

resulted in an increase in the amounts and activity of effector T cells, which is often followed by a decrease in size of the tumor and or alleviation of other cancer symptoms.

[0007] T cell activation results in an upregulation of GITR levels in both Tregs and effector T cells. Manners of modulating the activity of GITR, such that the Tregs immune suppressing function is reduced, and the activity of effector T cells is increased is an ongoing area of intense study. The GITR ligand, GITR-L, is expressed in a variety of cells including dendritic cells, macrophages and B cells. Previous studies have shown an association between increased anti-tumor immune activity following administration of exogenous GITR-L, or by alternate means of antagonizing GITR, in cancer models.

[0008] Given the increased presence, and the role that Tregs have in cancer, further attention to modulating the activity and presence of Tregs, via GITR, is paramount in further understanding and, ultimately, in the treatment of cancer. Therefore, there exists an urgent need for agents that can specifically bind and modulate the binding of GITR with its ligand, GITR-L, as a means to promote effector T cell activity and, as a result, anti-tumor activity.

SUMMARY

[0009] Disclosed is an isolated humanized monoclonal antibody or antigen-binding fragment thereof that binds to the human anti-glucocorticoid-induced tumor necrosis factor receptor (GITR). The antibody has a variable heavy chain region having the amino acid sequence of SEQ ID NO: 2, and a variable light chain region having the amino acid sequence of SEQ ID NO: 4; a variable heavy chain region having the amino acid sequence of SEQ ID NO: 6, and a variable light chain region having the amino acid sequence of SEQ ID NO: 8; a variable heavy chain region comprising the amino acid sequence of SEQ ID NO: 10, and a variable light chain region having the amino acid sequence of SEQ ID NO: 12; a variable heavy chain region having the amino acid sequence of SEQ ID NO: 14, and a variable light chain region having the amino acid sequence of SEQ ID NO: 16; a variable heavy chain region having the amino acid sequence of SEQ ID NO: 18, and a variable light chain region having the amino acid sequence of SEQ ID NO: 20; a variable heavy chain region having the amino acid sequence of SEQ ID NO: 22, and a variable light chain region having the amino acid sequence of SEQ ID NO: 24; a variable heavy chain region having the amino acid sequence of SEQ ID NO: 26, and a variable light chain region having the amino acid sequence of SEQ ID NO: 28; a variable heavy chain region having the amino acid sequence of SEQ ID NO: 30, and a variable light chain region having the amino acid sequence of SEQ ID NO: 32; a variable heavy chain

region having the amino acid sequence of SEQ ID NO: 34, and a variable light chain region having the amino acid sequence of SEQ ID NO: 36; a variable heavy chain region having the amino acid sequence of SEQ ID NO: 38, and a variable light chain region having the amino acid sequence of SEQ ID NO: 40; a variable heavy chain region having the amino acid sequence of SEQ ID NO: 42, and a variable light chain region having the amino acid sequence of SEQ ID NO: 44; a variable heavy chain region having the amino acid sequence of SEQ ID NO: 46, and a variable light chain region having the amino acid sequence of SEQ ID NO: 48; a variable heavy chain region having the amino acid sequence of SEQ ID NO: 50, and a variable light chain region having the amino acid sequence of SEQ ID NO: 52.

[0009a] In a first aspect, there is provided an isolated humanized monoclonal antibody or antigen-binding fragment thereof that binds to the human-glucocorticoid-induced tumor necrosis factor receptor (GITR) comprising:

- a. a variable heavy chain region comprising the amino acid sequence of SEQ ID NO: 2, and a variable light chain region comprising the amino acid sequence of SEQ ID NO: 4;
- b. a variable heavy chain region comprising the amino acid sequence of SEQ ID NO: 6, and a variable light chain region comprising the amino acid sequence of SEQ ID NO: 8;
- c. a variable heavy chain region comprising the amino acid sequence of SEQ ID NO: 10, and a variable light chain region comprising the amino acid sequence of SEQ ID NO: 12;
- d. a variable heavy chain region comprising the amino acid sequence of SEQ ID NO: 14, and a variable light chain region comprising the amino acid sequence of SEQ ID NO: 16;
- e. a variable heavy chain region comprising the amino acid sequence of SEQ ID NO: 18, and a variable light chain region comprising the amino acid sequence of SEQ ID NO: 20;
- f. a variable heavy chain region comprising the amino acid sequence of SEQ ID NO: 22, and a variable light chain region comprising the amino acid sequence of SEQ ID NO: 24;
- g. a variable heavy chain region comprising the amino acid sequence of SEQ ID NO: 26, and a variable light chain region comprising the amino acid sequence of SEQ ID NO: 28;
- h. a variable heavy chain region comprising the amino acid sequence of SEQ ID NO: 30, and a variable light chain region comprising the amino acid sequence of SEQ ID NO: 32;
- i. a variable heavy chain region comprising the amino acid sequence of SEQ ID NO: 34, and a variable light chain region comprising the amino acid sequence of SEQ ID NO: 36;
- j. a variable heavy chain region comprising the amino acid sequence of SEQ ID NO: 38, and a variable light chain region comprising the amino acid sequence of SEQ ID NO: 40; or
- k. a variable heavy chain region comprising the amino acid sequence of SEQ ID NO: 42, and

a variable light chain region comprising the amino acid sequence of SEQ ID NO: 44.

l. a variable heavy chain region comprising the amino acid sequence of SEQ ID NO: 46, and a variable light chain region comprising the amino acid sequence of SEQ ID NO: 48

m. a variable heavy chain region comprising the amino acid sequence of SEQ ID NO: 50, and a variable light chain region comprising the amino acid sequence of SEQ ID NO: 52.

[0010] Disclosed is an isolated humanized monoclonal antibody or antigen-binding fragment having a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) having the amino acid sequences of SEQ ID NO. 53, 54 or 55, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) comprising the amino acid sequences of SEQ ID NO. 56, 57, or 58; a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) having the amino acid sequences of SEQ ID NO. 59, 60, or 61, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) having the amino acid sequences of SEQ ID NO. 62, 63, or 64; a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) having the amino acid sequences of SEQ ID NO. 65, 66, or 67, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) having the amino acid sequences of SEQ ID NO. 68, 69, or 70; a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) having the amino acid sequences of SEQ ID NO. 71, 72, or 73, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) having the amino acid sequences of SEQ ID NO. 74, 75, or 76; a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) having the amino acid sequences of SEQ ID NO. 77, 78, or 79, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) having the amino acid sequences of SEQ ID NO. 80, 81, or 82; a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) having the amino acid sequences of SEQ ID NO. 83, 84, or 85, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) having the amino acid sequences of SEQ ID NO. 86, 87, or 88; a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) having the amino acid sequences of SEQ ID NO. 65, 72, or 89, respectively; and, a variable light chain complementarity

determining region 1, 2 or 3 (VL-CDR) having the amino acid sequences of SEQ ID NO. 90, 91, or 92; a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) having the amino acid sequences of SEQ ID NO. 93, 94, or 95, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) having the amino acid sequences of SEQ ID NO. 96, 97, or 98; a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) having the amino acid sequences of SEQ ID NO. 99, 100, or 101, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) having the amino acid sequences of SEQ ID NO. 102, 103, or 104; a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) having the amino acid sequences of SEQ ID NO. 65, 72, or 105, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) having the amino acid sequences of SEQ ID NO. 106, 107, or 108; a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) having the amino acid sequences of SEQ ID NO. 109, 72, or 110, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) having the amino acid sequences of SEQ ID NO. 111, 112, or 113; a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) having the amino acid sequences of SEQ ID NO. 65, 72, or 114, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) having the amino acid sequences of SEQ ID NO. 115, 116, or 117; and a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) having the amino acid sequences of SEQ ID NO. 101, 118, or 119, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) having the amino acid sequences of SEQ ID NO. 120, 121, or 122.

[0010a] In another aspect, there is provided an isolated humanized monoclonal antibody or antigen-binding fragment thereof wherein the antibody or antigen-binding fragment comprises:

- (a) a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) comprising the amino acid sequences of SEQ ID NO. 53, 54 or 55, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) comprising the amino acid sequences of SEQ ID NO. 56, 57, or 58;
- (b) a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) comprising the amino acid sequences of SEQ ID NO. 59, 60, or 61, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) comprising the

amino acid sequences of SEQ ID NO. 62, 63, or 64;

(c) a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) comprising the amino acid sequences of SEQ ID NO. 65, 66, or 67, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) comprising the amino acid sequences of SEQ ID NO. 68, 69, or 70;

(d) a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) comprising the amino acid sequences of SEQ ID NO. 71, 72, or 73, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) comprising the amino acid sequences of SEQ ID NO. 74, 75, or 76;

(e) a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) comprising the amino acid sequences of SEQ ID NO. 77, 78, or 79, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) comprising the amino acid sequences of SEQ ID NO. 80, 81, or 82;

(f) a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) comprising the amino acid sequences of SEQ ID NO. 83, 84, or 85, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) comprising the amino acid sequences of SEQ ID NO. 86, 87, or 88;

(g) a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) comprising the amino acid sequences of SEQ ID NO. 65, 72, or 89, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) comprising the amino acid sequences of SEQ ID NO. 90, 91, or 92;

(h) a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) comprising the amino acid sequences of SEQ ID NO. 93, 94, or 95, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) comprising the amino acid sequences of SEQ ID NO. 96, 97, or 98;

(i) a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) comprising the amino acid sequences of SEQ ID NO. 99, 100, or 101, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) comprising the amino acid sequences of SEQ ID NO. 102, 103, or 104;

(j) a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) comprising the amino acid sequences of SEQ ID NO. 65, 72, or 105, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) comprising the amino acid sequences of SEQ ID NO. 106, 107, or 108;

(k) a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) comprising the amino acid sequences of SEQ ID NO. 109, 72, or 110, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) comprising the amino acid sequences of SEQ ID NO. 111, 112, or 113;

(l) a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) comprising the amino acid sequences of SEQ ID NO. 65, 72, or 114, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) comprising the amino acid sequences of SEQ ID NO. 115, 116, or 117; or

(m) a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) comprising the amino acid sequences of SEQ ID NO. 101, 118, or 119, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) comprising the amino acid sequences of SEQ ID NO. 120, 121, or 122;

wherein said antibody or antibody binding fragment binds human-glucocorticoid-induced tumor necrosis factor receptor (GITR).

[0011] The antibody is monovalent or bivalent. For example the antibody is a single chain antibody. The antibody has a binding affinity within the range of 10^{-5} M to 10^{-12} M. In some embodiments the antibody has a IgG4 heavy chain constant region. In other embodiments the antibody has an Fc region that contains mutations at amino acid positions 234 and 235. The mutations are for example, L234A and L235A.

[0012] In other embodiments the disclosure includes a bi-specific antibody containing the human GITR antibody of the disclosure and an antibody that also binds to a tumor-associated antigen, a cytokine or a cell surface receptor.

[0013] Optionally the antibodies of the disclosure are s linked to a therapeutic agent, such as a toxin, a radiolabel, a siRNA, a small molecule, or a cytokine.

[0014] Also disclosed are cells producing the antibody according to the disclosure.

[0014a] In another aspect, there is provided a cell producing the antibody as described herein.

[0015] Disclosed are methods for depleting regulatory T-cells in a subject, by administering to a subject in need thereof a composition comprising an antibody according to the disclosure.

[0015a] In another aspect, there is provided use of a composition comprising an antibody as described herein in the manufacture of a medicament for depleting regulatory T-cells in a subject.

[0016] Other methods of the disclosure include augmenting an immune response to an antigen by administering to a subject in need thereof a composition comprising an antibody according to the disclosure. The antigen is a viral antigen, a bacterial antigen or a tumor associated antigen.

[0016a] In another aspect, there is provided use of a composition comprising an antibody as described herein in the manufacture of a medicament for augmenting an immune response to an antigen, wherein the composition is to be administered to a subject in need thereof.

[0017] In various embodiments administering an antibody according to the disclosure result in an increase in antigen specific T cell activity and/or an increase NK cell cytotoxicity.

[0018] In some embodiments the methods of the disclosure further includes administering to the subject IL-15.

[0019] Disclosed are methods of treating or alleviating a symptom of cancer by administering to a subject in need thereof a composition comprising an antibody according to the disclosure. The cancer is a cancer in which GITR or its ligand, GITR-L, is overexpressed. Optionally the subject is further administered a cytokine, such as IL-15 or a chemotherapeutic agent.

[0019a] In another aspect, there is provided use of a composition comprising an antibody as described herein in the manufacture of a medicament for treating or alleviating a symptom of cancer, wherein the composition is to be administered to a subject in need thereof.

[0020] The disclosure further provides a nucleic acid having the nucleic acid sequence of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, and 51.

[0020a] In another aspect, there is provided a nucleic acid comprising the nucleic acid sequence of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51.

[0021] Disclosed is a nucleic acid encoding the polypeptide of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52 or polypeptide having the amino acid sequence of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52. Vectors containing the nucleic acids according to the disclosure are also provided. Also included in the disclosure are cells containing the vectors according to the disclosure.

[0021a] In another aspect, there is provided a nucleic acid encoding the polypeptide of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52. In another aspect, there is provided a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52. In another aspect, there is provided a vector comprising the nucleic acid as described herein. In another aspect, there is provided a cell comprising the vector as described herein.

[0022] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entirety. In cases of

conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples described herein are illustrative only and are not intended to be limiting.

[0023] Other features and advantages of the disclosure will be apparent from and encompassed by the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] Figure 1 illustrates the design and results from an ELISA *in vitro* binding assay used for identifying anti-GITR antibodies. Plates were coated with 2ug/ml each of the A) hGITR-His; B) hGITR-mlgG2a; C) mGITR-His; or D) mlgG2a. OD measurements for each corresponding well are shown below the template.

[0025] Figure 2 is a pair of graphs showing binding activity of indicated anti-GITR phage antibodies in four different concentrations (1E10 to 1E13 particles/mL) to two different concentrations of hGITR-mlg determined by a meso scale discovery immunoassay..

[0026] Figure 3 is a pair of graphs showing binding activity for indicated anti-GITR phage antibodies to eight different concentrations of hGITR-mlg using a meso scale discovery immunoassay.

[0027] Figure 4 illustrates the data for the flow cytometry binding assay performed using anti-GITR phage antibodies. Four concentrations of anti-GITR phage AB were tested along with CHO cells expressing either stable GITR or control CA9.

[0028] Figure 5 is a graph showing flow cytometry GITR binding data with a single concentration of phage antibodies from culture supernatant of individual colonies. Orange bars indicate binding to CHO cells expressing GITR and blue bars indicate binding to CHO cells lacking GITR expression (CA9 control).

[0029] Figure 6 illustrates ELISA GITR binding data for phage supernatant from single colonies. The clone template, OD450 for individual clones and the coating pattern for each plate is shown.

[0030] Figure 7 illustrates flow cytometry and ELISA results for anti-GITR antibodies according to the invention.

[0031] Figure 8 is a graph showing GITR binding of anti-GITR antibodies expressed in full IgG1-Fc(LALA) mutant format as analyzed by flow cytometry assays. Anti-GITR mAb binding to the GITR(+) CHO cell lines were tested by 5-point 2X serial dilutions in duplicates.

- (j) a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) comprising the amino acid sequences of SEQ ID NO. 65, 72, or 105, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) comprising the amino acid sequences of SEQ ID NO. 106, 107, or 108;
- (k) a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) comprising the amino acid sequences of SEQ ID NO. 109, 72, or 110, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) comprising the amino acid sequences of SEQ ID NO. 111, 112, or 113;
- (l) a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) comprising the amino acid sequences of SEQ ID NO. 65, 72, or 114, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) comprising the amino acid sequences of SEQ ID NO. 115, 116, or 117; or
- (m) a variable heavy chain complementarity determining region 1, 2, or 3 (VH-CDR) comprising the amino acid sequences of SEQ ID NO. 101, 118, or 119, respectively; and, a variable light chain complementarity determining region 1, 2 or 3 (VL-CDR) comprising the amino acid sequences of SEQ ID NO. 120, 121, or 122;

wherein said antibody or antibody binding fragment binds human-glucocorticoid-induced tumor necrosis factor receptor (GITR).

3. The antibody of claim 1, wherein said antibody is monovalent or bivalent.
4. The antibody of claim 1, wherein said antibody is a single chain antibody.
5. The antibody of claim 1, wherein said antibody has a binding affinity within the range of 10^{-5} M to 10^{-12} M.
6. The antibody of claim 1, wherein said antibody has a IgG4 heavy chain constant region.
7. The antibody of claim 1, wherein the Fc region contains mutations at amino acid positions 234 and 235.

8. The antibody of claim 7, wherein the mutations are L234A and L235A.
9. The antibody according to claim 1 wherein said antibody is a bi-specific antibody that also binds to a tumor-associated antigen, a cytokine or a cell surface receptor.
10. The antibody according to any one of preceding claims linked to a therapeutic agent.
11. The antibody of claim 10, wherein said therapeutic agent is a toxin, a radiolabel, a siRNA, a small molecule, or a cytokine.
12. A cell producing the antibody of any one of claims 1-11.
13. Use of a composition comprising an antibody according to any one of claims 1-11 in the manufacture of a medicament for depleting regulatory T-cells in a subject.
14. Use of a composition comprising an antibody of any one of claims 1-11 in the manufacture of a medicament for augmenting an immune response to an antigen, wherein the composition is to be administered to a subject in need thereof.
15. The use of claim 14, wherein said antigen is a viral antigen, a bacterial antigen or a tumor associated antigen.
16. The use of claim 14, wherein said antibody causes an increase in antigen specific T cell activity.
17. The use of claim 14, wherein said antibody causes an increase NK cell cytotoxicity.
18. The use of claim 14, wherein IL-15 is to be further administered to said subject.
19. Use of a composition comprising an antibody according to any one of claims 1-11 in the manufacture of a medicament for treating or alleviating a symptom of cancer, wherein the composition is to be administered to a subject in need thereof.
20. The use of claim 19, wherein said cancer is a cancer in which GITR or its ligand, GITR-L, is overexpressed.
21. The use of claim 20, wherein a cytokine or a chemotherapeutic agent is to be further administered to said subject.

22. The use of claim 21, wherein the cytokine is IL-15.
23. A nucleic acid comprising the nucleic acid sequence of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51.
24. A nucleic acid encoding the polypeptide of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52.
25. A polypeptide comprising the amino acid sequence of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52.
26. A vector comprising the nucleic acid of claim 23 or 24.
27. A cell comprising the vector of claim 26.