

Claims:

1. An isolated monoclonal antibody, comprising a CD152-binding domain, wherein the CD152-binding domain comprises an immunoglobulin heavy chain variable region comprising CDR1, CDR2, and CDR3, wherein the CDR1, CDR2, and CDR3 comprise amino acid sequences having at least 80%, 85%, 88%, 90%, 92%, 95%, 97%, 98%, 99%, or 100% identity to of

(1) SEQ ID NOs: ~~4, 5~~184, 185 and ~~6~~186, respectively; or

(2) SEQ ID NOs: 10, 11 and 12, respectively;

(3) ~~SEQ ID NOs: 16, 17 and 18, respectively;~~

(4) ~~SEQ ID NOs: 22, 23 and 24, respectively;~~

(5) ~~SEQ ID NOs: 28, 29 and 30, respectively;~~

(6) ~~SEQ ID NOs: 34, 35 and 36, respectively;~~

(7) ~~SEQ ID NOs: 40, 41 and 42, respectively;~~

(8) ~~SEQ ID NOs: 46, 47 and 48, respectively;~~

(9) ~~SEQ ID NOs: 52, 53 and 54, respectively;~~

(10) ~~SEQ ID NOs: 58, 59 and 60, respectively;~~

(11) ~~SEQ ID NOs: 64, 65 and 66, respectively;~~

(12) ~~SEQ ID NOs: 70, 71 and 72, respectively;~~

(13) ~~SEQ ID NOs: 76, 77 and 78, respectively;~~

(14) ~~SEQ ID NOs: 82, 83 and 84, respectively;~~

(15) ~~SEQ ID NOs: 88, 89 and 90, respectively;~~

(16) ~~SEQ ID NOs: 94, 95 and 96, respectively;~~

(17) ~~SEQ ID NOs: 100, 101 and 102, respectively;~~

(18) ~~SEQ ID NOs: 106, 107 and 108, respectively;~~

(19) ~~SEQ ID NOs: 112, 113 and 114, respectively;~~

(20) ~~SEQ ID NOs: 118, 119 and 120, respectively;~~

(21) ~~SEQ ID NOs: 124, 125 and 126, respectively;~~

(22) ~~SEQ ID NOs: 130, 131 and 132, respectively;~~

(23) ~~SEQ ID NOs: 136, 137 and 138, respectively;~~

(24) ~~SEQ ID NOs: 142, 143 and 144, respectively;~~

(25) ~~SEQ ID NOs: 148, 149 and 150, respectively;~~

(26) ~~SEQ ID NOs: 154, 155 and 156, respectively;~~

(27) SEQ ID NOs: 160, 161 and 162, respectively;
(28) SEQ ID NOs: 166, 167 and 168, respectively;
(29) SEQ ID NOs: 172, 173 and 174, respectively;
(30) SEQ ID NOs: 178, 179 and 180, respectively;
(31) SEQ ID NOs: 184, 185 and 186, respectively; or
(32) SEQ ID NOs: 190, 191 and 192, respectively.

2. The isolated monoclonal antibody of claim 1, wherein the antibody is a heavy-chain-only antibody.

3. The isolated monoclonal antibody of claim 1 or 2, wherein the antibody comprises two immunoglobulin heavy chains.

4. The isolated monoclonal antibody of any one of claims 1 to 3, wherein the antibody consists of two immunoglobulin heavy chains.

5. The isolated monoclonal antibody of any one of claims 1 to 4, wherein the immunoglobulin heavy chain variable region comprises an amino acid sequence having at least ~~80%, 85%, 88%,~~ 90%, 92%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NOs: ~~3183, 9, 15, 21, 27, 33, 39,~~ 45, 51, 57, 63, 69, 75, 81, 87, 93, 99, or 105, 111, 117, 123, 129, ~~135, 141, 147, 153, 159, 165,~~ 171, 177, 183, ~~or 189.~~

6. The isolated monoclonal antibody of any one of claim 3 to 5, wherein at least one of the two immunoglobulin heavy chains comprises an amino acid sequence having at least ~~80%, 85%, 88%,~~ 90%, 92%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NOs: ~~2182, 8, 14, 20, 26, 32, 38,~~ 44, 50, 56, 62, 68, 74, 80, 86, 92, 98, 104, 110, 116, 122, 128, 134, 140, 146, 152, 158, 164, or 170, 176, 182, ~~or 188.~~

7. The isolated monoclonal antibody of any one of claims 1 to 6, which exhibits one or a combination of the following properties: (a) binding to human CD152; (b) ~~binds~~binding specifically to monkey CD152; (c) not binding to mouse CD152; (d) blocking the binding of CD152 to CD80, CD86, or both; (e) promoting secretion of IL-2 by immune cells; (f) inducing T-cell activation; (g) stimulating an anti-tumor immune response by immune cells.

8. The isolated monoclonal antibody of any one of claims 1 to 7, which exhibits one or a combination of the following properties: (a) binding to human CD152 with an affinity higher than that of an ipilimumab analogue; (b) binding to human CD152 with the affinity that is at least 2-fold, at least 5-fold, at least 10-fold, at least 20-fold, at least 30-fold, at least 50-fold, or at least 100-fold higher than that of an ipilimumab analogue; (c) dissociating from human CD152 with a K_d of 1.0×10^{-9} M or less; (d) dissociating from human CD152 with the K_d that is lower than that of an ipilimumab analogue; (e) dissociating from human CD152 with the K_d that is at least 2-fold, at least 5-fold, at least 10-fold, at least 20-fold, at least 30-fold, at least 50-fold, or at least 100-fold lower than that of an ipilimumab analogue.
9. The isolated monoclonal antibody of any one of claims 1 to 8, wherein the antibody dissociates from human CD152 with a K_d of 6.0×10^{-11} M or less.
10. The isolated monoclonal antibody of any one of claims 1 to 9, wherein the antibody is a human, ~~humanized, or chimeric~~ antibody.
11. A pharmaceutical composition, comprising the isolated monoclonal antibody of any of claims 1 to 10, and a pharmaceutically acceptable excipient.
12. The pharmaceutical composition of claim 11, wherein the pharmaceutically acceptable excipient is selected from the group consisting of carriers, surface active agents, thickening or emulsifying agents, solid binders, dispersion or suspension aids, solubilizers, colorants, flavoring agents, coatings, disintegrating agents, lubricants, sweeteners, preservatives, isotonic agents, and a combination thereof.
13. The pharmaceutical composition of claim 11 or 12, further comprising a second antibody, wherein the second antibody is an immunostimulatory antibody or costimulatory antibody.
14. The pharmaceutical composition of claim 13, wherein the immunostimulatory antibody is selected from the group consisting of an anti-PD-1 antibody, an anti-PD-L1 antibody, an anti-LAG-3 antibody, an anti-TIM 3 antibody, an anti-STAT3 antibody, and an anti-ROR1 antibody.
15. The pharmaceutical composition of claim 13 or 14, wherein the costimulatory antibody is an anti-CD137 antibody or an anti-GITR antibody.

16. A nucleic acid molecule encoding the isolated antibody of any one of claims 1 to 10.
17. The nucleic acid molecule of claim 16, wherein the nucleic acid molecule comprises a nucleotide sequence having at least 80%, 85%, 88%, 90%, 92%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: ~~1181~~, 7, ~~13, 19, 25, 31, 37, 43, 49, 55, 61, 67, 73, 79, 85, 91, 97, 103, 109, 115, 121, 127, 133, 139, 145, 151, 163, 169, 175, 181, or 187~~169.
18. An expression vector comprising the nucleic acid molecule of claim 16 or 17, wherein the nucleic acid molecule is operatively linked to regulatory sequences suitable for expression of the nucleic acid segment in a host cell.
19. A host cell comprising the expression vector of claim 18.
20. ~~A method of~~Use of the isolated antibody of any one of claims 1 to 10 in preparation of a composition for inducing an antibody-dependent cell-mediated cytotoxicity (ADCC) against a cell ~~CD152-expressing a tumor associated antigen, the method~~cell, wherein said inducing comprising contacting a ~~TNK~~ cell with the isolated antibody ~~of any one of claims 1 to 10, and~~ wherein said contacting is under conditions whereby the ADCC against the cell ~~CD152-expressing the tumor associated antigen cell~~ is induced.
21. Use of the isolated monoclonal antibody of any one of claims 1 to 10 or the pharmaceutical composition of any one of claims 11 to 15 in preparation of a medicament for treating a disorder, wherein the disorder is a cancer or an autoimmune disease.
22. The use of claim 21, wherein the disorder is a cancer.
23. The use of claim 22, wherein the cancer is selected from the group consisting of leukemia, lymphoma, CLL, small lymphocytic lymphoma, marginal cell B-Cell lymphoma, Burkett's Lymphoma, renal cell carcinoma, colon cancer, colorectal cancer, breast cancer, epithelial squamous cell cancer, melanoma, myeloma, stomach cancer, brain cancer, lung cancer, pancreatic cancer, cervical cancer, ovarian cancer, liver cancer, bladder cancer, prostate cancer, testicular cancer, thyroid cancer, and head and neck cancer.
24. The use of any one of claims 21 to 23, wherein the medicament further contains an additional therapeutic agent.

25. The use of claim 24, wherein the additional therapeutic agent is an anti-cancer agent.

26. The use of claim 24, wherein the additional therapeutic agent is Ipilimumab ~~and/or~~ and/or a biosimilar product thereof.

27. The use of claim 21, wherein the disorder is an autoimmune disease.