

SUMMARY

[0022] Anti-VISTA antibodies known prior to the instant disclosure have exhibited numerous shortcomings, including failing to address the fact that multiple ligands bind to the VISTA receptor, the potential for antibody-dependent cellular cytotoxicity (ADCC) of VISTA-expressing immune cells and toxic cytokine release, anti-drug antibody or immunogenicity, multiple binding epitopes on VISTA that have varying efficacy and toxicity, and un-optimized Fc binding. The inventors of the instant application have harnessed the knowledge of these shortcomings to design novel anti-VISTA antibodies, and antigen-binding fragments thereof, which overcome these concerns. Each of these aspects are described in more detail below.

[0023] To begin with, most known anti-VISTA antibodies bind to one of two dominant epitopes on the VISTA extracellular domain. The first epitope, R54/F62/Q63, is associated with anti-tumor efficacy, but is also associated with significant cytokine release and inflammation, creating serious safety concerns for therapeutic treatment. The second epitope, H121/H122/H123 confers pH sensitive binding and increased PK, but eliminates most anti-tumor activity. The inventors of the instant application have identified the anti-VISTA antibodies, and antigen-binding fragments thereof, disclosed herein, which bind to a third proprietary epitope, and which exhibit improved safety and excellent single agent efficacy in tumor models (see Examples herein).

[0024] Secondly, previously known anti-VISTA antibodies have been shown to block only one, two, or (at most) three of the known VISTA ligands either at pH 6.0 or pH 7.4. In contrast, the anti-VISTA antibodies, and antigen-binding fragments described herein, are able to block the binding of all five known ligands to VISTA over a range of pH's from 6.0 to 7.4, providing increased efficacy.

[0025] Additionally, the anti-VISTA antibodies, and antigen-binding fragments thereof, described herein, have been Fc-optimized to provide reduce Fcγ receptor binding and, therefore, reduced ADCC, CDC (complement-dependent cytotoxicity), and proinflammatory cytokine release, providing increased safety for therapeutic administration. Several anti-VISTA antibodies described herein have been further Fc-optimized to increase FcRn binding and, therefore, increase antibody recycling and prolonged exposure. Finally, the anti-VISTA antibodies and antigen-binding fragments described herein were developed using a genetically engineered humanized mouse model, conferring a further advantage related to decreased immunogenicity in humans. Thus, the anti-VISTA antibodies, and antigen-binding fragments thereof, described herein exhibit surprising and improved properties over anti-VISTA antibodies known prior to the instant disclosure, and uses thereof.

[0026] Accordingly, in one ~~aspect~~example, disclosed herein is a human anti-VISTA antibody, or an antigen-binding fragment thereof, which (i) blocks the binding of all five known ligands to VISTA (VSIG-3 (V-set and immunoglobulin domain containing 3), VSIG-8 (V-set and immunoglobulin domain containing 8), PSGL-1 (P-selectin glycoprotein ligand-1), LRIG1 (leucine rich repeats and immunoglobulin like domains 1) and VISTA) at pH 6.0 and/or pH 7.4; and/or (ii) binds to a unique

epitope including amino acid Tyrosine 37, Arginine 54, Valine 117 and Arginine 127 of VISTA-ECD (extracellular domain).

[0027] In one aspect, ~~the present disclosure refers to disclosed herein is~~ an antibody, or an antigen-binding fragment thereof, that binds to V-domain Ig-containing Suppressor of T cell Activation (VISTA), wherein the antibody, or antigen-binding fragment thereof, blocks binding of all five ligands to VISTA at pH 6.0 and pH 7.4, wherein the five known ligands to VISTA are VSIG-3 (V-set and immunoglobulin domain containing 3), VSIG-8 (V-set and immunoglobulin domain containing 8), PSGL-1 (P-selectin glycoprotein ligand-1), LRIG1 (leucine rich repeats and immunoglobulin like domains 1) and VISTA; and wherein the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region (VH) and a light chain variable region (VL).

[0028] In another ~~aspect~~example, disclosed herein is an antibody, or an antigen-binding fragment thereof, that binds to V-domain Ig-containing Suppressor of T cell Activation (VISTA), wherein the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to, comprises, or consists of any one of SEQ ID NOs: 584-597, 227-246, and 383-386, and wherein the VL comprises a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to, comprises, or consists of any one of SEQ ID NOs: 84-110. In one ~~embodiment~~example, the antibody, or antigen-binding fragment thereof, blocks binding of all five ligands to VISTA at pH 6.0 and pH 7.4, wherein the five known ligands to VISTA are VSIG-3 (V-set and immunoglobulin domain containing 3), VSIG-8 (V-set and immunoglobulin domain containing 8), PSGL-1 (P-selectin glycoprotein ligand-1), LRIG1 (leucine rich repeats and immunoglobulin like domains 1) and VISTA. In another ~~embodiment~~example, the antibody, or antigen-binding fragment thereof comprises a VH CDR1 of any one of SEQ ID NOs: 247-253 as defined by Kabat numbering system; any one of SEQ ID NOs: 284-291 as defined by IMGT numbering system; or any one of SEQ ID NOs: 318-325 as defined by Paratome numbering system; a VH CDR2 of any one of SEQ ID NOs: 254-265 as defined by Kabat numbering system; any one of SEQ ID NOs: 292-298 as defined by IMGT numbering system; or any one of SEQ ID NOs: 326-339 as defined by Paratome numbering system; a VH CDR3 of any one of SEQ ID NOs: 266-283 as defined by Kabat numbering system; any one of SEQ ID NOs: 299-317 as defined by IMGT numbering system; or any one of SEQ ID NOs: 340-359 as defined by Paratome numbering system; a VL CDR1 of any one of SEQ ID NOs: 111-122 as defined by Kabat numbering system; any one of SEQ ID NOs: 152-162 as defined by IMGT numbering system; or any one of SEQ ID NOs: 188-196 or 576-578 as defined by Paratome numbering system; a VL CDR2 of any one of SEQ ID NOs: 123-131 and 575 as defined by Kabat numbering system; any one of SEQ ID NOs: 163-167 as defined by IMGT numbering system; or any one of SEQ ID NOs: 197-206 as defined by Paratome numbering system, a VL CDR3 of any one of SEQ ID NOs: 132-151 as defined by Kabat numbering system; any one of SEQ ID NOs: 168-

186 as defined by IMGT numbering system; or any one of SEQ ID NOs: 207-226 as defined by Paratome numbering system.

[0029] In one aspect, the present disclosure refers to an antibody, or antigen-binding fragment thereof, that binds to VISTA, wherein the antibody or antigen-binding fragment thereof, comprises a VH and a VL, wherein the VH comprises: a VH CDR1 of any one of SEQ ID NOs: 249, 247, 248, or 250-253 as defined by Kabat numbering system; any one of SEQ ID NOs: 286, 284, 285, or 287-291 as defined by IMGT numbering system; or any one of SEQ ID NOs: 320, 318, 319, or 321-325 as defined by Paratome numbering system, a VH CDR2 of any one of SEQ ID NOs: 256, 254, 255, or 257-265 as defined by Kabat numbering system; any one of SEQ ID NOs: 294, 292, 293, or 295-298 as defined by IMGT numbering system; or any one of SEQ ID NOs: 328, 326, 327, or 329-339 as defined by Paratome numbering system, a VH CDR3 of any one of SEQ ID NOs: 268, 266, 267, or 269-283 as defined by Kabat numbering system; any one of SEQ ID NOs: 301, 299, 300, or 302-317 as defined by IMGT numbering system; or any one of SEQ ID NOs: 342, 340, 341, or 343-359 as defined by Paratome numbering system, and wherein the VL comprises: a VL CDR1 of any one of SEQ ID NOs: 113, 111, 112, or 114-122 as defined by Kabat numbering system; any one of SEQ ID NOs: 154, 152, 153, or 155-162 as defined by IMGT numbering system; or any one of SEQ ID NOs: 190, 188, 189, 191-196 or 576-578 as defined by Paratome numbering system, a VL CDR2 of any one of SEQ ID NOs: 125, 123, 124, or 126-131 and 575 as defined by Kabat numbering system; any one of SEQ ID NOs: 165, 163, 164, or 166-167 as defined by IMGT numbering system; or any one of SEQ ID NOs: 199, 197, 198, or 200-206 as defined by Paratome numbering system, and a VL CDR3 of any one of SEQ ID NOs: 134, 132, 133, or 135-151 as defined by Kabat numbering system; any one of SEQ ID NOs: 170, 168, 169, 171-186 as defined by IMGT numbering system; or any one of SEQ ID NOs: 209, 207, 208, or 210-226 as defined by Paratome numbering system. In another example, there is disclosed herein is an antibody, or antigen-binding fragment thereof, that binds to VISTA, wherein the antibody or antigen-binding fragment thereof, comprises a VH and a VL, wherein the VH comprises: a VH CDR1 of any one of SEQ ID NOs: 247-253 as defined by Kabat numbering system; any one of SEQ ID NOs: 284-291 as defined by IMGT numbering system; or any one of SEQ ID NOs: 318-325 as defined by Paratome numbering system, a VH CDR2 of any one of SEQ ID NOs: 254-265 as defined by Kabat numbering system; any one of SEQ ID NOs: 292-298 as defined by IMGT numbering system; or any one of SEQ ID NOs: 326-339 as defined by Paratome numbering system, a VH CDR3 of any one of SEQ ID NOs: 266-283 as defined by Kabat numbering system; any one of SEQ ID NOs: 299-317 as defined by IMGT numbering system; or any one of SEQ ID NOs: 340-359 as defined by Paratome numbering system, and wherein the VL comprises: a VL CDR1 of any one of SEQ ID NOs: 111-122 as defined by Kabat numbering system; any one of SEQ ID NOs: 152-162 as defined by IMGT numbering system; or any one of SEQ ID NOs: 188-196 or 576-578 as defined by Paratome numbering system, a VL CDR2 of any one of SEQ ID NOs: 123-131 and 575 as defined by Kabat numbering system; any one of SEQ ID NOs: 163-167

as defined by IMGT numbering system; or any one of SEQ ID NOs: 197-206 as defined by Paratome numbering system, and a VL CDR3 of any one of SEQ ID NOs: 132-151 as defined by Kabat numbering system; any one of SEQ ID NOs: 168-186 as defined by IMGT numbering system; or any one of SEQ ID NOs: 207-226 as defined by Paratome numbering system. In one

embodimentexample, the antibody, or antigen-binding fragment thereof, blocks binding of all five ligands to VISTA at pH 6.0 and pH 7.4, wherein the five known ligands to VISTA are VSIG-3 (V-set and immunoglobulin domain containing 3), VSIG-8 (V-set and immunoglobulin domain containing 8), PSGL-1 (P-selectin glycoprotein ligand-1), LRIG1 (leucine rich repeats and immunoglobulin like domains 1) and VISTA.

[0030] In one embodimentexample, the VH comprises a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to, comprises, or consists of any one of SEQ ID NOs: 584-597, 227-246, and 383-386, and the VL comprises a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to, comprises, or consists of any one of SEQ ID NOs: 84-110.

[0031] In another embodimentexample, the VH CDR1 comprises SEQ ID NO: 247, the VH CDR2 comprises SEQ ID NO: 254, the VH CDR3 comprises SEQ ID NO: 266, the VL CDR1 comprises SEQ ID NO: 111, the VL CDR2 comprises SEQ ID NO: 123, and the VL CDR3 comprises SEQ ID NO: 132; the VH CDR1 comprises SEQ ID NO: 284, the VH CDR2 comprises SEQ ID NO: 292, the VH CDR3 comprises SEQ ID NO: 299, the VL CDR1 comprises SEQ ID NO: 152, the VL CDR2 comprises SEQ ID NO: 163, and the VL CDR3 comprises SEQ ID NO: 168; the VH CDR1 comprises SEQ ID NO: 318, the VH CDR2 comprises SEQ ID NO: 326, the VH CDR3 comprises SEQ ID NO: 340, the VL CDR1 comprises SEQ ID NO: 188, the VL CDR2 comprises SEQ ID NO:

CDR2 comprises SEQ ID NO: 165, and the VL CDR3 comprises SEQ ID NO: 173; or the VH CDR1 comprises SEQ ID NO: 319, the VH CDR2 comprises SEQ ID NO: 331, the VH CDR3 comprises SEQ ID NO: 345, the VL CDR1 comprises SEQ ID NO: 193, the VL CDR2 comprises SEQ ID NO: 200, and the VL CDR3 comprises SEQ ID NO: 212.

[0032] In another example embodiment, the VH CDR1 comprises SEQ ID NO: 247, SEQ ID NO: 284 or SEQ ID NO: 318, the VH CDR2 comprises SEQ ID NO: 254, SEQ ID NO: 292 or SEQ ID NO: 326, the VH CDR3 comprises SEQ ID NO: 266, SEQ ID NO: 299 or SEQ ID NO: 340, the VL CDR1 comprises SEQ ID NO: 111, SEQ ID NO: 152 or SEQ ID NO: 188, the VL CDR2 comprises SEQ ID NO: 123, SEQ ID NO: 163 or SEQ ID NO: 197, and the VL CDR3 comprises SEQ ID NO: 132, SEQ ID NO: 168 or SEQ ID NO: 207; the VH CDR1 comprises SEQ ID NO: 248, SEQ ID NO: 285 or SEQ ID NO: 319, the VH CDR2 comprises SEQ ID NO: 255, SEQ ID NO: 293 or SEQ ID NO: 327, the VH CDR3 comprises SEQ ID NO: 267, SEQ ID NO: 300 or SEQ ID NO: 341, the VL CDR1 comprises SEQ ID NO: 112, SEQ ID NO: 153 or SEQ ID NO: 189, the VL CDR2 comprises SEQ ID NO: 124, SEQ ID NO: 164 or SEQ ID NO: 198, and the VL CDR3 comprises SEQ ID NO: 133, SEQ ID NO: 169 or SEQ ID NO: 208; the VH CDR1 comprises SEQ ID NO: 249, SEQ ID NO: 286 or SEQ ID NO: 320, the VH CDR2 comprises SEQ ID NO: 256, SEQ ID NO: 294 or SEQ ID NO: 328, the VH CDR3 comprises SEQ ID NO: 268, SEQ ID NO: 301 or SEQ ID NO: 342, the VL CDR1 comprises SEQ ID NO: 113, SEQ ID NO: 154 or SEQ ID NO: 190, the VL CDR2 comprises SEQ ID NO: 125, SEQ ID NO: 165, or SEQ ID NO: 199, and the VL CDR3 comprises SEQ ID NO: 134, SEQ ID NO: 170 or SEQ ID NO: 209; the VH CDR1 comprises SEQ ID NO: 250, SEQ ID NO: 287, or SEQ ID NO: 321, the VH CDR2 comprises SEQ ID NO: 257, SEQ ID NO: 295 or SEQ ID NO: 332, the VH CDR3 comprises SEQ ID NO: 269, SEQ ID NO: 302 or SEQ ID NO: 346, the VL CDR1 comprises SEQ ID NO: 114, SEQ ID NO: 155 or SEQ ID NO: 191, the VL CDR2 comprises SEQ ID NO: 126, SEQ ID NO: 165 or SEQ ID NO: 200, and the VL CDR3 comprises SEQ ID NO: 135, SEQ ID NO: 171 or SEQ ID NO: 210; the VH CDR1 comprises SEQ ID NO: 251, SEQ ID NO: 288 or SEQ ID NO: 322, the VH CDR2 comprises SEQ ID NO: 258, SEQ ID NO: 295 or SEQ ID NO: 333, the VH CDR3 comprises SEQ ID NO: 270, SEQ ID NO: 303 or SEQ ID NO: 344, the VL CDR1 comprises SEQ ID NO: 115, SEQ ID NO: 156 or SEQ ID NO: 192, the VL CDR2 comprises SEQ ID NO: 127, SEQ ID NO: 166 or SEQ ID NO: 201, and the VL CDR3 comprises SEQ ID NO: 136, SEQ ID NO: 172 or SEQ ID NO: 211; or the VH CDR1 comprises SEQ ID NO: 248, SEQ ID NO: 185 or SEQ ID NO: 319, the VH CDR2 comprises SEQ ID NO: 259, SEQ ID NO: 296 or SEQ ID NO: 331, the VH CDR3 comprises SEQ ID NO: 271, SEQ ID NO: 304 or SEQ ID NO: 345, the VL CDR1 comprises SEQ ID NO: 116, SEQ ID NO: 157 or SEQ ID NO: 193, the VL CDR2 comprises SEQ ID NO: 126, SEQ ID NO: 165 or SEQ ID NO: 200, and the VL CDR3 comprises SEQ ID NO: 137, SEQ ID NO: 173 or SEQ ID NO: 212.

[0033] In another example embodiment, (i) the VH comprises a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to, comprises, or consists of SEQ ID NO:

91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to, comprises, or consists of SEQ ID NO: 87; (xiii) the VH comprises a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to, comprises, or consists of SEQ ID NO: 594, and the VL comprises a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to, comprises, or consists of SEQ ID NO: 884; or (xiv) the VH comprises a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to, comprises, or consists of SEQ ID NO: 595, and the VL comprises a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to, comprises, or consists of SEQ ID NO: 89.

[0034] In one exampleembodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain (HC) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to, comprises, or consists of any one of SEQ ID NOs: 407-477, 572-574, and 604-609, and a light chain (LC) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to, comprises, or consists of any one of SEQ ID NOs: 387-406, 569-571, and 598-603.

[0035] In one exampleembodiment, the antibody, or antigen-binding fragment thereof, binds to human VISTA (amino acids 33-311 of SEQ ID NO:377). In one exampleembodiment, the antibody, or antigen-binding fragment thereof, specifically binds to human VISTA (amino acids 33-311 of SEQ ID NO:377). In one exampleembodiment, the antibody, or antigen-binding fragment thereof, binds to an epitope of human VISTA comprising the amino acid sequence HLHHG (amino acids 98-102 of SEQ ID NO: 377) or VVEIRHHHSEHR (amino acids 148-159 of SEQ ID NO: 377). In one exampleembodiment, the antibody, or antigen-binding fragment thereof, binds to an epitope of human VISTA comprising Tyrosine 37, Arginine 54, Valine 117 and Arginine 127 of SEQ ID NO:377.

[0036] In one exampleembodiment, the antibody, or antigen-binding fragment thereof, comprises an Fc region. In one exampleembodiment, the Fc region is a human Fc region or a variant of the human Fc region that has in the range of one to seven amino acid mutations in the Fc region relative to the native human Fc region. In one exampleembodiment, the human Fc region is of a human IgG1, human IgG2 or a human IgG4. In another exampleembodiment, the antibody comprises a constant region of a human IgG1 or a human IgG4 or a variant of the constant region that has in the range of one to seven amino acid mutations in the constant region relative to the native constant region.

[0037] In one exampleembodiment, (a) the Fc region is of a human IgG1, and wherein the mutations are selected from the group consisting of C220D, D221C, E233P, L234A, L234E, L234Y, L235A, L235E, L235F, G236A, G236W, G236R, G237A, P238S, S239D, F241A, M252Y, S254T, T256E, T256N, V264A, D265A, S267E, H268F, H268A, D270A, H268Q, E294deletion, N297A, N297G, N297E, S298A, T307P, E318A, K322A, S324T, K326A, K326M, L328R, P329A, P329G, A330L, A330S, P331A, P331S, I332E, E333A, E333S, K334A, A378V, S383N, M428L, N434S, and N434Y, wherein the residues are numbered using the EU numbering system; (b) the Fc region is of a human IgG2, and wherein the mutations are selected from the group consisting of C220D, G237A, P238S, S239D, F241A, M252Y, S254T, T256E, T256N, V264A, D265A, S267E, H268F, H268A, D270A,

H268Q, E294deletion, N297A, N297G, N297E, S298A, T307P, V309L, E318A, K322A, S324T, K326A, K326M, L328R, P329A, P329G, A330L, A330S, P331A, P331S, I332E, E333A, E333S, K334A, S383N, M428L, N434S, and N434Y, wherein the residues are numbered using the EU numbering system; or (c) the Fc region is of a human IgG4, and wherein the mutations are selected from the group consisting of S228P, E233P, F234A, L235A, L235E, L235F, G236A, G236W, G236R, G237A, P238S, S239D, F241A, M252Y, S254T, T256E, T256N, V264A, D265A, S267E, H268F, H268A, D270A, H268Q, E294deletion, N297A, N297G, N297E, S298A, T307P, V309L, E318A, K322A, S324T, K326A, K326M, L328R, P329A, P329G, I332E, E333A, E333S, K334A, A378V, S383N, M428L, N434S, and N434Y, wherein the residues are numbered using the EU numbering system.

[0038] In one ~~exampleembodiment~~, the antibody, or antigen-binding fragment thereof, is a bispecific antibody or a multispecific antibody. In one ~~exampleembodiment~~, the antigen-binding fragment is an Fv fragment, a Fab fragment, a F(ab')₂ fragment, or a single-chain Fv (scFv).

[0039] In one aspect, ~~the present disclosure refers to~~~~disclosed herein is~~ an antibody, or antigen-binding fragment thereof, which competes for binding to human VISTA (SEQ ID NO: 377) with any one of the antibodies, or antigen-binding fragments thereof, described herein. In one ~~aspectexample~~, disclosed herein is an antibody, or antigen-binding fragment thereof, which prevents binding of any one of the antibodies, or antigen-binding fragments thereof, described herein with human VISTA (SEQ ID NO: 377). In one ~~exampleembodiment~~, the binding is measured by an ELISA assay, surface plasmon resonance, or BLI, e.g., BLI on the Octet Red 96 (ForteBio System).

[0040] In another aspect, ~~the present disclosure refers to~~~~disclosed herein is~~ an antibody-drug conjugate comprising an antibody, or antigen-binding fragment thereof, disclosed herein and a therapeutic agent. In another aspect, ~~the present disclosure refers to~~~~disclosed herein is~~ a chimeric antigen receptor (CAR) comprising an scFv disclosed herein.

[0041] In another aspect, ~~disclosed herein is~~ the present disclosure refers to a polynucleotide comprising a nucleotide sequence encoding the VH, the VL, or the VH and the VL of the antibody, or antigen-binding fragment thereof, as disclosed herein. In another example, there is described a polynucleotide comprising a nucleotide sequence encoding the VH of an antibody, or antigen-binding fragment disclosed herein. In another ~~aspectexample~~, disclosed herein is a polynucleotide comprising a nucleotide sequence encoding the VL of an antibody, or antigen-binding fragment disclosed herein. In another ~~exampleaspect~~, disclosed herein is a polynucleotide comprising a nucleotide sequence encoding the VH and the VL of an antibody, or antigen-binding fragment disclosed herein.

[0042] In one aspect, ~~disclosed herein~~the present disclosure refers to is a cell comprising one or more polynucleotides encoding an antibody, or antigen-binding fragment thereof, disclosed herein.

[0043] In one aspect, ~~the present disclosure refers to~~~~disclosed herein is~~ a pharmaceutical composition comprising an antibody, or antigen-binding fragment thereof, an antibody-drug conjugate, or a CAR disclosed herein, and a pharmaceutically acceptable carrier.

[0044] In one aspect, ~~the present disclosure refers to~~~~disclosed herein is~~ a method of producing an antibody, or antigen-binding fragment thereof, disclosed herein, the method comprising culturing a cell under conditions

such that said one or more polynucleotides are expressed by the cell to produce the antibody, or antigen-binding fragment thereof, encoded by the polynucleotides.

[0045] In one aspect, the present disclosure refers to the use of the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating cancer, an autoimmune disease, and/or an infection in a subject in need thereof, optionally wherein the cancer is a non-small cell lung cancer, small cell lung cancer, a head and neck squamous cell carcinoma, an hepatocellular carcinoma, an ovarian cancer, a neuroblastoma, an oral cancer, a thyroid cancer, a breast cancer, a sarcoma, a pancreatic cancer, a colon cancer, a gastric cancer, a choriocarcinoma, a testicular cancer, a mesothelioma, a skin cancer, a renal cell carcinoma, a bladder cancer, a hematological cancer, a cervical cancer, a blood cancer, an acute myeloid leukemia, myelodysplastic syndrome, and/or a metastatic cancer. In one example, disclosed herein is a method of treating cancer, an autoimmune disease, and/or an infection in a subject in need thereof, comprising administering to the subject a pharmaceutical composition disclosed herein. In one ~~embodiment~~example, the method is for treating cancer. In one example~~embodiment~~, the method is for treating an autoimmune disease. In one example~~embodiment~~, the method is for treating an infection. In one example~~embodiment~~, the cancer is a non-small cell lung cancer, small cell lung cancer, a head and neck squamous cell carcinoma, an hepatocellular carcinoma, an ovarian cancer, a neuroblastoma, an oral cancer, a thyroid cancer, a breast cancer, a sarcoma, a pancreatic cancer, a colon cancer, a gastric cancer, a choriocarcinoma, a testicular cancer, a mesothelioma, a skin cancer, a renal cell carcinoma, a bladder cancer, a hematological cancer, or a cervical cancer. In one example~~embodiment~~, the cancer is a metastatic cancer. In one example~~embodiment~~, the cancer is a blood cancer, an acute myeloid leukemia, or a myelodysplastic syndrome. In one example~~embodiment~~, the method further comprises administering to the subject an additional therapy, optionally wherein the additional therapy is radiotherapy, a chemotherapeutic agent, a targeted therapy, a tyrosine kinase inhibitor, hormone therapy, and/or an immune checkpoint inhibitor. In one example~~embodiment~~, the immune checkpoint inhibitor is an inhibitor of Programmed Death-1 (PD-1), or Programmed death-ligand 1 (PDL1), or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4).

[0046] In one example~~aspect~~, provided-described herein is an antibody or an antigen-binding fragment thereof that binds, *e.g.*, specifically binds, to VISTA, wherein the antibody comprises a variable heavy chain region (VH) and a variable light chain region (VL). In one example~~embodiment~~, the VH comprises (i) a VH complementarity determining region (CDR) 1 of SEQ ID NO: 247, a VH CDR2 of SEQ ID NO: 254, and a VH CDR3 of SEQ ID NO: 266; (ii) a VH CDR 1 of SEQ ID NO: 284, a VH CDR2 of SEQ ID NO: 292, and a VH CDR3 of SEQ ID NO: 299; or (iii) a VH CDR1 of SEQ ID NO: 318, a VH CDR2 of SEQ ID NO: 326, and a VH CDR3 of SEQ ID NO: 340.

[0047] In another example~~aspect~~, provided-described herein is an antibody or an antigen-binding fragment thereof that specifically binds to VISTA, wherein the antibody comprises a VH and a VL, wherein the VH comprises (i) a VH CDR1 of SEQ ID NO: 248 a VH CDR2 of SEQ ID NO: 255, and

a VH CDR3 of SEQ ID NO: 267; (ii) a VH CDR1 of SEQ ID NO: 285, a VH CDR2 of SEQ ID NO: 293, and a VH CDR3 of SEQ ID NO: 300; or (iii) a VH CDR1 of SEQ ID NO: 319, a VH CDR2 of SEQ ID NO: 327, and a VH CDR3 of SEQ ID NO: 341.

[0048] In another ~~example~~ aspect, ~~provided-described~~ herein is an antibody or an antigen-binding fragment thereof that specifically binds to VISTA, wherein the antibody comprises a VH and a VL, wherein the VH comprises (i) a VH CDR1 of SEQ ID NO: 249, a VH CDR2 of SEQ ID NO: 256, and a VH CDR3 of SEQ ID NO: 268; (ii) a VH CDR 1 of SEQ ID NO: 286 a VH CDR2 of SEQ ID NO: 294, and a VH CDR3 of SEQ ID NO: 301; or (iii) a VH CDR 1 of SEQ ID NO: 320, a VH CDR2 of SEQ ID NO: 328, and a VH CDR3 of SEQ ID NO: 342.

[0049] In another example aspect, ~~provided-described~~ herein is an antibody or an antigen-binding fragment thereof that specifically binds to VISTA, wherein the antibody comprises a VH and a VL, wherein the VH comprises (i) a VH CDR1 of SEQ ID NO: 250, a VH CDR2 of SEQ ID NO: 257, and a VH CDR3 of SEQ ID NO: 269; (ii) a VH CDR1 of SEQ ID NO: 287, a VH CDR2 of SEQ ID NO: 295, and a VH CDR3 of SEQ ID NO: 302; or (iii) a VH CDR1 of SEQ ID NO: 321, a VH CDR2 of SEQ ID NO: 329, and a VH CDR3 of SEQ ID NO: 343.

[0050] In another example aspect, ~~provided-described~~ herein is an antibody or an antigen-binding fragment thereof that specifically binds to VISTA, wherein the antibody comprises a VH and a VL, wherein the VH comprises (i) a VH CDR1 of SEQ ID NO: 251, a VH CDR2 of SEQ ID NO: 258, and a VH CDR3 of SEQ ID NO: 270; (ii) a VH CDR1 of SEQ ID NO: 288, a VH CDR2 of SEQ ID NO: 295, and a VH CDR3 of SEQ ID NO: 303; or (iii) a VH CDR1 of SEQ ID NO: 322, a VH CDR2 of SEQ ID NO: 330, and a VH CDR3 of SEQ ID NO: 344.

[0051] In another example aspect, ~~provided-described~~ herein is an antibody or an antigen-binding fragment thereof that specifically binds to VISTA, wherein the antibody comprises a VH and a VL, wherein the VH comprises (i) a VH CDR1 of SEQ ID NO: 248, a VH CDR2 of SEQ ID NO: 259, and a VH CDR3 of SEQ ID NO: 271; (ii) a VH CDR1 of SEQ ID NO: 285, a VH CDR2 of SEQ ID NO: 296, and a VH CDR3 of SEQ ID NO: 304; or (iii) a VH CDR1 of SEQ ID NO: 319, a VH CDR2 of SEQ ID NO: 331, and a VH CDR3 of SEQ ID NO: 345.

[0052] In another example aspect, ~~provided-described~~ herein is an antibody or an antigen-binding fragment thereof that specifically binds to VISTA, wherein the antibody comprises a VH and a VL, wherein the VH comprises (i) a VH CDR1 of SEQ ID NO: 247, a VH CDR2 of SEQ ID NO: 254, and a VH CDR3 of SEQ ID NO: 277; (ii) a VH CDR1 of SEQ ID NO: 284, a VH CDR2 of SEQ ID NO: 292, and a VH CDR3 of SEQ ID NO: 310; or (iii) a CDR1 of SEQ ID NO: 318, a CDR2 of SEQ ID NO: 326, and a CDR3 of SEQ ID NO: 352.

[0053] In another example aspect, ~~provided-described~~ herein is an antibody or an antigen-binding fragment thereof that specifically binds to VISTA, wherein the antibody comprises a VH and a VL, wherein (i) the VH comprises a VH CDR1 of SEQ ID NO: 247, a VH CDR2 of SEQ ID NO: 254, and a VH CDR3 of SEQ ID NO: 266, and the VL comprises a VL CDR1 of SEQ ID NO: 111, a VL CDR2 of SEQ ID NO: 123, and a VL CDR3 of SEQ ID NO: 132; (ii) the VH comprises a VH CDR1 of SEQ ID NO: 284, a VH CDR2 of SEQ ID NO: 292, and a VH CDR3 of SEQ ID NO: 299, and the VL comprises a VL CDR1 of SEQ ID NO: 152, a VL CDR2 of SEQ ID NO: 163, and a VL CDR3 of SEQ ID NO: 168; or (iii) the VH comprises a VH CDR1 of SEQ ID NO: 318, a VH CDR2 of SEQ ID NO: 326, and a VH CDR3 of SEQ ID NO: 340, and the VL comprises a VL CDR1 of SEQ ID NO: 188, a VL CDR2 of SEQ ID NO: 197, and a VL CDR3 of SEQ ID NO: 207.

[0054] In another example aspect, ~~provided-described~~ herein is an antibody or an antigen-binding fragment thereof that specifically binds to VISTA, wherein the antibody comprises a VH and a VL, wherein (i) the VH comprises a VH CDR1 of SEQ ID NO: 248, a VH CDR2 of SEQ ID NO: 255, and a VH CDR3 of

SEQ ID NO: 267, and the VL comprises a VL CDR 1 of SEQ ID NO: 112, a VL CDR2 of SEQ ID NO: 124, and a VL CDR3 of SEQ ID NO: 133; (ii) the VH comprises a VH CDR1 of SEQ ID NO: 285, a VH CDR2 of SEQ ID NO: 293, and a VH CDR3 of SEQ ID NO: 300, and the VL comprises a VL CDR 1 of SEQ ID NO: 153, a VL CDR2 of SEQ ID NO: 164 and a VL CDR3 of SEQ ID NO: 169; or (iii) the VH comprises a VH CDR1 of SEQ ID NO: 319, a VH CDR2 of SEQ ID NO: 327, and a VH CDR3 of SEQ ID NO: 341, and the VL comprises a VL CDR 1 of SEQ ID NO: 189, a VL CDR2 of SEQ ID NO: 198, and a VL CDR3 of SEQ ID NO: 208.

[0055] In another ~~aspect~~example, ~~provided~~described herein is an antibody or an antigen-binding fragment thereof that specifically binds to VISTA, wherein the antibody comprises a VH and a VL, wherein (i) the VH comprises a VH CDR1 of SEQ ID NO: 249, a VH CDR2 of SEQ ID NO: 256, and a VH CDR3 of SEQ ID NO: 268, and the VL comprises a VL CDR1 of SEQ ID NO: 113, a VL CDR2 of SEQ ID NO: 125, and a VL CDR3 of SEQ ID NO: 134; (ii) the VH comprises a VH CDR1 of SEQ ID NO: 286, a VH CDR2 of SEQ ID NO: 294, and a VH CDR3 of SEQ ID NO: 301, and the VL comprises a VL CDR1 of SEQ ID NO: 154, a VL CDR2 of SEQ ID NO: 165, and a VL CDR3 of SEQ ID NO: 170; or (iii) the VH comprises a VH CDR1 of SEQ ID NO: 320, a VH CDR2 of SEQ ID NO: 328, and a VH CDR3 of SEQ ID NO: 342, and the VL comprises a VL CDR1 of SEQ ID NO: 190, a VL CDR2 of SEQ ID NO: 199, and a VL CDR3 of SEQ ID NO: 209.

[0056] In another ~~example~~aspect, ~~provided~~described herein is an antibody or an antigen-binding fragment thereof that specifically binds to VISTA, wherein the antibody comprises a VH and a VL, wherein (i) the VH comprises a VH CDR1 of SEQ ID NO: 250, a VH CDR2 of SEQ ID NO: 257, and a VH CDR3 of SEQ ID NO: 269, and the VL comprises a VL CDR1 of SEQ ID NO: 114, a VL CDR2 of SEQ ID NO: 126, and a VL CDR3 of SEQ ID NO: 135; (ii) the VH comprises a VH CDR1 of SEQ ID NO: 287, a VH CDR2 of SEQ ID NO: 295, and a VH CDR3 of SEQ ID NO: 302, and the VL comprises a VL CDR1 of SEQ ID NO: 155, a VL CDR2 of SEQ ID NO: 165, and a VL CDR3 of SEQ ID NO: 171; or (iii) the VH comprises a VH CDR1 of SEQ ID NO: 321, a VH CDR2 of SEQ ID NO: 329, and a VH CDR3 of SEQ ID NO: 343, and the VL comprises a VL CDR1 of SEQ ID NO: 191, a VL CDR2 of SEQ ID NO: 200, and a VL CDR3 of SEQ ID NO: 210.

[0057] In another ~~example~~aspect, ~~provided~~described herein is an antibody or an antigen-binding fragment thereof that specifically binds to VISTA, wherein the antibody comprises a VH and a VL, wherein (i) the VH comprises a VH CDR1 of SEQ ID NO: 251, a VH CDR2 of SEQ ID NO: 258, and a VH CDR3 of SEQ ID NO: 270, and the VL comprises a VL CDR1 of SEQ ID NO: 115, a VL CDR2 of SEQ ID NO: 127, and a VL CDR3 of SEQ ID NO: 136; (ii) the VH comprises a VH CDR1 of SEQ ID NO: 288, a VH CDR2 of SEQ ID NO: 295, and a VH CDR3 of SEQ ID NO: 303, and the VL comprises a VL CDR1 of SEQ ID NO: 156, a VL CDR2 of SEQ ID NO: 166, and a VL CDR3 of SEQ ID NO: 172; or (iii) the VH comprises a VH CDR1 of SEQ ID NO: 322, a VH CDR2 of SEQ ID NO: 330, and a VH CDR3 of SEQ ID NO: 344, and the VL comprises a VL CDR1 of SEQ ID NO: 192, a VL CDR2 of SEQ ID NO: 201, and a VL CDR3 of SEQ ID NO: 211.

[0058] In another ~~example~~aspect, ~~provided-described~~ herein is an antibody or an antigen-binding fragment thereof that specifically binds to VISTA, wherein the antibody comprises a VH and a VL, wherein (i) the VH comprises a VH CDR1 of SEQ ID NO: 248, a VH CDR2 of SEQ ID NO: 259, and a VH CDR3 of SEQ ID NO: 271, and the VL comprises a VL CDR1 of SEQ ID NO: 116, a VL CDR2 of SEQ ID NO: 126, and a VL CDR3 of SEQ ID NO: 137; (ii) the VH comprises a VH CDR1 of SEQ ID NO: 285, a VH CDR2 of SEQ ID NO: 296, and a VH CDR3 of SEQ ID NO: 304, and the VL comprises a VL CDR1 of SEQ ID NO: 157, a VL CDR2 of SEQ ID NO: 165, and a VL CDR3 of SEQ ID NO: 173; or (iii) the VH comprises a VH CDR1 of SEQ ID NO: 319, a VH CDR2 of SEQ ID NO: 331, and a VH CDR3 of SEQ ID NO: 345, and the VL comprises a VL CDR1 of SEQ ID NO: 193, a VL CDR2 of SEQ ID NO: 200, and a VL CDR3 of SEQ ID NO: 212.

[0059] In another ~~example~~aspect, ~~provided-described~~ herein is an antibody or an antigen-binding fragment thereof that specifically binds to VISTA, wherein the antibody comprises a VH and a VL, wherein (i) the VH comprises a VH CDR1 of SEQ ID NO: 247, a VH CDR2 of SEQ ID NO: 254, and a VH CDR3 of SEQ ID NO: 277, and the VL comprises a VL CDR1 of SEQ ID NO: 111, a VL CDR2 of SEQ ID NO: 123, and a VL CDR3 of SEQ ID NO: 132; (ii) the VH comprises a VH CDR1 of SEQ ID NO: 284, a VH CDR2 of SEQ ID NO: 292, and a VH CDR3 of SEQ ID NO: 310, and the VL comprises a VL CDR1 of SEQ ID NO: 152, a VL CDR2 of SEQ ID NO: 163, and a VL CDR3 of SEQ ID NO: 168; or (iii) the VH comprises a VH CDR1 of SEQ ID NO: 318, a VH CDR2 of SEQ ID NO: 326, and a VH CDR3 of SEQ ID NO: 352, and the VL comprises a VL CDR1 of SEQ ID NO: 168, a VL CDR2 of SEQ ID NO: 197, and a VL CDR3 of SEQ ID NO: 207.

[0060] In a specific ~~example~~embodiment, the VH comprises the sequence of SEQ ID NO: 584. In a specific ~~example~~embodiment, the VL comprises the sequence of SEQ ID NO: 84. In a specific ~~example~~embodiment, the VH comprises the sequence of SEQ ID NO: 584 and the VL comprises the sequence of SEQ ID NO: 84.

[0061] In a specific ~~example~~embodiment, the VH comprises the sequence of SEQ ID NO: 585. In a specific ~~example~~embodiment, the VL comprises the sequence of SEQ ID NO: 85. In a specific ~~example~~embodiment the VH comprises the sequence of SEQ ID NO: 585 and the VL comprises the sequence of SEQ ID NO: 85.

[0062] In a specific ~~example~~embodiment, the VH comprises the sequence of SEQ ID NO: 586. In a specific ~~example~~embodiment, the VL comprises the sequence of SEQ ID NO: 86. In a specific ~~embodiment-example~~ the VH comprises the sequence of SEQ ID NO: 586 and the VL comprises the sequence of SEQ ID NO: 86.

[0063] In a specific ~~example~~embodiment, the VH comprises the sequence of SEQ ID NO: 587. In a specific ~~example~~embodiment, the VL comprises the sequence of SEQ ID NO: 87. In a specific ~~example~~embodiment, the VH comprises the sequence of SEQ ID NO: 587 and the VL comprises the sequence of SEQ ID NO: 87.

least 95% identity to sequence of SEQ ID NO: 88. In a specific exampleembodiment, the VH comprises a sequence that has at least 95% identity to sequence of SEQ ID NO: 588 and the VL comprises a sequence that has at least 95% identity to sequence of SEQ ID NO: 88.

[0073] In a specific exampleembodiment, the VH comprises a sequence that has at least 95% identity to sequence of SEQ ID NO: 589. In a specific exampleembodiment, the VL comprises a sequence that has at least 95% identity to sequence of SEQ ID NO: 89. In a specific exampleembodiment, the VH comprises a sequence that has at least 95% identity to sequence of SEQ ID NO: 589 and the VL comprises a sequence that has at least 95% identity to sequence of SEQ ID NO: 89.

[0074] In a specific exampleembodiment, the VH comprises a sequence that has at least 95% identity to sequence of SEQ ID NO: 592. In a specific exampleembodiment, the VL comprises a sequence that has at least 95% identity to sequence of SEQ ID NO: 86. In a specific exampleembodiment, the VH comprises a sequence that has at least 95% identity to sequence of SEQ ID NO: 592 and the VL comprises a sequence that has at least 95% identity to sequence of SEQ ID NO: 86.

[0075] In a specific exampleembodiment, the VH comprises a sequence that has at least 95% identity to sequence of SEQ ID NO: 238. In a specific exampleembodiment, the VL comprises a sequence that has at least 95% identity to sequence of SEQ ID NO: 84. In a specific exampleembodiment, the VH comprises a sequence that has at least 95% identity to sequence of SEQ ID NO: 238 and the VL comprises a sequence that has at least 95% identity to sequence of SEQ ID NO: 84.

[0076] In another exampleaspect, ~~provided-described~~ herein is an antibody or an antigen-binding fragment thereof that specifically binds to VISTA, wherein the antibody comprises a VH and a VL, wherein the VH comprises a VH CDR1, a VH CDR2 and a VH CDR3, and wherein the VH CDR1 is of the SEQ ID NO: set forth in Table 1 as the VH CDR1 for an Antibody No. listed in Table 1, and the VH CDR2 is of the SEQ ID NO: set forth in Table 1 as the VH CDR2 for said antibody, and the VH CDR3 is of the SEQ ID NO: set forth in Table 1 as the VH CDR3 for said antibody.

[0077] In another exampleaspect, ~~provided-described~~ herein is an antibody or an antigen-binding fragment thereof that specifically binds to VISTA, wherein the antibody comprises a VH and a VL, wherein the VH comprises a VH CDR1, a VH CDR2 and a VH CDR3, and wherein the VH CDR1 is of the SEQ ID NO: set forth in Table 2 as the VH CDR1 for an Antibody No. listed in Table 2, and the VH CDR2 is of the SEQ ID NO: set forth in Table 2 as the VH CDR2 for said antibody, and the VH CDR3 is of the SEQ ID NO: set forth in Table 2 as the VH CDR3 for said antibody.

[0078] In another exampleaspect, ~~provided-described~~ herein is an antibody or an antigen-binding fragment thereof that specifically binds to VISTA, wherein the antibody comprises a VH and a VL, wherein the VH comprises a VH CDR1, a VH CDR2 and a VH CDR3, and wherein the VH CDR1 is of the SEQ ID NO: set forth in Table 3 as the VH CDR1 for an Antibody No. listed in Table 3, and the VH CDR2 is of the SEQ ID NO: set forth in Table 3 as the VH CDR2 for said antibody, and the VH CDR3 is of the SEQ ID NO: set forth in Table 3 as the VH CDR3 for said antibody.

[0079] In another ~~example~~aspect, ~~provided-described~~ herein is an antibody or an antigen-binding fragment thereof that specifically binds to VISTA, wherein the antibody comprises a VH and a VL, wherein (i) the VH comprises a VH CDR1, a VH CDR2 and a VH CDR3, and wherein the VH CDR1 is of the SEQ ID NO: set forth in Table 1 as the VH CDR1 for an Antibody No. listed in Table 1, and the VH CDR2 is of the SEQ ID NO: set forth in Table 1 as the VH CDR2 for said antibody, and the VH CDR3 is of the SEQ ID NO: set forth in Table 1 as the VH CDR3 for said antibody and (ii) the VL comprises a VL CDR1, a VL CDR2 and a VL CDR3, and wherein the VL CDR1 is of the SEQ ID NO: set forth in Table 4 as the VL CDR1 for said antibody, the VL CDR2 is of the SEQ ID NO: set forth in Table 4 as the VL CDR2 for said antibody, and the VL CDR3 is of the SEQ ID NO: set forth in Table 4 as the VL CDR3 for said antibody.

[0080] In another ~~example~~aspect, ~~provided-described~~ herein is an antibody or an antigen-binding fragment thereof that specifically binds to VISTA, wherein the antibody comprises a VH and a VL, wherein (i) the VH comprises a VH CDR1, a VH CDR2 and a VH CDR3, and wherein the VH CDR1 is of the SEQ ID NO: set forth in Table 2 as the VH CDR1 for an Antibody No. listed in Table 2, and the VH CDR2 is of the SEQ ID NO: set forth in Table 2 as the VH CDR2 for said antibody, and the VH CDR3 is of the SEQ ID NO: set forth in Table 2 as the VH CDR3 for said antibody and (ii) the VL comprises a VL CDR1, a VL CDR2 and a VL CDR3, and wherein the VL CDR1 is of the SEQ ID NO: set forth in Table 5 as the VL CDR1 for said antibody, the VL CDR2 is of the SEQ ID NO: set forth in Table 5 as the VL CDR2 for said antibody, and the VL CDR3 is of the SEQ ID NO: set forth in Table 5 as the VL CDR3 for said antibody.

[0081] In another ~~example~~aspect, ~~provided-described~~ herein is an antibody or an antigen-binding fragment thereof that specifically binds to VISTA, wherein the antibody comprises a VH and a VL, wherein (i) the VH comprises a VH CDR1, a VH CDR2 and a VH CDR3, and wherein the VH CDR1 is of the SEQ ID NO: set forth in Table 3 as the VH CDR1 for an Antibody No. listed in Table 3, and the VH CDR2 is of the SEQ ID NO: set forth in Table 3 as the VH CDR2 for said antibody, and the VH CDR3 is of the SEQ ID NO: set forth in Table 3 as the VH CDR3 for said antibody and (ii) the VL comprises a VL CDR1, a VL CDR2 and a VL CDR3, and wherein the VL CDR1 is of the SEQ ID NO: set forth in Table 6 as the VL CDR1 for said antibody, the VL CDR2 is of the SEQ ID NO: set forth in Table 6 as the VL CDR2 for said antibody, and the VL CDR3 is of the SEQ ID NO: set forth in Table 6 as the VL CDR3 for said antibody.

[0082] In a specific ~~example~~embodiment, the VH comprises the SEQ ID NO: set forth in Table 7 as the VH for an antibody. In a specific ~~example~~embodiment, the VH comprises the SEQ ID NO: set forth in Table 7 as the VH for an antibody and the VL comprises the SEQ ID NO: set forth in Table 8 as the VL for said antibody.

[0083] In another ~~example~~aspect, ~~provided-described~~ herein is an antibody or an antigen-binding fragment thereof that specifically binds to VISTA, wherein the antibody comprises a heavy chain and a light chain, and wherein the light chain is of the SEQ ID NO: set forth in Table 9 as the light chain for an Antibody

No. listed in Table 9, and the heavy chain is of the SEQ ID NO: set forth in Table 9 as the heavy chain for said antibody.

[0084] In a specific exampleembodiment, the antibody or antigen-binding fragment specifically binds to human VISTA (amino acids 33-311 of SEQ ID NO: 377).

[0085] In another exampleaspect, provided-described herein is an antibody or an antigen-binding fragment thereof that specifically binds to VISTA, wherein the antibody recognizes an epitope of human VISTA comprising the amino acid sequence HLHHG (amino acids 98-102 of SEQ ID NO: 377, numbering begins with the first amino acid after the signal sequence (signal sequence is underlined, in bold, Table 11)) or VVEIRHHHSEHR (amino acids 148-159 of SEQ ID NO: 377, numbering begins with the first amino acid after the signal sequence (underlined, in bold Table 11)). In another exampleembodiment, the antibody recognizes an epitope of human VISTA comprising Tyrosine 37, Arginine 54, Valine 117 and Arginine 127 of SEQ ID NO: 377 (numbering begins with the first amino acid after the signal sequence (underlined, in bold in Table 11)).

[0086] In another exampleaspect, provided-described herein is an antibody or antigen-binding fragment thereof which competes for binding to VISTA with a reference antibody selected from the group consisting of: (a) a first immunoglobulin comprising (i) a VH comprising the sequence of SEQ ID NO: 584 and (ii) a VL comprising the sequence of SEQ ID NO: 84; (b) a second immunoglobulin comprising (i) a VH comprising the sequence of SEQ ID NO: 585 and (ii) a VL comprising the sequence of SEQ ID NO: 85; (c) a third immunoglobulin comprising (i) a VH comprising the sequence of SEQ ID NO: 586 and (ii) a VL comprising the sequence of SEQ ID NO: 86; (d) a fourth immunoglobulin comprising (i) a VH comprising the sequence of SEQ ID NO: 587 and (ii) a VL comprising the sequence of SEQ ID NO: 87; (e) a fifth immunoglobulin comprising (i) a VH comprising the sequence of SEQ ID NO: 588 and (ii) a VL comprising the sequence of SEQ ID NO: 88; (f) a sixth immunoglobulin comprising (i) a VH comprising the sequence of SEQ ID NO: 589 and (ii) a VL comprising the sequence of SEQ ID NO: 89; (g) a seventh immunoglobulin comprising (i) a VH comprising the sequence of SEQ ID NO: 238 and (ii) a VL comprising the sequence of SEQ ID NO: 84; and (h) an eighth immunoglobulin comprising (i) a VH comprising the sequence of SEQ ID NO: 592 and (ii) a VL comprising the sequence of SEQ ID NO: 86.

[0087] In a specific exampleembodiment, the antibody is a monoclonal antibody. In a specific exampleembodiment, the antibody is a human antibody. In a specific exampleembodiment, the antibody is an immunoglobulin.

[0088] In a specific exampleembodiment, the antibody comprises an Fc region or a variant of the Fc region; optionally wherein the Fc region is a human Fc region or a variant of the human Fc region that has in the range of one to seven amino acid mutations in the Fc region relative to the native human Fc region, and/or optionally wherein the human Fc region is of a human IgG1, human IgG2 or a human IgG4, further optionally wherein the antibody comprises a constant region of a human IgG1 or a

human IgG4 or a variant of the constant region that has in the range of one to seven amino acid mutations in the constant region relative to the native constant region.

[0089] In a specific exampleembodiment, the antibody mediates antibody-dependent cell-mediated cytotoxicity (ADCC). In a specific exampleembodiment, the antibody mediates complement-dependent cell-mediated cytotoxicity (CDC). In a specific exampleembodiment, the antibody mediates antibody-dependent cellular phagocytosis (ADCP).

[0090] In a specific exampleembodiment, the antibody comprises said variant of the human Fc region. In a specific exampleembodiment, (a) the Fc region is of a human IgG1, wherein the mutations are selected from the group consisting of C220D, D221C, E233P, L234A, L234E, L234Y, L235A, L235E, L235F, G236A, G236W, G236R, G237A, P238S, S239D, F241A, M252Y, S254T, T256E, T256N, V264A, D265A, S267E, H268F, H268A, D270A, H268Q, E294deletion, N297A, N297G, N297E, S298A, T307P, E318A, K322A, S324T, K326A, K326M, L328R, P329A, P329G, A330L, A330S, P331A, P331S, I332E, E333A, E333S, K334A, A378V, S383N, M428L, N434S, and N434Y, wherein the residues are numbered using the EU numbering system; (b) the Fc region is of a human IgG2, and wherein the mutations are selected from the group consisting of C220D, G237A, P238S, S239D, F241A, M252Y, S254T, T256E, T256N, V264A, D265A, S267E, H268F, H268A, D270A, H268Q, E294deletion, N297A, N297G, N297E, S298A, T307P, V309L, E318A, K322A, S324T, K326A, K326M, L328R, P329A, P329G, A330L, A330S, P331A, P331S, I332E, E333A, E333S, K334A, S383N, M428L, N434S, and N434Y, wherein the residues are numbered using the EU numbering system; or (c) the Fc region is of a human IgG4, and wherein the mutations are selected from the group consisting of S228P, E233P, F234A, L235A, L235E, L235F, G236A, G236W, G236R, G237A, P238S, S239D, F241A, M252Y, S254T, T256E, T256N, V264A, D265A, S267E, H268F, H268A, D270A, H268Q, E294deletion, N297A, N297G, N297E, S298A, T307P, V309L, E318A, K322A, S324T, K326A, K326M, L328R, P329A, P329G, I332E, E333A, E333S, K334A, A378V, S383N, M428L, N434S, and N434Y, wherein the residues are numbered using the EU numbering system.

[0091] In a specific exampleembodiment, the Fc region (a) is of a human IgG1, wherein the mutations comprise L234A and L235A, and optionally P329G, wherein the residues are numbered using the EU numbering system; or (b) is of a human IgG4, and wherein the mutations comprise F234A and L235A, and optionally P329G, wherein the residues are numbered using the EU numbering system.

[0092] In a specific exampleembodiment, the Fc region is of a human IgG1, IgG2, or IgG4, wherein the mutations comprise M252Y, S254T, and T256E, wherein the residues are numbered using the EU numbering system.

[0093] In a specific exampleembodiment, the Fc region is of a human IgG1, IgG2 or IgG4, wherein the mutations comprise M428L and N434S, wherein the residues are numbered using the EU numbering system.

[0094] In a specific exampleembodiment, the Fc region is of a human IgG4, wherein the mutations comprise S228P and L235E, wherein the residues are numbered using the EU numbering system.

- [0095]** In one ~~example~~embodiment, the Fc region is a human IgG4, and the mutations comprise S228P, M252Y, S254T, and T256E, wherein the residues are numbered using the EU numbering system.
- [0096]** In one ~~example~~embodiment, the Fc region is of a human IgG4, wherein the mutations comprise S228P, M428L and N434S, wherein the residues are numbered using the EU numbering system.
- [0097]** In a specific ~~example~~embodiment, the antibody or antigen-binding fragment is a bispecific antibody or a trispecific antibody. In another ~~example~~embodiment, the antibody or antigen-binding fragment is a BiTE or TriKE.
- [0098]** In a specific ~~example~~embodiment, the antigen-binding fragment is an Fv fragment, a Fab fragment, or a F(ab')₂ fragment.
- [0099]** In a specific ~~example~~embodiment, the antibody or antigen-binding fragment thereof is purified. In another ~~example~~embodiment, the antibody, or antigen-binding fragment, is isolated.
- [00100]** In another ~~example~~aspect, ~~provided-described~~ herein is a single-chain Fv (scFv) comprising a VH and a VL separated by a linker sequence, wherein the VH comprises a VH CDR1, a VH CDR2 and a VH CDR3, the VH CDR1 is of the SEQ ID NO: set forth in a table selected from the group consisting of Tables 1-3 as the VH CDR1 for an Antibody No. listed in said table, and the VH CDR2 is of the SEQ ID NO: set forth in said table as the VH CDR2 for said antibody, and the VH CDR3 is of the SEQ ID NO: set forth in said table as the VH CDR3 for said antibody. In a specific ~~example~~embodiment, the VL comprises a VL CDR1, a VL CDR2 and a VL CDR3, and wherein the VL CDR1 is of the SEQ ID NO: set forth in a table selected from the group consisting of Tables 4-6 as the VL CDR1 for said antibody, the VL CDR2 is of the SEQ ID NO: set forth in said table as the VL CDR2 for said antibody, and the VL CDR3 is of the SEQ ID NO: set forth in said table as the VL CDR3 for said antibody, wherein the VL CDR1, VL CDR2, VL CDR3, VH CDR1, VH CDR2 and VH CDR3 all are defined by the same CDR numbering system. In a specific ~~example~~embodiment, the VH comprises the SEQ ID NO: set forth in Table 7 as the VH of said antibody. In a specific ~~example~~embodiment, the VL comprises the SEQ ID NO: set forth in Table 8 as the VL of said antibody.
- [00101]** In another ~~example~~aspect, ~~provided-described~~ herein is a fusion protein comprising an scFv ~~described~~ ~~provided~~ herein.
- [00102]** In another ~~example~~aspect, ~~provided-described~~ herein is an antibody-drug conjugate comprising the antibody or antigen-binding fragment, the scFv, or the fusion protein of any of the preceding ~~example~~embodiments bound (optionally covalently bound) to a therapeutic agent.
- [00103]** In another ~~example~~aspect, ~~provided-described~~ herein is a chimeric antigen receptor (CAR) comprising the scFv of any of the preceding ~~example~~embodiments. Also ~~provided-described~~ herein is a cell which expresses the CAR.
- [00104]** In another ~~example~~aspect, ~~provided-described~~ herein is a polynucleotide comprising a nucleotide sequence encoding the antibody or antigen-binding fragment, the scFv, the fusion protein, or the CAR of any of the preceding ~~example~~embodiments.
- [00105]** In another ~~example~~aspect, ~~provided-described~~ herein is an *ex vivo* cell containing one or more polynucleotides each comprising a nucleotide sequence encoding the antibody or antigen-binding fragment, the scFv, the fusion protein, or the CAR of any of the preceding ~~example~~embodiments. Also

~~provided-described~~ herein is a method of producing an antibody or antigen-binding fragment or scFv or fusion protein or CAR comprising culturing the cell under conditions such that said one or more polynucleotides are expressed by the cell to produce the antibody or antigen-binding fragment or scFv or fusion protein or CAR encoded by the polynucleotides.

[00106] In another ~~example~~aspect, ~~provided-described~~ herein is a pharmaceutical composition comprising (a) a therapeutically effective amount of the antibody or antigen-binding fragment, the scFv, the fusion protein, the CAR, the antibody-drug conjugate, or the cell of any of the preceding ~~example~~embodiments; and (b) a pharmaceutically acceptable carrier. Also ~~provided-described~~ herein is a method of treating cancer in a subject in need thereof, comprising administering to said subject the pharmaceutical composition. In a specific ~~example~~embodiment, the cancer is a non-small cell lung cancer, a small cell lung cancer, a head and neck squamous cell carcinoma, a blood cancer, an hepatocellular carcinoma, an ovarian cancer, a mesothelioma, a neuroblastoma, an oral cancer, a thyroid cancer, a breast cancer, a sarcoma, a pancreatic cancer, a colon cancer, a gastric cancer, a choriocarcinoma, a testicular cancer, a skin cancer, a renal cell carcinoma, a bladder cancer, a hematological cancer (*e.g.*, an acute myeloid leukemia), or a cervical cancer. In one ~~example~~embodiment, the cancer is a myelodysplastic syndrome. In a specific ~~example~~embodiment, the cancer is metastatic cancer. In a specific ~~example~~embodiment, the cancer is an acute myeloid leukemia, and wherein the pharmaceutical composition comprises a therapeutically effective amount of the antibody-drug conjugate, wherein the therapeutic agent optionally is a cytotoxic agent.

[00107] In a specific ~~example~~embodiment, the method of treating cancer further comprises administering to the subject an additional therapy. In a specific ~~example~~embodiment, the additional therapy is for treating the cancer. In a specific ~~example~~embodiment, the method of treating cancer further comprises administering to the subject a chemotherapeutic agent, a tyrosine kinase inhibitor, and/or an immune checkpoint inhibitor. In a specific ~~example~~embodiment, the method of treating cancer further comprises administering to the subject the immune checkpoint inhibitor, wherein the immune checkpoint inhibitor is an inhibitor of Programmed Death-1 (PD-1), or Programmed death-ligand 1 (PDL1), or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). In a specific ~~example~~embodiment, said subject is a human. In one ~~example~~embodiment, the additional therapy is radiotherapy.

BRIEF DESCRIPTION OF THE FIGURES

[00108] Figs. 1A-1N. Octet sensorgrams measuring affinity of anti-VISTA antibodies No. 269.1 (Fig. 1A), No. 321.1 (Fig. 1B), No. 245.1 (Fig. 1C), No. 465.1 (Fig. 1D), No. 457.1 (Fig. 1E), No. 173.1 (Fig. 1F), No. 833.1 (Fig. 1G), No. 150.1 (Fig. 1H), No. 474.1 (Fig. 1I), No. 80 (Fig. 1J), No. 85 (Fig. 1K), No. 87 (Fig. 1L), No. 91 (Fig. 1M) and No. 92 (Fig. 1N) to human VISTA. Antibody affinities were measured using biolayer interferometry on the Octet Red 96 (ForteBio) system. Sensorgrams showing antigen (his-tagged human VISTA Met 1 to Ala 194) association and

What is claimed is:

1. An antibody, or an antigen-binding fragment thereof, that binds to V-domain Ig-containing Suppressor of T cell Activation (VISTA),

wherein the antibody, or antigen-binding fragment thereof, blocks binding of all five ligands to VISTA at pH 6.0 and pH 7.4, wherein the five known ligands to VISTA are VSIG-3 (V-set and immunoglobulin domain containing 3), VSIG-8 (V-set and immunoglobulin domain containing 8), PSGL-1 (P-selectin glycoprotein ligand-1), LRIG1 (leucine rich repeats and immunoglobulin like domains 1) and VISTA; and

wherein the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region (VH) and a light chain variable region (VL).

- ~~2. An antibody, or an antigen-binding fragment thereof, that binds to V-domain Ig-containing Suppressor of T cell Activation (VISTA),~~

~~wherein the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region (VH) and a light chain variable region (VL);~~

~~wherein the VH comprises a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to, comprises, or consists of any one of SEQ ID NOs: 584-597, 227-246, and 383-386; and~~

~~wherein the VL comprises a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to, comprises, or consists of any one of SEQ ID NOs: 84-110.~~

- ~~3. The antibody, or antigen-binding fragment thereof, of claim 1 or claim 2, comprising~~

~~a VH CDR1 of any one of SEQ ID NOs: 247-253 as defined by Kabat numbering system; any one of SEQ ID NOs: 284-291 as defined by IMGT numbering system; or any one of SEQ ID NOs: 318-325 as defined by Paratome numbering system;~~

~~a VH CDR2 of any one of SEQ ID NOs: 254-265 as defined by Kabat numbering system; any one of SEQ ID NOs: 292-298 as defined by IMGT numbering system; or any one of SEQ ID NOs: 326-339 as defined by Paratome numbering system;~~

~~a VH CDR3 of any one of SEQ ID NOs: 266-283 as defined by Kabat numbering system; any one of SEQ ID NOs: 299-317 as defined by IMGT numbering system; or any one of SEQ ID NOs: 340-359 as defined by Paratome numbering system;~~

a VL CDR1 of any one of SEQ ID NOs: 111-122 as defined by Kabat numbering system; any one of SEQ ID NOs: 152-162 as defined by IMGT numbering system; or any one of SEQ ID NOs: 188-196 or 576-578 as defined by Paratome numbering system;

a VL CDR2 of any one of SEQ ID NOs: 123-131 and 575 as defined by Kabat numbering system; any one of SEQ ID NOs: 163-167 as defined by IMGT numbering system; or any one of SEQ ID NOs: 197-206 as defined by Paratome numbering system; and

a VL CDR3 of any one of SEQ ID NOs: 132-151 as defined by Kabat numbering system; any one of SEQ ID NOs: 168-186 as defined by IMGT numbering system; or any one of SEQ ID NOs: 207-226 as defined by Paratome numbering system.

4.2. An antibody, or antigen-binding fragment thereof, that binds to VISTA, wherein the antibody or antigen-binding fragment thereof, comprises a VH and a VL,

wherein the VH comprises:

a VH CDR1 of any one of SEQ ID NOs: 249, 247, 248, or 250-253 as defined by Kabat numbering system; any one of SEQ ID NOs: 286, 284, 285, or 287-291 as defined by IMGT numbering system; or any one of SEQ ID NOs: 320, 318, 319, or 321-325 as defined by Paratome numbering system,

a VH CDR2 of any one of SEQ ID NOs: 256, 254, 255, or 257-265 as defined by Kabat numbering system; any one of SEQ ID NOs: 294, 292, 293, or 295-298 as defined by IMGT numbering system; or any one of SEQ ID NOs: 328, 326, 327, or 329-339 as defined by Paratome numbering system,

a VH CDR3 of any one of SEQ ID NOs: 268, 266, 267, or 269-283 as defined by Kabat numbering system; any one of SEQ ID NOs: 301, 299, 300, or 302-317 as defined by IMGT numbering system; or any one of SEQ ID NOs: 342, 340, 341, or 343-359 as defined by Paratome numbering system, and

wherein the VL comprises:

a VL CDR1 of any one of SEQ ID NOs: 113, 111, 112, or 114-122 as defined by Kabat numbering system; any one of SEQ ID NOs: 154, 152, 153, or 155-162 as defined by IMGT numbering system; or any one of SEQ ID NOs: 190, 188, 189, 191-196 or 576-578 as defined by Paratome numbering system,

a VL CDR2 of any one of SEQ ID NOs: 125, 123, 124, or 126-131 and 575 as defined by Kabat numbering system; any one of SEQ ID NOs: 165, 163, 164, or 166-167 as defined by IMGT numbering system; or any one of SEQ ID NOs: 199, 197, 198, or 200-206 as defined by Paratome numbering system, and

a VL CDR3 of any one of SEQ ID NOs: 134, 132, 133, or 135-151 as defined by Kabat numbering system; any one of SEQ ID NOs: 170, 168, 169, 171-186 as defined by IMGT numbering system; or any one of SEQ ID NOs: 209, 207, 208, or 210-226 as defined by Paratome numbering system.

~~5.3.~~ The antibody, or antigen-binding fragment thereof, of claim 1 or claim 42,

wherein the VH comprises a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to, comprises, or consists of any one of SEQ ID NOs: 592, 584-591, 593-597, 227-246, and 383-386, and

wherein the VL comprises a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to, comprises, or consists of any one of SEQ ID NOs: 86, 84, 85, or 87-110.

~~6.4.~~ The antibody, or antigen-binding fragment thereof, of ~~claim 3 or~~ claim 42, wherein

~~the VH CDR1 comprises SEQ ID NO: 247, the VH CDR2 comprises SEQ ID NO: 254, the VH CDR3 comprises SEQ ID NO: 266, the VL CDR1 comprises SEQ ID NO: 111, the VL CDR2 comprises SEQ ID NO: 123, and the VL CDR3 comprises SEQ ID NO: 132;~~

~~the VH CDR1 comprises SEQ ID NO: 284, the VH CDR2 comprises SEQ ID NO: 292, the VH CDR3 comprises SEQ ID NO: 299, the VL CDR1 comprises SEQ ID NO: 152, the VL CDR2 comprises SEQ ID NO: 163, and the VL CDR3 comprises SEQ ID NO: 168;~~

~~the VH CDR1 comprises SEQ ID NO: 318, the VH CDR2 comprises SEQ ID NO: 326, the VH CDR3 comprises SEQ ID NO: 340, the VL CDR1 comprises SEQ ID NO: 188, the VL CDR2 comprises SEQ ID NO: 197, and the VL CDR3 comprises SEQ ID NO: 207;~~

~~the VH CDR1 comprises SEQ ID NO: 248, the VH CDR2 comprises SEQ ID NO: 255, the VH CDR3 comprises SEQ ID NO: 267, the VL CDR1 comprises SEQ ID NO: 112, the VL CDR2 comprises SEQ ID NO: 124, and the VL CDR3 comprises SEQ ID NO: 133;~~

~~the VH CDR1 comprises SEQ ID NO: 285, the VH CDR2 comprises SEQ ID NO: 293, the VH CDR3 comprises SEQ ID NO: 300, and the VL CDR1 comprises SEQ ID NO: 153, the VL CDR2 comprises SEQ ID NO: 164 and the VL CDR3 comprises SEQ ID NO: 169;~~

~~the VH CDR1 comprises SEQ ID NO: 319, the VH CDR2 comprises SEQ ID NO: 327, the VH CDR3 comprises SEQ ID NO: 341, and the VL CDR1 comprises SEQ ID NO: 189, the VL CDR2 comprises SEQ ID NO: 198, and the VL CDR3 comprises SEQ ID NO: 208;~~

the VH CDR1 comprises SEQ ID NO: 249, the VH CDR2 comprises SEQ ID NO: 256, the VH CDR3 comprises SEQ ID NO: 268, the VL CDR1 comprises SEQ ID NO: 113, the VL CDR2 comprises SEQ ID NO: 125, and the VL CDR3 comprises SEQ ID NO: 134;

the VH CDR1 comprises SEQ ID NO: 286, the VH CDR2 comprises SEQ ID NO: 294, the VH CDR3 comprises SEQ ID NO: 301, the VL CDR1 comprises SEQ ID NO: 154, the VL CDR2 comprises SEQ ID NO: 165, and the VL CDR3 comprises SEQ ID NO: 170; or

the VH CDR1 comprises SEQ ID NO: 320, the VH CDR2 comprises SEQ ID NO: 328, the VH CDR3 comprises SEQ ID NO: 342, the VL CDR1 comprises SEQ ID NO: 190, the VL CDR2 comprises SEQ ID NO: 199, and the VL CDR3 comprises SEQ ID NO: 209;

~~the VH CDR1 comprises SEQ ID NO: 250, the VH CDR2 comprises SEQ ID NO: 257, the VH CDR3 comprises SEQ ID NO: 269, the VL CDR1 comprises SEQ ID NO: 114, the VL CDR2 comprises SEQ ID NO: 126, and the VL CDR3 comprises SEQ ID NO: 135;~~

~~the VH CDR1 comprises SEQ ID NO: 287, the VH CDR2 comprises SEQ ID NO: 295, the VH CDR3 comprises SEQ ID NO: 302, the VL CDR1 comprises SEQ ID NO: 155, the VL CDR2 comprises SEQ ID NO: 165, and the VL CDR3 comprises SEQ ID NO: 171;~~

~~the VH CDR1 comprises SEQ ID NO: 321, the VH CDR2 comprises SEQ ID NO: 329, the VH CDR3 comprises SEQ ID NO: 343, the VL CDR1 comprises SEQ ID NO: 191, the VL CDR2 comprises SEQ ID NO: 200, and the VL CDR3 comprises SEQ ID NO: 210;~~

~~the VH CDR1 comprises SEQ ID NO: 251, the VH CDR2 comprises SEQ ID NO: 258, the VH CDR3 comprises SEQ ID NO: 270, the VL CDR1 comprises SEQ ID NO: 115, the VL CDR2 comprises SEQ ID NO: 127, and the VL CDR3 comprises SEQ ID NO: 136;~~

~~the VH CDR1 comprises SEQ ID NO: 288, the VH CDR2 comprises SEQ ID NO: 295, the VH CDR3 comprises SEQ ID NO: 303, the VL CDR1 comprises SEQ ID NO: 156, the VL CDR2 comprises SEQ ID NO: 166, and the VL CDR3 comprises SEQ ID NO: 172;~~

~~the VH CDR1 comprises SEQ ID NO: 322, the VH CDR2 comprises SEQ ID NO: 330, the VH CDR3 comprises SEQ ID NO: 344, the VL CDR1 comprises SEQ ID NO: 192, the VL CDR2 comprises SEQ ID NO: 201, and the VL CDR3 comprises SEQ ID NO: 211;~~

~~the VH CDR1 comprises SEQ ID NO: 248, the VH CDR2 comprises SEQ ID NO: 259, the VH CDR3 comprises SEQ ID NO: 271, the VL CDR1 comprises SEQ ID NO: 116, the VL CDR2 comprises SEQ ID NO: 126, and the VL CDR3 comprises SEQ ID NO: 137;~~

~~the VH CDR1 comprises SEQ ID NO: 285, the VH CDR2 comprises SEQ ID NO: 296, the VH CDR3 comprises SEQ ID NO: 304, the VL CDR1 comprises SEQ ID NO: 157, the VL CDR2 comprises SEQ ID NO: 165, and the VL CDR3 comprises SEQ ID NO: 173; or~~

~~the VH CDR1 comprises SEQ ID NO: 319, the VH CDR2 comprises SEQ ID NO: 331, the VH CDR3 comprises SEQ ID NO: 345, the VL CDR1 comprises SEQ ID NO: 193, the VL CDR2 comprises SEQ ID NO: 200, and the VL CDR3 comprises SEQ ID NO: 212.~~

7. — The antibody, or antigen-binding fragment thereof, of claim 3 or claim 4, wherein

the VH CDR1 comprises SEQ ID NO: 247, SEQ ID NO: 284 or SEQ ID NO: 318, the VH CDR2 comprises SEQ ID NO: 254, SEQ ID NO: 292 or SEQ ID NO: 326, the VH CDR3 comprises SEQ ID NO: 266, SEQ ID NO: 299 or SEQ ID NO: 340, the VL CDR1 comprises SEQ ID NO: 111, SEQ ID NO: 152 or SEQ ID NO: 188, the VL CDR2 comprises SEQ ID NO: 123, SEQ ID NO: 163 or SEQ ID NO: 197, and the VL CDR3 comprises SEQ ID NO: 132, SEQ ID NO: 168 or SEQ ID NO: 207;

the VH CDR1 comprises SEQ ID NO: 248, SEQ ID NO: 285 or SEQ ID NO: 319, the VH CDR2 comprises SEQ ID NO: 255, SEQ ID NO: 293 or SEQ ID NO: 327, the VH CDR3 comprises SEQ ID NO: 267, SEQ ID NO: 300 or SEQ ID NO: 341, the VL CDR1 comprises SEQ ID NO: 112, SEQ ID NO: 153 or SEQ ID NO: 189, the VL CDR2 comprises SEQ ID NO: 124, SEQ ID NO: 164 or SEQ ID NO: 198, and the VL CDR3 comprises SEQ ID NO: 133, SEQ ID NO: 169 or SEQ ID NO: 208;

the VH CDR1 comprises SEQ ID NO: 249, SEQ ID NO: 286 or SEQ ID NO: 320, the VH CDR2 comprises SEQ ID NO: 256, SEQ ID NO: 294 or SEQ ID NO: 328, the VH CDR3 comprises SEQ ID NO: 268, SEQ ID NO: 301 or SEQ ID NO: 342, the VL CDR1 comprises SEQ ID NO: 113, SEQ ID NO: 154 or SEQ ID NO: 190, the VL CDR2 comprises SEQ ID NO: 125, SEQ ID NO: 165, or SEQ ID NO: 199, and the VL CDR3 comprises SEQ ID NO: 134, SEQ ID NO: 170 or SEQ ID NO: 209;

the VH CDR1 comprises SEQ ID NO: 250, SEQ ID NO: 287, or SEQ ID NO: 321, the VH CDR2 comprises SEQ ID NO: 257, SEQ ID NO: 295 or SEQ ID NO: 332, the VH CDR3 comprises SEQ ID NO: 269, SEQ ID NO: 302 or SEQ ID NO: 346, the VL CDR1 comprises SEQ ID NO: 114, SEQ ID NO: 155 or SEQ ID NO: 191, the VL CDR2 comprises SEQ ID NO: 126, SEQ ID NO: 165 or SEQ ID NO: 200, and the VL CDR3 comprises SEQ ID NO: 135, SEQ ID NO: 171 or SEQ ID NO: 210;

the VH CDR1 comprises SEQ ID NO: 251, SEQ ID NO: 288 or SEQ ID NO: 322, the VH CDR2 comprises SEQ ID NO: 258, SEQ ID NO: 295 or SEQ ID NO: 333, the VH CDR3 comprises SEQ ID NO: 270, SEQ ID NO: 303 or SEQ ID NO: 344, the VL CDR1 comprises SEQ ID NO: 115, SEQ ID NO: 156 or SEQ ID NO: 192, the VL CDR2 comprises SEQ ID NO: 127, SEQ ID NO: 166 or SEQ ID NO: 201, and the VL CDR3 comprises SEQ ID NO: 136, SEQ ID NO: 172 or SEQ ID NO: 211; or

the VH CDR1 comprises SEQ ID NO: 248, SEQ ID NO: 185 or SEQ ID NO: 319, the VH CDR2 comprises SEQ ID NO: 259, SEQ ID NO: 296 or SEQ ID NO: 331, the VH CDR3 comprises SEQ ID NO: 271, SEQ ID NO: 304 or SEQ ID NO: 345, the VL CDR1 comprises SEQ ID NO: 116, SEQ ID NO: 157 or SEQ ID NO: 193, the VL CDR2 comprises SEQ ID NO: 126, SEQ ID NO: 165 or SEQ ID NO: 200, and the VL CDR3 comprises SEQ ID NO: 137, SEQ ID NO: 173 or SEQ ID NO: 212.

8.5. The antibody, or antigen-binding fragment thereof, of any one of the previous claims claims 1 to 4,

wherein the VL comprises a sequence having at least ~~90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%~~ identity to, comprises, or consists of SEQ ID NO: 84;

(x) wherein the VH comprises a sequence having at least ~~90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%~~ identity to, comprises, or consists of SEQ ID NO: 591238, and

wherein the VL comprises a sequence having at least ~~90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%~~ identity to, comprises, or consists of SEQ ID NO: 85;

(xi) wherein the VH comprises a sequence having at least ~~90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%~~ identity to, comprises, or consists of SEQ ID NO: 593, and

wherein the VL comprises a sequence having at least ~~90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%~~ identity to, comprises, or consists of SEQ ID NO: 86;

(xii) wherein the VH comprises a sequence having at least ~~90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%~~ identity to, comprises, or consists of SEQ ID NO: 593238, and

wherein the VL comprises a sequence having at least ~~90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%~~ identity to, comprises, or consists of SEQ ID NO: 87;

(xiii) wherein the VH comprises a sequence having at least ~~90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%~~ identity to, comprises, or consists of SEQ ID NO: 594, and

wherein the VL comprises a sequence having at least ~~90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%~~ identity to, comprises, or consists of SEQ ID NO: 884; or

(xiv) wherein the VH comprises a sequence having at least ~~90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%~~ identity to, comprises, or consists of SEQ ID NO: 595, and

wherein the VL comprises a sequence having at least ~~90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%~~ identity to, comprises, or consists of SEQ ID NO: 89.

9.6. The antibody, or antigen-binding fragment thereof, of any one of ~~the previous claims~~ claims 1 to 5,

comprising a heavy chain (HC) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to, comprises, or consists of any one of SEQ ID NOs: 573, 407-477, 572, 574, and 604-609, and

comprising a light chain (LC) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to, comprises, or consists of any one of SEQ ID NOs: 391, 387-390, 392-406, 569-571, and 598-603.

~~10.7.~~ The antibody, or antigen-binding fragment thereof, of any one of the previous claims, which binds to human VISTA (amino acids 33-311 of SEQ ID NO:377), optionally, which binds to an

epitope of human VISTA comprising the amino acid sequence ⁶⁶HLHHG₇₀ (amino acids 98-102 of SEQ ID NO: 377) or ¹¹⁶VVEIRHHHSEHR₁₂₇ (amino acids 148-159 of SEQ ID NO: 377), or optionally, which binds to an epitope of human VISTA comprising Tyrosine 37, Arginine 54, Valine 117 and Arginine 127 of SEQ ID NO:377 (respectively amino acids 69, 86, 149 and 159 of SEQ ID NO:377).

~~11. The antibody, or antigen-binding fragment thereof, of claim 10, which binds to an epitope of human VISTA comprising the amino acid sequence HLHHG (amino acids 98-102 of SEQ ID NO: 377) or VVEIRHHHSEHR (amino acids 148-159 of SEQ ID NO: 377).~~

~~12. The antibody, or antigen-binding fragment thereof, of claim 10, which binds to an epitope of human VISTA comprising Tyrosine 37, Arginine 54, Valine 117 and Arginine 127 of SEQ ID NO:377.~~

~~13.8.~~ The antibody, or antigen-binding fragment thereof, of any one of the previous claims, comprising an Fc region, optionally wherein the Fc region is a human Fc region or a variant of the human Fc region that has in the range of one to seven amino acid mutations in the Fc region relative to the native human Fc region, and/or optionally wherein the human Fc region is of a human IgG1, human IgG2, or a human IgG4, further optionally wherein the antibody comprises a constant region of a human IgG1 or a human IgG4 or a variant of the constant region that has in the range of one to seven amino acid mutations in the constant region relative to the native constant region, optionally wherein:

(a) the Fc region is of a human IgG1, and wherein the mutations are selected from the group consisting of C220D, D221C, E233P, L234A, L234E, L234Y, L235A, L235E, L235F, G236A, G236W, G236R, G237A, P238S, S239D, F241A, M252Y, S254T, T256E, T256N, V264A, D265A, S267E, H268F, H268A, D270A, H268Q, E294deletion, N297A, N297G, N297E, S298A, T307P, E318A, K322A, S324T, K326A, K326M, L328R, P329A, P329G, A330L, A330S, P331A, P331S, I332E, E333A, E333S, K334A, A378V, S383N, M428L, N434S, and N434Y, wherein the residues are numbered using the EU numbering system;

(b) the Fc region is of a human IgG2, and wherein the mutations are selected from the group consisting of C220D, G237A, P238S, S239D, F241A, M252Y, S254T, T256E, T256N, V264A, D265A, S267E, H268F, H268A, D270A, H268Q, E294deletion, N297A, N297G, N297E, S298A, T307P, V309L, E318A, K322A, S324T, K326A, K326M, L328R, P329A, P329G, A330L, A330S, P331A, P331S, I332E,

E333A, E333S, K334A, S383N, M428L, N434S, and N434Y, wherein the residues are numbered using the EU numbering system; or

(c) the Fc region is of a human IgG4, and wherein the mutations are selected from the group consisting of S228P, E233P, F234A, L235A, L235E, L235F, G236A, G236W, G236R, G237A, P238S, S239D, F241A, M252Y, S254T, T256E, T256N, V264A, D265A, S267E, H268F, H268A, D270A, H268Q, E294deletion, N297A, N297G, N297E, S298A, T307P, V309L, E318A, K322A, S324T, K326A, K326M, L328R, P329A, P329G, I332E, E333A, E333S, K334A, A378V, S383N, M428L, N434S, and N434Y, wherein the residues are numbered using the EU numbering system.

14. ~~The antibody, or antigen-binding fragment, of claim 13, wherein~~

~~(a) the Fc region is of a human IgG1, and wherein the mutations are selected from the group consisting of C220D, D221C, E233P, L234A, L234E, L234Y, L235A, L235E, L235F, G236A, G236W, G236R, G237A, P238S, S239D, F241A, M252Y, S254T, T256E, T256N, V264A, D265A, S267E, H268F, H268A, D270A, H268Q, E294deletion, N297A, N297G, N297E, S298A, T307P, E318A, K322A, S324T, K326A, K326M, L328R, P329A, P329G, A330L, A330S, P331A, P331S, I332E, E333A, E333S, K334A, A378V, S383N, M428L, N434S, and N434Y, wherein the residues are numbered using the EU numbering system;~~

~~(b) the Fc region is of a human IgG2, and wherein the mutations are selected from the group consisting of C220D, G237A, P238S, S239D, F241A, M252Y, S254T, T256E, T256N, V264A, D265A, S267E, H268F, H268A, D270A, H268Q, E294deletion, N297A, N297G, N297E, S298A, T307P, V309L, E318A, K322A, S324T, K326A, K326M, L328R, P329A, P329G, A330L, A330S, P331A, P331S, I332E, E333A, E333S, K334A, S383N, M428L, N434S, and N434Y, wherein the residues are numbered using the EU numbering system; or~~

~~(c) the Fc region is of a human IgG4, and wherein the mutations are selected from the group consisting of S228P, E233P, F234A, L235A, L235E, L235F, G236A, G236W, G236R, G237A, P238S, S239D, F241A, M252Y, S254T, T256E, T256N, V264A, D265A, S267E, H268F, H268A, D270A, H268Q, E294deletion, N297A, N297G, N297E, S298A, T307P, V309L, E318A, K322A, S324T, K326A, K326M, L328R, P329A, P329G, I332E, E333A, E333S, K334A, A378V, S383N, M428L, N434S, and N434Y, wherein the residues are numbered using the EU numbering system.~~

15.9. The antibody, or antigen-binding fragment thereof, of any one of the previous claims, which is a bispecific antibody or a multispecific antibody, or wherein the antigen-binding fragment is an Fv fragment, a Fab fragment, a F(ab')₂ fragment, or a single-chain Fv (scFv).

~~16.~~ The antibody, or antigen-binding fragment thereof, of any one of the previous claims, wherein the antigen-binding fragment is an Fv fragment, a Fab fragment, a F(ab')₂ fragment, or a single chain Fv (scFv).

~~17.~~10. An antibody, or antigen-binding fragment thereof, which competes for binding to human VISTA (SEQ ID NO: 377) with any one of the antibodies, or antigen-binding fragments thereof, of the previous claims.

~~18.~~11. An antibody-drug conjugate comprising the antibody, or antigen-binding fragment thereof, of any one of the previous claims and a therapeutic agent.

~~19.~~12. A chimeric antigen receptor (CAR) comprising the scFv of claim ~~16~~9.

~~20.~~13. A polynucleotide comprising a nucleotide sequence encoding the VH, the VL, or the VH and the VL of the antibody, or antigen-binding fragment thereof, of any one of claims 1-~~17~~10.

~~21.~~14. A cell comprising one or more polynucleotides encoding the antibody, or antigen-binding fragment thereof, of any one of claims 1-~~17~~10.

~~22.~~15. A pharmaceutical composition comprising the antibody, or antigen-binding fragment thereof, of any one of claims 1-~~17~~10, the antibody-drug conjugate of claim ~~18~~11, or the CAR of claim ~~19~~12, and a pharmaceutically acceptable carrier.

~~23.~~16. A method of producing ~~the an~~ antibody, or antigen-binding fragment thereof, ~~of any one of claims 1-17,~~ the method comprising culturing the cell of claim ~~21~~14 under conditions such that said one or more polynucleotides are expressed by the cell to produce the antibody, or antigen-binding fragment thereof, encoded by the polynucleotides.

~~24.~~17. A method of treating cancer, an autoimmune disease, and/or an infection in a subject in need thereof, comprising administering to the subject the Use of the pharmaceutical composition of claim ~~22~~15 in the manufacture of a medicament for treating cancer, an autoimmune disease, and/or an infection in a subject in need thereof, optionally wherein the cancer is a non-small cell lung cancer, small cell lung cancer, a head and neck squamous cell carcinoma, an hepatocellular carcinoma, an ovarian cancer, a neuroblastoma, an oral cancer, a thyroid cancer, a breast cancer, a sarcoma, a pancreatic cancer, a colon

cancer, a gastric cancer, a choriocarcinoma, a testicular cancer, a mesothelioma, a skin cancer, a renal cell carcinoma, a bladder cancer, a hematological cancer, a cervical cancer, a blood cancer, an acute myeloid leukemia, myelodysplastic syndrome, and/or a metastatic cancer.

~~25. — The method of claim 24, wherein the cancer is a non-small cell lung cancer, small cell lung cancer, a head and neck squamous cell carcinoma, an hepatocellular carcinoma, an ovarian cancer, a neuroblastoma, an oral cancer, a thyroid cancer, a breast cancer, a sarcoma, a pancreatic cancer, a colon cancer, a gastric cancer, a choriocarcinoma, a testicular cancer, a mesothelioma, a skin cancer, a renal cell carcinoma, a bladder cancer, a hematological cancer, or a cervical cancer.~~

~~26. — The method of claim 24 or 25, wherein the cancer is a metastatic cancer.~~

~~27. — The method of claim 24, wherein the cancer is a blood cancer, an acute myeloid leukemia, or a myelodysplastic syndrome.~~

~~28.18. The method of any one of claims 23-27~~use of claim 17, wherein the ~~method~~use further comprises administering to the subject an additional therapy to be administered to the subject, optionally wherein the additional therapy is radiotherapy, a chemotherapeutic agent, a targeted therapy, a tyrosine kinase inhibitor, hormone therapy, and/or an immune checkpoint inhibitor; optionally wherein the immune checkpoint inhibitor is an inhibitor of Programmed Death-1 (PD-1), or Programmed death-ligand 1 (PDL1), or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), or lymphocyte-activation gene 3 (LAG-3).

29. The method of claim 28, wherein the immune checkpoint inhibitor is an inhibitor of Programmed Death 1 (PD-1), or Programmed death ligand 1 (PDL1), or cytotoxic T lymphocyte associated protein 4 (CTLA-4).