcc agtgaccctt cctaagacag aaacggtaag agtaggatct 600
 ccactggttt ttacaaagcc aagggcacat cagatcagtg tgctgaatg ccacccggac 660
 aagagaagaa tgagctccat cctcagatgg caacctttct ttgaagtcct tcacctgaca 720
 gtgggctcca cactactccc tgacacaggg tcttga 756

35<210> 6

<400> 6

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40<210> 7

<211> 168

<212> DNA

<213> Artificial Sequence

<220>

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5

<400> 7

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tgccaccccg acaagagaag aatgagctcc atcctcagat ggcaaccttt ctttgaagtc      120
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10

<210> 8

<211> 55

<212> PRT

<213> Artificial Sequence

15

<220>

<223> Mutant CD83 sequence

<400> 8

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20Arg Val Gly Ser Pro Leu Val Phe Thr Lys Pro Arg Ala His Gln Ile
   1             5             10             15
Ser Val Pro Glu Cys His Pro Asp Lys Arg Arg Met Ser Ser Ile Leu
           20           25           30
Arg Trp Gln Pro Phe Phe Glu Val Leu His Leu Thr Val Gly Ser Thr
25           35           40           45
Leu Leu Pro Asp Thr Gly Ser
   50           55

```

<210> 9

30<211> 205

<212> PRT

<213> Homo sapiens

<400> 9

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35Met Ser Arg Gly Leu Gln Leu Leu Leu Leu Ser Cys Ala Tyr Ser Leu
   1             5             10             15
Ala Pro Ala Thr Pro Glu Val Lys Val Ala Cys Ser Glu Asp Val Asp
           20           25           30
Leu Pro Cys Thr Ala Pro Trp Asp Pro Gln Val Pro Tyr Thr Val Ser
40           35           40           45
Trp Val Lys Leu Leu Glu Gly Gly Glu Glu Arg Met Glu Thr Pro Gln
   50           55           60

```

Glu Asp His Leu Arg Gly Gln His Tyr His Gln Lys Gly Gln Asn Gly
 65 70 75 80
 Ser Phe Asp Ala Pro Asn Glu Arg Pro Tyr Ser Leu Lys Ile Arg Asn
 85 90 95
 5Thr Thr Ser Cys Asn Ser Gly Thr Tyr Arg Cys Thr Leu Gln Asp Pro
 100 105 110
 Asp Gly Gln Arg Asn Leu Ser Gly Lys Val Ile Leu Arg Val Thr Gly
 115 120 125
 Cys Pro Ala Gln Arg Lys Glu Glu Thr Phe Lys Lys Tyr Arg Ala Glu
 10 130 135 140
 Ile Val Leu Leu Leu Ala Leu Val Ile Phe Tyr Leu Thr Leu Ile Ile
 145 150 155 160
 Phe Thr Cys Lys Phe Ala Arg Leu Gln Ser Ile Phe Pro Asp Phe Ser
 165 170 175
 15Lys Ala Gly Met Glu Arg Ala Phe Leu Pro Val Thr Ser Pro Asn Lys
 180 185 190
 His Leu Gly Leu Val Thr Pro His Lys Thr Glu Leu Val
 195 200 205

20<210> 10

<211> 2574

<212> DNA

<213> Homo sapiens

25<400> 10

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 gcgaaggggg cggggacggg ggcgcccgcc ggcctaacgg gattaggagg gcgcgccacc 180
 cgcttccgct gcccgccggg gaatcccccg ggtggcgccc agggaagtgc ccgaacgggc 240
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 ctcccgcgac gccggaggtg aagggtggtt gctccgaaga tgtggacttg ccctgcaccg 420
 ccccttgga tccgcaggtt ccctacacgg tctcctgggt caagttattg gaggggtggtg 480
 aagagaggat ggagacaccc caggaagacc acctcagggg acagcactat catcagaagg 540
 35ggcaaatgg ttctttcgac gcccccaatg aaaggcccta ttccctgaag atccgaaaca 600
 ctaccagctg caactcgggg acatacaggt gcactctgca ggacccggat gggcagagaa 660
 acctaatgg caaggtgatc ttgagagtga caggatgccc tgcacagcgt aaagaagaga 720
 cttttaagaa atacagagcg gagattgtcc tgctgctggc tctggttatt ttctacttaa 780
 cactcatcat ttctacttgt aagtttgcac ggctacagag tatcttccca gatttttcta 840
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 tgactcctca caagacagaa ctggtatgag caggatttct gcaggttctt cttcctgaag 960
 ctgaggctca ggggtgtgcc tgtctgttac actggaggag agaagaatga gcctacgctg 1020

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gcttctccat ggccaccttt tcagcgatgt atgcagctat ctgggtcaacc tcctggacat 1200
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<210> 11

<211> 239

30<212> PRT

<213> *Oryctolagus cuniculus*

<400> 11

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Leu Pro Gly Ala Arg Cys Ala Asp Val Val Met Thr Gln Thr Pro Ala
          20          25          30
Ser Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ala
          35          40          45
40Ser Glu Ser Ile Ser Asn Tyr Leu Ser Trp Tyr Gln Gln Lys Pro Gly
          50          55          60
Gln Pro Pro Lys Leu Leu Ile Tyr Arg Thr Ser Thr Leu Ala Ser Gly

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9

65		70		75		80										
Val	Ser	Ser	Arg	Phe	Lys	Gly	Ser	Gly	Ser	Gly	Thr	Glu	Tyr	Thr	Leu	
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	Thr	Ile	Ser	Gly	Val	Gln	Cys	Asp	Asp	Val	Ala	Thr	Tyr	Tyr	Cys	Gln
5		100						105						110		
	Cys	Thr	Ser	Gly	Gly	Lys	Phe	Ile	Ser	Asp	Gly	Ala	Ala	Phe	Gly	Gly
		115						120						125		
	Gly	Thr	Glu	Val	Val	Val	Lys	Gly	Asp	Pro	Val	Ala	Pro	Thr	Val	Leu
		130						135						140		
10	Leu	Phe	Pro	Pro	Ser	Ser	Asp	Glu	Val	Ala	Thr	Gly	Thr	Val	Thr	Ile
		145						150						155		160
	Val	Cys	Val	Ala	Asn	Lys	Tyr	Phe	Pro	Asp	Val	Thr	Val	Thr	Trp	Glu
				165						170					175	
	Val	Asp	Gly	Thr	Thr	Gln	Thr	Thr	Gly	Ile	Glu	Asn	Ser	Lys	Thr	Pro
15		180						185						190		
	Gln	Asn	Ser	Ala	Asp	Cys	Thr	Tyr	Asn	Leu	Ser	Ser	Thr	Leu	Thr	Leu
		195						200						205		
	Thr	Ser	Thr	Gln	Tyr	Asn	Ser	His	Lys	Glu	Tyr	Thr	Cys	Lys	Val	Thr
		210						215						220		
20	Gln	Gly	Thr	Thr	Ser	Val	Val	Gln	Ser	Phe	Ser	Arg	Lys	Asn	Cys	
		225						230						235		

<210> 12

<211> 720

25<212> DNA

<213> *Oryctolagus cuniculus*

<400> 12

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	acagtcacca	tcaattgcc	ggcagtgaa	agcattagca	actacttato	ctggtatcag	180
	cagaaaccag	ggcagcctcc	caagctcctg	atctacagga	catccactct	ggcatctggg	240
	gtctcatcgc	ggttcaaagg	cagtggatct	gggacagagt	acactctcac	catcagcggc	300
	gtgcagtgtg	acgatgttgc	cacttactac	tgtcaatgca	cttctggtgg	gaagttcatt	360
35	agtgatggtg	ctgctttcgg	cggagggacc	gaggtggtgg	tcaaaggtga	tccagttgca	420
	cctactgtcc	tcctcttccc	accatctagc	gatgaggtgg	caactggaac	agtcaccatc	480
	gtgtgtgtgg	cgaataaata	ctttcccgat	gtcaccgtca	cctgggaggt	ggatggcacc	540
	acccaaacaa	ctggcatcga	gaacagtaaa	acaccgcaga	attctgcaga	ttgtacctac	600
	aacctcagca	gcactctgac	actgaccagc	acacagtaca	acagccacaa	agagtacacc	660
40	tgcaaggtga	cccagggcac	gacctcagtc	gtccagagct	tcagtaggaa	gaactgttaa	720

<210> 13

10

<211> 454

<212> PRT

<213> *Oryctolagus cuniculus*

5<400> 13

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Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
 1             5             10             15
Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
          20             25             30
10Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser
          35             40             45
Asn Asn Ala Ile Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
 50             55             60
Trp Ile Gly Tyr Ile Trp Ser Gly Gly Leu Thr Tyr Tyr Ala Asn Trp
1565             70             75             80
Ala Glu Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
          85             90             95
Lys Met Thr Ser Pro Thr Ile Glu Asp Thr Ala Thr Tyr Phe Cys Ala
          100            105            110
20Arg Gly Ile Asn Asn Ser Ala Leu Trp Gly Pro Gly Thr Leu Val Thr
          115            120            125
Val Ser Ser Gly Gln Pro Lys Ala Pro Ser Val Phe Pro Leu Ala Pro
          130            135            140
Cys Cys Gly Asp Thr Pro Ser Ser Thr Val Thr Leu Gly Cys Leu Val
25145            150            155            160
Lys Gly Tyr Leu Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Thr
          165            170            175
Leu Thr Asn Gly Val Arg Thr Phe Pro Ser Val Arg Gln Ser Ser Gly
          180            185            190
30Leu Tyr Ser Leu Ser Ser Val Val Ser Val Thr Ser Ser Ser Gln Pro
          195            200            205
Val Thr Cys Asn Val Ala His Pro Ala Thr Asn Thr Lys Val Asp Lys
          210            215            220
Thr Val Ala Pro Ser Thr Cys Ser Lys Pro Thr Cys Pro Pro Pro Glu
35225            230            235            240
Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp
          245            250            255
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
          260            265            270
40Val Ser Gln Asp Asp Pro Glu Val Gln Phe Thr Trp Tyr Ile Asn Asn
          275            280            285
Glu Gln Val Arg Thr Ala Arg Pro Pro Leu Arg Glu Gln Gln Phe Asn

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11

290 295 300
 Ser Thr Ile Arg Val Val Ser Thr Leu Pro Ile Ala His Gln Asp Trp
 305 310 315 320
 Leu Arg Gly Lys Glu Phe Lys Cys Lys Val His Asn Lys Ala Leu Pro
 5 325 330 335
 Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Arg Gly Gln Pro Leu Glu
 340 345 350
 Pro Lys Val Tyr Thr Met Gly Pro Pro Arg Glu Glu Leu Ser Ser Arg
 355 360 365
 10 Ser Val Ser Leu Thr Cys Met Ile Asn Gly Phe Tyr Pro Ser Asp Ile
 370 375 380
 Ser Val Glu Trp Glu Lys Asn Gly Lys Ala Glu Asp Asn Tyr Lys Thr
 385 390 395 400
 Thr Pro Ala Val Leu Asp Ser Asp Gly Ser Tyr Phe Leu Tyr Asn Lys
 15 405 410 415
 Leu Ser Val Pro Thr Ser Glu Trp Gln Arg Gly Asp Val Phe Thr Cys
 420 425 430
 Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Ile
 435 440 445
 20 Ser Arg Ser Pro Gly Lys
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<210> 14

<211> 1362

25<212> DNA

<213> *Oryctolagus cuniculus*

<400> 14

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 accgtctctg gattctccct cagtaacaat gcaataaact gggtcgccca ggctccaggg 180
 aaggggctag agtggatcgg atacatttgg agtgggtgggc ttacatacta cgcgaaactgg 240
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 35 tgggggccag gcaccctggc caccgtctcc tcagggcaac ctaaggctcc atcagtcttc 420
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 aaaggctaacc tcccggagcc agtgaccgtg acctggaact cgggcaccct caccaatggg 540
 gtacgcacct tcccgccgt cccggcagtc tcaggcctct actcgtgag cagcgtggtg 600
 agcgtgacct caagcagcca gcccgtcacc tgcaacgtgg cccaccagc caccaacacc 660
 40 aaagtggaca agaccgttgc gccctcgaca tgcagcaagc ccacgtgccc accccctgaa 720
 ctctgggggg gaccgtctgt cttcatcttc cccccaaaac ccaaggacac cctcatgatc 780
 tcacgcaccc ccgaggtcac atgcgtggtg gtggacgtga gccaggatga ccccgaggtg 840

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aaaaccatct ccaaagccag agggcagccc ctggagccga aggtctacac catgggccct      1080
5ccccgggagg agctgagcag caggtcggtc agcctgacct gcatgatcaa cggcttctac     1140
ccttccgaca tctcgggtgga gtgggagaag aacgggaagg cagaggacaa ctacaagacc     1200
acgccggccg tgctggacag cgacgggtcc tacttctctt acaacaagct ctcagtgtccc     1260
acgagttagt ggcagcgggg cgacgtcttc acctgtccg tgatgcacga ggccttgac      1320
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<210> 15

<211> 238

<212> PRT

<213> *Oryctolagus cuniculus*

15

<400> 15

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Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
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Leu Pro Gly Ala Arg Cys Ala Asp Val Val Met Thr Gln Thr Pro Ala
20              20              25              30
Ser Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ser
      35              40              45
Ser Lys Asn Val Tyr Asn Asn Asn Trp Leu Ser Trp Phe Gln Gln Lys
      50              55              60
25Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Tyr Ala Ser Thr Leu Ala
      65              70              75              80
Ser Gly Val Pro Ser Arg Phe Arg Gly Ser Gly Ser Gly Thr Gln Phe
      85              90              95
Thr Leu Thr Ile Ser Asp Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr
30              100              105              110
Cys Ala Gly Asp Tyr Ser Ser Ser Ser Asp Asn Gly Phe Gly Gly Gly
      115              120              125
Thr Glu Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu Leu
      130              135              140
35Phe Pro Pro Ser Ser Asp Glu Val Ala Thr Gly Thr Val Thr Ile Val
      145              150              155              160
Cys Val Ala Asn Lys Tyr Phe Pro Asp Val Thr Val Thr Trp Glu Val
      165              170              175
Asp Gly Thr Thr Gln Thr Thr Gly Ile Glu Asn Ser Lys Thr Pro Gln
40              180              185              190
Asn Ser Ala Asp Cys Thr Tyr Asn Leu Ser Ser Thr Leu Thr Leu Thr
      195              200              205

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13

Ser Thr Gln Tyr Asn Ser His Lys Glu Tyr Thr Cys Lys Val Thr Gln
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 Gly Thr Thr Ser Val Val Gln Ser Phe Ser Arg Lys Asn Cys
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<210> 16
 <211> 717
 <212> DNA
 <213> *Oryctolagus cuniculus*

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<400> 16
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 agtgataatg gtttcggcgg agggaccgag gtggtgggtca aaggtgatcc agttgcacct 420
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 20tgtgtggcga ataaatactt tcccgatgtc accgtcacct gggaggtgga tggcaccacc 540
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 ctccagcagca ctctgacact gaccagcaca cagtacaaca gccacaaaga gtacacctgc 660
 aaggtgaccc agggcacgac ctcagtcgtc cagagcttca gtaggaagaa ctgttaa 717

25<210> 17

<211> 452
 <212> PRT
 <213> *Oryctolagus cuniculus*

30<400> 17

Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
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 Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
 20 25 30
 35Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Thr Ile Ser
 35 40 45
 Asp Tyr Asp Leu Ser Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Lys
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 Tyr Ile Gly Phe Ile Ala Ile Asp Gly Asn Pro Tyr Tyr Ala Thr Trp
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 Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
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14

Lys Ile Thr Ala Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
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 Gly Asp Thr Pro Ser Ser Thr Val Thr Leu Gly Cys Leu Val Lys Gly
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 Tyr Leu Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Thr Leu Thr
 10 165 170 175
 Asn Gly Val Arg Thr Phe Pro Ser Val Arg Gln Ser Ser Gly Leu Tyr
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 Ser Leu Ser Ser Val Val Ser Val Thr Ser Ser Ser Gln Pro Val Thr
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 15Cys Asn Val Ala His Pro Ala Thr Asn Thr Lys Val Asp Lys Thr Val
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 Ala Pro Ser Thr Cys Ser Lys Pro Thr Cys Pro Pro Pro Glu Leu Leu
 225 230 235 240
 Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Thr Leu
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 Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
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 Gln Asp Asp Pro Glu Val Gln Phe Thr Trp Tyr Ile Asn Asn Glu Gln
 275 280 285
 25Val Arg Thr Ala Arg Pro Pro Leu Arg Glu Gln Gln Phe Asn Ser Thr
 290 295 300
 Ile Arg Val Val Ser Thr Leu Pro Ile Ala His Gln Asp Trp Leu Arg
 305 310 315 320
 Gly Lys Glu Phe Lys Cys Lys Val His Asn Lys Ala Leu Pro Ala Pro
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 Ile Glu Lys Thr Ile Ser Lys Ala Arg Gly Gln Pro Leu Glu Pro Lys
 340 345 350
 Val Tyr Thr Met Gly Pro Pro Arg Glu Glu Leu Ser Ser Arg Ser Val
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 35Ser Leu Thr Cys Met Ile Asn Gly Phe Tyr Pro Ser Asp Ile Ser Val
 370 375 380
 Glu Trp Glu Lys Asn Gly Lys Ala Glu Asp Asn Tyr Lys Thr Thr Pro
 385 390 395 400
 Ala Val Leu Asp Ser Asp Gly Ser Tyr Phe Leu Tyr Asn Lys Leu Ser
 40 405 410 415
 Val Pro Thr Ser Glu Trp Gln Arg Gly Asp Val Phe Thr Cys Ser Val
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Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Ile Ser Arg

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Ser Pro Gly Lys

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<213> *Oryctolagus cuniculus*

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gagtggcagc	ggggcgacgt	cttcacctgc	tccgtgatgc	acgaggcctt	gcacaaccac	1320
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<211> 238

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<213> *Oryctolagus cuniculus*

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Gln Ser Val Tyr Asp Asn Asp Glu Leu Ser Trp Tyr Gln Gln Lys Pro
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Gly Gln Pro Pro Lys Leu Leu Ile Tyr Leu Ala Ser Lys Leu Ala Ser
65      70          75          80
15Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Ala
      85          90          95
Leu Thr Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
      100          105          110
Gln Ala Thr His Tyr Ser Ser Asp Trp Tyr Leu Thr Phe Gly Gly Gly
20      115          120          125
Thr Glu Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu Leu
      130          135          140
Phe Pro Pro Ser Ser Asp Glu Val Ala Thr Gly Thr Val Thr Ile Val
145      150          155          160
25Cys Val Ala Asn Lys Tyr Phe Pro Asp Val Thr Val Thr Trp Glu Val
      165          170          175
Asp Gly Thr Thr Gln Thr Thr Gly Ile Glu Asn Ser Lys Thr Pro Gln
      180          185          190
Asn Ser Ala Asp Cys Thr Tyr Asn Leu Ser Ser Thr Leu Thr Leu Thr
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ggggtcccat cccgattcaa aggcaagtga tctgggacac agttcgctct caccatcagc      300
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tggtatctta ctttcggcgg agggaccgag gtggtggtca aaggatgatcc agttgcacct      420
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tgtgtggcga ataaatactt tcccgatgtc accgtcacct gggagggtgga tggcaccacc      540
caaacaactg gcatcgagaa cagtaaaaca ccgcagaatt ctgcagattg tacctacaac      600
10ctcagcagca ctctgacact gaccagcaca cagtacaaca gccacaaaga gtacacctgc      660
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          20          25          30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Arg Ser
          35          40          45
25Ser Tyr Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
          50          55          60
Trp Val Gly Val Ile Ser Thr Ala Tyr Asn Ser His Tyr Ala Ser Trp
65          70          75          80
Ala Lys Gly Arg Phe Thr Ile Ser Arg Thr Ser Thr Thr Val Asp Leu
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Lys Met Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
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Arg Gly Gly Ser Trp Leu Asp Leu Trp Gly Gln Gly Thr Leu Val Thr
          115          120          125
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Cys Cys Gly Asp Thr Pro Ser Ser Thr Val Thr Leu Gly Cys Leu Val
145          150          155          160
Lys Gly Tyr Leu Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Thr
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Leu Thr Asn Gly Val Arg Thr Phe Pro Ser Val Arg Gln Ser Ser Gly
          180          185          190

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18

Leu Tyr Ser Leu Ser Ser Val Val Ser Val Thr Ser Ser Ser Gln Pro
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 Val Thr Cys Asn Val Ala His Pro Ala Thr Asn Thr Lys Val Asp Lys
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 5Thr Val Ala Pro Ser Thr Cys Ser Lys Pro Thr Cys Pro Pro Pro Glu
 225 230 235 240
 Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp
 245 250 255
 Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
 10 260 265 270
 Val Ser Gln Asp Asp Pro Glu Val Gln Phe Thr Trp Tyr Ile Asn Asn
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 Glu Gln Val Arg Thr Ala Arg Pro Pro Leu Arg Glu Gln Gln Phe Asn
 290 295 300
 15Ser Thr Ile Arg Val Val Ser Thr Leu Pro Ile Ala His Gln Asp Trp
 305 310 315 320
 Leu Arg Gly Lys Glu Phe Lys Cys Lys Val His Asn Lys Ala Leu Pro
 325 330 335
 Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Arg Gly Gln Pro Leu Glu
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 Pro Lys Val Tyr Thr Met Gly Pro Pro Arg Glu Glu Leu Ser Ser Arg
 355 360 365
 Ser Val Ser Leu Thr Cys Met Ile Asn Gly Phe Tyr Pro Ser Asp Ile
 370 375 380
 25Ser Val Glu Trp Glu Lys Asn Gly Lys Ala Glu Asp Asn Tyr Lys Thr
 385 390 395 400
 Thr Pro Ala Val Leu Asp Ser Asp Gly Ser Tyr Phe Leu Tyr Asn Lys
 405 410 415
 Leu Ser Val Pro Thr Ser Glu Trp Gln Arg Gly Asp Val Phe Thr Cys
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Gly Gly Gly Ala Cys Ala Cys Cys Cys Cys Thr Gly Ala Cys Ala Cys			
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Thr Cys Ala Cys Cys Thr Gly Cys Ala Cys Ala Gly Cys Cys Thr Cys			
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Thr Gly Gly Ala Thr Thr Cys Thr Cys Cys Cys Gly Cys Ala Gly Cys			
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Ala Gly Cys Thr Ala Cys Gly Ala Cys Ala Thr Gly Ala Gly Cys Thr			
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20Gly Gly Gly Thr Cys Cys Gly Cys Cys Ala Gly Gly Cys Thr Cys Cys			
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Ala Gly Gly Gly Ala Ala Gly Gly Gly Gly Cys Thr Gly Gly Ala Ala			
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Thr Gly Gly Gly Thr Cys Gly Gly Ala Gly Thr Cys Ala Thr Thr Ala			
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Gly Thr Ala Cys Thr Gly Cys Thr Thr Ala Thr Ala Ala Cys Thr Cys			
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Cys Cys Ala Thr Cys Thr Cys Cys Ala Gly Ala Ala Cys Cys Thr Cys			
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Gly Ala Cys Cys Ala Cys Gly Gly Thr Gly Gly Ala Thr Cys Thr Gly			
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Cys Ala Ala Cys Cys Gly Ala Ala Gly Ala Cys Ala Cys Gly Gly Cys			
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20

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	Cys	Thr	Gly	Gly	Ala	Ala	Cys	Thr	Cys	Gly	Gly	Gly	Cys	Ala	Cys	Cys			
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	Thr Cys Ala Gly Cys Ala Cys Cys Cys Thr Cys Cys Cys Cys Ala Thr				
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	Thr Gly Gly Gly Cys Cys Cys Thr Cys Cys Cys Cys Gly Gly Gly Ala					
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10<210> 47

<211> 11

<212> PRT

<213> Oryctolagus cuniculus

15<400> 47

Ala Gly Asp Tyr Ser Ser Ser Ser Asp Asn Gly

1

5

10

<210> 48

20<211> 12

<212> PRT

<213> Oryctolagus cuniculus

<400> 48

25Gln Ala Thr His Tyr Ser Ser Asp Trp Leu Thr Tyr

1

5

10

<210> 49

<211> 5

30<212> RNA

<213> Artificial Sequence

<220>

<223> AU-rich sequence

35

<400> 49

auuua

5

<210> 50

40<211> 6

<212> RNA

<213> Artificial Sequence

<220>

<223> AU-rich sequence

<400> 50

5auuuuua

6

<210> 51

<211> 7

<212> RNA

10<213> Artificial Sequence

<220>

<223> AU-rich sequence

15<400> 51

auuuuua

7

<210> 52

<211> 157

20<212> PRT

<213> Oryctolagus cuniculus

<400> 52

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

30

145

150

155

<210> 53

<211> 154

5<212> PRT

<213> *Oryctolagus cuniculus*

<400> 53

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Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
10 1          5          10          15
Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Ser Pro
          20          25          30
Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Leu Ser
          35          40          45
15Ser Tyr Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
          50          55          60
Tyr Ile Gly Ile Ile Ser Ser Ser Gly Thr Thr Tyr Tyr Ala Asn Trp
65          70          75          80
Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
20          85          90          95
Lys Val Thr Ser Pro Thr Ile Gly Asp Thr Ala Thr Tyr Phe Cys Ala
          100          105          110
Arg Glu Gly Ala Gly Val Ser Met Thr Leu Trp Gly Pro Gly Thr Leu
          115          120          125
25Val Thr Val Ser Ser Gly Gln Pro Lys Ala Pro Ser Val Phe Pro Leu
          130          135          140
Ala Pro Cys Cys Gly Asp Thr Pro Ser Ser
145          150

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30<210> 54

<211> 154

<212> PRT

<213> *Oryctolagus cuniculus*

35<400> 54

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Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
1          5          10          15
Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
          20          25          30
40Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser
          35          40          45
Ser Tyr Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu

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31

50 55 60
 Trp Ile Gly Ile Ile Tyr Ala Ser Gly Ser Thr Tyr Tyr Ala Ser Trp
 65 70 75 80
 Ala Lys Gly Arg Val Ala Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
 5 85 90 95
 Lys Ile Thr Ser Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
 100 105 110
 Arg Glu Asp Ala Gly Phe Ser Asn Ala Leu Trp Gly Pro Gly Thr Leu
 115 120 125
 10Val Thr Val Ser Ser Gly Gln Pro Lys Ala Pro Ser Val Phe Pro Leu
 130 135 140
 Ala Pro Cys Cys Gly Asp Thr Pro Ser Ser
 145 150

15<210> 55
 <211> 147
 <212> PRT
 <213> *Oryctolagus cuniculus*

20<400> 55
 Met Asp Met Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1 5 10 15
 Leu Pro Gly Ala Arg Cys Ala Tyr Asp Met Thr Gln Thr Pro Ala Ser
 20 25 30
 25Val Glu Val Ala Val Gly Gly Thr Val Thr Ile Lys Cys Gln Ala Ser
 35 40 45
 Gln Ser Ile Ser Thr Tyr Leu Asp Trp Tyr Gln Gln Lys Pro Gly Gln
 50 55 60
 Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asp Leu Ala Ser Gly Val
 3065 70 75 80
 Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Thr Leu Thr
 85 90 95
 Ile Ser Asp Leu Glu Cys Ala Asp Ala Ala Thr Tyr Tyr Cys Gln Gln
 100 105 110
 35Gly Tyr Thr His Ser Asn Val Asp Asn Val Phe Gly Gly Gly Thr Glu
 115 120 125
 Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu Leu Phe Pro
 130 135 140
 Pro Ser Ser
 40145

<210> 56

<211> 147

<212> PRT

<213> Oryctolagus cuniculus

5<400> 56

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Met Asp Met Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1           5           10           15
Leu Pro Gly Ala Arg Cys Ala Tyr Asp Met Thr Gln Thr Pro Ala Ser
      20           25           30
10Val Glu Val Ala Val Gly Gly Thr Val Ala Ile Lys Cys Gln Ala Ser
      35           40           45
Gln Ser Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
 50           55           60
Pro Pro Lys Pro Leu Ile Tyr Glu Ala Ser Met Leu Ala Ala Gly Val
1565           70           75           80
Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
      85           90           95
Ile Ser Asp Leu Glu Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Gln Gln
      100          105          110
20Gly Tyr Ser Ile Ser Asp Ile Asp Asn Ala Phe Gly Gly Gly Thr Glu
      115          120          125
Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu Leu Phe Pro
      130          135          140
Pro Ser Ser
25145

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<210> 57

<211> 150

<212> PRT

30<213> Oryctolagus cuniculus

<400> 57

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

```

33

Val Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Glu Tyr Thr Leu
 85 90 95
 Thr Ile Ser Gly Val Gln Cys Asp Asp Val Ala Thr Tyr Tyr Cys Gln
 100 105 110
 5Cys Thr Ser Gly Gly Lys Phe Ile Ser Asp Gly Ala Ala Phe Gly Gly
 115 120 125
 Gly Thr Glu Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu
 130 135 140
 Leu Phe Pro Pro Ser Ser
 10145 150

<210> 58

<211> 236

<212> PRT

15<213> Oryctolagus cuniculus

<400> 58

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

34

195	200	205
Gln Tyr Asn Ser His Lys Glu Tyr Thr Cys Lys Val Thr Gln Gly Thr		
210	215	220
Thr Ser Val Val Gln Ser Phe Ser Arg Lys Asn Cys		
5225	230	235

<210> 59

<211> 711

<212> DNA

10<213> *Oryctolagus cuniculus*

<400> 59

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atggacatga gggccccac tcagctgctg gggctcctgc tgctctggct cccaggtgcc      60
agatgtgcct atgatatgac ccagactcca gcctctgtgg aggtagctgt gggaggcaca      120
15gtcaccatca agtgccaggc cagtcagagc attagtagctg acttagactg gtatcagcag      180
aaaccagggc agcctcccaa gctcctgata tatgatgcat ccgatctggc atctgggggc      240
ccatcgcggt tcaaaggcag tggatctggg acacagttca ctctcaccat cagcgacctg      300
gagtgtgccg atgctgccac ttactactgt caacagggtt atacacatag taatgttgat      360
aatgttttcg gcggaggggac cgagggtggtg gtcaaagggtg atccagttgc acctactgtc      420
20ctcctcttcc caccatctag cgatgagggtg gcaactggaa cagtcacat cgtgtgtgtg      480
gcgaataaat actttccga tgtcaccgtc acctgggagg tggatggcac caccctaaaca      540
actggcatcg agaacagtaa aacaccgcag aattctgcag attgtaccta caacctcagc      600
agcactctga cactgaccag cacacagtac aacagccaca aagagtacac ctgcaagggtg      660
accaggggca cgacctcagt cgtccagagc ttcagtagga agaactgtta a              711

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25

<210> 60

<211> 456

<212> PRT

<213> *Oryctolagus cuniculus*

30

<400> 60

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

35
 85 90 95
 Lys Val Thr Ser Pro Thr Ile Gly Asp Thr Ala Thr Tyr Phe Cys Ala
 100 105 110
 Arg Glu Gly Ala Gly Val Ser Met Thr Leu Trp Gly Pro Gly Thr Leu
 5 115 120 125
 Val Thr Val Ser Ser Gly Gln Pro Lys Ala Pro Ser Val Phe Pro Leu
 130 135 140
 Ala Pro Cys Cys Gly Asp Thr Pro Ser Ser Thr Val Thr Leu Gly Cys
 145 150 155 160
 10Leu Val Lys Gly Tyr Leu Pro Glu Pro Val Thr Val Thr Trp Asn Ser
 165 170 175
 Gly Thr Leu Thr Asn Gly Val Arg Thr Phe Pro Ser Val Arg Gln Ser
 180 185 190
 Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Ser Val Thr Ser Ser Ser
 15 195 200 205
 Gln Pro Val Thr Cys Asn Val Ala His Pro Ala Thr Asn Thr Lys Val
 210 215 220
 Asp Lys Thr Val Ala Pro Ser Thr Cys Ser Lys Pro Thr Cys Pro Pro
 225 230 235 240
 20Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Pro
 245 250 255
 Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
 260 265 270
 Val Asp Val Ser Gln Asp Asp Pro Glu Val Gln Phe Thr Trp Tyr Ile
 25 275 280 285
 Asn Asn Glu Gln Val Arg Thr Ala Arg Pro Pro Leu Arg Glu Gln Gln
 290 295 300
 Phe Asn Ser Thr Ile Arg Val Val Ser Thr Leu Pro Ile Ala His Gln
 305 310 315 320
 30Asp Trp Leu Arg Gly Lys Glu Phe Lys Cys Lys Val His Asn Lys Ala
 325 330 335
 Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Arg Gly Gln Pro
 340 345 350
 Leu Glu Pro Lys Val Tyr Thr Met Gly Pro Pro Arg Glu Glu Leu Ser
 35 355 360 365
 Ser Arg Ser Val Ser Leu Thr Cys Met Ile Asn Gly Phe Tyr Pro Ser
 370 375 380
 Asp Ile Ser Val Glu Trp Glu Lys Asn Gly Lys Ala Glu Asp Asn Tyr
 385 390 395 400
 40Lys Thr Thr Pro Ala Val Leu Asp Ser Asp Gly Ser Tyr Phe Leu Tyr
 405 410 415
 Asn Lys Leu Ser Val Pro Thr Ser Glu Trp Gln Arg Gly Asp Val Phe

	420		425		430										
Thr	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys
	435				440					445					
Ser	Ile	Ser	Arg	Ser	Pro	Gly	Lys								
5	450				455										

<210> 61

<211> 1368

<212> DNA

10<213> *Oryctolagus cuniculus*

<400> 61

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tcggtggagg	agtcgggggg	tgcctgggtc	acgcctggga	caccctgac	actcacctgc	120
15acagtctctg	gattctccct	cagcagctac	gacatgacct	gggtccgcca	ggctccaggg	180
aaggggctgg	aatggatcgg	aatcatttat	gctagtggta	ccacatacta	cgcgaactgg	240
gcgaaaggcc	gattcaccat	ctccaaaacc	tgcaccacgg	tggatctgaa	agtcaccagt	300
ccgacaatcg	gggacacggc	cacctatttc	tgtgccagag	agggggctgg	tgttagtatg	360
accttgtggg	gcccaggcac	cctggtcacc	gtctcctcag	ggcaacctaa	ggctccatca	420
20gtcttccccc	tggccccctg	ctgcggggac	acaccctcta	gcacggtgac	cttgggctgc	480
ctggtcaaag	gctacctccc	ggagccagtg	accgtgacct	ggaactcggg	caccctcacc	540
aatgggggtac	gcaccttccc	gtccgtccgg	cagtcctcag	gcctctactc	gctgagcagc	600
gtggtgagcg	tgacctcaag	cagccagccc	gtcacctgca	acgtggccca	cccagccacc	660
aacaccaaag	tggacaagac	cgttgcgccc	tgcacatgca	gcaagcccac	gtgccacccc	720
25cctgaactcc	tgggggggacc	gtctgtcttc	atcttccccc	caaaacccaa	ggacaccctc	780
atgatctcac	gcacccccga	ggtcacatgc	gtggtgggtg	acgtgagcca	ggatgacccc	840
gaggtgcagt	tcacatggta	cataaacaac	gagcaggtgc	gcaccgcccg	gccgccgcta	900
cgggagcagc	agttcaacag	cacgatccgc	gtggtcagca	ccctccccat	cgcgcaccag	960
gactggctga	ggggcaagga	gttcaagtgc	aaagtccaca	acaaggcaact	cccggccccc	1020
30atcgagaaaa	ccatctccaa	agccagaggg	cagcccctgg	agccgaaggt	ctacaccatg	1080
ggccctcccc	gggaggagct	gagcagcagg	tcggtcagcc	tgacctgcat	gatcaacggc	1140
ttctaccctt	ccgacatctc	ggtggagtgg	gagaagaacg	ggaaggcaga	ggacaactac	1200
aagaccacgc	cggccgtgct	ggacagcgac	ggctcctact	tcctctacaa	caagctctca	1260
gtgcccacga	gtgagtggca	gcggggcgac	gtcttcacct	gtcccgatg	gcacgaggcc	1320
35ttgcacaacc	actacacgca	gaagtccatc	tcccgtcttc	cgggtaaa		1368

<210> 62

<211> 236

<212> PRT

40<213> *Oryctolagus cuniculus*

<400> 62

37

Met Asp Met Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1 5 10 15
 Leu Pro Gly Ala Arg Cys Ala Tyr Asp Met Thr Gln Thr Pro Ala Ser
 20 25 30
 5Val Glu Val Ala Val Gly Gly Thr Val Ala Ile Lys Cys Gln Ala Ser
 35 40 45
 Gln Ser Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
 50 55 60
 Pro Pro Lys Pro Leu Ile Tyr Glu Ala Ser Met Leu Ala Ala Gly Val
 1065 70 75 80
 Ser Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 85 90 95
 Ile Ser Asp Leu Glu Cys Asp Asp Ala Ala Thr Tyr Tyr Cys Gln Gln
 100 105 110
 15Gly Tyr Ser Ile Ser Asp Ile Asp Asn Ala Phe Gly Gly Gly Thr Glu
 115 120 125
 Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu Leu Phe Pro
 130 135 140
 Pro Ser Ser Asp Glu Val Ala Thr Gly Thr Val Thr Ile Val Cys Val
 20145 150 155 160
 Ala Asn Lys Tyr Phe Pro Asp Val Thr Val Thr Trp Glu Val Asp Gly
 165 170 175
 Thr Thr Gln Thr Thr Gly Ile Glu Asn Ser Lys Thr Pro Gln Asn Ser
 180 185 190
 25Ala Asp Cys Thr Tyr Asn Leu Ser Ser Thr Leu Thr Leu Thr Ser Thr
 195 200 205
 Gln Tyr Asn Ser His Lys Glu Tyr Thr Cys Lys Val Thr Gln Gly Thr
 210 215 220
 Thr Ser Val Val Gln Ser Phe Ser Arg Lys Asn Cys
 30225 230 235

<210> 63

<211> 711

<212> DNA

35<213> *Oryctolagus cuniculus*

<400> 63

atggacatga gggccccac tcaactgctg gggctcctgc tgctctggct ccaggtgcc 60
 agatgtgcct atgatatgac ccagactcca gcctctgtgg aggtagctgt gggaggcaca 120
 40gtcgccatca agtgccaggc cagtcagagc gttagtagtt acttagcctg gtatcagcag 180
 aaaccagggc agcctccaa gccctgatc tacgaagcat ccatgctggc ggctggggtc 240
 tcatcgcggt tcaaaggcag tggatctggg acagacttca ctctcaccat cagcgacctg 300

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gagtgtgacg atgctgccac ttactattgt caacagggtt attctatcag tgatattgat      360
aatgcttttc gcggaggggac cgaggtgggtg gtcaaagggtg atccagttgc acctactgtc      420
ctcctcttcc caccatctag cgatgaggtg gcaactggaa cagtcaccat cgtgtgtgtg      480
gcgaataaat actttcccgga tgtcacccgtc acctggggagg tggatggcac cacccaaaca      540
5actggcatcg agaacagtaa aacaccgcag aattctgcag attgtaccta caacctcagc      600
agcactctga cactgaccag cacacagtac aacagccaca aagagtacac ctgcaagggtg      660
accaggggca cgacctcagt cgtccagagc ttcagtagga agaactgtta a              711

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<210> 64

10<211> 459

<212> PRT

<213> *Oryctolagus cuniculus*

<400> 64

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

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39

Thr Lys Val Asp Lys Thr Val Ala Pro Ser Thr Cys Ser Lys Pro Thr
 225 230 235 240
 Cys Pro Pro Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro
 245 250 255
 5Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
 260 265 270
 Cys Val Val Val Asp Val Ser Gln Asp Asp Pro Glu Val Gln Phe Thr
 275 280 285
 Trp Tyr Ile Asn Asn Glu Gln Val Arg Thr Ala Arg Pro Pro Leu Arg
 10 290 295 300
 Glu Gln Gln Phe Asn Ser Thr Ile Arg Val Val Ser Thr Leu Pro Ile
 305 310 315 320
 Ala His Gln Asp Trp Leu Arg Gly Lys Glu Phe Lys Cys Lys Val His
 325 330 335
 15Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Arg
 340 345 350
 Gly Gln Pro Leu Glu Pro Lys Val Tyr Thr Met Gly Pro Pro Arg Glu
 355 360 365
 Glu Leu Ser Ser Arg Ser Val Ser Leu Thr Cys Met Ile Asn Gly Phe
 20 370 375 380
 Tyr Pro Ser Asp Ile Ser Val Glu Trp Glu Lys Asn Gly Lys Ala Glu
 385 390 395 400
 Asp Asn Tyr Lys Thr Thr Pro Ala Val Leu Asp Ser Asp Gly Ser Tyr
 405 410 415
 25Phe Leu Tyr Asn Lys Leu Ser Val Pro Thr Ser Glu Trp Gln Arg Gly
 420 425 430
 Asp Val Phe Thr Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
 435 440 445
 Thr Gln Lys Ser Ile Ser Arg Ser Pro Gly Lys
 30 450 455

<210> 65

<211> 1377

<212> DNA

35<213> *Oryctolagus cuniculus*

<400> 65

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 tcggtggagg agtccggggg tcgcctgggc tcgcctggga caccctgac actcacctgc 120
 40acagcctctg gattctccct cagtagctac gacatgagct gggtcgcca ggctccaggg 180
 aaggggctgg aatacatcgg aatcattagt agtagtggtg gcacatacta cgcgagctgg 240
 gcgaaaggcc gattcacat ctccaaaacc tcgaccacgg tggatctgga agtgaccagt 300

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ctgacaaccg aggacacggc cacctatttc tgtagtagag aacatgctgg ttatagtgg 360
gatacgggtc acttgtgggg cccaggaacc ctggtcaccg tctcctcggg gcaacctaa 420
gctccatcag tcttcccact ggccccctgc tgcggggaca caccctctag cacggtgacc 480
ttgggctgcc tgggtcaaag ctacctcccg gagccagtga ccgtgacctg gaactcgggc 540
5accctcacca atggggtacg caccttcccg tccgtccggc agtcctcagg cctctactcg 600
ctgagcagcg tggtgagcgt gacctcaagc agccagcccg tcacctgcaa cgtggcccac 660
ccagccacca acaccaaagt ggacaagacc gttgcgccct cgacatgcag caagcccacg 720
tgcccacccc ctgaactcct ggggggaccg tctgtcttca tcttcccccc aaaaccaag 780
gacaccctca tgatctcacg ccccccgag gtcacatgcg tggtggtgga cgtgagccag 840
10gatgaccccg aggtgcagtt cacatggtac ataaacaacg agcaggtgcg caccgcccgg 900
ccgccgtac gggagcagca gttcaacagc acgatccgcg tggtcagcac cctccccatc 960
gcgccaccag actggctgag gggcaaggag ttcaagtga aagtccaca caaggcactc 1020
ccggccccca tcgagaaaac catctccaaa gccagagggc agcccctgga gccgaaggtc 1080
tacaccatgg gccctccccg ggaggagctg agcagcaggt cggtcagcct gacctgcatg 1140
15atcaacggct tctacccttc cgacatctcg gtggagtggg agaagaacg gaaggcagag 1200
gacaactaca agaccacgcc ggccgtgctg gacagcgacg gctcctactt cctctacaac 1260
aagctctcag tgcccacgag tgagtggcag cggggcgacg tcttcacctg ctccgtgatg 1320
cacgaggcct tgcacaacca ctacacgcag aagtccatct cccgctctcc gggtaaa 1377

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20<210> 66

<211> 150

<212> PRT

<213> *Oryctolagus cuniculus*

25<400> 66

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Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
  1             5             10             15
Val Gln Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
      20             25             30
30Gly Thr Pro Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Thr Ile Ser
      35             40             45
Asp Tyr Asp Leu Ser Trp Val Arg Gln Ala Pro Gly Glu Gly Leu Lys
      50             55             60
Tyr Ile Gly Phe Ile Ala Ile Asp Gly Asn Pro Tyr Tyr Ala Thr Trp
3565             70             75             80
Ala Lys Gly Arg Phe Thr Ile Ser Lys Thr Ser Thr Thr Val Asp Leu
      85             90             95
Lys Ile Thr Ala Pro Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
      100            105            110
40Arg Gly Ala Gly Asp Leu Trp Gly Pro Gly Thr Leu Val Thr Val Ser
      115            120            125
Ser Gly Gln Pro Lys Ala Pro Ser Val Phe Pro Leu Ala Pro Cys Cys

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41

130 135 140
 Gly Asp Thr Pro Ser Ser
 145 150

5<210> 67
 <211> 152
 <212> PRT
 <213> Oryctolagus cuniculus

10<400> 67
 Met Glu Thr Gly Leu Arg Trp Leu Leu Leu Val Ala Val Leu Lys Gly
 1 5 10 15
 Val His Cys Gln Ser Val Glu Glu Ser Gly Gly Arg Leu Val Thr Pro
 20 25 30
 15Gly Thr Pro Leu Thr Leu Thr Cys Thr Ala Ser Gly Phe Ser Arg Ser
 35 40 45
 Ser Tyr Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu
 50 55 60
 Trp Val Gly Val Ile Ser Thr Ala Tyr Asn Ser His Tyr Ala Ser Trp
 2065 70 75 80
 Ala Lys Gly Arg Phe Thr Ile Ser Arg Thr Ser Thr Thr Val Asp Leu
 85 90 95
 Lys Met Thr Ser Leu Thr Thr Glu Asp Thr Ala Thr Tyr Phe Cys Ala
 100 105 110
 25Arg Gly Gly Ser Trp Leu Asp Leu Trp Gly Gln Gly Thr Leu Val Thr
 115 120 125
 Val Ser Ser Gly Gln Pro Lys Ala Pro Ser Val Phe Pro Leu Ala Pro
 130 135 140
 Cys Cys Gly Asp Thr Pro Ser Ser
 30145 150

<210> 68
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 35<213> Oryctolagus cuniculus

<400> 68
 Met Asp Thr Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Trp
 1 5 10 15
 40Leu Pro Gly Ala Arg Cys Ala Asp Val Val Met Thr Gln Thr Pro Ala
 20 25 30
 Ser Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ser

42

35 40 45
 Ser Lys Asn Val Tyr Asn Asn Asn Trp Leu Ser Trp Phe Gln Gln Lys
 50 55 60
 Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Tyr Ala Ser Thr Leu Ala
 565 70 75 80
 Ser Gly Val Pro Ser Arg Phe Arg Gly Ser Gly Ser Gly Thr Gln Phe
 85 90 95
 Thr Leu Thr Ile Ser Asp Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr
 100 105 110
 10Cys Ala Gly Asp Tyr Ser Ser Ser Ser Asp Asn Gly Phe Gly Gly Gly
 115 120 125
 Thr Glu Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu Leu
 130 135 140
 Phe Pro Pro Ser Ser

15145

<210> 69

<211> 149

<212> PRT

20<213> Oryctolagus cuniculus

<220>

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<222> (1)...(149)

25<223> Xaa = any amino acid

<400> 69

Met Asp Xaa Arg Ala Pro Thr Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1 5 10 15
 30Leu Pro Gly Ala Arg Cys Ala Leu Val Met Thr Gln Thr Pro Ala Ser
 20 25 30
 Val Ser Ala Ala Val Gly Gly Thr Val Thr Ile Asn Cys Gln Ser Ser
 35 40 45
 Gln Ser Val Tyr Asp Asn Asp Glu Leu Ser Trp Tyr Gln Gln Lys Pro
 35 50 55 60
 Gly Gln Pro Pro Lys Leu Leu Ile Tyr Leu Ala Ser Lys Leu Ala Ser
 65 70 75 80
 Gly Val Pro Ser Arg Phe Lys Gly Ser Gly Ser Gly Thr Gln Phe Ala
 85 90 95
 40Leu Thr Ile Ser Gly Val Gln Cys Asp Asp Ala Ala Thr Tyr Tyr Cys
 100 105 110
 Gln Ala Thr His Tyr Ser Ser Asp Trp Tyr Leu Thr Phe Gly Gly Gly

43

115	120	125
Thr Glu Val Val Val Lys Gly Asp Pro Val Ala Pro Thr Val Leu Leu		
130	135	140
Phe Pro Pro Ser Ser		

5145