

CLAIMS

1. An isolated antibody that specifically binds to human V-domain Ig Suppressor of T cell Activation (human VISTA), which antibody comprises an FcR binding human IgG2 Fc or constant region, wherein the antibody agonizes or promotes one or more of the suppressive effects of VISTA on T cell immunity and in the absence of said FcR binding human IgG2 Fc or constant region or when it comprises a human Ig Fc or constant region other than an FcR binding human IgG2 Fc or constant region the antibody antagonizes or inhibits the suppressive effects of VISTA on T cell immunity; and which antibody:
 - (i) comprises the VH CDRs of SEQ ID NO:120, 121 and 122 and the VL CDRs of SEQ ID NO:123, 124 and 125;
 - (ii) comprises the VH CDRs of SEQ ID NO:140, 141 and 142 and the VL CDRs of SEQ ID NO:143, 144 and 145;
 - (iii) comprises the VH CDRs of SEQ ID NO:370, 371 and 372 and the VL CDRs of SEQ ID NO:373, 374 and 375;
 - (iv) comprises the VH CDRs of SEQ ID NO:380, 381 and 382 and the VL CDRs of SEQ ID NO:383, 384 and 385;
 - (v) comprises the VH CDRs of SEQ ID NO:400, 401 and 402 and the VL CDRs of SEQ ID NO:403, 404 and 405;
 - (vi) comprises the VH CDRs of SEQ ID NO:470, 471 and 472 and the VL CDRs of SEQ ID NO:473, 474 and 475;
 - (vii) comprises the VH CDRs of SEQ ID NO:500, 501 and 502 and the VL CDRs of SEQ ID NO:503, 504 and 505;
 - (viii) comprises the VH CDRs of SEQ ID NO:740, 741 and 742 and the VL CDRs of SEQ ID NO:743, 744 and 745; or
 - (ix) comprises the VH CDRs of SEQ ID NO:770, 771 and 772 and the VL CDRs of SEQ ID NO:773, 774 and 775.
2. The isolated antibody of claim 1, wherein the human IgG2 constant or Fc region binds to Fc gamma receptors including human CD32A.

3. The isolated antibody of claim 1 or 2, wherein the IgG2 constant or Fc region comprises native human IgG2 binding to Fc gamma receptors.
4. The isolated antibody of claim 3 wherein said FcγRs include one or more of hFcγRI(CD64), FcγRIIA or hFcγRIIB, (CD32 or CD32A) and FcγRIIIA (CD16A) or FcγRIIIB (CD16B).
5. The isolated antibody or antibody fragment of any one of claims 1-4 which competes for binding to human VISTA any of the anti-human VISTA antibodies having the identical variable sequences as any of the anti-human VISTA antibodies having the following sequences:
 - (i) comprises the VH polypeptide of SEQ ID NO:126 and the VL polypeptide of SEQ ID NO:128;
 - (ii) comprises the VH polypeptide of SEQ ID NO:146 and the VL polypeptide of SEQ ID NO:148;
 - (iii) comprises the VH polypeptide of SEQ ID NO:376 and the VL polypeptide of SEQ ID NO:378;
 - (iv) comprises the VH polypeptide of SEQ ID NO:386 and the VL polypeptide of SEQ ID NO:388;
 - (v) comprises the VH polypeptide of SEQ ID NO:406 and the VL polypeptide of SEQ ID NO:408;
 - (vi) comprises the VH polypeptide of SEQ ID NO:476 and the VL polypeptide of SEQ ID NO:478;
 - (vii) comprises the VH polypeptide of SEQ ID NO:506 and the VL polypeptide of SEQ ID NO:508;
 - (viii) comprises the VH polypeptide of SEQ ID NO:746 and the VL polypeptide of SEQ ID NO:748; or
 - (ix) comprises the VH polypeptide of SEQ ID NO:776 and the VL polypeptide of SEQ ID NO:778.
6. The anti-human VISTA antibody of any one of Claims 1-5 which promotes or enhances the suppressive effect of VISTA on one or more of activation of monocytes, induction of T-cell proliferation; induction or suppression of cytokine expression, increased survival of monocytes, induction of antibody-dependent cell-mediated cytotoxicity (ADCC) in cells-expressing VISTA; or induction of antibody-dependent cellular phagocytosis (ADCP) in cells expressing VISTA.

7. The antibody of any one of Claims 1-6, wherein said human IgG2 Fc region comprises the following modifications:
 - a. either or both of the heavy chain cysteine residue at position 127 and the light chain cysteine residue at position 214 (wherein numbering is according to Kabat) are deleted or changed to a different amino acid residue, resulting in an increase in the agonistic properties of the resultant modified antibody relative to an antibody lacking said Fc modifications or
 - b. the cysteine residue at position 214 of said IgG2 Fc region is mutated or substituted with another amino acid and/or one or more of the cysteine residues at positions 127, 232 or 233 of the heavy chain are deleted or substituted with another amino acid resulting in an increase in the agonistic properties of the resultant modified antibody relative to an antibody lacking said Fc modifications.
8. A pharmaceutical composition comprising at least one agonistic antibody according to any one of claims 1-7 and a pharmaceutically acceptable carrier.
9. A diagnostic composition comprising at least one agonistic antibody according to any one of claims 1-7 and a diagnostically acceptable carrier.
10. Use of the antibody according to any one of claims 1-7 or pharmaceutical composition according to claim 8 in the treatment or prevention of allergy, autoimmunity, inflammation or sepsis or the treatment of a transplant or gene therapy recipient, wherein a therapeutically effective amount of at least one of the agonistic antibody is to be administered to a human subject in need thereof.
11. The use of claim 10, which further comprises detecting VISTA expression in the subject optionally using a diagnostic composition according to claim 9.
12. Use of an agonistic antibody according to any one of claims 1-7 in the preparation of a medicament for suppressing T cell immunity and/or promoting the suppressive effects of human VISTA on immunity in a subject in need thereof.
13. Use of any agonistic antibody according to any one of claims 1-7 or a composition containing according to claim 8 in the manufacture of a medicament for suppressing T cell immunity and/or promoting the suppressive effects of human VISTA on immunity in a subject in need thereof, optionally wherein the subject has an autoimmune, inflammatory, allergic condition, and/or is at risk of developing an autoimmune, inflammatory or allergic response because the subject has or is to receive a transplant and/or the subject exhibits symptoms of an autoimmune, inflammatory or allergic response or sepsis.
14. The use according to any one of claims 9-13, further comprising another immunoinhibitory antibody or immunoinhibitory fusion protein which is selected from immunoinhibitory antibodies or fusion proteins targeting one or more of

CTLA4, PD-1, PDL-1, LAG-3, TIM-3, BTLA, B7-H4, B7-H3, VISTA, CD40, CD137, OX40, GITR, CD27, CD28 or ICOS to be administered.

15. The use of any one of claims 10-14, which includes assaying:

- a. VISTA protein expression by the individual's cells or in bodily fluids prior, concurrent and/or after treatment;
- b. VISTA expression levels on hematopoietic cells; and/or
- c. VISTA expression levels on hematopoietic cells selected from any one or more of myeloid lineage cells and/or a lymphocytes, monocyte or a neutrophils, T cells, B cells, a natural killer (NK) cells or a natural killer T (NKT) cells.

16. The antibody of any one of claims 1-7, or use of any one of claims 13-15, wherein the anti-human VISTA antibody or fragment comprises an affinity or K_D for human VISTA which is:

- a. 50nM or less as determined by surface plasmon resonance at 37° C; or
- b. 1nM or less as determined by surface plasmon resonance at 37° C.

17. A pharmaceutical composition comprising a pharmaceutically effective amount of an antibody according to claim 16 and a pharmaceutically acceptable carrier.

18. A diagnostic composition comprising a pharmaceutically effective amount of an antibody according to claim 16 and a diagnostically acceptable carrier.

19. The agonistic antibody according to any one of claims 1-7 or pharmaceutical composition according to claim 8 for use in therapy.