

CLAIMS

What is claimed is:

1. A T-cell modulatory multimeric polypeptide comprising:
 - at least one heterodimer, ~~wherein the at least one heterodimer comprises comprising:~~
 - a) a first polypeptide comprising:
 - i) a Wilms tumor-1 (WT-1) peptide epitope, ~~wherein the WT-1 peptide epitope has a length from 8 amino acids to 16 amino acids,~~
 - ~~ii) a beta-2 microglobulin (β 2M) polypeptide, and~~
 - ~~iii) a linker between the WT-1 peptide and the β 2M polypeptide, wherein the linker comprises a Cys residue; and comprising the amino acid sequence $X_1X_2X_3$ TWNQMNL (SEQ ID NO:460) or X_2X_3 TWNQMNL (SEQ ID NO:461), wherein each of X_1 , X_2 , and X_3 is independently any amino acid, with the proviso that the N terminal amino acid is not a Cys, and wherein the WT-1 peptide epitope has a length from 9 to 25 amino acids; and~~
 - ~~ii) a first Class I major histocompatibility complex (MHC) polypeptide;~~
 - b) a second polypeptide comprising ~~a second class I MHC polypeptide, and~~
 - ~~i) a major histocompatibility complex (MHC) class I heavy chain polypeptide,~~
 - ~~ii) an immunoglobulin (Ig) Fc polypeptide, and~~
 - ~~iii) at least one activating immunomodulatory polypeptide,~~
 - ~~wherein the heterodimer comprises a first disulfide bond formed between (i) the Cys residue in the linker between the WT-1 peptide epitope and the β 2M polypeptide, and (ii) a Cys residue in the MHC class I heavy chain polypeptide,~~
 - ~~wherein the heterodimer comprises a second disulfide bond formed between a Cys residue in the β 2M polypeptide and a Cys residue in the MHC class I heavy chain polypeptide, and wherein the Ig Fc polypeptide does not comprise a C-terminal lysine) at least one activating immunomodulatory polypeptide,~~
 - ~~wherein the first and/or the second polypeptide comprises the at least one immunomodulatory polypeptide, and optionally wherein the first or the second polypeptide comprises an immunoglobulin (Ig) Fc polypeptide.~~
2. A T-cell modulatory multimeric polypeptide of claim 1, wherein ~~at least one of the one or more immunomodulatory polypeptides is a variant immunomodulatory polypeptide that exhibits reduced affinity to a cognate co-immunomodulatory polypeptide compared to the affinity of a corresponding wild-type immunomodulatory polypeptide for the cognate co-immunomodulatory polypeptide~~

a) the first polypeptide comprises, in order from N-terminus to C-terminus:

- i) the WT-1 peptide epitope;
- ii) the Cys-containing linker; and
- iii) the β 2M polypeptide, and

b) the second polypeptide comprises, in order from N-terminus to C-terminus:

- i) the at least one immunomodulatory polypeptide;
- ii) an optional linker;
- iii) the MHC class I heavy chain polypeptide;
- iv) an optional linker; and
- v) the Ig Fc polypeptide,

wherein, when the TMMP comprises more than one immunomodulatory polypeptide, the TMMP may comprise one or more linkers between the immunomodulatory polypeptides.

3. A T-cell modulatory multimeric polypeptide of claim ~~21~~, wherein ~~the ratio of the binding affinity of the wild type immunomodulatory polypeptide to a cognate co-immunomodulatory polypeptide to the binding affinity of the variant immunomodulatory polypeptide to the cognate co-immunomodulatory polypeptide, when measured by bio-layer interferometry, is at least 1.5:1~~a) the first polypeptide comprises, in order from N-terminus to C-terminus:

- i) the WT-1 peptide epitope;
- ii) the Cys-containing linker; and
- iii) the β 2M polypeptide, and

b) the second polypeptide comprises, in order from N-terminus to C-terminus:

- i) the MHC class I heavy chain polypeptide;
- ii) an optional linker;
- iii) the Ig Fc polypeptide;
- iv) an optional linker, and
- v) the at least one immunomodulatory polypeptide,

wherein, when the TMMP comprises more than one immunomodulatory polypeptide, the TMMP may comprise one or more linkers between the immunomodulatory polypeptides.

4. ~~A T cell modulatory multimeric polypeptide of claim 2 or 3, wherein the variant immunomodulatory polypeptide binds the co-immunomodulatory polypeptide with an affinity selected~~

from the group consisting of from about 10^{-4} M to about 10^{-7} M, from about 10^{-4} M to about 10^{-6} M, and from about 10^{-4} M to about 10^{-5} M.

5. ~~_____ A T cell modulatory multimeric polypeptide of any one of claims 1-4, wherein:~~

~~a1) the first polypeptide comprises, in order from N terminus to C terminus:~~

~~_____ i) the WT-1 peptide epitope; and~~

~~_____ ii) the first MHC polypeptide; and~~

~~b1) the second polypeptide comprises, in order from N terminus to C terminus:~~

~~_____ i) the at least one immunomodulatory polypeptide;~~

~~_____ ii) the second MHC polypeptide; and~~

~~_____ iii) an Ig Fc polypeptide; or~~

~~a2) the first polypeptide comprises, in order from N terminus to C terminus:~~

~~_____ i) the WT-1 peptide epitope; and~~

~~_____ ii) the first MHC polypeptide; and~~

~~b2) the second polypeptide comprises, in order from N terminus to C terminus:~~

~~_____ i) the second MHC polypeptide;~~

~~_____ ii) the at least one immunomodulatory polypeptide; and~~

~~_____ iii) an Ig Fc polypeptide; or~~

~~a3) the first polypeptide comprises, in order from N terminus to C terminus:~~

~~_____ i) the WT-1 peptide epitope; and~~

~~_____ ii) the first MHC polypeptide; and~~

~~b3) the second polypeptide comprises, in order from N terminus to C terminus:~~

~~_____ i) the second MHC polypeptide;~~

~~_____ ii) an Ig Fc polypeptide; and~~

~~_____ iii) the at least one immunomodulatory polypeptide; or~~

~~a4) the first polypeptide comprises, in order from N terminus to C terminus:~~

~~_____ i) the at least one immunomodulatory polypeptide; _____~~

~~_____ ii) the WT-1 peptide epitope;~~

~~_____ ii) the first MHC polypeptide; and~~

~~b4) the second polypeptide comprises, in order from N terminus to C terminus:~~

~~_____ i) the second MHC polypeptide; and~~

~~_____ ii) the Ig Fc polypeptide; or~~

~~a5) the first polypeptide comprises, in order from N-terminus to C-terminus:~~

- ~~_____ i) the WT-1 peptide epitope;~~
- ~~_____ ii) the first MHC polypeptide; and~~
- ~~_____ iii) the at least one immunomodulatory polypeptide; and~~

~~b5) the second polypeptide comprises, in order from N-terminus to C-terminus:~~

- ~~_____ i) the second MHC polypeptide; and~~
- ~~_____ ii) an immunoglobulin (Ig)-Fc polypeptide.~~

~~6. _____ A T-cell modulatory multimeric polypeptide of any one of claims 1-4, wherein:~~

- ~~_____ a) the first MHC polypeptide is a β 2-microglobulin polypeptide; and the second MHC polypeptide is an MHC class I heavy chain polypeptide; or~~
- ~~_____ b) the first MHC polypeptide is an MHC class I heavy chain polypeptide; and the second MHC polypeptide is a β 2-microglobulin polypeptide.~~

~~7. _____ A T-cell modulatory multimeric polypeptide of claim 6, wherein:~~

- ~~_____ a) the first polypeptide comprises, in order from N-terminus to C-terminus:~~
 - ~~_____ i) the WT-1 peptide epitope; and~~
 - ~~_____ ii) the β 2-microglobulin polypeptide; and~~
- ~~_____ b) the second polypeptide comprises, in order from N-terminus to C-terminus:~~
 - ~~_____ i) the at least one immunomodulatory polypeptide;~~
 - ~~_____ ii) the MHC class I heavy chain polypeptide; and~~
 - ~~_____ iii) an Ig-Fc polypeptide.~~

~~8. _____ A T-cell modulatory multimeric polypeptide of claim 6, wherein:~~

- ~~_____ a) the first polypeptide comprises, in order from N-terminus to C-terminus:~~
 - ~~_____ i) the WT-1 peptide epitope; and~~
 - ~~_____ ii) the β 2-microglobulin polypeptide; and~~
- ~~_____ b) the second polypeptide comprises, in order from N-terminus to C-terminus:~~
 - ~~_____ i) the MHC class I heavy chain polypeptide; and~~
 - ~~_____ ii) an Ig-Fc polypeptide; and~~
 - ~~_____ iii) at least one immunomodulatory polypeptide~~

94. A T-cell modulatory multimeric polypeptide of any one of claims 1-83, wherein the at least one immunomodulatory polypeptide is selected from the group consisting of a cytokine, a 4-1BBL

polypeptide, an ICOS-L polypeptide, an OX-40L polypeptide, a CD80 polypeptide, a CD86 polypeptide, a CD40 polypeptide, a CD70 polypeptide, and combinations thereof.

~~105.~~ A T-cell modulatory multimeric polypeptide of any one of claims 1-~~94~~, wherein the at least one immunomodulatory polypeptide comprises an IL-2 polypeptide.

~~116.~~ A T-cell modulatory multimeric polypeptide of any one of claims 1-~~105~~, wherein the multimeric polypeptide comprises at least two immunomodulatory polypeptides, and wherein at least two of the immunomodulatory polypeptides are the same, optionally wherein the 2 or more immunomodulatory polypeptides are in tandem.

~~127.~~ A T-cell modulatory multimeric polypeptide of any one of claims 1-~~116~~, wherein one or more of the at least one immunomodulatory polypeptide is a variant IL-2 polypeptide that exhibits reduced affinity to an IL-2 receptor compared to the affinity of a wild-type IL-2 polypeptide for the IL-2 receptor, optionally wherein the variant IL-2 polypeptide comprises: i) an H16 substitution and an F42 substitution.

~~138.~~ A T-cell modulatory multimeric polypeptide of claim ~~127~~, wherein the one or more variant IL-2 polypeptides comprises: i) an H16A substitution and an F42A substitution; or ii) an H16T substitution and an F42A substitution.

~~14.~~ A T-cell modulatory multimeric polypeptide of any one of claims 1-13, wherein the first polypeptide and the second polypeptide are covalently linked to one another, optionally wherein the covalent linkage is via a disulfide bond.

~~15.~~ A T-cell modulatory multimeric polypeptide of any one of claims 1-14, wherein the first MHC polypeptide or a linker between the epitope and the first MHC polypeptide comprises an amino acid substitution to provide a first Cys residue, wherein the second MHC polypeptide comprises an amino acid substitution to provide a second Cys residue, and wherein the disulfide linkage is between the first and the second Cys residues.

~~169.~~ A T-cell modulatory multimeric polypeptide of any one of claims 1-~~158~~, wherein:
a) the first polypeptide comprises a disulfide bond is between: i) a the Cys present in a the linker between the WT-1 peptide epitope and the first MHC class I polypeptide, wherein the first MHC class I

~~polypeptide is a β 2M polypeptide; and ii) a Cys residue at position 84 in the MHC class I heavy chain polypeptide; and~~

~~b) the second disulfide bond is between: i) a Cys residue at position 12 of the β 2M polypeptide; and ii) a Cys residue at position 236 of the MHC class I heavy chain polypeptide introduced via a Y84C substitution in the second MHC class I polypeptide, wherein the second MHC class I polypeptide is a MHC Class I heavy chain polypeptide.~~

~~17. A T-cell modulatory multimeric polypeptide of any one of claims 1-15, wherein the polypeptide comprises a disulfide bond between: i) a Cys residue introduced into the first MHC class I polypeptide via an R12C substitution, wherein the first MHC class I polypeptide is a β 2M polypeptide; and ii) a Cys residue introduced into the second MHC class I polypeptide, via an A236C substitution, wherein second MHC class I polypeptide is an MHC Class I heavy chain polypeptide.~~

~~18. A T-cell modulatory multimeric polypeptide of any one of claims 1-15, wherein the polypeptide comprises a first disulfide bond between: i) a Cys present in a linker between the WT-1 peptide epitope and the first MHC class I polypeptide, wherein the first MHC class I polypeptide is a β 2M polypeptide; and ii) a Cys residue introduced via a Y84C substitution in the second MHC class I polypeptide, wherein the second MHC class I polypeptide is a MHC Class I heavy chain polypeptide, and a second disulfide bond between i) a Cys residue introduced into the β 2M polypeptide via an R12C substitution; and ii) a Cys residue introduced into the MHC Class I heavy chain polypeptide via an A236C substitution.~~

~~19~~10. A T-cell modulatory multimeric polypeptide of any one of claims 1-9, wherein the linker between the WT-1 peptide epitope and the β 2M polypeptide first MHC is GCGGS(GGGGS)_n (SEQ ID NO:319), where n is 1, 2, 3, 4, 5, 6, 7, 8, or 9.

~~20~~11. A T-cell modulatory multimeric polypeptide of any one of claims 1-~~19~~10, wherein the WT-1 peptide epitope has a length of 9 or 10 amino acids.

~~21~~12. A T-cell modulatory multimeric polypeptide of any one of claims 1-~~20~~11, wherein the Ig Fc polypeptide comprises an amino acid sequence having at least 95% sequence identity to one of the amino acid sequences depicted in FIG. 5D, FIG. 5E, FIG. 5F, FIG. 5G, and FIG. 5H.

~~22. A T-cell modulatory multimeric polypeptide of any one of claims 1-21, wherein the WT-1 peptide comprises the amino acid sequence SMTWNQMNL (SEQ ID NO:451), GCMTWNQMNL (SEQ ID NO:452), SYTWNQMNL (SEQ ID NO:453), or GCYTWNQMNL (SEQ ID NO:454).~~

~~23~~13. A T-cell modulatory multimeric polypeptide of any one of claims 1-~~24~~12, wherein the first or the second MHC polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to [SEQ ID NO:455](#), or at least 95% amino acid sequence identity to SEQ ID NO:342, or at least 95% amino acid sequence identity to SEQ ID NO:344.

~~24~~14. A T-cell modulatory multimeric polypeptide of ~~any one of claims 1-23~~claim 1, wherein the first polypeptide of the at least one heterodimer has the amino acid sequence set forth in SEQ ID NO:423; and the second polypeptide of the at least one heterodimer has the amino acid sequence set forth in SEQ ID NO:486 wherein the first MHC polypeptide is a β 2M polypeptide, and wherein the second MHC polypeptide comprises an amino acid sequence having at least 95% amino acid sequence identity to an HLA-A*24 polypeptide, wherein the epitope is selected from the group consisting of: SMTWNQMNL (SEQ ID NO:451), GCMTWNQMNL (SEQ ID NO:452), SYTWNQMNL (SEQ ID NO:453), and GCYTWNQMNL (SEQ ID NO:454), and wherein the Ig Fc polypeptide comprises the amino acid sequence depicted in FIG. 5G or FIG. 5H.

~~25~~. — A T-cell modulatory multimeric polypeptide of claim 1, wherein:

- a) the first polypeptide comprises the amino acid sequence depicted in FIG. 37B; and
- b) the second polypeptide comprises the amino acid sequence depicted in FIG. 20B.

~~26~~15. A T-cell modulatory multimeric polypeptide of any one of claims 1-~~25~~14, wherein the multimeric polypeptide comprises a first and a second heterodimer, and wherein the first and second heterodimers are covalently bound by one or more disulfide bonds between the Ig Fc polypeptides of the first and second heterodimers.

~~16~~. A T-cell modulatory multimeric polypeptide of claim 15,
wherein the first polypeptide of both the first and second heterodimers has the amino acid
sequence set forth in SEQ ID NO:423,
wherein the second polypeptide of both the first and second heterodimers has the amino acid
sequence set forth in SEQ ID NO:486.

~~27~~17. ~~A A composition comprising one or more nucleic acids encoding the first and second polypeptides of a T cell modulatory multimeric polypeptide according to any one of claims 1-14 comprising a nucleotide sequence encoding a first or second polypeptide according to any one of claims 1-26.~~

2818. A composition comprising one or more~~An~~ expression vectors comprising the one or more nucleic acids of claim 2717.

2919. Use of a T-cell modulatory multimeric polypeptide according to any one of claims 1-16 in the manufacture of a medicament for ~~A method of~~ selectively modulating the activity of a T cell specific for a Wilms tumor-1 (WT-1) epitope, ~~the method comprising contacting the T cell with a T-cell modulatory multimeric polypeptide according to any one of claims 1-26, wherein said contacting selectively modulates the activity of the WT-1 epitope specific T cell.~~

3020. Use of a pharmaceutical composition comprising T-cell modulatory multimeric polypeptide according to any one of claims 1-16 in the manufacture of a medicament for ~~A method of~~ treating a patient having a cancer in a patient, ~~the method comprising administering to the patient an effective amount of a pharmaceutical composition comprising T-cell modulatory multimeric polypeptide according to any one of claims 1-26.~~

3121. The use of claim 20~~method of claim 30~~, wherein the cancer is acute myeloid leukemia, myeloma, ovarian cancer, pancreatic cancer, non-small cell lung cancer, colorectal cancer, breast cancer, Wilms tumor, mesothelioma, soft tissue sarcoma, neuroblastoma, or nephroblastoma.

3222. The use of claim of 20 or 21~~A method of 30 or 31~~, wherein the patient also receives further ~~comprising administering one or more checkpoint inhibitors to the individual.~~

3323. The use of claim 22~~A method according to claim 32~~, wherein the checkpoint inhibitor is an antibody that binds to a polypeptide selected from the group consisting of CD27, CD28, CD40, CD122, CD96, CD73, CD47, OX40, GITR, CSF1R, JAK, PI3K delta, PI3K gamma, TAM, arginase, CD137, ICOS, A2AR, B7-H3, B7-H4, BTLA, CTLA-4, LAG3, TIM3, VISTA, CD96, TIGIT, CD122, PD-1, PD-L1, and PD-L2.

3424. The use of claim 23~~A method according to claim 33~~, wherein the checkpoint inhibitor is an antibody specific for PD-1, PD-L1, or CTLA4.

3525. The use of claim 23 or 24~~A method according to claim 33 or 34~~, wherein the one or more checkpoint inhibitors is selected from the group consisting of nivolumab, pembrolizumab, pidilizumab, AMP-224, MPDL3280A, MDX-1105, MEDI-4736, arelumab, ipilimumab, tremelimumab, pidilizumab,

IMP321, MGA271, BMS-986016, lirilumab, urelumab, PF-05082566, IPH2101, MEDI-6469, CP-870,893, Mogamulizumab, Varlilumab, Avelumab, Galiximab, AMP-514, AUNP 12, Indoximod, NLG-919, INCB024360, KN035, and combinations thereof.

~~36. — A method of modulating an immune response in an individual, the method comprising administering to the individual an effective amount of the T-cell modulatory multimeric polypeptide of any one of claims 1-26, wherein said administering induces an epitope-specific T cell response and an epitope-non-specific T cell response, and wherein the ratio of the epitope-specific T cell response to the epitope-non-specific T cell response is at least 2:1.~~

~~3726. Use of a T-cell modulatory multimeric polypeptide of any one of claims 1-16 in the manufacture of a medicament for A method of delivering an immunomodulatory polypeptide selectively to a target T cell in a mixed population comprising non-target T cells and the target T cell, wherein the target T cell is specific for the WT-1 epitope present within the T-cell modulatory multimeric polypeptide, and wherein said immunomodulatory polypeptide present within the T-cell modulatory multimeric polypeptide is delivered to the target T cell, the method comprising contacting a mixed population of T cells with a T-cell modulatory multimeric polypeptide of any one of claims 1-26, wherein the mixed population of T cells comprises the target T cell and non-target T cells, wherein the target T cell is specific for the WT-1 epitope present within the T-cell modulatory multimeric polypeptide, and wherein said contacting delivers the one or more immunomodulatory polypeptides present within the T-cell modulatory multimeric polypeptide to the target T cell.~~

~~3827. A method of detecting, in a mixed population of T cells obtained from an individual, the presence of a target T cell that binds a WT-1 epitope, the method comprising:~~

~~a) contacting *in vitro* the mixed population of T cells with the T-cell modulatory multimeric polypeptide of any one of claims 1-2616, wherein the T-cell modulatory multimeric polypeptide comprises the WT-1 epitope; and~~

~~b) detecting activation and/or proliferation of T cells in response to said contacting, wherein activated and/or proliferated T cells indicates the presence of the target T cell.~~

~~39. — A T-cell modulatory multimeric polypeptide (TMMP) comprising:
at least one heterodimer comprising:~~

~~—— a) a first polypeptide comprising, in order from N-terminus to C-terminus:~~

- _____ i) a Wilms tumor 1 (WT-1) peptide, wherein the WT-1 peptide has the amino acid sequence VLDFAPPGA (SEQ ID NO:259);
- _____ ii) a linker having the amino acid sequence GCGSGGGSGGGGS (SEQ ID NO:317); and
- _____ iii) a $\beta 2$ -microglobulin polypeptide comprising the amino acid sequence set forth in SEQ ID NO:311; and
- _____ b) a second polypeptide comprising, in order from N-terminus to C-terminus:
 - _____ i) a variant IL-2 polypeptide comprising the amino acid sequence set forth in SEQ ID NO:188, where X_1 is Ala and where X_2 is Ala;
 - _____ ii) a (GGGS)₄ linker;
 - _____ iii) a variant IL-2 polypeptide comprising the amino acid sequence set forth in SEQ ID NO:188, where X_1 is Ala and where X_2 is Ala;
 - _____ iv) a major histocompatibility complex (MHC) heavy chain polypeptide comprising the amino acid sequence set forth in SEQ ID NO:341;
 - _____ v) a linker comprising the amino acid sequence AAAGG; and
 - _____ vi) an immunoglobulin (Ig)-Fc polypeptide.

40. _____ A TMMP of claim 39, wherein the Ig-Fc polypeptide is a variant Ig-Fc polypeptide comprising one or more sequence variations relative to the wild-type polypeptide, wherein the ability of the Ig-Fc polypeptide to induce cell lysis through complement-dependent cytotoxicity (CDC) and/or antibody-dependent cellular cytotoxicity (ADCC) is reduced or substantially eliminated, optionally wherein the Ig-Fc polypeptide comprises an amino acid sequence having at least at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to an amino acid sequence of an Fc region depicted in FIG. 5A-5G or 5H.

41. _____ A TMMP of claim 40, wherein the Ig-Fc polypeptide is a variant human IgG1-Fc polypeptide comprising comprises an L234A and/or L235A substitutions (L14 and L15 in the amino acid sequence depicted in FIG. 5H).

42. _____ A TMMP of any one of claims 39-41, wherein the first polypeptide comprises construct 2380 having the amino acid sequence set forth in FIG. 14B and SEQ ID NO:423; and where the second polypeptide comprises construct 1715A having the amino acid sequence set forth in FIG. 14J and SEQ ID NO:486.

43. _____ A TMMP comprising a homodimer of the heterodimer of any one of claims 39-42.

44. — A nucleic acid comprising a nucleotide sequence encoding the first and/or the second polypeptide of any one of claims 39-42.
45. — An expression vector comprising the nucleic acid of claim 44.
46. — A genetically modified host cell, wherein the host cell is genetically modified with a nucleic acid of claim 44 or an expression vector of claim 45.
47. — A method of making a T-cell modulatory multimeric polypeptide (TMMP), the method comprising culturing the genetically modified host cell of claim 46 *in vitro* in a culture medium under conditions such that the host cell synthesizes the TMMP.
48. — A method of selectively modulating the activity of T-cell specific for a Wilms tumor-1 (WT-1) epitope, the method comprising contacting the T-cell with a T-cell modulatory multimeric polypeptide according to any one of claims 39-43, wherein said contacting selectively modulates the activity of the WT-1 epitope-specific T-cell.
49. — A method of treating a patient having a cancer associated with WT-1, the method comprising administering to the patient an effective amount of a pharmaceutical composition comprising T-cell modulatory multimeric polypeptide according to any one of claims 39-43.
50. — A method of claim 49, wherein the cancer is acute myeloid leukemia, myeloma, ovarian cancer, pancreatic cancer, non-small cell lung cancer, colorectal cancer, breast cancer, Wilms tumor, mesothelioma, soft tissue sarcoma, neuroblastoma, or nephroblastoma.
51. — A method of 49 or 50, further comprising administering one or more immune checkpoint inhibitors to the individual.
52. — A method according to claim 51, wherein the immune checkpoint inhibitor is an antibody that binds to a polypeptide selected from the group consisting of CD27, CD28, CD40, CD122, CD96, CD73, CD47, OX40, GITR, CSF1R, JAK, PI3K delta, PI3K gamma, TAM, arginase, CD137, ICOS, A2AR, B7-H3, B7-H4, BTLA, CTLA-4, LAG3, TIM3, VISTA, CD96, TIGIT, CD122, PD-1, PD-L1, and PD-L2.

~~53. — A method according to claim 52, wherein the immune checkpoint inhibitor is an antibody specific for PD-1, PD-L1, or CTLA4.~~

~~54. — A method according to claim 52 or 53, wherein the one or more immune checkpoint inhibitors is selected from the group consisting of nivolumab, pembrolizumab, pidilizumab, AMP 224, MPDL3280A, MDX 1105, MEDI 4736, avelumab, ipilimumab, tremelimumab, pidilizumab, IMP321, MGA271, BMS-986016, lirilumab, urelumab, PF 05082566, IPH2101, MEDI 6469, CP 870,893, Mergamulizumab, Varlilumab, Avelumab, Galiximab, AMP 514, AUNP 12, Indoximod, NLG 919, INCB024360, KN035, and combinations thereof.~~