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Anti-human VISTA antibodies and use thereof

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ABSTRACT

The invention provides antagonistic and agonistic anti-human VISTA antibodies and antibody fragments. These antagonist antibodies and antibody fragments may be used to inhibit or block VISTA's suppressive effects on T cell immunity and thereby promote T cell immunity. These agonist antibodies and antibody fragments may be used to potentiate or enhance or mimic VISTA's suppressive effects on T cell immunity and thereby suppress T cell immunity. These antagonist antibodies and antibody fragments are especially useful in the treatment of cancer and infectious conditions. These agonist antibodies and antibody fragments are especially useful in the treatment of autoimmunity, allergy, inflammatory conditions, GVHD, sepsis and transplant recipients. Screening assays for identifying these agonists are also provided.

ANTI-HUMAN VISTA ANTIBODIES AND USE THEREOF

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application Nos. 62/323,193 filed April 15, 2016, 62/343,355 filed May 31, 2016, 62/372,362 filed August 9, 2016, 62/385,627 filed September 9, 2016, 62/425,184 filed November 22, 2016, 62/363,929 filed July 19, 2016, 62/365,085 filed July 21, 2016, 62/385,805 filed September 9, 2016, 62/363,931 filed July 19, 2016, 62/365,102 filed July 21, 2016, 62/385,871 filed September 9, 2016, 62/363,917 filed July 19, 2016, 62/365,081 filed July 21, 2016, 62/385,888 filed September 9, 2016, 62/364,073 filed July 19, 2016, 62/365,166 filed July 21, 2016, 62/385,893 filed September 9, 2016, 62/363,925 filed July 19, 2016, 62/365,087 filed July 21, 2016, 62/385,785 filed September 9, 2016, 62/406,632 filed October 11, 2016, each and all of which are incorporated herein by reference. This application relates to PCT application PCT/US2017/027765 filed April 14, 2017 "ANTI-HUMAN VISTA ANTIBODIES AND USE THEREOF" (Attorney Docket No. 43260.2214) which is being incorporated by reference and to which priority is also claimed.

The entire disclosure in the complete specification of our Australian Patent Application No. 2017250294 is by this cross-reference incorporated into the present specification.

FIELD

[1] The invention relates to the identification of novel anti-human VISTA antibodies and antibody fragments, i.e., anti-human **VISTA** (**V**-region **I**mmunoglobulin-containing **S**uppressor of **T** cell **A**ctivation(1)), ("VISTA") antibodies and antibody fragments. More specifically, the present application provides novel human VISTA agonists, i.e., anti-human VISTA antibodies and antibody fragments which agonize or promote the suppressive effects of human VISTA on immunity, particularly T cell immunity. Also, the invention relates to the use of such agonists to enhance or mimic the suppressive effects of VISTA on immunity such as its suppressive effects on $CD4^+$ or $CD8^+$ T cell proliferation, $CD4^+$ or $CD8^+$ T cell activation and its suppressive effect on the production of immune cytokines, particularly proinflammatory cytokines. Also the invention relates to the specific use of these agonistic antibodies and antibody fragments as prophylactics or therapeutics, especially in treating conditions wherein the prevention or inhibition of T cell immunity and the expression of proinflammatory cytokines is therapeutically beneficial such as autoimmunity, inflammation, allergic disorders, sepsis, GVHD or in alleviating the inflammatory side effects of some conditions such as cancer.

[2] The present application also provides novel antagonists, i.e., anti-human VISTA antibodies and antibody fragments which antagonize or inhibit the suppressive effects of human VISTA on immunity, particularly VISTA's effects on T cell immunity. Also, the invention relates to the use of such novel antagonists to block or inhibit the suppressive effects of VISA on immunity, i.e., its suppressive effects on $CD4^+$ or $CD8^+$ T cell proliferation, $CD4^+$ or $CD8^+$ T cell activation and the production of immune cytokines. Also the invention

also relates to the specific use of these antagonistic antibodies and antibody fragments as prophylactics or therapeutics, especially in treating conditions wherein promoting T cell immunity is therapeutically beneficial such as in the treatment of cancer and infectious diseases.

BACKGROUND

[3] Immune negative checkpoint regulator (NCR) pathways have proven to be extraordinary clinical targets in the treatment of human immune-related diseases. Blockade of two NCRs, CTLA-4 and PD-1, using monoclonal antibodies (mAbs) to enhance tumor immunity is revolutionizing the treatment of cancer and has established these pathways as clinically validated targets in human disease. Also soluble versions of NCR ligands that trigger NCR pathways have entered the clinic as immunosuppressive drugs to treat autoimmunity (i.e., AMP-110/B7-H4-Ig for Rheumatoid arthritis).

[4] VISTA (*see* Ref 1), is an NCR ligand, whose closest phylogenetic relative is PD-L1. VISTA bears homology to PD-L1 but displays a unique expression pattern that is restricted to the hematopoietic compartment. Specifically, VISTA is constitutively and highly expressed on CD11b ^{high} myeloid cells, and expressed at lower levels on $CD4^+$ and $CD8^+$ T cells. Like PD-L1, VISTA is a ligand that profoundly suppresses immunity (Ref 1), and like PD-L1, blocking VISTA allows for the development of therapeutic immunity to cancer in pre-clinical oncology models (*see* Ref 2). Whereas blocking VISTA enhances immunity, especially $CD8^+$ and $CD4^+$ mediated T cell immunity, treatment with a soluble Ig fusion protein of the extracellular domain of VISTA (VISTA-Ig) suppresses immunity and has been shown to arrest the progression of multiple murine models of autoimmune disease.

[5] Clear scientific evidence has shown that VISTA is a ligand that induces profound T cell suppression. Numerous antagonistic anti-human VISTA antibodies have been reported by different groups including Dartmouth College and Jannsen. These antibodies are useful in the treatment of conditions wherein the suppression of the immunosuppressive effects of VISTA on T cell immunity is desired such as cancer and infection. However, to the best of the inventors' knowledge no anti-human VISTA antibody or antibody fragment has been previously identified which agonizes the effects of human VISTA. Such agonistic anti-human VISTA antibodies and antibody fragments would be desirable in treating conditions wherein the suppression of immunity, particularly T cell immunity is desired and/or conditions wherein VISTA expression is aberrantly downregulated.

SUMMARY

[6] It is an object of the invention to provide novel antibodies and antibody fragments which specifically bind to human VISTA and variants thereof, e.g., chimeric, human, humanized or multispecific anti-human VISTA antibodies which specifically bind to human VISTA and which promote or mimic the effects of human VISTA on immunity.

[7] It is a specific object of the invention to provide agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA wherein the agonistic antibody or antibody fragment binds to the same or overlapping epitope as any one of the anti-human VISTA antibodies having the CDR and variable heavy and light polypeptides shown in **Figure 4.**

[8] It is a specific object of the invention to provide an isolated antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human V-domain Ig Suppressor of T cell Activation (human VISTA), wherein the antibody or antibody fragment agonizes or promotes one or more of the effects of VISTA on immunity, e.g., comprising a human IgG2 constant or human IgG2 Fc region optionally wherein the human IgG2 constant or Fc region binds to Fc gamma receptors including human CD32A and/or containing a human IgG2 constant or Fc region which comprises the native human IgG2 binding to Fc gamma receptors and/or an IgG2 which binds to FcγRs including one or more of hFcγRI(CD64), FcγRIIA or hFcγRIIB, (CD32 or CD32A) and FcγRIIIA (CD16A) or FcγRIIIB (CD16B).

[9] It is a specific object of the invention to provide agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA wherein the agonistic antibody or antibody fragment binds to a VISTA epitope which includes or overlaps with the epitope bound by any of the anti-human VISTA antibodies having the sequences of Figure 4.

[10] It is a specific object of the invention to provide agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA wherein the agonistic antibody or antibody fragment binds or interacts with one of more residues of an epitope comprising residues of LLDSGLYCCLVVEIRHHHSEHRVH.

[11] It is a specific object of the invention to provide agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA wherein the agonistic antibody or antibody fragment binds or interacts with one of more residues of an epitope comprising one or more residues of 79EVQTCSERRPIR90 , 48NVTLTCRLLGPV60, 153HHHSEHRVHGAM164 , 52LTCRLLGPV60 , 56LLGPVDKGHDVTFYK70, 113LAQRHGLESASDHHG127, 153HHHSEHRVHGAM164, 93TFQDLHLHHGGHQAA107, 146CLVVEIRHHHSEH158, 53TCRLLGPVDKG63, 123SDHHG127 and/or 153HHHSEHRVHGAM164.

[12] It is a specific object of the invention to provide agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA wherein the agonistic antibody or antibody fragment binds or interacts with one of more residues of an epitope comprising one or more residues of 79EVQTCSERRPIR90 .

[13] It is a specific object of the invention to provide agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA wherein the agonistic antibody or antibody fragment promotes or enhances at least

one effect of human VISTA on immunity, e.g. its suppressive effect on any one or more of T cell immunity, activation of monocytes, induction of T-cell proliferation; induction or suppression of cytokine expression, increased survival of monocytes, induction of antibody-dependent cell-mediated cytotoxicity (ADCC) in cells-expressing VISTA; and induction of antibody-dependent cellular phagocytosis (ADCP) in cells-expressing VISTA.

[14] It is a specific object of the invention to provide agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA wherein the agonistic antibody or antibody fragment comprising an antigen binding region that specifically binds to human VISTA, wherein the antibody or antibody fragment which comprises variable heavy and light sequences having the identical CDR polypeptides as any one of the anti-human VISTA antibodies having the CDR and variable heavy and light polypeptides shown in Figure 4, with the proviso that if said antibody or fragment comprises an antagonist anti-human VISTA antibody or antibody fragment then the antibody or antibody fragment does not comprise the same CDRs as any one of VSTB112, VSTB116, VSTB95, VSTB50, VSTB53 or VSTB60.

[15] It is a specific object of the invention to provide agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA wherein the agonistic antibody or antibody which comprises an antagonist anti-human VISTA antibody or fragment then the antibody or antibody fragment does not comprise the same CDRs as any one of VSTB112, VSTB116, VSTB95, VSTB50, VSTB53 or VSTB60.

[16] It is a specific object of the invention to provide agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA wherein the agonistic antibody or antibody fragment comprises a variable heavy and/or variable light polypeptide having at least 90% sequence identity to those of an anti-human VISTA antibody selected from any one of VSTB49-VSTB116, wherein the variable heavy and light polypeptide sequences thereof are shown in Figure 4, with the proviso that if said antibody or fragment comprises an antagonist anti-human VISTA antibody or fragment then the antibody or antibody fragment does not comprise the same CDRs as any one of VSTB112, VSTB116, VSTB95, VSTB50, VSTB53 or VSTB60.

[17] It is a specific object of the invention to provide agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA wherein the agonistic antibody or antibody comprises an antigen binding region that specifically binds to human VISTA wherein the agonistic antibody or antibody fragment comprises a variable heavy and/or variable light polypeptide having at least 95% sequence identity to those of an anti-human VISTA antibody selected from any one of VSTB49-VSTB116, wherein the variable heavy and light polypeptide sequences thereof are shown in Figure 4, with the proviso that if said antibody or fragment comprises an antagonist anti-human VISTA antibody or antibody fragment then the antibody or antibody fragment does

not comprise the same CDRs as any one of VSTB112, VSTB116, VSTB95, VSTB50, VSTB53 or VSTB60.

[18] It is a specific object of the invention to provide agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA wherein the agonistic antibody or antibody fragment comprises a variable heavy and/or variable light polypeptide having at least 96-99% sequence identity to those of an anti-human VISTA antibody selected from any one of VSTB49-VSTB116, wherein the variable heavy and light polypeptide sequences thereof are shown in Figure 4, with the proviso that if said antibody or fragment comprises an antagonist anti-human VISTA antibody or antibody fragment then the antibody or antibody fragment does not comprise the same CDRs as any one of VSTB112, VSTB116, VSTB95, VSTB50, VSTB53 or VSTB60.

[19] It is a specific object of the invention to provide agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA wherein the agonistic antibody or antibody fragment which comprises a variable heavy and/or variable light polypeptide identical to those of an anti-human VISTA antibody selected from one of VSTB49-VSTB116, wherein the variable heavy and light polypeptide sequences thereof are shown in Figure 4, with the proviso that if said antibody or fragment comprises an antagonist anti-human VISTA antibody or antibody fragment then the antibody or antibody fragment does not comprise the same CDRs as any one of VSTB112, VSTB116, VSTB95, VSTB50, VSTB53 or VSTB60.

[20] It is a specific object of the invention to provide an antagonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA according to any of the foregoing which antagonizes or blocks at least one effect of human VISTA on immunity.

[21] It is a specific object of the invention to provide an agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA according to any of the foregoing which agonizes or promotes at least one effect of human VISTA on immunity.

[22] It is a specific object of the invention to provide an agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA according to any of the foregoing which comprises a human constant domain.

[23] It is a specific object of the invention to provide agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA according to any of the foregoing which comprises a human constant domain selected from IgG1, IgG2, IgG3 and IgG4, which optionally is modified, e.g., by deletion, substitution or addition mutations or any combination of the foregoing.

[24] It is a specific object of the invention to provide agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human

VISTA according to any of the foregoing wherein the antibody fragment comprises or is a Fab, F(ab')2, or scFv antibody fragment.

[25] It is a specific object of the invention to provide an antagonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA according to any of the foregoing which blocks or suppresses at least one of the effects of human VISTA on immunity, e.g., selected from its suppressive effect on T cell immunity, activation of monocytes, or T-cell proliferation; induction or suppression of cytokine expression, increased survival of monocytes, suppression of antibody-dependent cell-mediated cytotoxicity (ADCC) of cells-expressing VISTA; and suppression of antibody-dependent cellular phagocytosis (ADCP) of cells-expressing VISTA.

[26] It is a specific object of the invention to provide agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA according to any of the foregoing which promotes or enhances at least one of the effects of human VISTA on immunity, e.g., selected from its suppressive effect T cell immunity, activation of monocytes, suppression of T-cell proliferation; induction or suppression of cytokine expression, increased survival of monocytes, suppression of antibody-dependent cell-mediated cytotoxicity (ADCC) in cells-expressing VISTA; and suppression of antibody-dependent cellular phagocytosis (ADCP) of cells-expressing VISTA.

[27] It is a specific object of the invention to provide agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA according to any of the foregoing which comprises a human IgG2 constant or Fc region.

[28] It is a specific object of the invention to provide agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA according to any of the foregoing that promotes or enhances the suppressive effect of human VISTA on immunity, e.g. its effect on any one or more of T cell immunity, activation of monocytes, T-cell proliferation; cytokine expression, survival of monocytes, antibody-dependent cell-mediated cytotoxicity (ADCC) in cells-expressing VISTA; and antibody-dependent cellular phagocytosis (ADCP) in cells-expressing VISTA.

[29] It is a specific object of the invention to provide an agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA according to any of the foregoing which inhibits T cell immunity and/or proinflammatory cytokine expression.

[30] It is a specific object of the invention to provide an agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA according to any of the foregoing which is a human, humanized or chimeric antibody that comprises a human Fc region, e.g., human IgG1, IgG2, IgG3 and IgG4 or a chimera of any of the foregoing.

[31] It is a specific object of the invention to provide an agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA according to any of the foregoing which is chimeric, human or humanized.

[32] It is a specific object of the invention to provide agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA according to any of the foregoing which comprises a human IgG2 constant domain or Fc region which potentially may be mutated.

[33] It is a specific object of the invention to provide an agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA according to any of the foregoing which comprises a human IgG2 constant domain or fragment thereof or an hIgG1, hIgG3, hIgG4, IgA, IgD, IgE, or IgM, wherein the entire or substantially the entire hinge and CH1 domains of said antibody and optionally the entire or substantially the entire light chain constant region have been replaced with the corresponding entire or substantially the entire light chain, and the hinge and CH1 domains ("H2 regions" or "H2 domains") of hIgG2.

[34] It is a specific object of the invention to provide agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA according to any of the foregoing which (i) comprises an IgG2 Fc region wherein either or both of the heavy chain cysteine residue at position 127 and the light chain cysteine residue at position 214 (wherein numbering is according to Kabat) are deleted or changed to a different amino acid residue, resulting in an increase in the agonistic properties of the resultant modified antibody relative to an antibody wherein these residues are unchanged, (ii) the cysteine residue at position 214 in the H2 region of said antibody is mutated or substituted with another amino acid and/or one or more of the cysteine residues at positions 127, 232 or 233 of the heavy chain are deleted or substituted with another amino acid, (iii) it comprises a human IgG2 constant domain wherein at least one cysteine residue is deleted or changed to another amino acid, (iv) it competes with or binds to the same epitope on human VISTA as VSTB95 (variable heavy and light sequences shown in Figure 4).

[35] It is a specific object of the invention to provide agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA according to any of the foregoing which:

(i) comprises the V_H CDRs of SEQ ID NO:100, 101 and 102 and the V_L CDRs of SEQ ID NO:103, 104 and 105;
(ii) comprises the V_H CDRs of SEQ ID NO:110, 111 and 112 and the V_L CDRs of SEQ ID NO:113, 114 and 115;
(iii) comprises the V_H CDRs of SEQ ID NO:120, 121 and 122 and the V_L CDRs of SEQ ID NO:123, 124 and 125;
(iv) comprises the V_H CDRs of SEQ ID NO:130, 131 and 132 and the V_L CDRs of SEQ ID NO:133, 134 and 135;

(v) comprises the V_H CDRs of SEQ ID NO:140, 141 and 142 and the V_L CDRs of SEQ ID NO:143, 144 and 145;

(vi) comprises the V_H CDRs of SEQ ID NO:150, 151 and 152 and the V_L CDRs of SEQ ID NO:153, 154 and 155;

(vii) comprises the V_H CDRs of SEQ ID NO:160, 161 and 162 and the V_L CDRs of SEQ ID NO:163, 164 and 165;

(viii) comprises the V_H CDRs of SEQ ID NO:170, 171 and 172 and the V_L CDRs of SEQ ID NO:173, 174 and 175;

(ix) comprises the V_H CDRs of SEQ ID NO:180, 181 and 182 and the V_L CDRs of SEQ ID NO:183, 184 and 185;

(x) comprises the V_H CDRs of SEQ ID NO:190, 191 and 192 and the V_L CDRs of SEQ ID NO:193, 194 and 195;

(xi) comprises the V_H CDRs of SEQ ID NO:200, 201 and 202 and the V_L CDRs of SEQ ID NO:203, 204 and 205;

(xii) comprises the V_H CDRs of SEQ ID NO:210, 211 and 212 and the V_L CDRs of SEQ ID NO:213, 214 and 215;

(xiii) comprises the V_H CDRs of SEQ ID NO:220, 221 and 222 and the V_L CDRs of SEQ ID NO:223, 224 and 225;

(xiv) comprises the V_H CDRs of SEQ ID NO:230, 231 and 232 and the V_L CDRs of SEQ ID NO:233, 234 and 235;

(xv) comprises the V_H CDRs of SEQ ID NO:240, 241 and 242 and the V_L CDRs of SEQ ID NO:243, 244 and 245;

(xvi) comprises the V_H CDRs of SEQ ID NO:250, 251 and 252 and the V_L CDRs of SEQ ID NO:253, 254 and 255;

(xvii) comprises the VH CDRs of SEQ ID NO:260, 261 and 262 and the V_L CDRs of SEQ ID NO:263, 264 and 265;

(xviii) comprises the V_H CDRs of SEQ ID NO:270, 271 and 272 and the V_L CDRs of SEQ ID NO:273, 274 and 275;

(xix) comprises the V_H CDRs of SEQ ID NO:280, 281 and 282 and the V_L CDRs of SEQ ID NO:283, 284 and 285;

(xx) comprises the V_H CDRs of SEQ ID NO:290, 291 and 292 and the V_L CDRs of SEQ ID NO:293, 294 and 295;

(xxi) comprises the V_H CDRs of SEQ ID NO:300, 301 and 302 and the V_L CDRs of SEQ ID NO:303, 304 and 305;

(xxii) comprises the V_H CDRs of SEQ ID NO:310, 311 and 312 and the V_L CDRs of SEQ ID NO:313, 314 and 315;

(xxiii) comprises the V_H CDRs of SEQ ID NO:320, 321 and 322 and the V_L CDRs of SEQ ID NO:323, 324 and 325;

(xxiv) comprises the V_H CDRs of SEQ ID NO:330, 331 and 332 and the V_L CDRs of SEQ ID NO:333, 334 and 335;

(xxv) comprises the V_H CDRs of SEQ ID NO:340, 341 and 342 and the V_L CDRs of SEQ ID NO:343, 344 and 345;

(xxvi) comprises the V_H CDRs of SEQ ID NO:350, 351 and 352 and the V_L CDRs of SEQ ID NO:353, 354 and 355;

(xxvii) comprises the V_H CDRs of SEQ ID NO:360, 361 and 362 and the V_L CDRs of SEQ ID NO:363, 364 and 365;

(xxviii) comprises the V_H CDRs of SEQ ID NO:370, 371 and 372 and the V_L CDRs of SEQ ID NO:373, 374 and 375;

(xxix) comprises the V_H CDRs of SEQ ID NO:380, 381 and 382 and the V_L CDRs of SEQ ID NO:383, 384 and 385;

(xxx) comprises the V_H CDRs of SEQ ID NO:390, 391 and 392 and the V_L CDRs of SEQ ID NO:393, 394 and 395;

(xxxi) comprises the V_H CDRs of SEQ ID NO:400, 401 and 402 and the V_L CDRs of SEQ ID NO:403, 404 and 405;

(xxxii) comprises the V_H CDRs of SEQ ID NO:410, 411 and 412 and the V_L CDRs of SEQ ID NO:413, 414 and 415;

(xxxiii) comprises the V_H CDRs of SEQ ID NO:420, 421 and 422 and the V_L CDRs of SEQ ID NO:423, 424 and 425;

(xxxiv) comprises the V_H CDRs of SEQ ID NO:430, 431 and 432 and the V_L CDRs of SEQ ID NO:433, 434 and 435;

(xxxv) comprises the V_H CDRs of SEQ ID NO:440, 441 and 442 and the V_L CDRs of SEQ ID NO:443, 444 and 445;

(xxxvi) comprises the V_H CDRs of SEQ ID NO:450, 451 and 452 and the V_L CDRs of SEQ ID NO:453, 454 and 455;

(xxxvii) comprises the V_H CDRs of SEQ ID NO:460, 461 and 462 and the V_L CDRs of SEQ ID NO:463, 464 and 465;

(xxxviii) comprises the V_H CDRs of SEQ ID NO:470, 471 and 472 and the V_L CDRs of SEQ ID NO:473, 474 and 475;

(xxxix) comprises the V_H CDRs of SEQ ID NO:480, 481 and 482 and the V_L CDRs of SEQ ID NO:483, 484 and 485;

(xl) comprises the V_H CDRs of SEQ ID NO:490, 491 and 492 and the VL CDR polypeptides of SEQ ID NO:493, 494 and 495;

(xli) comprises the V_H CDRs of SEQ ID NO:500, 501 and 502 and the VL CDR polypeptides of SEQ ID NO:503, 504 and 505;

(xlii) comprises the V_H CDRs of SEQ ID NO:510, 511 and 512 and the VL CDR polypeptides of SEQ ID NO:513, 514 and 515;

(xliii) comprises the V_H CDRs of SEQ ID NO:520, 521 and 522 and the VL CDR polypeptides of SEQ ID NO:523, 524 and 525;

(xliv) comprises the V_H CDRs of SEQ ID NO:530, 531 and 532 and the VL CDR polypeptides of SEQ ID NO:533, 534 and 535;

(xlv) comprises the V_H CDRs of SEQ ID NO:540, 541 and 542 and the VL CDR polypeptides of SEQ ID NO:543, 544 and 545;

(xlvi) comprises the V_H CDRs of SEQ ID NO:550, 551 and 552 and the VL CDR polypeptides of SEQ ID NO:553, 554 and 555;

(xlvii) comprises the V_H CDRs of SEQ ID NO:560, 561 and 562 and the V_L CDRs of SEQ ID NO:563, 564 and 565;

(xlviii) comprises the V_H CDRs of SEQ ID NO:570, 571 and 572 and the V_L CDRs of SEQ ID NO:573, 574 and 575;

(xlix) comprises the V_H CDRs of SEQ ID NO:580, 581 and 582 and the V_L CDRs of SEQ ID NO:583, 584 and 585;

(l) comprises the V_H CDRs of SEQ ID NO:590, 591 and 592 and the V_L CDRs of SEQ ID NO:593, 594 and 595;

(li) comprises the V_H CDRs of SEQ ID NO:600, 601 and 602 and the V_L CDRs of SEQ ID NO:603, 604 and 605;

(lii) comprises the V_H CDRs of SEQ ID NO:610, 611 and 612 and the V_L CDRs of SEQ ID NO:613, 614 and 615;

(liii) comprises the V_H CDRs of SEQ ID NO:620, 621 and 622 and the V_L CDRs of SEQ ID NO:623, 624 and 625;

(liv) comprises the V_H CDRs of SEQ ID NO:630, 631 and 632 and the V_L CDRs of SEQ ID NO:633, 634 and 635;

(lv) comprises the V_H CDRs of SEQ ID NO:640, 641 and 642 and the V_L CDRs of SEQ ID NO:643, 644 and 645;

(lvi) comprises the V_H CDRs of SEQ ID NO:650, 651 and 652 and the V_L CDRs of SEQ ID NO:653, 654 and 655;

(lvii) comprises the V_H CDRs of SEQ ID NO:660, 661 and 662 and the V_L CDRs of SEQ ID NO:663, 664 and 665;

(lviii) comprises the V_H CDRs of SEQ ID NO:670, 671 and 672 and the V_L CDRs of SEQ ID NO:673, 674 and 675;

(lix) comprises the V_H CDRs of SEQ ID NO:680, 681 and 682 and the V_L CDRs of SEQ ID NO:683, 684 and 685;

(lx) comprises the V_H CDRs of SEQ ID NO:690, 691 and 692 and the V_L CDRs of SEQ ID NO:693, 694 and 695;

(lxi) comprises the V_H CDRs of SEQ ID NO:700, 701 and 702 and the V_L CDRs of SEQ ID NO:703, 704 and 705;

(lxii) comprises the V_H CDRs of SEQ ID NO:710, 711 and 712 and the V_L CDRs of SEQ ID NO:713, 714 and 715;

(lxiii) comprises the V_H CDRs of SEQ ID NO:720, 721 and 722 and the V_L CDRs of SEQ ID NO:723, 724 and 725;

(lxiv) comprises the V_H CDRs of SEQ ID NO:730, 731 and 732 and the V_L CDRs of SEQ ID NO:733, 734 and 735;

(lxv) comprises the V_H CDRs of SEQ ID NO:740, 741 and 742 and the V_L CDRs of SEQ ID NO:743, 744 and 745;

(lxvi) comprises the V_H CDRs of SEQ ID NO:750, 751 and 752 and the V_L CDRs of SEQ ID NO:753, 754 and 755;

(lxvii) comprises the V_H CDRs of SEQ ID NO:760, 761 and 762 and the V_L CDRs of SEQ ID NO:763, 764 and 765;

(lxviii) comprises the V_H CDRs of SEQ ID NO:770, 771 and 772 and the V_L CDRs of SEQ ID NO:773, 774 and 775;

(lxix) comprises the V_H CDRs of SEQ ID NO:780, 781 and 782 and the V_L CDRs of SEQ ID NO:783, 784 and 785;

(lxx) comprises the V_H CDRs of SEQ ID NO:790, 791 and 792 and the V_L CDRs of SEQ ID NO:793, 794 and 795;

(lxxi) comprises the V_H CDRs of SEQ ID NO:800, 801 and 802 and the V_L CDRs of SEQ ID NO:803, 804 and 805;

(lxxii) comprises the V_H CDRs of SEQ ID NO:810, 811 and 812 and the V_L CDRs of SEQ ID NO: 813, 814 and 815.

[36] It is an object of the invention to provide a VISTA agonist according to any of the foregoing which:

(i) comprises the V_H polypeptide of SEQ ID NO:106 and the V_L polypeptide of SEQ ID NO:108;

(ii) comprises the V_H polypeptide of SEQ ID NO:116 and the V_L polypeptide of SEQ ID NO:118;

(iii) comprises the V_H polypeptide of SEQ ID NO:126 and the V_L polypeptide of SEQ ID NO:128;

(iv) comprises the V_H polypeptide of SEQ ID NO:136 and the V_L polypeptide f SEQ ID NO:138;

(v) comprises the V_H polypeptide of SEQ ID NO:146 and the V_L polypeptide of SEQ ID NO:148;

(vi) comprises the V_H polypeptide of SEQ ID NO:156 and the V_L polypeptide of SEQ ID NO:158;

(vii) comprises the V_H polypeptide of SEQ ID NO:166 and the V_L polypeptide of SEQ ID NO:168;

(viii) comprises the V_H polypeptide of SEQ ID NO:176 and the V_L polypeptide of SEQ ID NO:178;

(ix) comprises the V_H polypeptide of SEQ ID NO:186 and the V_L polypeptide of SEQ ID NO:188;

(x) comprises the V_H polypeptide of SEQ ID NO:196 and the V_L polypeptide of SEQ ID NO:198;

(xi) comprises the V_H polypeptide of SEQ ID NO:206 and the V_L polypeptide of SEQ ID NO:208;

(xii) comprises the V_H polypeptide of SEQ ID NO:216 and the V_L polypeptide of SEQ ID NO:218;

(xiii) comprises the V_H polypeptide of SEQ ID NO:226 and the V_L polypeptide of SEQ ID NO:228;

(xiv) comprises the V_H polypeptide of SEQ ID NO:236 and the V_L polypeptide of SEQ ID NO:238;

(xv) comprises the V_H polypeptide of SEQ ID NO:246 and the V_L polypeptide of SEQ ID NO:248;

(xvi) comprises the V_H polypeptide of SEQ ID NO:256 and the V_L polypeptide of SEQ ID NO:258;

(xvii) comprises the V_H polypeptide of SEQ ID NO:266 and the V_L polypeptide of SEQ ID NO:268;

(xviii) comprises the V_H polypeptide of SEQ ID NO:276 and the VL polypeptide of SEQ ID NO:278;

(xix) comprises the V_H polypeptide of SEQ ID NO:286 and the V_L polypeptide of SEQ ID NO:288;

(xx) comprises the V_H polypeptide of SEQ ID NO:296 and the V_L polypeptide of SEQ ID NO:298;

(xxi) comprises the V_H polypeptide of SEQ ID NO:306 and the V_L polypeptide of SEQ ID NO:308;

(xxii) comprises the V_H polypeptide of SEQ ID NO:316 and the V_L polypeptide of SEQ ID NO:318;

(xxiii) comprises the V_H polypeptide of SEQ ID NO:326 and the V_L polypeptide of SEQ ID NO:328;

(xxiv) comprises the V_H polypeptide of SEQ ID NO:336 and the V_L polypeptide of SEQ ID NO:338;

(xxv) comprises the V_H polypeptide of SEQ ID NO:346 and the V_L polypeptide of SEQ ID NO:348;

(xxvi) comprises the V_H polypeptide of SEQ ID NO:356 and the V_L polypeptide of SEQ ID NO:358;

(xxvii) comprises the V_H polypeptide of SEQ ID NO:366 and the V_L polypeptide of SEQ ID NO:368;

(xxviii) comprises the V_H polypeptide of SEQ ID NO:376 and the V_L polypeptide of SEQ ID NO:378;

(xxix) comprises the V_H polypeptide of SEQ ID NO:386 and the V_L polypeptide of SEQ ID NO:388;

(xxx) comprises the V_H polypeptide of SEQ ID NO:396 and the V_L polypeptide of SEQ ID NO:398;

(xxxi) comprises the V_H polypeptide of SEQ ID NO:406 and the V_L polypeptide of SEQ ID NO:408;

(xxxii) comprises the V_H polypeptide of SEQ ID NO:416 and the V_L polypeptide of SEQ ID NO:418;

(xxxiii) comprises the V_H polypeptide of SEQ ID NO:426 and the V_L polypeptide of SEQ ID NO:428;

(xxxiv) comprises the V_H polypeptide of SEQ ID NO:436 and the V_L polypeptide of SEQ ID NO:438;

(xxxv) comprises the V_H polypeptide of SEQ ID NO:446 and the V_L polypeptide of SEQ ID NO:448;

(xxxvi) comprises the V_H polypeptide of SEQ ID NO:456 and the V_L polypeptide of SEQ ID NO:458;

(xxxvii) comprises the V_H polypeptide of SEQ ID NO:466 and the V_L polypeptide of SEQ ID NO:468;

(xxxviii) comprises the V_H polypeptide of SEQ ID NO:476 and the V_L polypeptide of SEQ ID NO:478;

(xxxix) comprises the V_H polypeptide of SEQ ID NO:486 and the V_L polypeptide of SEQ ID NO:488;

(xl) comprises the V_H polypeptide of SEQ ID NO:496 and the V_L polypeptide of SEQ ID NO:498;

(xli) comprises the V_H polypeptide of SEQ ID NO:506 and the V_L polypeptide of SEQ ID NO:508;

(xlii) comprises the V_H polypeptide of SEQ ID NO:516 and the V_L polypeptide of SEQ ID NO:518;

(xliii) comprises the V_H polypeptide of SEQ ID NO:526 and the V_L polypeptide of SEQ ID NO:528;

(xliv) comprises the V_H polypeptide of SEQ ID NO:536 and the V_L polypeptide of SEQ ID NO:533, 534 and 535;

(xlv) comprises the V_H polypeptide of SEQ ID NO:546 and the V_L polypeptide of SEQ ID NO:548;

(xlvi) comprises the V_H polypeptide of SEQ ID NO:556 and the V_L polypeptide of SEQ ID NO:558;

(xlvii) comprises the V_H polypeptide of SEQ ID NO:566 and the V_L polypeptide of SEQ ID NO:568;

(xlviii) comprises the V_H polypeptide of SEQ ID NO:576 and the V_L polypeptide of SEQ ID NO:578;

(xlix) comprises the V_H polypeptide of SEQ ID NO:586 and the V_L polypeptide of SEQ ID NO:588;

(l) comprises the V_H polypeptide of SEQ ID NO:596 and the V_L polypeptide of SEQ ID NO:598;

(li) comprises the V_H polypeptide of SEQ ID NO:606 and the V_L polypeptide of SEQ ID NO:608;

(lii) comprises the V_H polypeptide of SEQ ID NO:616 and the V_L polypeptide of SEQ ID NO:618;

(liii) comprises the V_H polypeptide of SEQ ID NO:626 and the V_L polypeptide of SEQ ID NO:628;

(liv) comprises the V_H polypeptide of SEQ ID NO:636 and the V_L polypeptide of SEQ ID NO:638;

(lv) comprises the V_H polypeptide of SEQ ID NO:646 and the V_L polypeptide of SEQ ID NO:648;

(lvi) comprises the V_H polypeptide of SEQ ID NO:656 and the V_L polypeptide of SEQ ID NO:658;

(lvii) comprises the V_H polypeptide of SEQ ID NO:666 and the V_L polypeptide of SEQ ID NO:668;

(lviii) comprises the V_H polypeptide of SEQ ID NO:676 and the V_L polypeptide of SEQ ID NO:678;

(lix) comprises the V_H polypeptide of SEQ ID NO:686 and the V_L polypeptide of SEQ ID NO:688;

(lx) comprises the V_H polypeptide of SEQ ID NO:696 and the V_L polypeptide of SEQ ID NO:698;

(lxi) comprises the V_H polypeptide of SEQ ID NO:706 and the V_L polypeptide of SEQ ID NO:708;

(lxii) comprises the V_H polypeptide of SEQ ID NO:716 and the V_L polypeptide of SEQ ID NO:718;

(lxiii) comprises the V_H polypeptide of SEQ ID NO:726 and the V_L polypeptide of SEQ ID NO:728;

(lxiv) comprises the V_H polypeptide of SEQ ID NO:736 and the V_L polypeptide of SEQ ID NO:738;

(lxv) comprises the V_H polypeptide of SEQ ID NO:746 and the V_L polypeptide of SEQ ID NO:748;

(lxvi) comprises the V_H polypeptide of SEQ ID NO:756 and the V_L polypeptide of SEQ ID NO:758;

(lxvii) comprises the V_H polypeptide of SEQ ID NO:766 and the V_L polypeptide of SEQ ID NO:768;

(lxviii) comprises the V_H polypeptide of SEQ ID NO:776 and the V_L polypeptide of SEQ ID NO:778;

(lxix) comprises the V_H polypeptide of SEQ ID NO:786 and the V_L polypeptide of SEQ ID NO:788;

(lxx) comprises the V_H polypeptide of SEQ ID NO:796 and the V_L polypeptide of SEQ ID NO:798;

(lxxi) comprises the V_H polypeptide of SEQ ID NO:806 and the V_L polypeptide of SEQ ID NO:808; and

(lxxii) comprises the V_H polypeptide of SEQ ID NO:816 and the V_L polypeptide of SEQ ID NO: 818.

[37] It is a specific object of the invention to provide an agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA according to any of the foregoing which comprises a human IgG2 constant domain wherein optionally at least one cysteine residue is deleted or changed to another amino acid.

[38] It is a specific object of the invention to provide an agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA according to any of the foregoing which mediates any one or combination of at least one of the following immmunoinhibitory effects: (i) decreases immune response, (ii) decreases T cell activation, (iii) decreases cytotoxic T cell activity, (iv) decreases natural killer (NK) cell activity, (v) decreases T-cell activity, (vi) decreases pro-inflammatory cytokine secretion, (vii) decreases IL-2 secretion; (viii) decreases interferon-γ production, (ix) decreases Th1 response, (x) decreases Th2 response, (xi) increases cell number and/or activity of regulatory T cells, (xii) increases regulatory cell activity and/or one or more of myeloid derived suppressor cells (MDSCs), iMCs, mesenchymal stromal cells, TIE2-expressing monocytes, (xiii) increases regulatory cell activity and/or the activity of one or more of myeloid derived suppressor cells (MDSCs), iMCs, mesenchymal stromal cells, TIE2-expressing monocytes, (xiii) increases M2 macrophages, (xiv) increases M2 macrophage activity, (xv) increases N2 neutrophils, (xvi) increases N2 neutrophils activity, (xvii) increases inhibition of T cell activation, (xviii) increases inhibition of CTL activation, (xix) increases inhibition of NK cell activation, (xx) increases T cell exhaustion, (xxi) decreases T cell response, (xxii) decreases activity of cytotoxic cells, (xxiii) reduces antigen-specific memory responses, (xxiv) inhibits apoptosis or lysis of cells, (xxv) decreases cytotoxic or cytostatic effect on cells, (xxvi) reduces direct killing of cells, (xxvii) decreases Thl7 activity, and/or (xxviii) reduces complement dependent cytotoxicity and/or antibody dependent cell-mediated cytotoxicity, with the proviso that said anti-VISTA antibody or antigen-binding fragment may elicit an opposite effect to one or more of (i)-(xxviii) and optionally is used to treat autoimmunity, allergy, inflammation, transplant or sepsis.

[39] It is a specific object of the invention to provide a pharmaceutical or diagnostic composition comprising an agonistic antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human VISTA according to any of the foregoing.

[40] It is a specific object of the invention to provide a method of treatment and/or diagnosis, or use of a composition containing at least one antagonistic antibody or antibody fragment according to any of the foregoing claims for diagnostic or therapeutic use, which

method or use comprises the administration to a subject in need thereof at least one dosage or composition comprising a therapeutically or diagnostically effective amount of at least one at least one antagonistic antibody or antibody fragment according to any of the foregoing, e.g., cancer or an infectious disorder, optionally wherein the cancer is a blood cancer or solid tumor, e.g., one surrounded by a tumor stroma comprising myeloid cells, T-cells, or a combination of myeloid cells and T-cells or a cancer selected from leukemia, lymphoma, myelodysplastic syndrome or myeloma, lung cancer or a combination thereof or a leukemia which comprises acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myeloid (myelogenous) leukemia (AML), chronic myelogenous leukemia (CML); hairy cell leukemia, T-cell prolymphocytic leukemia, large granular lymphocytic leukemia, or adult T-cell leukemia.

[41] It is a specific object of the invention to provide a method of treatment and/or diagnosis, or use of a composition containing at least one agonistic antibody or antibody fragment according to any of the foregoing claims for diagnostic or therapeutic use, which method or use comprises the administration to a subject in need thereof at least one dosage or composition comprising a therapeutically or diagnostically effective amount of at least one at least one agonistic antibody or antibody fragment according to any of the foregoing or composition containing according to any of the foregoing.

[42] It is a specific object of the invention to provide a method or use of any agonistic antibody or antibody fragment according to any of the foregoing for effecting in vitro and/or in vivo any one or combination of at least one of the following immmunoinhibitory effects: (i) decreases immune response, (ii) decreases T cell activation, (iii) decreases cytotoxic T cell activity, (iv) decreases natural killer (NK) cell activity, (v) decreases T-cell activity, (vi) decreases pro-inflammatory cytokine secretion, (vii) decreases IL-2 secretion; (viii) decreases interferon-γ production, (ix) decreases Th1 response, (x) decreases Th2 response, (xi) increases cell number and/or activity of regulatory T cells, (xii) increases regulatory cell activity and/or one or more of myeloid derived suppressor cells (MDSCs), iMCs, mesenchymal stromal cells, TIE2-expressing monocytes, (xiii) increases regulatory cell activity and/or the activity of one or more of myeloid derived suppressor cells (MDSCs), iMCs, mesenchymal stromal cells, TIE2-expressing monocytes, (xiii) increases M2 macrophages, (xiv) increases M2 macrophage activity, (xv) increases N2 neutrophils, (xvi) increases N2 neutrophils activity, (xvii) increases inhibition of T cell activation, (xviii) increases inhibition of CTL activation, (xix) increases inhibition of NK cell activation, (xx) increases T cell exhaustion, (xxi) decreases T cell response, (xxii) decreases activity of cytotoxic cells, (xxiii) reduces antigen-specific memory responses, (xxiv) inhibits apoptosis or lysis of cells, (xxv) decreases cytotoxic or cytostatic effect on cells, (xxvi) reduces direct killing of cells, (xxvii) decreases Thl7 activity, and/or (xxviii) reduces complement dependent cytotoxicity and/or antibody dependent cell-mediated cytotoxicity, with the proviso that said anti-VISTA antibody or antigen-binding fragment may elicit an opposite effect to one or

more of (i)-(xxviii) and optionally is used to treat autoimmunity, allergy, inflammation, transplant or sepsis.

[43] It is a specific object of the invention to provide a method or use of any agonistic antibody or antibody fragment according to any of the foregoing for use in the treatment or prevention of allergy, autoimmunity, transplant, gene therapy, inflammation, cancer, GVHD or sepsis, or to treat or prevent inflammatory, autoimmune, or allergic side effects associated with any of the foregoing therewith in a human subject.

[44] An anti-VISTA antibody or antigen-binding fragment or composition, or method or use according to any of the foregoing, further comprising another immunomodulatory antibody or fusion protein which is selected from immmunoinhibitory antibodies or fusion proteins targeting one or more of CTLA4, PD-1, PDL-1, LAG-3, TIM-3, BTLA, B7-H4, B7-H3, VISTA, and/or agonistic antibodies or fusion protein targeting one or more of CD40, CD137, OX40, GITR, CD27, CD28 or ICOS.

[45] A method or use of any of the foregoing which includes assaying VISTA protein by the individual's cells or in bodily fluids prior, concurrent and/or after treatment.

[46] A method or use of any of the foregoing which includes assaying VISTA levels on hematopoietic cells.

[47] A method or use of any of the foregoing which includes assaying VISTA levels on hematopoietic cells selected from any one or more of myeloid lineage cells and/or a lymphocytes, monocyte or a neutrophils, T cells, B cells, a natural killer (NK) cells or a natural killer T (NKT) cells.

[48] A method or use of any of the foregoing wherein the agonist anti-human VISTA antibody or fragment comprises the same CDRs as an antibody selected from VSTB49-VSTB116 and a human IgG2 Fc region which optionally may be mutated or wherein the IgG2 constant or Fc region retains native FcR binding and/or the ability to bind CD32A.

[49] The antibody, composition, method or use of any of the foregoing wherein the anti-human VISTA antibody or fragment comprises an affinity or KD for human VISTA which is 50M or less as determined by surface plasmon resonance at 37° C.

[50] The antibody, composition, method or use of any of the foregoing wherein the anti-human VISTA antibody or fragment comprises an affinity or KD for human VISTA which is 1nM or less as determined by surface plasmon resonance at 37° C.

[51] It is a specific object of the invention to provide isolated antagonistic and agonistic anti-human VISTA antibodies and agonistic antibody fragments comprising an antigen binding region that specifically binds to human VISTA wherein the antibodies or antibody fragments comprise variable heavy and light sequences having the CDR polypeptides of any one of the anti-human VISTA antibodies having the sequences shown in **Figure 4**, with the proviso that if said antibody or fragment comprises an antagonist anti-human VISTA antibody or antibody fragment then the antibody or antibody fragment does

not comprise the same CDRs as any one of VSTB112, VSTB116, VSTB95, VSTB50, VSTB53 or VSTB60.

[52] It is a specific object of the invention to provide isolated antagonistic and agonistic anti-human VISTA antibodies and agonistic antibody fragments comprising an antigen binding region that specifically binds to human VISTA wherein the antibodies or antibody fragments comprise variable heavy and light sequences having the CDR polypeptides of an anti-human VISTA antibody selected from VSTB49-VSTB116, with the proviso that if said antibody or fragment comprises an antagonistic anti-human VISTA antibody or anti-human VISTA antibody fragment then the anti-human VISTA antibody or antibody fragment does not comprise the same CDRs as any one of VSTB112, VSTB116, VSTB95, VSTB50, VSTB53 or VSTB60.

[53] It is another specific object of the invention to provide isolated antagonistic and agonistic antibodies and antibody fragments comprising the CDRs of an anti-human VISTA antibody selected from VSTB49-VSTB116, which comprise a variable heavy and/or variable light polypeptide having at least 90%, 95%, or 96-99% sequence identity to the variable heavy and light polypeptide sequences of VSTB49-VSTB116, with the proviso that if said antibody or fragment comprises an antagonistic anti-human VISTA antibody or fragment then the antibody or antibody fragment does not comprise the same CDRs as any one of VSTB112, VSTB116, VSTB95, VSTB50, VSTB53 or VSTB60.

[54] It is another specific object of the invention to provide isolated antagonistic and agonistic antibodies or antibody fragments comprising the same CDRs any one of VSTB49-VSTB116, which comprise a variable heavy and/or variable light polypeptide which is/are identical to the variable heavy and light polypeptide sequences of VSTB49-VSTB116, with the proviso that if said antibody or fragment comprises an antagonistic anti-human VISTA antibody or fragment then the antibody or antibody fragment does not comprise the same CDRs as any one of VSTB112, VSTB116, VSTB95, VSTB50, VSTB53 or VSTB60.

[55] It is another specific object of the invention to provide isolated antagonistic or agonistic chimeric, human, humanized, multispecific (e.g., bispecific) anti-human VISTA antibodies or antibody fragments comprising an antigen binding region that specifically binds to human VISTA which comprise variable heavy and light sequences having the CDR polypeptides as any one of the anti-human VISTA antibodies comprising the CDR and variable heavy and light polypeptides disclosed in **Figure 4**, with the proviso that if said antibody or fragment comprises an antagonistic anti-human VISTA antibody or antibody fragment then the antibody or antibody fragment does not comprise the same CDRs as any one of VSTB112, VSTB116, VSTB95, VSTB50, VSTB53 or VSTB60.

[56] It is another specific object of the invention to provide novel immunosuppressants, i.e., anti-human VISTA antibodies and antibody fragments, e.g., those containing human IgG2 constant domains or IgG2 Fc regions, optionally wherein the FcR binding capability of the human IgG2 constant domains or IgG2 Fc regions are maintained or

are enhanced compared to the wild-type human IgG2 constant domains or IgG2 Fc regions, which agonize, elicit or mimic the effects of human VISTA on immunity, e.g., its suppressive effects on T cell activity, differentiation and proliferation and its suppressive effects on the expression of proinflammatory cytokines.

[57] It is another specific object of the invention to provide novel antagonists, i.e., novel anti-human VISTA antibodies and antibody fragments which antagonize or block the effects of human VISTA on immunity, particularly its suppressive effects on T cell activity, differentiation and proliferation and its suppressive effects on the expression of proinflammatory cytokines.

[58] It is another specific object of the invention to provide novel immunosuppressive antibodies and antibody fragments which enhance or mimic the suppressive effects of VISTA on T cell immunity, i.e., which suppress $CD4^+$ or $CD8^+$ T cell proliferation, $CD4^+$ or $CD8^+$ T cell activation and its suppression of the production of immune cytokines, particularly proinflammatory cytokines such as IL-2, IL-4, IL-6, IL-17, TNF-α, and/or GM-CSF(granulocyte-macrophage colony-stimulating factor), and its promoting effects on the expression of chemokines or chemoattractants such as KC (keratinocyte chemoattractant) or MIP-2(Macrophage inflammatory protein 2).

[59] It is another specific object of the invention to provide novel antibodies and antibody fragments which block or reduce the suppressive effects of VISTA on T cell immunity, i.e., which enhance $CD4^+$ or $CD8^+$ T cell proliferation, $CD4^+$ or $CD8^+$ T cell activation, and its suppressive effects on the production of proinflammatory immune cytokines, particularly proinflammatory cytokines such as IL-2, IL-4, IL-6, IL-17, TNF-α, and/or GM-CSF(granulocyte-macrophage colony-stimulating factor), and its promoting effects on the expression of chemokines or chemoattractants such as KC (keratinocyte chemoattractant) or MIP-2(Macrophage inflammatory protein 2).

[60] It is another specific object of the invention to provide novel immunosuppressive or agonistic anti-human VISTA antibodies and antibody fragments of specific epitopic specificity or which compete for binding to human VISTA with specific anti-human VISTA antibodies.

[61] It is another specific object of the invention to provide novel immunosuppressive or agonistic anti-human VISTA antibodies and antibody fragments of specific epitopic specificity or which compete for binding to human VISTA with specific anti-human VISTA antibodies which agonize (enhance, elicit or mimic) the suppressive effects of VISTA on immunity, e.g., its suppressive effects on T cell immunity, i.e., $CD4^+$ or $CD8^+$ T cell proliferation, $CD4^+$ or $CD8^+$ T cell activation, and/or which suppress the production of proinflammatory immune cytokines such as IL-2, IL-4, IL-6, IL-17, TNF-α, and/or GM-CSF(granulocyte-macrophage colony-stimulating factor), and its promoting effects on the expression of chemokines or chemoattractants such as KC (keratinocyte chemoattractant) or MIP-2(Macrophage inflammatory protein 2).

[62] Also the invention also relates to the specific use of these agonistic anti-human VISTA antibodies and antibody fragments as prophylactics or therapeutics, especially in treating conditions wherein preventing or inhibiting or reducing immune reactions is therapeutically desirable, and more particularly wherein the preventing or inhibiting or reducing T cell immunity, or more specifically $CD4^+$ or $CD8^+$ mediated T cell immunity is therapeutically beneficial such as autoimmunity, inflammation, allergic disorders, sepsis, GVHD, and/or in treating transplant or cell therapy recipients, e.g., CAR-T recipients, or in alleviating the inflammatory side effects of some conditions such as cancer.

[63] Also the invention relates to the use of novel antagonistic anti-human VISTA antibodies and antibody fragments as prophylactics or therapeutics, especially in treating conditions wherein promoting immunity is desired, e.g., T cell immunity or $CD4^+$ or $CD8^+$-mediated T cell immunity is therapeutically beneficial such as cancer and infectious disease.

[64] It is another specific object of the invention to provide an agonist or antagonist anti-human VISTA antibody according to the invention which is attached to a detectable label, linker or a therapeutic moiety.

[65] It is another specific object of the invention to provide a diagnostic or therapeutic composition comprising a diagnostically or therapeutically effective amount of an agonist or antagonist anti-human VISTA antibody according to the invention, e.g., one containing the same CDRs as any of the antibodies having the sequences shown in **Figure 4** which is suitable for use in human therapy, such as an intravenous, subcutaneous or intramuscular administrable composition.

[66] It is another specific object of the invention to provide a diagnostic or therapeutic methods which use an agonist antibody according to the invention in association with another immune agonist, e.g., a PD-1 or PD-L1 agonist, e.g., wherein the PD-1 or PD-L1 agonist is selected from an anti-PD-1 antibody or antibody fragment, an anti-PD-L1 antibody or antibody fragment, a PD-L1 polypeptide or fragment thereof which may be monovalent or multimeric, a PD-1 polypeptide or fragment thereof which may be monovalent or multimeric, or a complex or fusion protein comprising any of the foregoing.

[67] It is another specific object of the invention to provide diagnostic or therapeutic methods which use an antagonist antibody according to the invention in association with another immune antagonist, e.g., a PD-1 or PD-L1 antagonist, e.g., wherein the PD-1 or PD-L1 agonist is selected from an antagonist anti-PD-1 antibody or antibody fragment, an antagonist anti-PD-L1 antibody or antibody fragment.

[68] It is another specific object of the invention to provide methods of contacting immune cells *in vitro* or *in vivo* with an antagonist or agonist antibody according to the invention, e.g., human immune cells, e.g., wherein the contacted cells are infused into a human subject such as a subject who has cancer or an infectious disease or one who has an inflammatory, allergic or autoimmune condition.

BRIEF DESCRIPTION OF THE FIGURES

[69] **Figure 1A-D**. This figure shows in vitro and in vivo screening assays which can be used to identify suppressive VISTA mAbs. **A**) Purified T cells were plated on top of anti-CD3 in the presence of the indicated mAb for 72 hours. Proliferation was measured by H3 incorporation. **B**) Purified DO11.10 T cells were stimulated by ISQ pulsed APCs for 6 days in the presence of the indicated antibody. Proliferation was measured through use of CTV dilution dye. **C**) GVHD was induced by transfer of C57BL/6 cells into irradiated BALB/c recipients. Mice were injected I.P. with 200 μg of antibody on day 0, 2 and 4 post transfer and survival was analyzed. **D**) Mice were treated with 10 mpk of the indicated antibody 3 hours prior to administration of ConA (15 mpk) and IL-2 was analyzed in plasma at 6 by Luminex.

[70] **Figure 2A-F.** This figure shows that agonist VISTA antibodies are immunosuppressive in multiple models of autoimmune disease. **A**) NZB/W F1 mice were treated 3X/week with either 8G8 or Ham Ig (200 μg) starting at 25 weeks until the end of the experiment. "X" denotes time points where the control treated group had all been sacrificed. B) Mice were treated with 200 μg of antibody 3 hours prior to administration of 15 mg/kg (mpk) of ConA and survival was followed for 80 hours. **C**) Mice were treated sequentially with Collagen II mAb followed by LPS and arthritis was measured by measuring for paw swelling. 8G8 and Ham-Ig were administered (200 μg) 3X every other day. **D**) Imiquimod was applied to the ear of mice daily. At day 14, 8G8 or Ham-Ig (200 μg) were administered every other day and ear thickness was measured with calipers. **E, F**) Imiquimod was applied to the backs of mice daily. At day 9, mice were euthanized and skin was sectioned & stained for CD3 expression by IHC.

[71] **Figure 3.** This figure shows the expression of VISTA in WT and hV-KI mice. CD4+ T cells, $CD8^+$ T cells, Tregs ($CD4^+$ $FoxP3^+$), and monocytes, $CD11b^+$, $Ly6C^+$, $Ly6G^-$ were isolated from the lymph nodes of WT and VISTA KI mice, and stained with αVISTA antibodies against mouse or human protein respectively.

[72] **Figure 4** contains the sequences of different anti-human VISTA antibodies including those of INX800, INX801, and INX900-INX919.

[73] **Figure 5** shows the effects of exemplary anti-human VISTA antibodies, i.e., INX800 and INX801 in a ConA hepatitis model which assesses the effects thereof on the expression of different cytokines, chemokines and chemoattractants.

[74] **Figure 6** shows the effects of exemplary anti-human VISTA antibodies, i.e., INX800 and INX801 in an in vivo graft versus host disease (GVHD) animal model.

[75] **Figure 7** shows the effects of exemplary agonistic anti-human VISTA antibodies, i.e., INX800 or INX801 on CD3-driven T cell immune responses.

[76] **Figure 8** shows the effects of exemplary agonistic anti-human VISTA antibodies, i.e., INX800 or INX801 on the number of specific T cell populations or on total T cell numbers.

[77] **Figure 9** compares the effects of exemplary anti-human VISTA antibodies in ConA assays and on the expression of select proinflammatory cytokines and inflammation markers, i.e., IL-2, ɣ interferon and IL-12p70.

[78] **Figure 10A-C:** shows different IgG2 Isoforms. (**A**) Disulfide shuffling leads to isoforms A and B, along with the transition for A/B (figure from Zhang, A. et al., 2015). (**B**) Isoforms are distinguishable by RP-HPLC. (**C**) Observed RP-HPLC chromatogram for INX901.

[79] **Figure 11:** shows chemical enrichment of IgG2 A or B isoforms. (**Black line, top**) Chromatogram shows a dominant left-most peak defining the B-form. (**Red line, bottom**) Chromatogram shows a dominant right peak defining the A-form.

[80] **Figure 12**: compares INX901 Fc-silent variants with respect to disulfide shuffling. (**Top**) INX901 on an IgG2 backbone exhibits an expected mixture of A, A/B, and B isoforms. (**Middle**) INX901Si on a silent IgG1 backbone exists as a single isoform. (**Bottom**) INX901HSi possesses an IgG1 silent Fc region with a CH1/hinge from IgG2, which enables disulfide shuffling equivalent to native IgG2.

[81] **Figure 13**. Biochemically skewed INX901 forms can still reduce cytokine production in the MLR. Supernatants from two separate MLRs were analyzed for cytokine production at the 72-hour time point by Luminex analysis. INX901 parental, A skew and B skew all reduced the production of TNFα and IL-2 in a dose dependent fashion.

[82] **Figure 14**. Genetically locked INX901 forms can still reduce cytokine production in the MLR, but Fc silent variants cannot. Supernatants from each MLR were analyzed for cytokine production at the 72-hour time point by Luminex analysis. INX901 parental, A lock and B lock all reduced the production of TNFα and IL-2 in a dose dependent fashion. The Si and HSi variants, which contain mutations to silence the Fc domain, did not consistently suppress cytokine production.

[83] **Figure 15.** Genetically locked INX908 forms can still reduce cytokine production in the MLR, but Fc silent variants cannot. Supernatants from each MLR were analyzed for cytokine production at the 72-hour time point by Luminex analysis. INX908 parental, A lock and B lock all reduced the production of TNFα and IL-2 in a dose dependent fashion. The Si and HSi variants, which contain mutations to silence the Fc domain, did not consistently suppress cytokine production.

[84] **Figure 16.** This figure schematically describes the Pepscan® technology used to identify linear and discontinuous epitopes bound by agonist anti-human VISTA antibodies.

[85] **Figure 17:** This figure shows that agonist anti-human VISTA antibodies bind to the same core sequence.

[86] **Figure 18:** This figure summarizes the epitope analysis for different anti-human VISTA antibodies according to the invention.

[87] **Figure 19:** This figure shows the epitopes bound by agonist anti-human VISTA antibodies and further identifies important residues involved in binding.

DETAILED DESCRIPTION

[88] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as those commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein may be used in the invention or testing of the present invention, suitable methods and materials are described herein. The materials, methods and examples are illustrative only, and are not intended to be limiting. The nomenclatures utilized in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art. Standard techniques may be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

[89] As used in the description herein and throughout the claims that follow, the meaning of "a," "an," and "the" includes plural reference unless the context clearly dictates otherwise.

[90] "Activating receptor," as used herein, refers broadly to immune cell receptors that bind antigen, complexed antigen (e.g., in the context of MHC molecules), Ig-fusion proteins, ligands, or antibodies. Activating receptors but are not limited to T cell receptors (TCRs), B cell receptors (BCRs), cytokine receptors, LPS receptors, complement receptors, and Fc receptors. For example, T cell receptors are present on T cells and are associated with CD3 molecules. T cell receptors are stimulated by antigen in the context of MHC molecules (as well as by polyclonal T cell activating reagents). T cell activation via the TCR results in numerous changes, e.g., protein phosphorylation, membrane lipid changes, ion fluxes, cyclic nucleotide alterations, RNA transcription changes, protein synthesis changes, and cell volume changes. For example, T cell receptors are present on T cells and are associated with CD3 molecules. T cell receptors are stimulated by antigen in the context of MHC molecules (as well as by polyclonal T cell activating reagents). T cell activation via the TCR results in numerous changes, e.g., protein phosphorylation, membrane lipid changes, ion fluxes, cyclic nucleotide alterations, RNA transcription changes, protein synthesis changes, and cell volume changes.

[91] "Adjuvant" as used herein, refers to an agent used to stimulate the immune system and increase the response to a vaccine, without having any specific antigenic effect in itself.

[92] "Agonist" herein refers to a molecule, generally an antibody or fusion proteins which enhances or mimics the effects of a specific molecule on immunity. Generally in the present application this will refer to anti-human VISTA agonist antibodies and antibody fragments which enhance or mimic the effects of human VISTA on immunity, particularly VISTA's suppressive effects on T cell immunity (CD4+ and/or CD8+ T cell immunity), the expression of proinflammatory cytokines and its effects of the expression of specific chemokines and chemoattractants.

[93] "Aids in the diagnosis" or "aids in the detection" of a disease herein means that the expression level of a particular marker polypeptide or expressed RNA is detected alone or in association with one or more other markers in order to assess whether a subject has cells characteristic of a particular disease condition or the onset of a particular disease condition or comprises immune dysfunction such as immunosuppression characterized by VISTA expression or abnormal immune upregulation characterized by cells having reduced VISTA levels, such as during autoimmunity, inflammation or allergic responses, e.g., in individuals with chronic and non-chronic diseases.

[94] "Allergic disease," as used herein, refers broadly to a disease involving allergic reactions. More specifically, an "allergic disease" is defined as a disease for which an allergen is identified, where there is a strong correlation between exposure to that allergen and the onset of pathological change, and where that pathological change has been proven to have an immunological mechanism. Herein, an immunological mechanism means that leukocytes show an immune response to allergen stimulation.

[95] "Amino acid," as used herein refers broadly to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified (e.g., hydroxyproline, γ -carboxyglutamate, and O-phosphoserine.) Amino acid analogs refers to compounds that have the same basic chemical structure as a naturally occurring amino acid (i. e., a carbon that is bound to a hydrogen, a carboxyl group, an amino group), and an R group (e.g., homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium.) Analogs may have modified R groups (e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid.

[96] "Anergy" or "tolerance," or "prolonged antigen-specific T cell suppression" or "prolonged immunosuppression" as used herein refers broadly to refractivity to activating receptor-mediated stimulation. Refractivity is generally antigen-specific and persists after exposure to the tolerizing antigen has ceased. For example, anergy in T cells (as opposed to unresponsiveness) is characterized by lack of cytokine production, e.g., IL-2. T cell anergy occurs when T cells are exposed to antigen and receive a first signal (a T cell receptor or CD-

3 mediated signal) in the absence of a second signal (a costimulatory signal). Under these conditions, reexposure of the cells to the same antigen (even if reexposure occurs in the presence of a costimulatory molecule) results in failure to produce cytokines and, thus, failure to proliferate. Anergic T cells can, however, mount responses to unrelated antigens and can proliferate if cultured with cytokines (e.g., IL-2). For example, T cell anergy can also be observed by the lack of IL-2 production by T lymphocytes as measured by ELISA or by a proliferation assay using an indicator cell line. Alternatively, a reporter gene construct can be used. For example, anergic T cells fail to initiate IL-2 gene transcription induced by a heterologous promoter under the control of the 5' IL- 2 gene enhancer or by a multimer of the API sequence that can be found within the enhancer (Kang et al. (1992) Science 257: 1134). Modulation of a costimulatory signal results in modulation of effector function of an immune cell.

[97] "Antagonist" herein refers to a molecule, generally an antibody or fusion proteins which blocks or reduces the effects of a specific molecule on immunity. Generally in the present application this will refer to anti-human VISTA antagonist antibodies and antibody fragments which block or reduce the effects of human VISTA on immunity, particularly VISTA's suppressive effects on T cell immunity ($CD4^+$ and/or CD8+ T cell immunity), the expression of proinflammatory cytokines and VISTA's effects of the expression of specific chemokines and chemoattractants.

[98] "Antibody", as used herein, refers broadly to an "antigen-binding portion" of an antibody (also used interchangeably with "antibody portion," "antigen-binding fragment," "antibody fragment"), as well as whole antibody molecules. The term "antigen-binding portion", as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., VISTA or specific portions thereof)). The term "antibody" as referred to herein includes whole polyclonal and monoclonal antibodies and any antigen-binding fragment (i. e., "antigen-binding portion") or single chains thereof as well as bispecific and multispecific antibodies, e.g., those that bind to multiple antigens or multiple antigen epitopes. An "antibody" refers to a glycoprotein comprising at least two heavy (H) chains and two light (L) chains interconnected by disulfide bonds, or an antigen-binding portion thereof. Each heavy chain is comprised of at least one heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, C_{H1}, Cm and Cm- Each light chain is comprised of at least one light chain variable region (abbreviated herein as V_L) and a light chain constant region. The light chain constant region is comprised of one domain, CL-The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FRs). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the

antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (C1q) of the classical complement system. More generally, the term "antibody" is intended to include any polypeptide chain-containing molecular structure with a specific shape that fits to and recognizes an epitope, where one or more non-covalent binding interactions stabilize the complex between the molecular structure and the epitope. The archetypal antibody molecule is the immunoglobulin, and all types of immunoglobulins, IgG, IgM, IgA, IgE, IgD, etc., from all sources, e.g. human, rodent, rabbit, cow, sheep, pig, dog, other mammals, chicken, other avians, etc., are considered to be "antibodies."

[99] The antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Non-limiting examples of antigen-binding fragments encompassed within the term "antigen-binding portion" of an antibody include (a) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and C_{H1} domains; (b) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (c) a Fd fragment consisting of the V_H and C_{H1} domains; (d) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody; (e) a dAb fragment (Ward, et al. (1989) *Nature* 341 : 544-546), which consists of a V_H domain; and (f) an isolated complementarily determining region (CDR). Furthermore, although the two domains of the Fv fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the V_L and V_H regions pair to form monovalent molecules (known as single chain Fv (scFv). See e.g., Bird, et al. (1988) *Science* 242: 423-426; Huston, et al. (1988) *Proc Natl. Acad. Sci.* USA 85: 5879-5883; and Osbourn, et al. (1998) *Nat. Biotechnol*. 16: 778. Single chain antibodies are also intended to be encompassed within the term "antigen-binding portion" of an antibody. Any V_H and V_L sequences of specific scFv can be linked to human immunoglobulin constant region cDNA or genomic sequences, in order to generate expression vectors encoding complete IgG molecules or other isotypes. VH and V_L can also be used in the generation of Fab, Fv, or other fragments of immunoglobulins using either protein chemistry or recombinant DNA technology. Other forms of single chain antibodies, such as diabodies are also encompassed. Diabodies are bivalent, bispecific antibodies in which V_H and V_L domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen-binding sites. See e.g. Holliger, et al. (1993) *Proc Natl. Acad. Sci. USA* 90: 6444-6448; Poljak, et al. (1994) *Structure 2*: 1121-1123. Still further, an antibody or antigen-binding portion thereof (antigen-binding fragment, antibody fragment, antibody portion) may be part of a larger immunoadhesion molecules, formed by covalent or noncovalent association of the antibody or antibody portion with one or more other proteins or peptides. Examples of immunoadhesion molecules include use of the streptavidin core region to make a tetrameric scFv molecule (Kipriyanov, et al. (1995) *Hum. Antibodies Hybridomas* 6: 93-101) and use of a cysteine residue, a marker peptide and a C-terminal polyhistidine tag to make

bivalent and biotinylated scFv molecules. Kipriyanov, et al. (1994) *Mol. Immunol*. 31: 1047-1058. Antibody portions, such as Fab and F(ab')$_2$ fragments, can be prepared from whole antibodies using conventional techniques, such as papain or pepsin digestion, respectively, of whole antibodies. Moreover, antibodies, antibody portions and immunoadhesion molecules can be obtained using standard recombinant DNA techniques, as described herein. Antibodies may be polyclonal, monoclonal, xenogeneic, allogeneic, syngeneic, or modified forms thereof, e.g., humanized, chimeric, bispecific or multispecific antibodies.

[100] "Antibody recognizing an antigen" and "an antibody specific for an antigen" is used interchangeably herein with the term "an antibody which binds specifically to an antigen" and refers to an immunoglobulin or fragment thereof that specifically binds an antigen.

[101] "Antigen," as used herein, refers broadly to a molecule or a portion of a molecule capable of being bound by an antibody which is additionally capable of inducing an animal to produce an antibody capable of binding to an epitope of that antigen. An antigen may have one epitope, or have more than one epitope. The specific reaction referred to herein indicates that the antigen will react, in a highly selective manner, with its corresponding antibody and not with the multitude of other antibodies which may be evoked by other antigens. In the case of a desired enhanced immune response to particular antigens of interest, antigens include, but are not limited to; infectious disease antigens for which a protective immune response may be elicited are exemplary.

[102] "Antigen presenting cell," as used herein, refers broadly to professional antigen presenting cells (e.g., B lymphocytes, monocytes, dendritic cells, and Langerhans cells) as well as other antigen presenting cells (e.g., keratinocytes, endothelial cells, astrocytes, fibroblasts, and oligodendrocytes).

[103] "Antisense nucleic acid molecule," as used herein, refers broadly to a nucleotide sequence which is complementary to a "sense" nucleic ac*id encoding a protein (e.g., complementary to the coding strand of a double-stranded cDNA molecule) complementary to an mRNA sequence or complementary to the coding strand of a gene. Accordingly, antisense nucleic acid molecules can hydrogen bond to sense nucleic acid molecules.

[104] "Apoptosis," as used herein, refers broadly to programmed cell death which can be characterized using techniques which are known in the art. Apoptotic cell death can be characterized by cell shrinkage, membrane blebbing, and chromatin condensation culminating in cell fragmentation. Cells undergoing apoptosis also display a characteristic pattern of internucleosomal DNA cleavage.

[105] "Autoimmunity" or "autoimmune disease or condition," as used herein, refers broadly to a disease or disorder arising from and directed against an individual's own tissues or a co-segregate or manifestation thereof or resulting condition therefrom, and includes. Herein autoimmune conditions include inflammatory or allergic conditions, e.g., chronic

diseases characterized by a host immune reaction against self-antigens potentially associated with tissue destruction such as rheumatoid arthritis.

[106] "B cell receptor" (BCR)," as used herein, refers broadly to the complex between membrane Ig (mIg) and other transmembrane polypeptides (e.g., IgA. and Ig) found on B cells. The signal transduction function of mIg is triggered by crosslinking of receptor molecules by oligomeric or multimeric antigens. B cells can also be activated by anti-immunoglobulin antibodies. Upon BCR activation, numerous changes occur in B cells, including tyrosine phosphorylation.

[107] "Cancer," as used herein, refers broadly to any neoplastic disease (whether invasive or metastatic) characterized by abnormal and uncontrolled cell division causing malignant growth or tumor (e.g., unregulated cell growth.) The term "cancer" or "cancerous" as used herein should be understood to encompass any neoplastic disease (whether invasive, non-invasive or metastatic) which is characterized by abnormal and uncontrolled cell division causing malignant growth or tumor, non-limiting examples of which are described herein. This includes any physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer are exemplified in the working examples. Further cancers include but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia. More particular examples of such cancers include squamous cell cancer, lung cancer (including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, and squamous carcinoma of the lung), cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer (including gastrointestinal cancer), pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma and various types of head and neck cancer, as well as B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; mantle cell lymphoma; AIDS-related lymphoma; and Waldenström's Macroglobulinemia); chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); Hairy cell leukemia; chronic myeloblasts leukemia; multiple myeloma and post-transplant lymphoproliferative disorder (PTLD). Other cancers amenable for treatment by the present invention include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include colorectal, bladder, ovarian, melanoma, squamous cell cancer, lung cancer (including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, and squamous carcinoma of the lung), cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer (including gastrointestinal cancer), pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or

uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma and various types of head and neck cancer, as well as B-cell lymphoma (including low grade/follicular non-Hodgkin's lymphoma (NHL); small lymphocytic (SL) NHL; intermediate grade/follicular NHL; intermediate grade diffuse NHL; high grade immunoblastic NHL; high grade lymphoblastic NHL; high grade small non-cleaved cell NHL; bulky disease NHL; mantle cell lymphoma; AIDS-related lymphoma; and Waldenström's Macroglobulinemia); chronic lymphocytic leukemia (CLL); acute lymphoblastic leukemia (ALL); Hairy cell leukemia; chronic myeloblastic leukemia; and post-transplant lymphoproliferative disorder (PTLD), as well as abnormal vascular proliferation associated with phakomatoses, edema (such as that associated with brain tumors), and Meigs' syndrome. Preferably, the cancer is selected from the group consisting of colorectal cancer, breast cancer, colorectal cancer, rectal cancer, non-small cell lung cancer, non-Hodgkin's lymphoma (NHL), renal cell cancer, prostate cancer, liver cancer, pancreatic cancer, soft-tissue sarcoma, Kaposi's sarcoma, carcinoid carcinoma, head and neck cancer, melanoma, ovarian cancer, mesothelioma, and multiple myeloma. In an exemplary embodiment the cancer is an early or advanced (including metastatic) bladder, ovarian or melanoma. In another embodiment the cancer is colorectal cancer. The cancerous conditions amenable for treatment of the invention include cancers that express or do not express VISTA and further include non-metastatic or non-invasive as well as invasive or metastatic cancers wherein VISTA expression by immune, stromal or diseased cells suppress antitumor responses and anti-invasive immune responses. The method of the present invention is particularly suitable for the treatment of vascularized tumors. Cancers according to the invention include cancers that express or do not express VISTA and further include non-metastatic or non-invasive as well as invasive or metastatic cancers wherein VISTA expression by immune, stromal or diseased cells suppress antitumor responses and anti-invasive immune responses, and those characterized by vascularized tumors.

[108] "Chimeric antibody," as used herein, refers broadly to an antibody molecule in which the constant region, or a portion thereof, is altered, replaced or exchanged so that the antigen-binding site (variable region) is linked to a constant region of a different or altered class, effector function and/or species, or an entirely different molecule which confers new properties to the chimeric antibody, e.g., an enzyme, toxin, hormone, growth factor, drug, the variable region or a portion thereof, is altered, replaced or exchanged with a variable region having a different or altered antigen specificity.

[109] "Coding region," as used herein, refers broadly to regions of a nucleotide sequence comprising codons which are translated into amino acid residues, whereas the term "noncoding region" refers to regions of a nucleotide sequence that are not translated into amino acids (e.g., 5' and 3' untranslated regions).

[110] "Conservatively modified variants," as used herein, applies to both amino acid and nucleic acid sequences, and with respect to particular nucleic acid sequences, refers broadly to conservatively modified variants refers to those nucleic acids which encode

identical or essentially identical amino acid sequences, or where the nucleic acid does not encode an amino acid sequence, to essentially identical sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given protein. "Silent variations" are one species of conservatively modified nucleic acid variations. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) may be modified to yield a functionally identical molecule.

[111] "Complementarity determining region," "hypervariable region," or "CDR," as used herein, refers broadly to one or more of the hyper-variable or complementarily determining regions (CDRs) found in the variable regions of light or heavy chains of an antibody. See Kabat, et al. (1987) Sequences of Proteins of Immunological Interest National Institutes of Health, Bethesda, Md. These expressions include the hypervariable regions as defined by Kabat, et al. (1983) *Sequences of Proteins of Immunological Interest*, U. S. Dept. of Health and Human Services or the hypervariable loops in 3-dimensional structures of antibodies. Chothia and Lesk (1987) *J. Mol. Biol.* 196: 901-917. The CDRs in each chain are held in close proximity by framework regions and, with the CDRs from the other chain, contribute to the formation of the antigen-binding site. Within the CDRs there are select amino acids that have been described as the selectivity determining regions (SDRs) which represent the critical contact residues used by the CDR in the antibody-antigen interaction. (Kashmiri *Methods* 36: 25-34(2005)).

[112] "Control amount," as used herein, refers broadly to a marker can be any amount or a range of amounts to be compared against a test amount of a marker. For example, a control amount of a marker may be the amount of a marker in a patient with a particular disease or condition or a person without such a disease or condition. A control amount can be either in absolute amount (e.g., microgram/ml) or a relative amount (e.g., relative intensity of signals).

[113] "Costimulatory receptor," as used herein, refers broadly to receptors which transmit a costimulatory signal to an immune cell, e.g., CD28 or ICOS. As used herein, the term "inhibitory receptors" includes receptors which transmit a negative signal to an immune cell, e.g., a T cell or an NK cell.

[114] "Costimulate," as used herein, refers broadly to the ability of a costimulatory molecule to provide a second, non-activating, receptor-mediated signal (a "costimulatory signal") that induces proliferation or effector function. For example, a costimulatory signal can result in cytokine secretion (e.g., in a T cell that has received a T cell-receptor-mediated signal) Immune cells that have received a cell receptor-mediated signal (e.g., via an activating receptor) may be referred to herein as "activated immune cells." With respect to T cells, transmission of a costimulatory signal to a T cell involves a signaling pathway that is not inhibited by cyclosporin A. In addition, a costimulatory signal can induce cytokine

secretion (e.g., IL-2 and/or IL-10) in a T cell and/or can prevent the induction of unresponsiveness to antigen, the induction of anergy, or the induction of cell death in the T cell.

[115] "Costimulatory polypeptide" or "costimulatory molecule" herein refers to a polypeptide that, upon interaction with a cell-surface molecule on T cells, modulates T cell responses.

[116] "Costimulatory signaling" as used herein is the signaling activity resulting from the interaction between costimulatory polypeptides on antigen presenting cells and their receptors on T cells during antigen-specific T cell responses. Without wishing to be limited by a single hypothesis, the antigen-specific T cell response is believed to be mediated by two signals: 1) engagement of the T cell Receptor (TCR) with antigenic peptide presented in the context of MHC (signal 1), and 2) a second antigen-independent signal delivered by contact between different costimulatory receptor/ligand pairs (signal 2). Without wishing to be limited by a single hypothesis, this "second signal" is critical in determining the type of T cell response (activation vs inhibition) as well as the strength and duration of that response, and is regulated by both positive and negative signals from costimulatory molecules, such as the B7 family of proteins.

[117] "B7" polypeptide herein means a member of the B7 family of proteins that costimulate T cells including, but not limited to B7-1, B7-2, B7-DC, B7-H5, B7-Hl, B7-H2, B7-H3, B7-H4, B7-H6, B7-S3 and biologically active fragments and/or variants thereof. Representative biologically active fragments include the extracellular domain or fragments of the extracellular domain that costimulate T cells.

[118] "Cytoplasmic domain," as used herein, refers broadly to the portion of a protein which extends into the cytoplasm of a cell.

[119] "Diagnostic," as used herein, refers broadly to identifying the presence or nature of a pathologic condition. Diagnostic methods differ in their sensitivity and specificity. The "sensitivity" of a diagnostic assay is the percentage of diseased individuals who test positive (percent of "true positives"). Diseased individuals not detected by the assay are "false negatives." Subjects who are not diseased and who test negative in the assay are termed "true negatives." The "specificity" of a diagnostic assay is 1 minus the false positive rate, where the "false positive" rate is defined as the proportion of those without the disease who test positive. While a particular diagnostic method may not provide a definitive diagnosis of a condition, it suffices if the method provides a positive indication that aids in diagnosis.

[120] "Diagnosing," or "aiding in the diagnosis" as used herein refers broadly to classifying a disease or a symptom, and/or determining the likelihood that an individual has a disease condition (e.g., based on absence or presence of VISTA expression, and/or increased or decreased expression by immune, stromal and/or putative diseased cells); determining a severity of the disease, monitoring disease progression, forecasting an

outcome of a disease and/or prospects of recovery. The term "detecting" may also optionally encompass any of the foregoing. Diagnosis of a disease according to the present invention may, in some embodiments, be affected by determining a level of a polynucleotide or a polypeptide of the present invention in a biological sample obtained from the subject, wherein the level determined can be correlated with predisposition to, or presence or absence of the disease. It should be noted that a "biological sample obtained from the subject" may also optionally comprise a sample that has not been physically removed from the subject.

[121] "Effective amount," as used herein, refers broadly to the amount of a compound, antibody, antigen, or cells that, when administered to a patient for treating a disease, is sufficient to effect such treatment for the disease. The effective amount may be an amount effective for prophylaxis, and/or an amount effective for prevention. The effective amount may be an amount effective to reduce, an amount effective to prevent the incidence of signs/symptoms, to reduce the severity of the incidence of signs/symptoms, to eliminate the incidence of signs/symptoms, to slow the development of the incidence of signs/symptoms, to prevent the development of the incidence of signs/symptoms, and/or effect prophylaxis of the incidence of signs/symptoms. The "effective amount" may vary depending on the disease and its severity and the age, weight, medical history, susceptibility, and pre-existing conditions, of the patient to be treated. The term "effective amount" is synonymous with "therapeutically effective amount" for purposes of this invention.

[122] "Extracellular domain" or "ECD" as used herein refers broadly to the portion of a protein that extends from the surface of a cell.

[123] "Expression vector," as used herein, refers broadly to any recombinant expression system for the purpose of expressing a nucleic acid sequence of the invention in vitro or in vivo, constitutively or inducibly, in any cell, including prokaryotic, yeast, fungal, plant, insect or mammalian cell. The term includes linear or circular expression systems. The term includes expression systems that remain episomal or integrate into the host cell genome. The expression systems can have the ability to self -replicate or not, i. e., drive only transient expression in a cell. The term includes recombinant expression cassettes which contain only the minimum elements needed for transcription of the recombinant nucleic acid.

[124] "Family," as used herein, refers broadly to the polypeptide and nucleic acid molecules of the invention is intended to mean two or more polypeptide or nucleic acid molecules having a common structural domain or motif and having sufficient amino acid or nucleotide sequence homology as defined herein. Family members can be naturally or non-naturally occurring and can be from either the same or different species. For example, a family can contain a first polypeptide of human origin, as well as other, distinct polypeptides of human origin or alternatively, can contain homologues of non-human origin (e.g.,

monkey polypeptides.) Members of a family may also have common functional characteristics.

[125] "Fc receptor" (FcRs) as used herein, refers broadly to cell surface receptors for the Fc portion of immunoglobulin molecules (Igs). Fc receptors are found on many cells which participate in immune responses. Among the human FcRs that have been identified so far are those which recognize IgG (designated FcγR), IgE (FceRI), IgA (FcaR), and polymerized IgM/A (FcεμR). FcRs are found in the following cell types: FceRI (mast cells), FceRII (many leukocytes), FcaR (neutrophils), and FcμR (glandular epithelium, hepatocytes). (Hogg Immunol. Today 9: 185-86 (1988)). The widely studied FcγRs are central in cellular immune defenses, and are responsible for stimulating the release of mediators of inflammation and hydrolytic enzymes involved in the pathogenesis of autoimmune disease. (Unkeless, Annu. Rev. Immunol. 6: 251-87 (1988)). The FcγRs provide a crucial link between effector cells and the lymphocytes that secrete Ig, since the macrophage/monocyte, polymorphonuclear leukocyte, and natural killer (NK) cell FcγRs confer an element of specific recognition mediated by IgG. Human leukocytes have at least three different types of FcγRs for IgG: hFcγRI(CD64) (found on monocytes/macrophages), hFcγRIIA or hFcγRIIB, (CD32 or CD32A) (found on monocytes, neutrophils, eosinophils, platelets, possibly B cells, and the K562 cell line) and FcγRIIIA (CD16A) or FcγRIIIB (CD16B) (found on NK cells, neutrophils, eosinophils, and macrophages).

[126] "Framework region" or "FR," as used herein refers broadly to one or more of the framework regions within the variable regions of the light and heavy chains of an antibody. See Kabat, et al. *Sequences of Proteins of Immunological Interest* National Institutes of Health, Bethesda, Md (1987). These expressions include those amino acid sequence regions interposed between the CDRs within the variable regions of the light and heavy chains of an antibody.

[127] "Heterologous," as used herein, refers broadly to portions of a nucleic acid indicates that the nucleic acid comprises two or more subsequences that are not found in the same relationship to each other in nature. For instance, the nucleic acid is typically recombinantly produced, having two or more sequences from unrelated genes arranged to make a new functional nucleic acid (e.g., a promoter from one source and a coding region from another source.) Similarly, a heterologous protein indicates that the protein comprises two or more subsequences that are not found in the same relationship to each other in nature (e.g., a fusion protein).

[128] "High affinity," as used herein, refers broadly to an antibody or fusion protein having a KD of at least 10^{-6} M, more preferably 10^{-7} M, even more preferably at least 10^{-8} M and even more preferably at least 10^{-9} M, 10^{-10} M, 10^{-11} M, or 10^{-12} M for a target antigen or receptor. "High affinity" for an IgG antibody or fusion protein herein refers to an antibody having a KD of 10^{-6} M or less, more preferably 10^{-7} M or less, preferably 10^{-8} M or less, more preferably 10^{-9} M or less and even more preferably 10^{-10} M, 10^{-11} M, or 10^{-12} M or less for a target antigen or receptor. With particular respect to antibodies, "high affinity" binding can

vary for different antibody isotypes. For example, "high affinity" binding for an IgM isotype refers to an antibody having a K_D of 10^{-7} M or less, more preferably 10^{-8} M or less.

[129] "Homology," as used herein, refers broadly to a degree of similarity between a nucleic acid sequence and a reference nucleic acid sequence or between a polypeptide sequence and a reference polypeptide sequence. Homology may be partial or complete. Complete homology indicates that the nucleic acid or amino acid sequences are identical. A partially homologous nucleic acid or amino acid sequence is one that is not identical to the reference nucleic acid or amino acid sequence. The degree of homology can be determined by sequence comparison, for example using BlastP software of the National Center of Biotechnology Information (NCBI) using default parameters. The term "sequence identity" may be used interchangeably with "homology."

[130] "Host cell," as used herein, refers broadly to refer to a cell into which a nucleic acid molecule of the invention, such as a recombinant expression vector of the invention, has been introduced. Host cells may be prokaryotic cells (e.g., E. coli), or eukaryotic cells such as yeast, insect (e.g., SF9), amphibian, or mammalian cells such as CHO, HeLa, HEK-293, e.g., cultured cells, explants, and cells in vivo. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It should be understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

[131] "Human monoclonal antibody" refers to antibodies displaying a single binding specificity which have variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. In one embodiment, the human monoclonal antibodies are produced by a hybridoma which includes a B cell obtained from a transgenic nonhuman animal, e.g., a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell. This includes fully human monoclonal antibodies and conjugates and variants thereof, e.g., which are bound to effector agents such as therapeutics or diagnostic agents.

[132] "Humanized antibody," as used herein, refers broadly to include antibodies made by a non-human cell having variable and constant regions which have been altered to more closely resemble antibodies that would be made by a human cell. For example, by altering the non-human antibody amino acid sequence to incorporate amino acids found in human germline immunoglobulin sequences. The humanized antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation in vivo), for example in the CDRs. The term "humanized antibody", as used herein, also includes antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

[133] "Hybridization," as used herein, refers broadly to the physical interaction of complementary (including partially complementary) polynucleotide strands by the formation of hydrogen bonds between complementary nucleotides when the strands are arranged antiparallel to each other.

[134] "IgV domain" and "IgC domain" as used herein, refer broadly to Ig superfamily member domains. These domains correspond to structural units that have distinct folding patterns called Ig folds. Ig folds are comprised of a sandwich of two β sheets, each consisting of antiparallel β strands of 5-10 amino acids with a conserved disulfide bond between the two sheets in most, but not all, domains. IgC domains of Ig, TCR, and MHC molecules share the same types of sequence patterns and are called the CI set within the Ig superfamily. Other IgC domains fall within other sets. IgV domains also share sequence patter and are called V set domains. IgV domains are longer than C-domains and form an additional pair of β strands.

[135] "Immune cell," as used herein, refers broadly to cells that are of hematopoietic origin and that play a role in the immune response. Immune cells include but are not limited to lymphocytes, such as B cells and T cells; natural killer cells; dendritic cells, and myeloid cells, such as monocytes, macrophages, eosinophils, mast cells, basophils, and granulocytes.

[136] "Immunoassay," as used herein, refers broadly to an assay that uses an antibody to specifically bind an antigen. The immunoassay may be characterized by the use of specific binding properties of a particular antibody to isolate, target, and/or quantify the antigen.

[137] "Immune related disease (or disorder or condition)" as used herein should be understood to encompass any disease disorder or condition selected from the group including but not limited to autoimmune diseases, inflammatory disorders and immune disorders associated with graft transplantation rejection, such as acute and chronic rejection of organ transplantation, allogenic stem cell transplantation, autologous stem cell transplantation, bone marrow transplantation, and graft versus host disease.

[138] "Immune response," as used herein, refers broadly to T cell-mediated and/or B cell-mediated immune responses that are influenced by modulation of T cell costimulation. Exemplary immune responses include B cell responses (e.g., antibody production) T cell responses (e.g., cytokine production, and cellular cytotoxicity) and activation of cytokine responsive cells, e.g., macrophages. As used herein, the term "downmodulation" with reference to the immune response includes a diminution in any one or more immune responses, while the term "upmodulation" with reference to the immune response includes an increase in any one or more immune responses. It will be understood that upmodulation of one type of immune response may lead to a corresponding downmodulation in another type of immune response. For example, upmodulation of the production of certain cytokines (e.g., IL-10) can lead to downmodulation of cellular immune responses.

[139] "Immunologic", "immunological" or "immune" response herein refer to the development of a humoral (antibody mediated) and/or a cellular (mediated by antigen-

specific T cells or their secretion products) response directed against a peptide in a recipient patient. Such a response can be an active response induced by administration of immunogen or a passive response induced by administration of antibody or primed T-cells. Without wishing to be limited by a single hypothesis, a cellular immune response is elicited by the presentation of polypeptide epitopes in association with Class II or Class I MHC molecules to activate antigen-specific $CD4^+$ T helper cells and/or $CD8_+$ cytotoxic T cells, respectively. The response may also involve activation of monocytes, macrophages, NK cells, basophils, dendritic cells, astrocytes, microglia cells, eosinophils, activation or recruitment of neutrophils or other components of innate immunity. The presence of a cell-mediated immunological response can be determined by proliferation assays ($CD4^+$ T cells) or CTL (cytotoxic T lymphocyte) assays. The relative contributions of humoral and cellular responses to the protective or therapeutic effect of an immunogen can be distinguished by separately isolating antibodies and T cells from an immunized syngeneic animal and measuring protective or therapeutic effect in a second subject.

[140] "Immunogenic agent" or "immunogen" is a moiety capable of inducing an immunological response against itself on administration to a mammal, optionally in conjunction with an adjuvant.

[141] "Inflammatory disorders", "inflammatory conditions" and/or "inflammation", used interchangeably herein, refers broadly to chronic or acute inflammatory diseases, and expressly includes inflammatory autoimmune diseases and inflammatory allergic conditions. These conditions include by way of example inflammatory abnormalities characterized by dysregulated immune response to harmful stimuli, such as pathogens, damaged cells, or irritants. Inflammatory disorders underlie a vast variety of human diseases. Non-immune diseases with etiological origins in inflammatory processes include cancer, atherosclerosis, and ischemic heart disease. Examples of disorders associated with inflammation include: Chronic prostatitis, Glomerulonephritis, Hypersensitivities, Pelvic inflammatory disease, Reperfusion injury, Sarcoidosis, Vasculitis, Interstitial cystitis, normocomplementemic urticarial vasculitis, pericarditis, myositis, anti-synthetase syndrome, scleritis, macrophage activation syndrome, Behçet's Syndrome, PAPA Syndrome, Blau's Syndrome, gout, adult and juvenile Still's disease, cryropyrinopathy, Muckle- Wells syndrome, familial cold-induced auto-inflammatory syndrome, neonatal onset multisystemic inflammatory disease, familial Mediterranean fever, chronic infantile neurologic, cutaneous and articular syndrome, systemic juvenile idiopathic arthritis, Hyper IgD syndrome, Schnitzler's syndrome, TNF receptor-associated periodic syndrome (TRAPSP), gingivitis, periodontitis, hepatitis, cirrhosis, pancreatitis, myocarditis, vasculitis, gastritis, gout, gouty arthritis, and inflammatory skin disorders, selected from the group consisting of psoriasis, atopic dermatitis, eczema, rosacea, urticaria, and acne.

[142] "Inhibitory signal," as used herein, refers broadly to a signal transmitted via an inhibitory receptor molecule on an immune cell. A signal antagonizes a signal via an activating receptor (e.g., via a TCR, CD3, BCR, or Fc molecule) and can result, e.g., in

inhibition of: second messenger generation; proliferation; or effector function in the immune cell, e.g., reduced phagocytosis, antibody production, or cellular cytotoxicity, or the failure of the immune cell to produce mediators (e.g., cytokines (e.g., IL-2) and/or mediators of allergic responses); or the development of anergy.

[143] "Isolated," as used herein, refers broadly to material removed from its original environment in which it naturally occurs, and thus is altered by the hand of man from its natural environment and includes "recombinant" polypeptides. Isolated material may be, for example, exogenous nucleic acid included in a vector system, exogenous nucleic acid contained within a host cell, or any material which has been removed from its original environment and thus altered by the hand of man (e.g., "isolated antibody"). For example, "isolated" or "purified," as used herein, refers broadly to a protein, DNA, antibody, RNA, or biologically active portion thereof, that is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the biological substance is derived, or substantially free from chemical precursors or other chemicals when chemically synthesized. As used herein the term "isolated" refers to a compound of interest (for example a polynucleotide or a polypeptide) that is in an environment different from that in which the compound naturally occurs e.g., separated from its natural milieu such as by concentrating a peptide to a concentration at which it is not found in nature. "Isolated" includes compounds that are within samples that are substantially enriched for the compound of interest and/or in which the compound of interest is partially or substantially purified.

[144] "Isolated antibody", as used herein, is intended to refer to an antibody that is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody that specifically binds VISTA) is substantially free of antibodies that specifically bind antigens other than VISTA). Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[145] "Isotype" herein refers to the antibody class (e.g., IgM or IgG1) that is encoded by the heavy chain constant region genes.

[146] "K-assoc" or "Ka", as used herein, refers broadly to the association rate of a particular antibody-antigen interaction, whereas the term "Kdiss" or "Kd," as used herein, refers to the dissociation rate of a particular antibody-antigen interaction.

[147] The term "K_D", as used herein, is intended to refer to the dissociation constant, which is obtained from the ratio of Kd to Ka (i. e., Kd/Ka) and is expressed as a molar concentration (M). K_D values for antibodies can be determined using methods well established in the art such as plasmon resonance (BIAcore®), ELISA and KINEXA. A preferred method for determining the K_D of an antibody is by using surface Plasmon resonance, preferably using a biosensor system such as a BIAcore® system or by ELISA. Typically these methods are effected at 25° or 37° C. Antibodies for therapeutic usage generally will possess

a K_D when determined by surface Plasmon resonance of 50 nM or less or more typically 1nM or less at 25° or 37° C.

[148] "Label" or a "detectable moiety" as used herein, refers broadly to a composition detectable by spectroscopic, photochemical, biochemical, immunochemical, chemical, or other physical means.

[149] "Low stringency," "medium stringency," "high stringency," or "very high stringency conditions," as used herein, refers broadly to conditions for nucleic acid hybridization and washing. Guidance for performing hybridization reactions can be found in Ausubel, et al., *Short Protocols in Molecular Biology* (5th Ed.) John Wiley & Sons, NY (2002). Exemplary specific hybridization conditions include but are not limited to: (1) low stringency hybridization conditions in 6 X sodium chloride/sodium citrate (SSC) at about 45° C, followed by two washes in 0. 2XSSC, 0.1% SDS at least at 50°C. (the temperature of the washes can be increased to 55 °C. for low stringency conditions); (2) medium stringency hybridization conditions in 6XSSC at about 45°C. , followed by one or more washes in 0. 2X SSC, 0. 1% SDS at 60°C. ; (3) high stringency hybridization conditions in 6XSSC at about 45°C followed by one or more washes in 0. 2X. SSC, 0. 1% SDS at 65°C.; and (4) very high stringency hybridization conditions are 0. 5M sodium phosphate, 7% SDS at 65°C, followed by one or more washes at 0.2XSSC, and 1 % SDS at 65° C.

[150] "Mammal," as used herein, refers broadly to any and all warm-blooded vertebrate animals of the class Mammalia, including humans, characterized by a covering of hair on the skin and, in the female, milk-producing mammary glands for nourishing the young. Examples of mammals include but are not limited to alpacas, armadillos, capybaras, cats, camels, chimpanzees, chinchillas, cattle, dogs, goats, gorillas, hamsters, horses, humans, lemurs, llamas, mice, non-human primates, pigs, rats, sheep, shrews, squirrels, tapirs, and voles. Mammals include but are not limited to bovine, canine, equine, feline, murine, ovine, porcine, primate, and rodent species. Mammal also includes any and all those listed on the Mammal Species of the World maintained by the National Museum of Natural History, Smithsonian Institution in Washington D. C.

[151] “Multispecific antibody” refers to an antibody with 2 or more antigen binding regions. This includes bispecific antibodies. These antigen binding regions may bind to different antigens or to different epitopes of the same antigen.

[152] "Naturally-occurring nucleic acid molecule," as used herein, refers broadly refers to an RNA or DNA molecule having a nucleotide sequence that occurs in nature (e.g., encodes a natural protein).

[153] "Nucleic acid" or "nucleic acid sequence," as used herein, refers broadly to a deoxy-ribonucleotide or ribonucleotide oligonucleotide in either single- or double-stranded form. The term encompasses nucleic acids, i.e., oligonucleotides, containing known analogs of natural nucleotides. The term also encompasses nucleic- acid-like structures with synthetic backbones. Unless otherwise indicated, a particular nucleic acid sequence also

implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions) and complementary sequences, as well as the sequence explicitly indicated. The term nucleic acid is used interchangeably with gene, cDNA, mRNA, oligonucleotide, and polynucleotide.

[154] "Operatively linked", as used herein, refers broadly to when two DNA fragments are joined such that the amino acid sequences encoded by the two DNA fragments remain in-frame.

[155] "Paratope," as used herein, refers broadly to the part of an antibody which recognizes an antigen (e.g., the antigen-binding site of an antibody.) Paratopes may be a small region (e.g., 15-22 amino acids) of the antibody's Fv region and may contain parts of the antibody's heavy and light chains. See Goldsby, et al. Antigens (Chapter 3) Immunology (5th Ed.) New York: W. H. Freeman and Company, pages 57-75.

[156] "Patient," or "subject" or "recipient", "individual", or "treated individual" are used interchangeably herein, and refers broadly to any animal that is in need of treatment either to alleviate a disease state or to prevent the occurrence or reoccurrence of a disease state. Also, "Patient" as used herein, refers broadly to any animal that has risk factors, a history of disease, susceptibility, symptoms, and signs, was previously diagnosed, is at risk for, or is a member of a patient population for a disease. The patient may be a clinical patient such as a human or a veterinary patient such as a companion, domesticated, livestock, exotic, or zoo animal.

[157] "Polypeptide," "peptide" and "protein," are used interchangeably and refer broadly to a polymer of amino acid residues s of any length, regardless of modification (e.g., phosphorylation or glycosylation). The terms apply to amino acid polymers in which one or more amino acid residue is an analog or mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer. Polypeptides can be modified, e.g., by the addition of carbohydrate residues to form glycoproteins. The terms "polypeptide," "peptide" and "protein" expressly include glycoproteins, as well as non-glycoproteins.

[158] "Promoter," as used herein, refers broadly to an array of nucleic acid sequences that direct transcription of a nucleic acid. As used herein, a promoter includes necessary nucleic acid sequences near the start site of transcription, such as, in the case of a polymerase II type promoter, a TATA element. A promoter also optionally includes distal enhancer or repressor elements, which can be located as much as several thousand base pairs from the start site of transcription. A constitutive" promoter is a promoter that is active under most environmental and developmental conditions. An "inducible" promoter is a promoter that is active under environmental or developmental regulation.

[159] "Prophylactically effective amount," as used herein, refers broadly to the amount of a compound that, when administered to a patient for prophylaxis of a disease or prevention of the reoccurrence of a disease, is sufficient to effect such prophylaxis for the disease or reoccurrence. The prophylactically effective amount may be an amount effective to prevent the incidence of signs and/or symptoms. The "prophylactically effective amount" may vary depending on the disease and its severity and the age, weight, medical history, predisposition to conditions, preexisting conditions, of the patient to be treated.

[160] "Prophylactic vaccine" and/or "Prophylactic vaccination" refers to a vaccine used to prevent a disease or symptoms associated with a disease such as cancer or an infectious condition.

[161] "Prophylaxis," as used herein, refers broadly to a course of therapy where signs and/or symptoms are not present in the patient, are in remission, or were previously present in a patient. Prophylaxis includes preventing disease occurring subsequent to treatment of a disease in a patient. Further, prevention includes treating patients who may potentially develop the disease, especially patients who are susceptible to the disease (e.g., members of a patent population, those with risk factors, or at risk for developing the disease).

[162] "Recombinant" as used herein, refers broadly with reference to a product, e.g., to a cell, or nucleic acid, protein, or vector, indicates that the cell, nucleic acid, protein or vector, has been modified by the introduction of a heterologous nucleic acid or protein or the alteration of a native nucleic acid or protein, or that the cell is derived from a cell so modified. Thus, for example, recombinant cells express genes that are not found within the native (non-recombinant) form of the cell or express native genes that are otherwise abnormally expressed, under expressed or not expressed at all.

[163] The term "recombinant human antibody", as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (e.g., a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom (described further below), (b) antibodies isolated from a host cell transformed to express the human antibody, e.g., from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable regions in which the framework and CDR regions are derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies can be subjected to in vitro mutagenesis (or, when an animal transgenic for human Ig sequences is used, in vivo somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire in vivo.

[164] "Signal sequence" or "signal peptide," as used herein, refers broadly to a peptide containing about 15 or more amino acids which occurs at the N-terminus of secretory and membrane bound polypeptides and which contains a large number of hydrophobic amino acid residues. For example, a signal sequence contains at least about 10-30 amino acid residues, preferably about 15-25 amino acid residues, more preferably about 18-20 amino acid residues, and even more preferably about 19 amino acid residues, and has at least about 35-65%, preferably about 38-50%, and more preferably about 40-45% hydrophobic amino acid residues (e.g., Valine, Leucine, Isoleucine or Phenylalanine). A "signal sequence," also referred to in the art as a "signal peptide," serves to direct a polypeptide containing such a sequence to a lipid bilayer, and is cleaved in secreted.

[165] "Specifically (or selectively) binds" to an antibody or "specifically (or selectively) immunoreactive with," or "specifically interacts or binds," as used herein, refers broadly to a protein or peptide (or other epitope), refers, in some embodiments, to a binding reaction that is determinative of the presence of the protein in a heterogeneous population of proteins and other biologies. For example, under designated immunoassay conditions, the specified antibodies bind to a particular protein at least two times greater than the background (non-specific signal) and do not substantially bind in a significant amount to other proteins present in the sample. Typically a specific or selective reaction will be at least twice background signal or noise and more typically more than about 10 to 100 times background.

[166] "Specifically hybridizable" and "complementary" as used herein, refer broadly to a nucleic acid can form hydrogen bond(s) with another nucleic acid sequence by either traditional Watson-Crick or other non-traditional types. The binding free energy for a nucleic acid molecule with its complementary sequence is sufficient to allow the relevant function of the nucleic acid to proceed, e.g., RNAi activity. Determination of binding free energies for nucleic acid molecules is well known in the art. (See, e.g., Turner, et al. *CSH Symp. Quant. Biol. LII*: 123-33 (1987); Frier, et al. *PNAS* 83: 9373-77 1986); Turner, et al. *J. Am. Chem. Soc.* 109:3783-85 (1987)). A percent complementarity indicates the percentage of contiguous residues in a nucleic acid molecule that can form hydrogen bonds (e.g., Watson-Crick base pairing) with a second nucleic acid sequence (e.g., about at least 5, 6, 7, 8, 9, 10 out of 10 being about at least 50%, 60%, 70%, 80%, 90%, and 100% complementary, inclusive). "Perfectly complementary" or 100% complementarity refers broadly all of the contiguous residues of a nucleic acid sequence hydrogen bonding with the same number of contiguous residues in a second nucleic acid sequence.

[167] "Substantial complementarity" refers to polynucleotide strands exhibiting about at least 90% complementarity, excluding regions of the polynucleotide strands, such as overhangs, that are selected so as to be noncomplementary. Specific binding requires a sufficient degree of complementarity to avoid non-specific binding of the oligomeric compound to non-target sequences under conditions in which specific binding is desired, i. e., under physiological conditions in the case of in vivo assays or therapeutic treatment, or

in the case of *in vitro* assays, under conditions in which the assays are performed. The non-target sequences typically may differ by at least 5 nucleotides.

[168] "Signs" of disease, as used herein, refers broadly to any abnormality indicative of disease, discoverable on examination of the patient; an objective indication of disease, in contrast to a symptom, which is a subjective indication of disease.

[169] "Solid support," "support," and "substrate," as used herein, refers broadly to any material that provides a solid or semi-solid structure with which another material can be attached including but not limited to smooth supports (e.g., metal, glass, plastic, silicon, and ceramic surfaces) as well as textured and porous materials.

[170] "Soluble ectodomain (ECD)" or "ectodomain" or "soluble VISTA protein(s)/molecule(s)" of VISTA as used herein means non-cell-surface-bound VISTA molecules or any portion thereof, including, but not limited to: VISTA fusion proteins or VISTA ECD-Ig fusion proteins, wherein the extracellular domain of VISTA or fragment thereof is fused to an immunoglobulin (Ig) moiety rendering the fusion molecule soluble, or fragments and derivatives thereof, proteins with the extracellular domain of VISTA fused or joined with a portion of a biologically active or chemically active protein such as the papillomavirus E7 gene product, melanoma-associated antigen p97 or HIV env protein, or fragments and derivatives thereof; hybrid (chimeric) fusion proteins such as VISTA -Ig, or fragments and derivatives thereof. Such fusion proteins are described in greater detail below.

[171] "Soluble VISTA protein(s)/molecule(s)" herein also include VISTA molecules with the transmembrane domain removed to render the protein soluble, or fragments and derivatives thereof; fragments, portions or derivatives thereof, and soluble VISTA mutant molecules. The soluble VISTA molecules used in the methods according to at least some embodiments of the invention may or may not include a signal (leader) peptide sequence.

[172] "Subject" or "patient" or "individual" in the context of therapy or diagnosis herein includes any human or nonhuman animal. The term "nonhuman animal" includes all vertebrates, e.g., mammals and non-mammals, such as nonhuman primates, sheep, dogs, cats, horses, cows, chickens, amphibians, reptiles, etc., i.e., anyone suitable to be treated according to the present invention include, but are not limited to, avian and mammalian subjects, and are preferably mammalian. Any mammalian subject in need of being treated according to the present invention is suitable. Human subjects of both genders and at any stage of development (i. e., neonate, infant, juvenile, adolescent, and adult) can be treated according to the present invention. The present invention may also be carried out on animal subjects, particularly mammalian subjects such as mice, rats, dogs, cats, cattle, goats, sheep, and horses for veterinary purposes, and for drug screening and drug development purposes. "Subjects" is used interchangeably with "individuals" and "patients."

[173] "Substantially free of chemical precursors or other chemicals," as used herein, refers broadly to preparations of VISTA protein in which the protein is separated from

chemical precursors or other chemicals which are involved in the synthesis of the protein. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of VISTA protein having less than about 30% (by dry weight) of chemical precursors or non-VISTA chemicals, more preferably less than about 20% chemical precursors or non-VISTA chemicals, still more preferably less than about 10% chemical precursors or non-VISTA chemicals, and most preferably less than about 5% chemical precursors or non-VISTA chemicals.

[174] "Symptoms" of disease as used herein, refers broadly to any morbid phenomenon or departure from the normal in structure, function, or sensation, experienced by the patient and indicative of disease.

[175] "T cell," as used herein, refers broadly to CD4+ T cells and CD8+ T cells. The term T cell also includes both T helper 1 type T cells and T helper 2 type T cells.

[176] "Therapy," "therapeutic," "treating," or "treatment", as used herein, refers broadly to treating a disease, arresting, or reducing the development of the disease or its clinical symptoms, and/or relieving the disease, causing regression of the disease or its clinical symptoms. Therapy encompasses prophylaxis, treatment, remedy, reduction, alleviation, and/or providing relief from a disease, signs, and/or symptoms of a disease. Therapy encompasses an alleviation of signs and/or symptoms in patients with ongoing disease signs and/or symptoms (e.g., inflammation, pain). Therapy also encompasses "prophylaxis". The term "reduced", for purpose of therapy, refers broadly to the clinical significant reduction in signs and/or symptoms. Therapy includes treating relapses or recurrent signs and/or symptoms (e.g., inflammation, pain). Therapy encompasses but is not limited to precluding the appearance of signs and/or symptoms anytime as well as reducing existing signs and/or symptoms and eliminating existing signs and/or symptoms. Therapy includes treating chronic disease ("maintenance") and acute disease. For example, treatment includes treating or preventing relapses or the recurrence of signs and/or symptoms (e.g., inflammation, pain).

[177] "Treg cell" (sometimes also referred to as suppressor T cells or inducible Treg cells or iTregs) as used herein refers to a subpopulation of T cells which modulate the immune system and maintain tolerance to self-antigens and can abrogate autoimmune diseases. $Foxp3^+ CD4^+ CD25^+$ regulatory T cells (Tregs) are critical in maintaining peripheral tolerance under normal conditions.

[178] "Transmembrane domain," as used herein, refers broadly to an amino acid sequence of about 15 amino acid residues in length which spans the plasma membrane. More preferably, a transmembrane domain includes about at least 20, 25, 30, 35, 40, or 45 amino acid residues and spans the plasma membrane. Transmembrane domains are rich in hydrophobic residues, and typically have an a-helical structure. In an embodiment, at least 50%, 60%, 70%, 80%, 90%, 95% or more of the amino acids of a transmembrane domain are

hydrophobic, e.g., leucines, isoleucines, tyrosines, or tryptophans. Transmembrane domains are described in, for example, Zagotta, et al. *Annu. Rev. Neurosci*. 19:235-263 (1996).

[179] "Transgenic animal," as used herein, refers broadly to a non-human animal, preferably a mammal, more preferably a mouse, in which one or more of the cells of the animal includes a "transgene". The term "transgene" refers to exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, for example directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal.

[180] "Unresponsiveness," as used herein, refers broadly to refractivity of immune cells to stimulation, e.g., and stimulation via an activating receptor or a cytokine. Unresponsiveness can occur, e.g., because of exposure to immunosuppressants or high doses of antigen.

[181] "Variable region" or "VR," as used herein, refers broadly to the domains within each pair of light and heavy chains in an antibody that are involved directly in binding the antibody to the antigen. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each light chain has a variable domain (V_L) at one end and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain.

[182] "Vector," as used herein, refers broadly to a nucleic acid molecule capable of transporting another nucleic acid molecule to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Vectors are referred to herein as "recombinant expression vectors" or simply "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions. The techniques and procedures are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. See, e.g., Sambrook, et al. *Molec. Cloning: Lab. Manual* [3rd Ed] Cold Spring Harbor Laboratory Press (2001). Standard techniques may

be used for recombinant DNA, oligonucleotide synthesis, and tissue culture, and transformation (e.g., electroporation, lipofection). Enzymatic reactions and purification techniques may be performed according to manufacturer's specifications or as commonly accomplished in the art or as described herein.

[183] Having defined certain terms and phrases used in the present application, the anti-VISTA antibodies and antigen binding antibody fragments and methods for the production and use thereof which are embraced by the invention are further described below.

[184] The present invention relates to antibodies and antibody fragments comprising an antigen binding region that binds to a V-domain Ig Suppressor of T cell Activation (VISTA). VISTA is a checkpoint regulator that negatively suppresses immune responses. See Wang et al., "VISTA, a novel mouse Ig superfamily ligand that negatively regulates T cell responses," *J. Exp. Med.*, 208(3) 577-92 (2011). This protein is expressed on normal human neutrophils, monocytes and T cells subsets. In addition, cynomolgus monkey cells express VISTA in a similar pattern to normal human cells. VISTA is also expressed in the peripheral blood cells e.g., of cancer patients.

[185] The binding of an antagonist anti-VISTA antibody or antibody fragment to VISTA according to the invention will antagonize at least one of the effects of VISTA on immunity thereby suppressing the suppressive effects of VISTA on immunity, e.g., T cell immunity and/or cytokine expression. By contrast, the binding of an agonist anti-VISTA antibody or antibody fragment to VISTA according to the invention will agonize, elicit or mimic at least one of the effects of VISTA on immunity thereby promoting at least one of the suppressive effects of VISTA on immunity, e.g., the suppression of T cell immunity or the suppression of the expression of specific proinflammatory cytokines or its promoting effect on the expression of certain chemoattractants and chemokines.

[186] Such antibody fragments include by way of example Fab, $F(ab')_2$, and scFv antibody fragments. These antibody or antibody fragments can comprise an antibody constant region or fragment or variant thereof. Such antibodies and antibody fragments include those which bind to VISTA proteins expressed on hematopoietic and other cells, for example, myeloid cells and/or lymphocytes, monocytes, neutrophils, T cells, natural killer (NK) cells, natural killer T (NKT) cells, a tumor cell, and/or in the tumor microenvironment (TME). The tumor microenvironment is the cellular environment of the tumor. It can include surrounding immune cells, fibroblasts, blood vessels, other cells, signaling molecules, and the extracellular matrix.

[187] Antibodies that block or inhibit the effects of VISTA may be used to enhance human immune responses, in particular immune responses to malignancies and infection. By contrast molecules that agonize VISTA such as soluble VISTA, e.g., VISTA-Ig and the subject agonist anti-human VISTA antibodies and fragments may be used to suppress

undesired human immune responses such as autoimmune, allergic, GVHD, sepsis or undesirable inflammatory immune responses.

[188] The subject application provides novel antagonist and agonist anti-human VISTA antibodies including those comprising the same CDRS as any of the anti-human VISTA antibodies having the sequences shown in **Figure 4**. While prior to the present invention a number of antagonist anti-human VISTA antibodies have been reported in the literature, no agonistic anti-human VISTA antibodies or antibody fragments have been reported.

[189] As disclosed in the experimental examples which follow the inventors initially produced 2 chimeric anti-human VISTA antibodies derived from a murine anti-human VISTA antibody (1E8 having sequences in **Figure 4**) which respectively contain unmodified IgG2 human constant regions or IgG2 constant regions wherein the cysteine residue at position 127 of the kappa chain was changed to a serine residue. As shown in the Examples and the Figures referenced therein, both antibodies were found to agonize or mimic the suppressive effects of VISTA on immunity at least based on (i) their ability to decrease the expression of certain proinflammatory cytokines such as IL-2, IL-4, IL-6, IL-17, granulocyte macrophage colony stimulating factor (GM-CSF) and tumor necrosis factor-alpha (TNF-α) as well as reducing the expression of certain chemokines or chemoattractants such as KC (keratinocyte derived chemokine) or MIP-2 (Macrophage Inflammatory Protein- 2); (ii) suppress T cell activity in GVHD model; and to (iii) suppress CD3-driven T cell responses.

[190] Additionally after isolation of these 2 agonist antibodies another 10 chimeric agonist anti-human VISTA antibodies containing human IgG2 constant or Fc regions have been obtained using analogous methods. These antibodies were derived from the antibodies referred to herein as GG8, VSTB95 (INX903), VSTB103 (INX904), VSTB53 (INX905), VSTB92(INX908), VSTB50(INX900), VSTB56(INX901), VSTB63(INX902), VSTB54(INX906) and VSTB66(INX907)(having the sequences in **Figure 4**).

[191] Particularly, these chimeric anti-human VISTA antibodies have the variable sequences shown in **Figure 4** and human IgG2 constant regions. As reported in the **Summary Tables 1** and **2** *infra* these anti-human VISTA antibodies when assessed by use of antibody binning were found to bind to 2 different epitope groups designated Group 1 and Group 2. As noted in **Figure 4** the epitope corresponding to Group 2 includes residues in 2 different peptides present in human VISTA, i.e., NLTLLDSGL and VQTGKDAPSNC.

[192] As is indicated in the **Tables 1 and 2** *infra* these 12 different anti-human VISTA antibodies were found to be immunosuppressive in at least one model of immunosuppression and many in several immunosuppression models. Particularly INX905, INX908, INX901, INX902 and INX906 were shown to be immunosuppressive in 2 different assay formats. While all of these antibodies were immunosuppressive and appear to elicit, promote or agonize the immunosuppressive effects of VISTA, INX901, INX902 and INX906 and INX908 appear to be the most immunosuppressive.

[193] Also, other chimeric anti-human VISTA antibodies comprising human IgG2 constant domains containing the variable sequences of other anti-VISTA antibodies shown in **Figure 4** are to be screened for their immunosuppressive properties and their ability to agonize or mimic the immunosuppressive and other effects of human VISTA. Based on the results obtained to date this screening should identify other agonist anti-human VISTA antibodies, particularly those which bind the same epitope. Additionally agonist anti-human VISTA antibodies according to the invention have been shown to be effective (immunosuppressive) in numerous autoimmune and inflammatory animal disease models including arthritis, lupus or SLE, GVHD, inflammatory bowel disease (IBD) or colitis, chronic and acute infectious disease or hepatotoxicity and psoriasis animal models. Based thereon the subject anti-human VISTA agonist antibodies should be well suited for use in therapeutic and prophylactic treatment of autoimmune, allergic and inflammatory conditions.

[194] As noted chimeric IgG2 anti-human VISTA antibodies having the sequences shown in **Figure 4** were shown to be immunosuppressive in different models of immunosuppression. These antibodies moreover elicit these immunosuppressive effects in a specific immunomodulatory manner rather than by effecting the depletion of specific types of T cells or by depleting T cells in general.

[195] As further shown in the examples chimeric IgG2 agonistic anti-human VISTA antibodies containing a mutation in the hinge region elicited substantially the same suppressive effects on immunity, i.e., the mutation within in IgG2 constant region appeared to elicit no enhancement in suppression under the tested experimental conditions. Rather both the IgG2A and IgG2 B forms and mixtures thereof elicited the same immunosuppressive effects. Additionally, based on experiments disclosed in the examples it would appear that FcγR binding may contribute to the agonist properties of the subject anti-human VISTA antibodies. In particular it was found that the inclusion of silent IgG2 constant regions ablated the immunosuppressive properties of the tested agonist antibodies. Based on these results it is hypothesized that one or more FcγRs may affect the agonistic properties of these antibodies and in particular it is hypothesized that FcγRIIA (CD32 or CD32A) or FcγRIIB (CD32B) binding may be involved in the agonist properties of the subject agonist antibodies.

[196] Using these same methods it is expected that other agonist anti-human VISTA IgG2 antibodies may be obtained, e.g., others derived from anti-human VISTA antibodies having the sequences shown in **Figure 4**. As mentioned 12 agonist anti-human VISTA antibodies have been obtained to date including those having the sequences contained in **Figure 4**. Based on these results it is anticipated that other agonistic anti-human VISTA antibodies may be generated and shown to be immunosuppressive. Also it is anticipated that other agonistic anti-human VISTA antibodies may be generated which bind to the same or overlapping epitope and/or compete with any of the antibodies containing the sequences shown in **Figure 4**. In exemplary embodiments these antibodies will bind to the epitope

corresponding to Group 1 or Group 2 antibodies or will compete for binding to human VISTA with such antibodies.

[197] Methods for identifying the specific epitope(s) bound by an antibody are known in the art. In the working examples Applicants disclose the elucidation of the epitope bound by a number of anti-VISTA antibodies according to the invention. Thus, in exemplary embodiments agonist anti-human VISTA antibodies according to the invention will comprise IgG2 constant regions or fragments thereof, of the A form, B form or a mixture of the foregoing. In exemplary embodiments these antibodies will bind to one or more FcγRs, e.g., they will bind to the same FcγRs as an intact or wild-type human IgG2 Fc region. In other exemplary embodiments the antibody will bind to CD32 (CD32A and/or CD32B). This may be accomplished by the use of wild-type or modified IgG2 constant regions which bind to CD32 (CD32A and/or CD32B). Further, the agonist antibody may be modified to incorporate another polypeptide such as another Fc polypeptide or antigen binding region which binds to FcγRs such as CD32A and/or CD32B.

[198] The IgG2 Fc or constant regions contained in the inventive agonist anti-human VISTA antibodies optionally may be modified, e.g., in order to alter effector function, e.g., to alter FcR binding, FcRN binding, complement binding, glycosylation and the like. In particular, the IgG2 Fc or constant regions contained in the inventive agonist anti-human VISTA antibodies optionally may be modified by the conversion of the cysteine at position 27 or further optionally by the conversion of another cysteine residue or other residues, e.g., in the hinge region to another amino acid, e.g., a serine. Other potential Fc modifications are disclosed *infra*.

[199] These VISTA agonist antibodies may be used in treating or preventing diseases conditions or for treating or reducing, ameliorating the pathological effects associated therewith, e.g., inflammation, in treating or preventing conditions wherein the suppression of T cell immunity or the expression of proinflammatory cytokines and or increased expression of chemokines and chemoattractants is therapeutically or prophylactically beneficial. These conditions include in particular autoimmunity, allergy, inflammatory disorders, sepsis, GVHD and for inhibiting unwanted T cell immune responses against transplanted cells, tissues or organs such as CAR-T cell or gene therapy constructs or cells containing.

[200] As mentioned exemplary conditions which may be treated therapeutically or prophylactically using an agonist anti-human VISTA antibody according to the invention include autoimmune conditions, allergy conditions, inflammatory conditions, GVHD, transplant and sepsis. As mentioned, agonist anti-human VISTA antibodies according to the invention have been shown to be therapeutically effective and to be immunosuppressive in numerous animal disease models including arthritis, inflammatory bowel disease (IBD), lupus, GVHD, chronic acute infection/hepatotoxicity and psoriasis disease models. Therefore the inventive antibodies should be well suited for use in treating conditions wherein the

suppression of immunity, especially T cell immunity is therapeutically desired.

A. USE OF AGONISTIC OR ANTAGONISTIC ANTI-HUMAN VISTA ANTIBODIES AND FRAGMENTS IN THERAPY AND DIAGNOSIS

[201] Compositions containing agonists according to the invention may be used to inhibit T cell immunity and to treat conditions where this is therapeutically desirable such as autoimmunity, allergy or inflammatory conditions. These compositions will comprise an amount of an agonist antibody or antibody fragment according to the invention effective to suppress T cell activation or proliferation or cytokine expression or other effects of VISTA in a subject in need thereof. Such autoimmune, inflammatory and allergic conditions include for example arthritic conditions such as RA, psoriatic arthritis, psoriasis, scleroderma, multiple sclerosis, lupus, IBD, ITP, diabetes, GVHD, sarcoidosis, allergic asthma, hepatitis associated hepatotoxicity and for inhibiting unwanted T cell immune responses against transplanted cells, tissues or organs such as CAR-T cell or gene therapy constructs or cells containing and the like.

[202] Specific conditions wherein the inventive antibodies may be used alone or in association with other therapeutics, especially other immunosuppressant molecules include acquired immune deficiency syndrome (AIDS), acquired splenic atrophy, acute anterior uveitis, Acute Disseminated Encephalomyelitis (ADEM), acute gouty arthritis, acute necrotizing hemorrhagic leukoencephalitis, acute or chronic sinusitis, acute purulent meningitis (or other central nervous system inflammatory disorders), acute serious inflammation, Addison's disease, adrenalitis, adult onset diabetes mellitus (Type II diabetes), adult-onset idiopathic hypoparathyroidism (AOIH), Agammaglobulinemia, agranulocytosis, vasculitides, including vasculitis, optionally, large vessel vasculitis, optionally, polymyalgia rheumatica and giant cell (Takayasu's) arthritis, allergic conditions, allergic contact dermatitis, allergic dermatitis, allergic granulomatous angiitis, allergic hypersensitivity disorders, allergic neuritis, allergic reaction, alopecia areata, alopecia totalis, Alport's syndrome, alveolitis, optionally allergic alveolitis or fibrosing alveolitis, Alzheimer's disease, amyloidosis, amylotrophic lateral sclerosis (ALS; Lou Gehrig's disease), an eosinophil-related disorder, optionally eosinophilia, anaphylaxis, ankylosing spondylitis, angiectasis, antibody-mediated nephritis, Anti-GBM/Anti-TBM nephritis, antigen-antibody complex-mediated diseases, antiglomerular basement membrane disease, anti-phospholipid antibody syndrome, antiphospholipid syndrome (APS), aphthae, aphthous stomatitis, aplastic anemia, arrhythmia, arteriosclerosis, arteriosclerotic disorders, arthritis, optionally rheumatoid arthritis such as acute arthritis, or chronic rheumatoid arthritis, arthritis chronica progrediente, arthritis deformans, ascariasis, aspergilloma, granulomas containing eosinophils, aspergillosis, aspermiogenese, asthma, optionally asthma bronchiale, bronchial asthma, or auto-immune asthma, ataxia telangiectasia, ataxic sclerosis, atherosclerosis, autism, autoimmune angioedema, autoimmune aplastic anemia, autoimmune atrophic

gastritis, autoimmune diabetes, autoimmune disease of the testis and ovary including autoimmune orchitis and oophoritis, autoimmune disorders associated with collagen disease, autoimmune dysautonomia, autoimmune ear disease, optionally autoimmune inner ear disease (AGED), autoimmune endocrine diseases including thyroiditis such as autoimmune thyroiditis, autoimmune enteropathy syndrome, autoimmune gonadal failure, autoimmune hearing loss, autoimmune hemolysis, Autoimmune hepatitis, autoimmune hepatological disorder, autoimmune hyperlipidemia, autoimmune immunodeficiency, autoimmune inner ear disease (AIED), autoimmune myocarditis, autoimmune neutropenia, autoimmune pancreatitis, autoimmune polyendocrinopathies, autoimmune polyglandular syndrome type I, autoimmune retinopathy, autoimmune thrombocytopenic purpura (ATP), autoimmune thyroid disease, autoimmune urticaria, autoimmune-mediated gastrointestinal diseases, Axonal & neuronal neuropathies, Balo disease, Behçet's disease, benign familial and ischemia-reperfusion injury, benign lymphocytic angiitis, Berger's disease (IgA nephropathy), bird-fancier's lung, blindness, Boeck's disease, bronchiolitis obliterans (non-transplant) vs NSIP, bronchitis, bronchopneumonic aspergillosis, Bruton's syndrome, bullous pemphigoid, Caplan's syndrome, Cardiomyopathy, cardiovascular ischemia, Castleman's syndrome, Celiac disease, celiac sprue (gluten enteropathy), cerebellar degeneration, cerebral ischemia, and disease accompanying vascularization, Chagas disease, channelopathies, optionally epilepsy, channelopathies of the CNS, chorioretinitis, choroiditis, an autoimmune hematological disorder, chronic active hepatitis or autoimmune chronic active hepatitis, chronic contact dermatitis, chronic eosinophilic pneumonia, chronic fatigue syndrome, chronic hepatitis, chronic hypersensitivity pneumonitis, chronic inflammatory arthritis, Chronic inflammatory demyelinating polyneuropathy (CIDP), chronic intractable inflammation, chronic mucocutaneous candidiasis, chronic neuropathy, optionally IgM polyneuropathies or IgM-mediated neuropathy, chronic obstructive airway disease, chronic pulmonary inflammatory disease, Chronic recurrent multifocal osteomyelitis (CRMO), chronic thyroiditis (Hashimoto's thyroiditis) or subacute thyroiditis, Churg-Strauss syndrome, cicatricial pemphigoid/benign mucosal pemphigoid, CNS inflammatory disorders, CNS vasculitis, Coeliac disease, Cogan's syndrome, cold agglutinin disease, colitis polyposa, colitis such as ulcerative colitis, colitis ulcerosa, collagenous colitis, conditions involving infiltration of T cells and chronic inflammatory responses, congenital heart block, congenital rubella infection, Coombs positive anemia, coronary artery disease, Coxsackie myocarditis, CREST syndrome (calcinosis, Raynaud's phenomenon), Crohn's disease, cryoglobulinemia, Cushing's syndrome, cyclitis, optionally chronic cyclitis, heterochronic cyclitis, iridocyclitis, or Fuch's cyclitis, cystic fibrosis, cytokine-induced toxicity, deafness, degenerative arthritis, demyelinating diseases, optionally autoimmune demyelinating diseases, demyelinating neuropathies, dengue, dermatitis herpetiformis and atopic dermatitis, dermatitis including contact dermatitis, dermatomyositis, dermatoses with acute inflammatory components, Devic's disease (neuromyelitis optica), diabetic large-artery disorder, diabetic nephropathy, diabetic retinopathy, Diamond Blackfan anemia, diffuse interstitial pulmonary fibrosis, dilated cardiomyopathy, discoid lupus, diseases involving leukocyte diapedesis, Dressler's syndrome,

Dupuytren's contracture, echovirus infection, eczema including allergic or atopic eczema, encephalitis such as Rasmussen's encephalitis and limbic and/or brainstem encephalitis, encephalomyelitis, optionally allergic encephalomyelitis or encephalomyelitis allergica and experimental allergic encephalomyelitis (EAE), endarterial hyperplasia, endocarditis, endocrine ophthalmopathy, endometriosis, endomyocardial fibrosis, endophthalmia phacoanaphylactica, endophthalmitis, enteritis allergica, eosinophilia-myalgia syndrome, eosinophilic fascitis, epidemic keratoconjunctivitis, epidermolysis bullosa acquisita (EBA), episclera, episcleritis, Epstein-Barr virus infection, erythema elevatum et diutinum, erythema multiforme, erythema nodosum leprosum, erythema nodosum, erythroblastosis fetalis, esophageal dysmotility, Essential mixed cryoglobulinemia, ethmoid, Evan's syndrome, Experimental Allergic Encephalomyelitis (EAE), Factor VIII deficiency, farmer's lung, febris rheumatica, Felty's syndrome, fibromyalgia, fibrosing alveolitis, filariasis, focal segmental glomerulosclerosis (FSGS), food poisoning, frontal, gastric atrophy, giant cell arthritis (temporal arthritis), giant cell hepatitis, giant cell polymyalgia, glomerulonephritides, glomerulonephritis (GN) with and without nephrotic syndrome such as chronic or acute glomerulonephritis (e.g., primary GN), Goodpasture's syndrome, gouty arthritis, granulocyte transfusion-associated syndromes, granulomatosis including lymphomatoid granulomatosis, granulomatosis with polyangiitis (GPA), granulomatous uveitis, Grave's disease, Guillain-Barre syndrome, gutatte psoriasis, hemoglobinuria paroxysmatica, Hamman-Rich's disease, Hashimoto's disease, Hashimoto's encephalitis, Hashimoto's thyroiditis, hemochromatosis, hemolytic anemia or immune hemolytic anemia including autoimmune hemolytic anemia (AIHA), hemolytic anemia, hemophilia A, Henoch-Schönlein purpura, Herpes gestationis, human immunodeficiency virus (HIV) infection, hyperalgesia, hypogammaglobulinemia, hypogonadism, hypoparathyroidism, idiopathic diabetes insipidus, idiopathic facial paralysis, idiopathic hypothyroidism, idiopathic IgA nephropathy, idiopathic membranous GN or idiopathic membranous nephropathy, idiopathic nephritic syndrome, idiopathic pulmonary fibrosis, idiopathic sprue, Idiopathic thrombocytopenic purpura (ITP), IgA nephropathy, IgE-mediated diseases, optionally anaphylaxis and allergic or atopic rhinitis, IgG4-related sclerosing disease, ileitis regionalis, immune complex nephritis, immune responses associated with acute and delayed hypersensitivity mediated by cytokines and T-lymphocytes, immune-mediated GN, immunoregulatory lipoproteins, including adult or acute respiratory distress syndrome (ARDS), Inclusion body myositis, infectious arthritis, infertility due to antispermatozoan antibodies, inflammation of all or part of the uvea, inflammatory bowel disease (IBD) inflammatory hyperproliferative skin diseases, inflammatory myopathy, insulin-dependent diabetes (type 1), insulitis, Interstitial cystitis, interstitial lung disease, interstitial lung fibrosis, iritis, ischemic re-perfusion disorder, joint inflammation, Juvenile arthritis, juvenile dermatomyositis, juvenile diabetes, juvenile onset (Type I) diabetes mellitus, including pediatric insulin-dependent diabetes mellitus (IDDM), juvenile-onset rheumatoid arthritis, Kawasaki syndrome, keratoconjunctivitis sicca, kypanosomiasis, Lambert-Eaton syndrome, leishmaniasis, leprosy, leucopenia, leukocyte adhesion deficiency, Leukocytoclastic vasculitis, leukopenia, lichen planus, lichen sclerosus, ligneous conjunctivitis,

linear IgA dermatosis, Linear IgA disease (LAD), Loffler's syndrome, lupoid hepatitis, lupus (including nephritis, cerebritis, pediatric, non-renal, extra-renal, discoid, alopecia), Lupus (SLE), lupus erythematosus disseminatus, Lyme arthritis, Lyme disease, lymphoid interstitial pneumonitis, malaria, male and female autoimmune infertility, maxillary, medium vessel vasculitis (including Kawasaki's disease and polyarteritis nodosa), membrano- or membranous proliferative GN (MPGN), including Type I and Type II, and rapidly progressive GN, membranous GN (membranous nephropathy), Meniere's disease, meningitis, microscopic colitis, microscopic polyangiitis, migraine, minimal change nephropathy, Mixed connective tissue disease (MCTD), mononucleosis infectiosa, Mooren's ulcer, Mucha-Habermann disease, multifocal motor neuropathy, multiple endocrine failure, multiple organ injury syndrome such as those secondary to septicemia, trauma or hemorrhage, multiple organ injury syndrome, multiple sclerosis (MS) such as spino-optical MS, multiple sclerosis, mumps, muscular disorders, myasthenia gravis such as thymoma-associated myasthenia gravis, myasthenia gravis, myocarditis, myositis, narcolepsy, necrotizing enterocolitis, and transmural colitis, and autoimmune inflammatory bowel disease, necrotizing, cutaneous, or hypersensitivity vasculitis, neonatal lupus syndrome (NLE), nephrosis, nephrotic syndrome, neurological disease, neuromyelitis optica (Devic's), neuromyelitis optica, neuromyotonia, neutropenia, non-cancerous lymphocytosis, nongranulomatous uveitis, non-malignant thymoma, ocular and orbital inflammatory disorders, ocular cicatricial pemphigoid, oophoritis, ophthalmia symphatica, opsoclonus myoclonus syndrome (OMS), opsoclonus or opsoclonus myoclonus syndrome (OMS), and sensory neuropathy, optic neuritis, orchitis granulomatosa, osteoarthritis, palindromic rheumatism, pancreatitis, pancytopenia, PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus), paraneoplastic cerebellar degeneration, paraneoplastic syndrome, paraneoplastic syndromes, including neurologic paraneoplastic syndromes, optionally Lambert-Eaton myasthenic syndrome or Eaton-Lambert syndrome, parasitic diseases such as Leishmania, paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, pars planitis (peripheral uveitis), Parsonnage-Turner syndrome, parvovirus infection, pemphigoid such as pemphigoid bullous and skin pemphigoid, pemphigus (including pemphigus vulgaris), pemphigus erythematosus, pemphigus foliaceus, pemphigus mucus-membrane pemphigoid, pemphigus, peptic ulcer, periodic paralysis, peripheral neuropathy, perivenous encephalomyelitis, pernicious anemia (anemia perniciosa), pernicious anemia, phacoantigenic uveitis, pneumonocirrhosis, POEMS syndrome, polyarteritis nodosa, Type I, II, & III, polyarthritis chronica primaria, polychondritis (e.g., refractory or relapsed polychondritis), polyendocrine autoimmune disease, polyendocrine failure, polyglandular syndromes, optionally autoimmune polyglandular syndromes (or polyglandular endocrinopathy syndromes), polymyalgia rheumatica, polymyositis, polymyositis/dermatomyositis, polyneuropathies, polyradiculitis acuta, post-cardiotomy syndrome, posterior uveitis, or autoimmune uveitis, postmyocardial infarction syndrome, postpericardiotomy syndrome, post-streptococcal nephritis, post-vaccination syndromes, presenile dementia, primary biliary cirrhosis, primary hypothyroidism, primary idiopathic

myxedema, primary lymphocytosis, which includes monoclonal B cell lymphocytosis, optionally benign monoclonal gammopathy and monoclonal garnmopathy of undetermined significance, MGUS, primary myxedema, primary progressive MS (PPMS), and relapsing remitting MS (RRMS), primary sclerosing cholangitis , progesterone dermatitis, progressive systemic sclerosis, proliferative arthritis, psoriasis such as plaque psoriasis, psoriasis, psoriatic arthritis, pulmonary alveolar proteinosis, pulmonary infiltration eosinophilia, pure red cell anemia or aplasia (PRCA), pure red cell aplasia, purulent or nonpurulent sinusitis, pustular psoriasis and psoriasis of the nails, pyelitis, pyoderma gangrenosum, Quervain's thyroiditis, Raynaud's phenomenon, reactive arthritis, recurrent abortion, reduction in blood pressure response, reflex sympathetic dystrophy, refractory sprue, Reiter's disease or syndrome, relapsing polychondritis, reperfusion injury of myocardial or other tissues, reperfusion injury, respiratory distress syndrome, restless legs syndrome, retinal autoimmunity, retroperitoneal fibrosis, Reynaud's syndrome, rheumatic diseases, rheumatic fever, rheumatism, rheumatoid arthritis, rheumatoid spondylitis, rubella virus infection, Sampter's syndrome, sarcoidosis, schistosomiasis, Schmidt syndrome, SCID and Epstein-Barr virus-associated diseases, sclera, scleritis, sclerodactyl, scleroderma, optionally systemic scleroderma, sclerosing cholangitis, sclerosis disseminata, sclerosis such as systemic sclerosis, sensoneural hearing loss, seronegative spondyloarthritides, Sheehan's syndrome, Shulman's syndrome, silicosis, Sjögren's syndrome, sperm & testicular autoimmunity, sphenoid sinusitis, Stevens-Johnson syndrome, stiff-man (or stiff-person) syndrome, subacute bacterial endocarditis (SBE), subacute cutaneous lupus erythematosus, sudden hearing loss, Susac's syndrome, Sydenham's chorea, sympathetic ophthalmia, systemic lupus erythematosus (SLE) or systemic lupus erythematodes, cutaneous SLE, systemic necrotizing vasculitis, ANCA-associated vasculitis, optionally Churg-Strauss vasculitis or syndrome (CSS), tabes dorsalis, Takayasu's arteritis, telangiectasia, temporal arteritis/Giant cell arteritis, thromboangiitis ubiterans, thrombocytopenia, including thrombotic thrombocytopenic purpura (TTP) and autoimmune or immune -mediated thrombocytopenia such as idiopathic thrombocytopenic purpura (ITP) including chronic or acute ITP, thrombocytopenic purpura (TTP), thyrotoxicosis, tissue injury, Tolosa-Hunt syndrome, toxic epidermal necrolysis, toxic-shock syndrome, transfusion reaction, transient hypogammaglobulinemia of infancy, transverse myelitis, traverse myelitis, tropical pulmonary eosinophilia, tuberculosis, ulcerative colitis, undifferentiated connective tissue disease (UCTD), urticaria, optionally chronic allergic urticaria and chronic idiopathic urticaria, including chronic autoimmune urticaria, uveitis, anterior uveitis, uveoretinitis, valvulitis, vascular dysfunction, vasculitis, vertebral arthritis, vesiculobullous dermatosis, vitiligo, Wegener's granulomatosis (Granulomatosis with Polyangiitis (GPA)), Wiskott-Aldrich syndrome, or x-linked hyper IgM syndrome.

[203] By contrast compositions containing VISTA antagonist antibodies according to the invention may be used to promote T cell immunity and to treat conditions where this is therapeutically desirable such as cancer and infectious conditions such as viral, bacterial, yeast, fungal, protozoal and parasite infections. These compositions will comprise an

amount of an antagonist according to the invention effective to promote T cell activation or proliferation or cytokine expression or other effects of VISTA in a subject in need thereof. Such cancer conditions include for example blood cancers, and solid tumors such as leukemias, lymphomas, myelodysplastic syndrome, myeloma, lung cancer, and other cancers identified herein.

[204] It should be understood that the disease conditions identified herein are intended to be exemplary and not exhaustive.

[205] The subject agonists and antagonists may be combined with other therapeutics which may be administered in the same or different compositions, at the same or different time. For example, the subject agonists may be administered in a therapeutic regimen that includes the administration ofd a PD-1 or PD-L1 agonist, CTLA4-Ig, a cytokine, a cytokine agonist or antagonist, or another receptor agonist or antagonist.

Downregulation of Immune Responses

[206] Upregulating or enhancing the inhibitory function of a VISTA polypeptide may be used to downregulate immune responses. Downregulation can be in the form of inhibiting or blocking an immune response already in progress, or may involve preventing the induction of an immune response. The functions of activated immune cells can be inhibited by downregulating immune cell responses or by inducing specific anergy in immune cells, or both. For example, VISTA agonist antibodies may bind to the VISTA polypeptide which is expressed on various immune cells and thereby downmodulate the immune response. This agonist antibody may be monospecific or multispecific, e.g., it may comprise a bispecific antibody such as a BiTE. For example, such an antibody can comprise a VISTA antigen binding moiety and another antigen binding moiety, e.g., which targets a cell surface receptor on an immune cell, e.g., a T cell, a B cell, or a myeloid cell. Such an antibody, in addition to comprising a VISTA antigen binding site, may comprise a binding site which binds to a B cell antigen receptor, a T cell antigen receptor, or an Fc or other receptor, in order to target the molecule to a specific cell population. Selection of this second antigen for the bispecific antibody provides flexibility in selection of cell population to be targeted. VISTA agonist antibodies that promote or mimic VISTA activity may enhance the interaction of VISTA with its natural binding partners. As disclosed herein other human VISTA activating or agonist antibodies can be identified by their ability to inhibit T cell activity or proliferation and/or based on their immunosuppressive effects in vitro or inflammatory, allergic or autoimmune disease models.

[207] A number of art-recognized readouts of cell activation can be employed to measure, e.g., cell proliferation or effector function (e.g., antibody production, cytokine production, phagocytosis) in the presence of the activating agent. The ability of a test antibody to agonize or promote the effects of human VISTA and thereby block this activation can be readily determined by measuring the ability of the agent to affect a decrease in proliferation or effector function being measured. Accordingly, the ability of a

test antibody to be immunosuppressive and to block immune activation can be determined by measuring cytokine production and/or proliferation at different concentrations of antigen.

[208] Tolerance may be induced against specific antigens by co-administering an antigen with a VISTA agonist antibody according to the invention. For example, tolerance may be induced to specific polypeptides Immune responses to allergens or foreign polypeptides to which an immune response is undesirable can be inhibited. For example, patients that receive Factor VIII frequently generate antibodies against this clotting factor. Co-administration of a VISTA agonist antibody according to the invention that stimulates or mimics VISTA activity or interaction with its natural binding partner, with recombinant factor VIII may suppress this undesired immune response.

[209] A VISTA agonist antibody according to the invention may be used in combination with another agent that blocks the activity of costimulatory receptors on an immune cell or which agonizes the activity of another immunosuppressive receptor or ligand expressed on immune cells in order to downmodulate immune responses. Exemplary molecules include: PD-1, PDL-1 agonists, soluble forms of CTLA-4, anti-B7-1 antibodies, anti-B7-2 antibodies, antagonistic antibodies targeting one or more of LAG-3, TIM-3, BTLA, B7-H4, B7H3, et al. and/or agonistic antibodies targeting one or more of CD40, CD137, OX40, GITR, CD27, CD28 or ICOS or combinations thereof. These moieties can be combined in a single composition or compound, e.g., a bispecific antibody containing a VISTA agonist antibody according to the invention and further comprising another immune agonist antibody or it may comprise a fusion polypeptide containing a VISTA agonist antibody according to the invention which is fused to another immunosuppressive polypeptide or other active agent. Alternatively these moieties may be administered as separate or discrete entities (simultaneously or sequentially) in the same or different compositions to downregulate immune cell mediated immune responses in a subject.

[210] Examples of specific immmunoinhibitory molecules that may be combined with VISTA agonist antibodies according to the invention include antibodies that block a costimulatory signal (e.g., against CD28 or ICOS), antibodies that activate an inhibitory signal via CTLA4, and/or antibodies against other immune cell markers (e.g., against CD40, CD40 ligand, or cytokines), fusion proteins (e.g., CTLA4-Fc or PD-1-Fc), and immunosuppressive drugs (e.g., rapamycin, cyclosporine A, or FK506).

[211] In a further embodiment, bispecific antibodies containing VISTA agonist antibodies according to the invention are useful for targeting a specific cell population, e.g., using a marker found only on a certain type of cell, e.g., B lymphocytes, monocytes, dendritic cells, or Langerhans cells. Downregulating immune responses by activating VISTA activity or VISTA-immune cell interactions (and thus stimulating the negative signaling function of VISTA) is useful in downmodulating the immune response, e.g., in situations of tissue, skin and organ transplantation, in graft-versus-host disease (GVHD), or allergies, or in autoimmune and inflammatory diseases such as systemic lupus erythematosus, IBD, RA,

psoriasis and multiple sclerosis. For example, blockage of immune cell function results in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by immune cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which promotes the activity of VISTA or the interaction of VISTA with its natural binding partner(s), on immune cells alone or in conjunction with another downmodulatory agent prior to or at the time of transplantation can inhibit the generation of a costimulatory signal. Moreover, promotion of VISTA activity may also be sufficient to anergize the immune cells, thereby inducing tolerance in a subject.

[212] To achieve sufficient immunosuppression or tolerance in some diseases or in some subjects, it may necessary to block the costimulatory function of other molecules. For example, it may be desirable to block the function of B7-1 and B7-2 by administering a soluble form of a combination of peptides having an activity of each of these antigens or blocking antibodies against these antigens (separately or together in a single composition) prior to or at the time of transplantation. Alternatively, it may be desirable to promote inhibitory activity of VISTA and to further inhibit a costimulatory activity of B7-1 and/or B7-2.

[213] The subject anti-human VISTA agonist antibodies are especially useful in treating autoimmune disease. Many autoimmune disorders are the result of inappropriate activation of immune cells that are reactive against self-tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive immune cells may reduce or eliminate disease symptoms. Administration of the subject anti-human VISTA agonist antibodies that promote activity of VISTA or VISTA interaction with its natural binding partner(s), may induce antigen-specific tolerance of autoreactive immune cells which could lead to long-term relief from the disease. Additionally, co-administration of agents which block costimulation of immune cells by disrupting receptor-ligand interactions of B7 molecules with costimulatory receptors may be useful in inhibiting immune cell activation to prevent production of autoantibodies or cytokines which may be involved in the disease process.

[214] Downregulation of an immune response via stimulation of VISTA activity or VISTA interaction with its natural binding partner(s) using the subject anti-human VISTA agonist antibodies may also be useful in treating an autoimmune attack of autologous tissues. Thus, conditions that are caused or exacerbated by autoimmune attack (e.g., heart disease, myocardial infarction or atherosclerosis) may be ameliorated or improved by increasing VISTA activity or VISTA binding to its natural binding partner. It is therefore within the scope of the invention to modulate conditions exacerbated by autoimmune attack, such as autoimmune disorders (as well as conditions such as heart disease, myocardial infarction, and atherosclerosis) by stimulating VISTA activity or VISTA interaction with its counter receptor using the subject anti-human VISTA agonist antibodies.

[215] As mentioned previously the efficacy of agonist anti-human VISTA antibodies according to the invention for preventing or alleviating autoimmune and inflammatory disorders can be determined using a number of well-characterized animal models of human autoimmune and inflammatory diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythematosus in MRL/lpr/lpr mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis. *See* Paul ed., *Fundamental Immunology*, Raven Press, New York, 1989, pages 840-856.

[216] Inhibition of immune cell activation is further useful therapeutically in the treatment of allergies and allergic reactions, e.g., by inhibiting IgE production. The subject anti-human VISTA agonist antibodies which promote or mimic VISTA activity or VISTA interaction with its natural binding partner(s) can be administered to an allergic subject to inhibit immune cell-mediated allergic responses in the subject. Stimulation of VISTA activity or interaction with its natural binding partner(s), can be accompanied by exposure to allergen in conjunction with appropriate MHC molecules. Allergic reactions can be systemic or local in nature, depending on the route of entry of the allergen and the pattern of deposition of IgE on mast cells or basophils. Thus, immune cell-mediated allergic responses can be inhibited locally or systemically by administration of the subject anti-human VISTA agonist antibodies.

Selection of Anti-VISTA Antibodies that Bind to the Same Epitope

[217] In certain embodiments, an agonistic anti-VISTA antibody according to the invention possesses desired functional properties such as modulation of immune stimulation and related functions. As shown in **Figure 4** and disclosed in the working examples, the epitopic specificity of a number of anti-human VISTA agonist antibodies according to the invention has been elucidated. As a number of antibodies which have been shown to bind to the same epitope have been found to be immunosuppressive it is expected that other VISTA agonist antibodies may be identified which bind to the same or overlapping epitope, i.e., they will interact with one or more of the amino acid residues of human VISTA polypeptide with which the exemplary VISTA agonist antibodies bind. Other antibodies with the same epitopic specificity may be selected and/or those which have the ability to cross-compete for binding to VISTA antigen with the desired antibodies. For example, the epitopic specificity of a desired antibody may be determined using a library of overlapping peptides comprising the entire VISTA polypeptide, e.g., 15-mers or an overlapping peptide library constituting a portion containing a desired epitope of VISTA and antibodies which bind to the same peptides or one or more residues thereof in the library are determined to bind the same linear or conformational epitope. In the examples the epitopic specificity was determined using Pepscan® methods which may be used to identify linear and conformational epitopes.

Modification of Agonist Antibodies According to the Invention

[218] In addition or as an alternative to modifications made within the framework or CDR regions, antibodies according to at least some embodiments of the invention may be engineered to include modifications within the Fc region, typically to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding, and/or antigen-dependent cellular cytotoxicity. Furthermore, an antibody according to at least some embodiments of the invention may be chemically modified (e.g., one or more chemical moieties can be attached to the antibody) or be modified to alter its glycosylation, again to alter one or more functional properties of the antibody. Such embodiments are described further below. The numbering of residues in the Fc region is that of the EU index of Kabat.

[219] In one embodiment, the hinge region of CH1 is modified such that the number of cysteine residues in the hinge region is altered, e.g., increased or decreased. This approach is described further in U.S. Pat. No. 5,677,425 by Bodmer et al. The number of cysteine residues in the hinge region of CHI is altered to, for example, facilitate assembly of the light and heavy chains or to increase or decrease the stability of the antibody.

[220] In another embodiment, the Fc hinge region of an antibody is mutated to decrease the biological half-life of the antibody. More specifically, one or more amino acid mutations are introduced into the CH2-CH3 domain interface region of the Fc -hinge fragment such that the antibody has impaired Staphylococcal protein A (SpA) binding relative to native Fc -hinge domain SpA binding. This approach is described in further detail in U.S. Pat. No. 6,165,745 by Ward et al.

[221] In another embodiment, the antibody is modified to increase its biological half-life. Various approaches are possible. For example, one or more of the following mutations can be introduced: T252L, T254S, and T256F, as described in U.S. Pat. No. 6,277,375 to Ward. Alternatively, to increase the biological half-life, the antibody can be altered within the CHI or CL region to contain a salvage receptor binding epitope taken from two loops of a CH2 domain of an Fc region of an IgG, as described in U.S. Pat. Nos. 5,869,046 and 6,121,022 by Presta et al.

[222] In yet other embodiments, the Fc region is altered by replacing at least one amino acid residue with a different amino acid residue to alter the effector functions of the antibody. For example, one or more amino acids selected from amino acid residues 234, 235, 236, 237, 297, 318, 320 and 322 can be replaced with a different amino acid residue such that the antibody has an altered affinity for an effector ligand but retains the antigen-binding ability of the parent antibody. The effector ligand to which affinity is altered can be, for example, an Fc receptor or the Cl component of complement. This approach is described in further detail in U.S. Pat. Nos. 5,624,821 and 5,648,260, both by Winter et al.

[223] In another example, one or more amino acids selected from amino acid residues 329, 331 and 322 can be replaced with a different amino acid residue such that the antibody has altered C1q binding and/or reduced or abolished complement dependent cytotoxicity

(CDC). This approach is described in further detail in U.S. Pat. Nos. 6,194,551 by Idusogie et al.

[224] In another example, one or more amino acid residues within amino acid positions 231 and 239 are altered to thereby alter the ability of the antibody to fix complement. This approach is described further in PCT Publication WO 94/29351 by Bodmer et al.

[225] In yet another example, the Fc region is modified to increase the affinity of the antibody for an Fγ receptor by modifying one or more amino acids at the following positions: 238, 239, 248, 249, 252, 254, 255, 256, 258, 265, 267, 268, 269, 270, 272, 276, 278, 280, 283, 285, 286, 289, 290, 292, 293, 294, 295, 296, 298, 301, 303, 305, 307, 309, 312, 315, 320, 322, 324, 326, 327, 329, 330, 331, 333, 334, 335, 337, 338, 340, 360, 373, 376, 378, 382, 388, 389, 398, 414, 416, 419, 430, 434, 435, 437, 438 or 439. This approach is described further in PCT Publication WO 00/42072 by Presta. Moreover, the binding sites on human IgGl for FcγRI, FcγRII, FcγRIII and FcRn have been mapped and variants with improved binding have been described (see Shields, R. L. et al. (2001) *J. Biol. Chem.* 276:6591-6604). Specific mutations at positions 256, 290, 298, 333, 334 and 339 are shown to improve binding to FcγRIII. Additionally, the following combination mutants are shown to improve FcγRIII binding: T256A/S298A, S298A/E333A, S298A/K224A and S298A/E333A/K334A. Furthermore, mutations such as M252Y/S254T/T256E or M428L/N434S improve binding to FcRn and increase antibody circulation half-life (see Chan CA and Carter PJ (2010) *Nature Rev Immunol* 10:301-316).

[226] In still another embodiment, the antibody can be modified to abrogate in vivo Fab arm exchange. Specifically, this process involves the exchange of IgG4 half-molecules (one heavy chain plus one light chain) between other IgG4 antibodies that effectively results in b specific antibodies which are functionally monovalent. Mutations to the hinge region and constant domains of the heavy chain can abrogate this exchange (see Aalberse, RC, Schuurman J., 2002, *Immunology* 105:9-19).

[227] In still another embodiment, the glycosylation of an antibody is modified. For example, an aglycosylated antibody can be made (i.e., the antibody lacks glycosylation). Glycosylation can be altered to, for example, increase the affinity of the antibody for antigen. Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence. For example, one or more amino acid substitutions can be made that result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site. Such aglyclosylation may increase the affinity of the antibody for antigen. Such an approach is described in further detail in U.S. Pat. Nos. 5,714,350 and 6,350,861 by Co et al.

[228] Additionally or alternatively, an antibody can be made that has an altered type of glycosylation, such as a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNac structures. Such altered

glycosylation patterns have been demonstrated to increase the ADCC ability of antibodies. Such carbohydrate modifications can be accomplished by, for example, expressing the antibody in a host cell with altered glycosylation machinery. Cells with altered glycosylation machinery have been described in the art and can be used as host cells in which to express recombinant antibodies according to at least some embodiments of the invention to thereby produce an antibody with altered glycosylation. For example, the cell lines Ms704, Ms705, and Ms709 lack the fucosyltransferase gene, FUT8 (a (1,6) fucosyltransferase), such that antibodies expressed in the Ms704, Ms705, and Ms709 cell lines lack fucose on their carbohydrates. The Ms704, Ms705, and Ms709 FUT8 cell lines are created by the targeted disruption of the FUT8 gene in CHO/DG44 cells using two replacement vectors (see U.S. Patent Publication No. 20040110704 by Yamane et al. and Yamane-Ohnuki et al. (2004) *Biotechnol Bioeng* 87:614-22). As another example, EP 1,176,195 by Hanai et al. describes a cell line with a functionally disrupted FUT8 gene, which encodes a fucosyl transferase, such that antibodies expressed in such a cell line exhibit hypofucosylation by reducing or eliminating the a 1,6 bond-related enzyme. Hanai et al. also describe cell lines which have a low enzyme activity for adding fucose to the N-acetylglucosamine that binds to the Fc region of the antibody or does not have the enzyme activity, for example the rat myeloma cell line YB2/0 (ATCC CRL 1662). PCT Publication WO 03/035835 by Presta describes a variant CHO cell line, Lecl3 cells, with reduced ability to attach fucose to Asn(297)-linked carbohydrates, also resulting in hypofucosylation of antibodies expressed in that host cell (see also Shields, R. L. et al. (2002) *J. Biol. Chem*. 277:26733-26740). PCT Publication WO 99/54342 by Umana et al. describes cell lines engineered to express glycoprotein-modifying glycosyl transferases (e.g., P(l,4)-N-acetylglucosaminyltransferase III (GnTIII)) such that antibodies expressed in the engineered cell lines exhibit increased bisecting GlcNac structures which results in increased ADCC activity of the antibodies (see also Umana et al. (1999) *Nat. Biotech*. 17: 176-180). Alternatively, the fucose residues of the antibody may be cleaved off using a fucosidase enzyme. For example, the fucosidase α-L-fucosidase removes fucosyl residues from antibodies (Tarentino, A. L. et al. (1975) *Biochem.* 14:5516-23).

[229] Another modification of the antibodies herein that is contemplated by the invention is pegylation or the addition of other water soluble moieties, typically polymers, e.g., in order to enhance half-life. An antibody can be pegylated to, for example, increase the biological (e.g., serum) half-life of the antibody. To pegylate an antibody, the antibody, or fragment thereof, typically is reacted with polyethylene glycol (PEG), such as a reactive ester or aldehyde derivative of PEG, under conditions in which one or more PEG groups become attached to the antibody or antibody fragment. Preferably, the pegylation is carried out via an acylation reaction or an alkylation reaction with a reactive PEG molecule (or an analogous reactive water-soluble polymer). As used herein, the term "polyethylene glycol" is intended to encompass any of the forms of PEG that have been used to derivatize other proteins, such as mono (Ci-Cio) alkoxy- or aryloxy-polyethylene glycol or polyethylene glycol-maleimide. In certain embodiments, the antibody to be pegylated is an aglycosylated antibody. Methods for pegylating proteins are known in the art and can be applied to the

antibodies according to at least some embodiments of the invention. See for example, EP 0 154 316 by Nishimura et al. and EP 0 401 384 by Ishikawa et al.

Methods of Engineering Antibodies

[230] In certain embodiments, an agonist anti-VISTA antibody according to the invention having V_H and V_L sequences can be used to create new anti-VISTA antibodies, respectively, by modifying the V_H and/or V_L sequences, or the constant regions attached thereto. Thus, in another aspect according to at least some embodiments of the invention, the structural features of an anti-VISTA antibody according to at least some embodiments of the invention, are used to create structurally related anti-VISTA antibodies that retain at least one functional property of the antibodies according to at least some embodiments of the invention, such as binding to human VISTA. For example, one or more CDR regions of one VISTA antibody or mutations thereof can be combined recombinantly with known framework regions and/or other CDRs to create additional, recombinantly-engineered, anti-VISTA antibodies according to at least some embodiments of the invention, as discussed above. Other types of modifications include those described in the previous section. The starting material for the engineering method is one or more of the V_H and/or V_L sequences provided herein, or one or more CDR regions thereof. To create the engineered antibody, it is not necessary to actually prepare (i.e., express as a protein) an antibody having one or more of the V_H and/or VL sequences provided herein, or one or more CDR regions thereof. Rather, the information contained in the sequences is used as the starting material to create a "second generation" sequences derived from the original sequences and then the "second generation" sequences is prepared and expressed as a protein.

[231] Standard molecular biology techniques can be used to prepare and express altered antibody sequence. Preferably, the anti-VISTA antibody encoded by the altered antibody sequences is one that retains one, some or all of the functional properties of the anti-VISTA antibodies, respectively, produced by methods and with sequences provided herein, which functional properties include binding to VISTA antigen with a specific K_D level or less and/or modulating immune responses and/or selectively binding to desired target cells such as for example, that express VISTA antigen.

[232] The functional properties of the altered antibodies can be assessed using standard assays available in the art and/or described herein. In certain embodiments of the methods of engineering antibodies according to at least some embodiments of the invention, mutations can be introduced randomly or selectively along all or part of an anti-VISTA antibody coding sequence and the resulting modified anti-VISTA antibodies can be screened for binding activity and/or other desired functional properties.

[233] Mutational methods have been described in the art. For example, PCT Publication WO 02/092780 by Short describes methods for creating and screening antibody mutations using saturation mutagenesis, synthetic ligation assembly, or a combination thereof. Alternatively, PCT Publication WO 03/074679 by Lazar et al. describes methods of

using computational screening methods to optimize physiochemical properties of antibodies.

Nucleic Acid Molecules Encoding Antibodies

[234] The invention further provides nucleic acids which encode an anti-VISTA antibody according to the invention, or a fragment or conjugate thereof. The nucleic acids may be present in whole cells, in a cell lysate, or in a partially purified or substantially pure form. A nucleic acid is "isolated" or "rendered substantially pure" when purified away from other cellular components or other contaminants, e.g., other cellular nucleic acids or proteins, by standard techniques, including alkaline/SDS treatment, CsCl banding, column chromatography, agarose gel electrophoresis and others well known in the art. See, F. Ausubel, et al., ed. (1987) *Current Protocols in Molecular Biology*, Greene Publishing and Wiley Interscience, New York. A nucleic acid according to at least some embodiments of the invention can be, for example, DNA or RNA and may or may not contain intronic sequences. In a preferred embodiment, the nucleic acid is a cDNA molecule.

[235] Nucleic acids according to at least some embodiments of the invention can be obtained using standard molecular biology techniques. For antibodies expressed by hybridomas (e.g., hybridomas prepared from transgenic mice carrying human immunoglobulin genes as described further below), cDNAs encoding the light and heavy chains of the antibody made by the hybridoma can be obtained by standard PCR amplification or cDNA cloning techniques. For antibodies obtained from an immunoglobulin gene library (e.g., using phage display techniques), nucleic acid encoding the antibody can be recovered from the library.

[236] Once DNA fragments encoding V_H and V_L segments are obtained, these DNA fragments can be further manipulated by standard recombinant DNA techniques, for example to convert the variable region genes to full-length antibody chain genes, to Fab fragment genes or to a scFv gene. In these manipulations, a V_L- or V_H-encoding DNA fragment is operatively linked to another DNA fragment encoding another protein, such as an antibody constant region or a flexible linker. As previously defined, "operatively linked" means that that the two DNA fragments are joined such that the amino acid sequences encoded by the two DNA fragments remain in-frame.

[237] The isolated DNA encoding the V_H region can be converted to a full-length heavy chain gene by operatively linking the V_H -encoding DNA to another DNA molecule encoding heavy chain constant regions (CH1, CH2 and CH3). The sequences of human heavy chain constant region genes are known in the art (see e.g., Kabat, E. A., el al. (1991) *Sequences of Proteins of Immunological Interest*, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242) and DNA fragments encompassing these regions can be obtained by standard PCR amplification. The heavy chain constant region can be an IgGl, IgG2, IgG3, IgG4, IgA, IgE, IgM or IgD constant region, but most preferably is an IgGl, IgG2 or IgG4 constant region. For a Fab fragment heavy chain gene, the VH-encoding DNA can be

operatively linked to another DNA molecule encoding only the heavy chain C_{H1} constant region.

[238] The isolated DNA encoding the V_L region can be converted to a full-length light chain gene (as well as a Fab light chain gene) by operatively linking the V_L-encoding DNA to another DNA molecule encoding the light chain constant region, C_L-The sequences of human light chain constant region genes are known in the art (see e.g., Kabat, E. A., et al. (1991) *Sequences of Proteins of Immunological Interest*, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242) and DNA fragments encompassing these regions can be obtained by standard PCR amplification. The light chain constant region can be a kappa (κ) or lambda (λ) constant region, but most preferably is a κ constant region.

[239] To create a scFv gene, the V_H- and V_L-encoding DNA fragments are operatively linked to another fragment encoding a flexible linker, e.g., encoding the amino acid sequence (Gly4-Ser)3, such that the V_H and V_L sequences can be expressed as a contiguous single-chain protein, with the V_L and V_H regions joined by the flexible linker (see e.g., Bird et al. (1988) *Science* 242:423-426; Huston et al. (1988) *Proc. Natl. Acad. Sci., USA* 85:5879-5883; McCafferty et al., (1990) *Nature* 348:552-554).

Production of Anti-VISTA Monoclonal Antibodies

[240] Anti-VISTA monoclonal antibodies (mAbs) and antigen-binding fragments according to the present invention can be produced by a variety of techniques, including conventional monoclonal antibody methodology e.g., the standard somatic cell hybridization technique of Kohler and Milstein (1975) *Nature* 256:495. Although somatic cell hybridization procedures are preferred, in principle, other techniques for producing monoclonal antibody can be employed e.g., viral or oncogenic transformation of B lymphocytes.

[241] A preferred animal system for preparing hybridomas is the murine system. Hybridoma production in the mouse is a very well-established procedure. Immunization protocols and techniques for isolation of immunized splenocytes for fusion are known in the art. Fusion partners (e.g., murine myeloma cells) and fusion procedures are also known. Chimeric or humanized antibodies of the present invention can be prepared based on the sequence of a murine monoclonal antibody prepared as described above. DNA encoding the heavy and light chain immunoglobulins can be obtained from the murine hybridoma of interest and engineered to contain non-murine (e.g., human) immunoglobulin sequences using standard molecular biology techniques. For example, to create a chimeric antibody, the murine variable regions can be linked to human constant regions using methods known in the art (see e.g., U.S. Pat. No. 4,816,567 to Cabilly et al.). To create a humanized antibody, the murine CDR regions can be inserted into a human framework using methods known in the art (see e.g., U.S. Pat. No. 5,225,539 to Winter and U.S. Pat. Nos. 5,530,101; 5,585,089; 5,693,762 and 6,180,370 to Queen et al.).

[242] According to at least some embodiments of the invention, the antibodies are human monoclonal antibodies. Such human monoclonal antibodies directed against VISTA can be generated using transgenic or transchromosomic mice carrying parts of the human immune system rather than the mouse system. These transgenic and transchromosomic mice include mice referred to herein as the HuMAb Mouse™ and KM Mouse™, respectively, and are collectively referred to herein as "human Ig mice." The HuMAb Mouse™ (Medarex Inc.) contains human immunoglobulin gene miniloci that encode unrearranged human heavy μ and γ and κ light chain immunoglobulin sequences, together with targeted mutations that inactivate the endogenous μ and κ chain loci (see e.g., Lonberg, et al. (1994) *Nature* 368(6474): 856-859). Accordingly, the mice exhibit reduced expression of mouse IgM or κ and in response to immunization, the introduced human heavy and light chain transgenes undergo class switching and somatic mutation to generate high affinity human IgG κ monoclonal (Lonberg, N. et al. (1994), supra; reviewed in Lonberg, N. (1994) *Handbook of Experimental Pharmacology* 113:49-101; Lonberg, N. and Huszar, D. (1995) Intern. Rev. Immunol. 13: 65-93, and Harding, F. and Lonberg, N. (1995) *Ann. N.Y. Acad. Sci*. 764:536-546). The preparation and use of the HuMab Mouse ®, and the genomic modifications carried by such mice, is further described in Taylor, L. et al. (1992) *Nucleic Acids Research* 20:6287-6295; Chen, J. et al. (1993) International Immunology 5:647-656; Tuaillon et al. (1993) *Proc. Natl. Acad. Sci. USA* 90:3720-3724; Choi et al. (1993) *Nature Genetics* 4: 117-123; Chen, J. et al. (1993) EMBO J. 12: 821-830; Tuaillon et al. (1994) *J. Immunol*. 152:2912-2920; Taylor, L. et al. (1994) *International Immunology* 6:579-591; and Fishwild, D. et al. (1996) *Nature Biotechnology* 14: 845-851, the contents of all of which are hereby specifically incorporated by reference in their entirety. See further, U.S. Pat. Nos. 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,789,650; 5,877,397; 5,661,016; 5,814,318; 5,874,299; and 5,770,429; all to Lonberg and Kay; U.S. Pat. No. 5,545,807 to Surani et al.; PCT Publication Nos. WO 92/03918, WO 93/12227, WO 94/25585, WO 97/13852, WO 98/24884 and WO 99/45962, all to Lonberg and Kay; and PCT Publication No. WO 01/14424 to Korman et al.

[243] In another embodiment, human antibodies according to at least some embodiments of the invention can be raised using a mouse that carries human immunoglobulin sequences on transgenes and transchomosomes, such as a mouse that carries a human heavy chain transgene and a human light chain transchromosome. Such mice, referred to herein as "KM mice™", are described in detail in PCT Publication WO 02/43478 to Ishida et al.

[244] Still further, alternative transgenic animal systems expressing human immunoglobulin genes are available in the art and can be used to raise anti-VISTA antibodies according to at least some embodiments of the invention. For example, an alternative transgenic system referred to as the Xenomouse (Abgenix, Inc.) can be used; such mice are described in, for example, U.S. Pat. Nos. 5,939,598; 6,075,181; 6,114,598; 6, 150,584 and 6,162,963 to Kucherlapati et al.

[245] Moreover, alternative transchromosomic animal systems expressing human immunoglobulin genes are available in the art and can be used to raise anti-VISTA antibodies according to at least some embodiments of the invention. For example, mice carrying both a human heavy chain transchromosome and a human light chain transchromosome, referred to as "TC mice" can be used; such mice are described in Tomizuka et al. (2000) *Proc. Natl. Acad Sci. USA* 97:722-727. Furthermore, cows carrying human heavy and light chain transchromosomes have been described in the art (Kuroiwa et al. (2002) *Nature Biotechnology* 20:889-894) and can be used to raise anti-VISTA antibodies according to at least some embodiments of the invention.

[246] Human monoclonal antibodies according to at least some embodiments of the invention can also be prepared using phage display methods for screening libraries of human immunoglobulin genes. Such phage display methods for isolating human antibodies are established in the art. See for example: U.S. Pat. Nos. 5,223,409; 5,403,484; and 5,571,698 to Ladner et al.; U.S. Pat. Nos. 5,427,908 and 5,580,717 to Dower et al.; U.S. Pat. Nos. 5,969,108 and 6,172,197 to McCafferty et al.; and U.S. Pat. Nos. 5,885,793; 6,521,404; 6,544,731; 6,555,313; 6,582,915 and 6,593,081 to Griffiths et al.

[247] Human monoclonal antibodies according to at least some embodiments of the invention can also be prepared using SCID mice into which human immune cells have been reconstituted such that a human antibody response can be generated upon immunization. Such mice are described in, for example, U.S. Pat. Nos. 5,476,996 and 5,698,767 to Wilson et al.

Immunization of Human Ig Mice

[248] In some embodiments human Ig mice are used to raise human anti-VISTA antibodies according to the invention, e.g., by immunizing such mice with a purified or enriched preparation of VISTA antigen and/or recombinant VISTA, or VISTA fusion protein, as described by Lonberg, N. et al. (1994) *Nature* 368(6474): 856-859; Fishwild, D. et al. (1996) *Nature Biotechnology* 14: 845-851; and PCT Publication WO 98/24884 and WO 01/14424. Preferably, the mice will be 6-16 weeks of age upon the first infusion. For example, a purified or recombinant preparation (dose ranging from .5-500 μg) of VISTA antigen can be used to immunize the human Ig mice intraperitoneally.

[249] In general transgenic mice respond when initially immunized intraperitoneally (IP) with antigen in complete Freund's adjuvant, followed by every other week IP immunizations (up to a total of 6) with antigen in incomplete Freund's adjuvant. However, adjuvants other than Freund's are also found to be effective. In addition, whole cells in the absence of adjuvant are found to be highly immunogenic. The immune response can be monitored over the course of the immunization protocol with plasma samples being obtained by retroorbital bleeds. The plasma can be screened by ELISA (as described below), and mice with sufficient titers of anti-VISTA human immunoglobulin can be used for fusions. Mice can be boosted intravenously with antigen 3 days before sacrifice and removal of the

spleen. It is expected that 2-3 fusions for each immunization may need to be performed. Between 6 and 24 mice are typically immunized for each antigen. Usually both HCo7 and HCol2 strains are used. In addition, both HCo7 and HCol2 transgene can be bred together into a single mouse having two different human heavy chain transgenes (HCo7/HCo 12). Alternatively or additionally, the KM Mouse™ strain can be used. In an exemplary embodiment these mice will be engineered to selectively produce human IgG2 antibodies.

Generation of Hybridomas Producing Human Monoclonal Antibodies

[250] In certain embodiments, hybridomas producing a human monoclonal anti-VISTA antibody according to the invention may be generated using splenocytes and/or lymph node cells from immunized mice can be isolated and fused to an appropriate immortalized cell line, such as a mouse myeloma cell line. The resulting hybridomas can be screened for the production of antigen-specific antibodies. For example, single cell suspensions of splenic lymphocytes from immunized mice can be fused to one-sixth the numbers of P3X63-Ag8.653 nonsecreting mouse myeloma cells (ATCC, CRL 1580) with 50% PEG. Cells are plated at approximately 2X105 in flat bottom microtiter plate, followed by a two week incubation in selective medium containing 20% fetal Clone Serum, 18% "653" conditioned media, 5% origen (IGEN), 4 mM L-glutamine, 1 mM sodium pyruvate, 5 mM HEPES, 0.055 mM 2-mercaptoethanol, 50 units/ml penicillin, 50 mg/ml streptomycin, 50 mg/ml gentamycin and IX HAT (Sigma; the HAT is added 24 hours after the fusion). After approximately two weeks, cells can be cultured in medium in which the HAT is replaced with HT. Individual wells can then be screened by ELISA for human monoclonal IgM and IgG antibodies. Once extensive hybridoma growth occurs, medium can be observed usually after 10-14 days. The antibody secreting hybridomas can be replated, screened again, and if still positive for human IgG, the monoclonal antibodies can be subcloned at least twice by limiting dilution. The stable subclones can then be cultured in vitro to generate small amounts of antibody in tissue culture medium for characterization.

[251] To purify human monoclonal antibodies, selected hybridomas can be grown in two-liter spinner-flasks for monoclonal antibody purification. Supernatants can be filtered and concentrated before affinity chromatography with protein A-Sepharose (Pharmacia, Piscataway, N.J.). Eluted IgG can be checked by gel electrophoresis and high performance liquid chromatography to ensure purity. The buffer solution can be exchanged into PBS, and the concentration can be determined by OD280 using 1.43 extinction coefficient. The monoclonal antibodies can be aliquoted and stored at -80 °C.

Generation of Transfectomas Producing Monoclonal Antibodies

[252] In certain embodiments, an anti-VISTA antibody according to the invention can be produced in a host cell transfectoma using, for example, a combination of recombinant DNA techniques and gene transfection methods as is well known in the art (e.g., Morrison, S. (1985) *Science* 229: 1202). For example, to express the antibodies, or antibody fragments thereof, DNAs encoding partial or full-length light and heavy chains, can be obtained by

standard molecular biology techniques (e.g., PCR amplification or cDNA cloning using a hybridoma that expresses the antibody of interest) and the DNAs can be inserted into expression vectors such that the genes are operatively linked to transcriptional and translational control sequences. In this context, the term "operatively linked" is intended to mean that an antibody gene is ligated into a vector such that transcriptional and translational control sequences within the vector serve their intended function of regulating the transcription and translation of the antibody gene. The expression vector and expression control sequences are chosen to be compatible with the expression host cell used. The antibody light chain gene and the antibody heavy chain gene can be inserted into separate vector or, more typically, both genes are inserted into the same expression vector. The antibody genes are inserted into the expression vector by standard methods (e.g., ligation of complementary restriction sites on the antibody gene fragment and vector, or blunt end ligation if no restriction sites are present). The light and heavy chain variable regions of the antibodies described herein can be used to create full-length antibody genes of any antibody isotype by inserting them into expression vectors already encoding heavy chain constant and light chain constant regions of the desired isotype such that the V_H segment is operatively linked to the C_H segments within the vector and the V_L segment is operatively linked to the C_L segment within the vector. Additionally or alternatively, the recombinant expression vector can encode a signal peptide that facilitates secretion of the antibody chain from a host cell. The antibody chain gene can be cloned into the vector such that the signal peptide is linked in-frame to the amino terminus of the antibody chain gene. The signal peptide can be an immunoglobulin signal peptide or a heterologous signal peptide (i.e., a signal peptide from a non-immunoglobulin protein).

Characterization Of Antibody Binding To Antigen

[253] In certain embodiments, the binding specificity of an agonistic anti-VISTA antibody according to the invention is determined by known antibody binding assay techniques such as ELISA. In an exemplary ELISA, microtiter plates are coated with a purified antigen, herein VISTA at 0.25μg/ml in PBS, and then blocked with 5% bovine serum albumin in PBS. Dilutions of antibody (e.g., dilutions of plasma from -immunized mice) are added to each well and incubated for 1-2 hours at 37 °C. The plates are washed with PBS/Tween and then incubated with secondary reagent (e.g., for human antibodies, a goat-anti-human IgG Fc-specific polyclonal reagent) conjugated to alkaline phosphatase for 1 hour at 37 °C. After washing, the plates are developed with pNPP substrate (1 mg/ml), and analyzed at OD of 405-650. Preferably, mice which develop the highest titers will be used for fusions.

[254] An ELISA assay as described above can also be used to screen for hybridomas that show positive reactivity with VISTA immunogen. Hybridomas that bind with high avidity to VISTA are subcloned and further characterized. One clone from each hybridoma, which retains the reactivity of the parent cells (by ELISA), can be chosen for making a 5-10 vial cell bank stored at -140 °C, and for antibody purification.

[255] To purify anti-VISTA antibodies, selected hybridomas can be grown in two-liter spinner-flasks for monoclonal antibody purification. Supernatants can be filtered and concentrated before affinity chromatography with protein A-Sepharose (Pharmacia, Piscataway, N.J.). Eluted IgG can be checked by gel electrophoresis and high performance liquid chromatography to ensure purity. The buffer solution can be exchanged into PBS, and the concentration can be determined by OD280 using 1.43 extinction coefficient. The monoclonal antibodies can be aliquoted and stored at -80 °C.

[256] To determine if the selected anti-VISTA monoclonal antibodies bind to unique epitopes, each antibody can be biotinylated using commercially available reagents (Pierce, Rockford, Il.). Competition studies using unlabeled monoclonal antibodies and biotinylated monoclonal antibodies can be performed using VISTA coated-ELISA plates as described above. Biotinylated mAb binding can be detected with a strep-avidin-alkaline phosphatase probe.

[257] To determine the isotype of purified antibodies, isotype ELISAs can be performed using reagents specific for antibodies of a particular isotype, e.g., IgG2's. For example, to determine the isotype of a human monoclonal antibody, wells of microtiter plates can be coated with ^g/ml of anti-human immunoglobulin overnight at 4°C. After blocking with 1% BSA, the plates are reacted with 1 mug /ml or less of test monoclonal antibodies or purified isotype controls, at ambient temperature for one to two hours. The wells can then be reacted with either human IgG1 or human IgM- specific alkaline phosphatase-conjugated probes. Plates are developed and analyzed as described above.

[258] Anti-VISTA human IgGs can be further tested for reactivity with VISTA antigen, respectively, by Western blotting. Briefly, VISTA antigen can be prepared and subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis. After electrophoresis, the separated antigens are transferred to nitrocellulose membranes, blocked with 10% fetal calf serum, and probed with the monoclonal antibodies to be tested. Human IgG binding can be detected using anti-human IgG alkaline phosphatase and developed with BCIP/NBT substrate tablets (Sigma Chem. Co., St. Louis, Mo.).

[259] In another aspect, the present invention features antibody-drug conjugates (ADCs), consisting of an antibody (or antibody fragment such as a single-chain variable fragment (scFv) linked to a payload drug (often cytotoxic). The antibody causes the ADC to bind to the target cancer cells. Often the ADC is then internalized by the cell and the drug is released into the cell. Because of the targeting, the side effects are lower and give a wider therapeutic window. Hydrophilic linkers (e.g., PEG4Mal) help prevent the drug being pumped out of resistant cancer cells through MDR (multiple drug resistance) transporters.

[260] In another aspect, the present invention features immunoconjugates comprising an anti-VISTA antibody, or a fragment thereof, conjugated to a therapeutic agent, such as a cytotoxin, a drug (e.g., an immunosuppressant) or a radiotoxin. Such conjugates are referred to herein as "immunoconjugates". Immunoconjugates that include one or more cytotoxins

are referred to as "immunotoxins." A cytotoxin or cytotoxic agent includes any agent that is detrimental to (e.g., kills) cells. Examples include Taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, teniposide, vincristine, vinblastine, colchicine, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents also include, for example, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thiotepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

[261] Other examples of therapeutic cytotoxins that can be conjugated to an antibody according to at least some embodiments of the invention include duocarmycins, calicheamicin, maytansines and auristatins, and derivatives thereof. An example of a calicheamicin antibody conjugate is commercially available (Mylotarg™ Wyeth).

[262] Cytotoxins can be conjugated to antibodies according to at least some embodiments of the invention using linker technology available in the art. Examples of linker types that have been used to conjugate a cytotoxin to an antibody include, but are not limited to, hydrazones, thioethers, esters, disulfides and peptide-containing linkers. A linker can be chosen that is, for example, susceptible to cleavage by low pH within the lysosomal compartment or susceptible to cleavage by proteases, such as proteases preferentially expressed in tumor tissue such as cathepsins (e.g., cathepsins B, C, D). For further discussion of types of cytotoxins, linkers and methods for conjugating therapeutic agents to antibodies, see also Saito, G. et al. (2003) *Adv. Drug Deliv. Rev*. 55: 199-215; Trail, P. A. et al. (2003) *Cancer Immunol. Immunother*. 52:328-337; Payne, G. (2003) *Cancer Cell* 3:207-212; Allen, T. M. (2002) *Nat. Rev. Cancer* 2:750-763; Pastan, I. and Kreitman, R. J. (2002) *Curr. Opin. Investig*. Drugs 3: 1089-1091; Senter, P. D. and Springer, C. J. (2001) *Adv. Drug Deliv. Rev*. 53:247-264.

[263] Antibodies of the present invention also can be conjugated to a radioactive isotope to generate cytotoxic radiopharmaceuticals, also referred to as radioimmunoconjugates. Examples of radioactive isotopes that can be conjugated to antibodies for use diagnostically or therapeutically include, but are not limited to, iodine 131, indium 111, yttrium 90 and lutetium 177. Methods for preparing radioimmunoconjugates are established in the art. Radioimmunoconjugates are commercially available, including Zevalin® (BiogenIDEC) and Bexxar®. (Corixa Pharmaceuticals), and similar methods can be used to prepare radioimmunoconjugates using the antibodies according to at least some embodiments of the invention.

[264] The agonist anti-human VISTA antibodies and conjugates containing according to at least some embodiments of the invention can be used to modify a given biological response, and the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, an enzymatically active toxin, or active fragment thereof, such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor or interferon-γ; or, biological response modifiers such as, for example, lymphokines, interleukin- 1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

[265] Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.*, 62: 119-58 (1982).

Bispecific Molecules

[266] According to at least some embodiments the invention also encompasses multispecific anti-VISTA agonist antibodies. Multispecific antibodies are monoclonal antibodies that have binding specificities for at least two different sites. In another aspect, the present invention features bispecific molecules comprising an anti-VISTA antibody, or a fragment thereof, according to at least some embodiments of the invention. An antibody according to at least some embodiments of the invention, or antigen-binding portions thereof, can be derivatized or linked to another functional molecule, e.g., another peptide or protein (e.g., another antibody or ligand for a receptor) to generate a bispecific molecule that binds to at least two different binding sites or target molecules. The antibody according to at least some embodiments of the invention may in fact be derivatized or linked to more than one other functional molecule to generate multispecific molecules that bind to more than two different binding sites and/or target molecules; such multispecific molecules are also intended to be encompassed by the term "bispecific molecule" as used herein. To create a bispecific molecule according to at least some embodiments of the invention, an antibody can be functionally linked (e.g., by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other binding molecules, such as another antibody, antibody fragment, peptide or binding mimetic, such that a bispecific molecule results. In certain embodiments, one of the binding specificities of the bispecific antibodies

is for VISTA and the other is for any other antigen. In certain embodiments, bispecific antibodies may bind to two different epitopes of VISTA. Bispecific antibodies may also be used to localize cytotoxic agents to cells which express VISTA. Bispecific antibodies can be prepared as full length antibodies or antibody fragments.

[267] A bispecific antibody according to at least some embodiments of the invention is an antibody which can bind simultaneously to two targets which are of different structure. Bispecific antibodies (bsAb) and bispecific antibody fragments (bsFab) according to at least some embodiments of the invention have at least one arm that specifically binds to a B-cell antigen or epitope and at least one other arm that specifically binds a targetable conjugate.

[268] According to at least some embodiments the invention encompasses also a fusion antibody protein, which is a recombinantly produced antigen-binding molecule in which two or more different single-chain antibody or antibody fragment segments with the same or different specificities are linked. A variety of bispecific fusion antibody proteins can be produced using molecular engineering. In one form, the bispecific fusion antibody protein is monovalent, consisting of, for example, a sent with a single binding site for one antigen and a Fab fragment with a single binding site for a second antigen. In another form, the bispecific fusion antibody protein is divalent, consisting of, for example, an IgG with two binding sites for one antigen and two scFv with two binding sites for a second antigen.

[269] The invention further encompasses engineered antibodies with three or more functional antigen-binding sites, including "Octopus antibodies" (see, e.g. US 2006/0025576A1), and "Dual Acting FAb" or "DAF" antibodies comprising an antigen-binding site that binds to VISTA as well as another, different antigen (see e.g. US 2008/0069820). Accordingly, the present invention includes bispecific molecules comprising at least one first binding specificity for VISTA and a second binding specificity for a second target epitope. According to at least some embodiments of the invention, the second target epitope is an Fc receptor, e.g., human FcγRI (CD64) or a human FcαR receptor (CD89). Therefore, the invention includes bispecific molecules capable of binding both to FcγR, FcαR or FcsR expressing effector cells (e.g., monocytes, macrophages or polymorphonuclear cells (PMNs)), and to target cells expressing VISTA, respectively. These bispecific molecules target VISTA expressing cells to effector cell and trigger Fc receptor-mediated effector cell activities, such as phagocytosis of an VISTA expressing cells, antibody dependent cell-mediated cytotoxicity (ADCC), cytokine release, or generation of superoxide anion.

[270] According to at least some embodiments of the invention in which the bispecific molecule is multispecific, the molecule can further include a third binding specificity, in addition to an anti-Fc binding specificity. In one embodiment, the third binding specificity is an anti-enhancement factor (EF) portion, e.g., a molecule which binds to a surface protein involved in cytotoxic activity and thereby increases the immune response against the target cell.

[271] The "anti-enhancement factor portion" can be an antibody, functional antibody fragment or a ligand that binds to a given molecule, e.g., an antigen or a receptor, and thereby results in an enhancement of the effect of the binding determinants for the Fc receptor or target cell antigen. The "anti-enhancement factor portion" can bind an Fc receptor or a target cell antigen. Alternatively, the anti-enhancement factor portion can bind to an entity that is different from the entity to which the first and second binding specificities bind. For example, the anti-enhancement factor portion can bind a cytotoxic T-cell (e.g., via CD2, CD3, CD8, CD28, CD4, CD40, ICAM-1 or other immune cell that results in an increased immune response against the target cell).

[272] According to at least some embodiments of the invention, the bispecific molecules comprise as a binding specificity at least one antibody, or an antibody fragment thereof, including, e.g., an Fab, Fab', F(ab')2, Fv, or a single chain Fv. The antibody may also be a light chain or heavy chain dimer, or any minimal fragment thereof such as a Fv or a single chain construct as described in Ladner et al. U.S. Pat. No. 4,946,778, the contents of which are expressly incorporated by reference.

[273] In one embodiment, the binding specificity for an Fcɣ receptor is provided by a monoclonal antibody, the binding of which is not blocked by human immunoglobulin G (IgG). As used herein, the term "IgG receptor" refers to any of the eight γ-chain genes located on chromosome 1. These genes encode a total of twelve transmembrane or soluble receptor isoforms which are grouped into three Fcɣ receptor classes: FcγRI (CD64), FcγRII(CD32), and FcγRIII (CD16). In one preferred embodiment, the Fcɣ receptor is a human high affinity FcγRI. The human FcγRI is a 72 kDa molecule, which shows high affinity for monomeric IgG. The production and characterization of certain preferred anti-Fcɣ monoclonal antibodies are described by Fanger et al. in PCT Publication WO 88/00052 and in U.S. Pat. No. 4,954,617, the teachings of which are fully incorporated by reference herein. These antibodies bind to an epitope of FcɣRI, FcɣRII or FcɣRIII at a site which is distinct from the Fey binding site of the receptor and, thus, their binding is not blocked substantially by physiological levels of IgG. Known anti-FcγRI antibodies include mAb 22, mAb 32, mAb 44, mAb 62 and mAb 197. The hybridoma producing mAb 32 is available from the American Type Culture Collection, ATCC Accession No. HB9469. In other embodiments, the anti-Fcɣ receptor antibody is a humanized form of monoclonal antibody 22 (H22). The production and characterization of the H22 antibody is described in Graziano, R.F. et al. (1995) *J. Immunol.* 155 (10): 4996-5002 and PCT Publication WO 94/10332. The H22 antibody producing cell line is deposited at the American Type Culture Collection under the designation HA022CLI and has the accession no. CRL 11177.

[274] In still other embodiments, the binding specificity for an Fc receptor is provided by an antibody that binds to a human IgA receptor, e.g., an Fc-α receptor (Fc αRI(CD89)), the binding of which is preferably not blocked by human immunoglobulin A (IgA). The term "IgA receptor" is intended to include the gene product of one a-gene (FcαRI) located on chromosome 19. This gene is known to encode several alternatively spliced transmembrane

isoforms of 55 to 10 kDa. FcαRI (CD89) is constitutively expressed on monocytes/macrophages, eosinophilic and neutrophilic granulocytes, but not on non-effector cell populations. Fc αRI has medium affinity (Approximately $5X10^{-7}$ M^{-1}) for both IgA1 and IgA2, which is increased upon exposure to cytokines such as G-CSF or GM-CSF (Morton, H. C. et al. (1996) *Critical Reviews in Immunology* 16:423-440). Four FcαRI- specific monoclonal antibodies, identified as A3, A59, A62 and A77, which bind FcαRI outside the IgA ligand binding domain, have been described (Monteiro, R. C. et al. (1992) *J. Immunol*. 148: 1764).

[275] While human monoclonal antibodies are preferred, other antibodies which can be employed in the bispecific molecules according to at least some embodiments of the invention are murine, chimeric and humanized monoclonal antibodies. The bispecific molecules of the present invention can be prepared by conjugating the constituent binding specificities, e.g., the anti-FcR and anti-VISTA binding specificities, using methods known in the art. For example, the binding specificity of each bispecific molecule can be generated separately and then conjugated to one another. When the binding specificities are proteins or peptides, a variety of coupling or cross-linking agents can be used for covalent conjugation. Examples of cross-linking agents include protein A, carbodiimide, N-succinimidyl-S-acetyl-thioacetate (SATA), 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB), o-phenylenedimaleimide (oPDM), N-succinimidyl-3-(2-pyridyld- dithio propionate (SPDP), and sulfosuccinimidyl 4-(N-maleimidomethyl) cyclohexane-l-carboxylate (sulfo-SMCC) (see e.g., Karpovsky et al. (1984) *J. Exp. Med*. 160: 1686; Liu, M A et al. (1985) *Proc. Natl. Acad. Sci. USA* 82:8648). Other methods include those described in Paulus (1985) Behring Ins. Mitt. No. 78, 118-132; Brennan et al. (1985) *Science* 229:81-83), and Glennie et al. (1987) *J. Immunol*. 139: 2367-2375). Preferred conjugating agents are SATA and sulfo-SMCC, both available from Pierce Chemical Co. (Rockford, Il.). When the binding moieties are antibodies, they can be conjugated via sulfhydryl bonding of the C-terminus hinge regions of the two heavy chains. In a particularly preferred embodiment, the hinge region is modified to contain an odd number of sulfhydryl residues, preferably one, prior to conjugation.

[276] Alternatively, both binding specificities can be encoded in the same vector and expressed and assembled in the same host cell. This method is particularly useful where the bispecific molecule is a mAbXmAb, mAbXFab, FabXF(ab')2 or ligandXFab fusion protein. A bispecific molecule according to at least some embodiments of the invention can be a single chain molecule comprising one single chain antibody and a binding determinant, or a single chain bispecific molecule comprising two binding determinants. Bispecific molecules may comprise at least two single chain molecules. Methods for preparing bispecific molecules are described for example in U.S. Pat. No. 5,260,203; U.S. Pat. No. 5,455,030; U.S. Pat. No. 4,881,175; U.S. Pat. No. 5,132,405; U.S. Pat. No. 5,091,513; U.S. Pat. No. 5,476,786; U.S. Pat. No. 5,013,653; U.S. Pat. No. 5,258,498; and U.S. Pat. No. 5,482,858.

[277] Techniques for making multispecific antibodies include, but are not limited to, recombinant co-expression of two immunoglobulin heavy chain-light chain pairs having

different specificities (see Milstein and Cuello, *Nature* 305: 537 (1983)), WO 93/08829, and Traunecker et al., *EMBO J.* 10: 3655 (1991)), and "knob-in-hole" engineering (see, e.g., U.S. Pat. No. 5,731,168). Multi-specific antibodies may also be made by engineering electrostatic steering effects for making antibody Fc-heterodimeric molecules (WO 2009/089004A1); controlled Fab-arm exchange (see Labrijn et al., *Proc. Natl. Acad. Sci. USA* 110(13):5145-50 (2013)); cross-linking two or more antibodies or fragments (see, e.g., U.S. Pat. No. 4,676,980, and Brennan et al., *Science*, 229: 81 (1985)); using leucine zippers to produce bi-specific antibodies (see, e.g., Kostelny et al., J. Immunol., 148(5): 1547-1553 (1992)); using "diabody" technology for making bispecific antibody fragments (see, e.g., Hollinger et al., *Proc. Natl. Acad. Sci. USA* 90:6444-6448 (1993)); and using single-chain Fv (sFv) dimers (see, e.g. Gruber et al., *J. Immunol.*, 152:5368 (1994)); and preparing trispecific antibodies as described, e.g., in Tutt et al. *J. Immunol.* 147: 60 (1991).

[278] Binding of the bispecific molecules to their specific targets can be confirmed by, for example, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), FACS analysis, bioassay (e.g., growth inhibition), or Western Blot assay. Each of these assays generally detects the presence of protein-antibody complexes of particular interest by employing a labeled reagent (e.g., an antibody) specific for the complex of interest. For example, the FcR-antibody complexes can be detected using e.g., an enzyme-linked antibody or antibody fragment which recognizes and specifically binds to the antibody-FcR complexes. Alternatively, the complexes can be detected using any of a variety of other immunoassays. For example, the antibody can be radioactively labeled and used in a radioimmunoassay (RIA) (see, for example, Weintraub, B., *Principles of Radioimmunoassays*, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986, which is incorporated by reference herein). The radioactive isotope can be detected by such means as the use of a γ counter or a scintillation counter or by autoradiography.

USES OF ANTAGONIST ANTIBODIES AND PHARMACEUTICAL COMPOSITIONS CONTAINING

Cancer Immunotherapy

[279] Unlike tumor-targeted therapies, which are aimed at inhibiting molecular pathways that are crucial for tumor growth and development, and/or depleting tumor cells, cancer immunotherapy is aimed to stimulate the patient's own immune system to eliminate cancer cells, providing long-lived tumor destruction. Various approaches can be used in cancer immunotherapy, among them are therapeutic cancer vaccines to induce tumor-specific T cell responses, and immunostimulatory antibodies (i.e. antagonists of inhibitory receptors = immune checkpoints) to remove immunosuppressive pathways.

[280] Clinical responses with targeted therapy or conventional anti-cancer therapies tend to be transient as cancer cells develop resistance, and tumor recurrence takes place. However, the clinical use of cancer immunotherapy in the past few years has shown that this type of therapy can have durable clinical responses, showing dramatic impact on long term survival. However, although responses are long term, only a small number of patients

respond (as opposed to conventional or targeted therapy, where a large number of patients respond, but responses are transient).

[281] By the time a tumor is detected clinically, it has already evaded the immune-defense system by acquiring immunoresistant and immunosuppressive properties and creating an immunosuppressive tumor microenvironment through various mechanisms and a variety of immune cells. Thus, in cancer immunotherapy it is becoming increasingly clear that a combination of therapies is be required for clinical efficacy.

[282] Combination approaches are needed and expected to increase the number of patients benefiting from immunotherapy and expand the number and types of cancers that are responsive, expanding the potential cancer indications for checkpoint agents well beyond the initial indications currently showing efficacy of immune checkpoint blockade as monotherapy. The combination of immunomodulatory approaches is meant to maximize the outcomes and overcome the resistance mechanisms of most tumors to a single approach. Thus, tumors traditionally thought of as non-immunogenic can likely become immunogenic and respond to immunotherapy though co-administration of pro-immunogenic therapies designed to increase the patient's anti-tumor immune responses. Potential priming agents are detailed herein below.

[283] The underlying scientific rationale for the dramatic increased efficacy of combination therapy claims that immune checkpoint blockade as a monotherapy will induce tumor regressions only when there is pre-existing strong anti-tumor immune response to be 'unleashed' when the pathway is blocked. According to at least some embodiments of the present invention, VISTA -specific antibodies, antibody fragments, conjugates and compositions comprising same, are used for treatment of all types of cancer in cancer immunotherapy in combination therapy.

[284] The term "treatment" as used herein, refers to both therapeutic treatment and prophylactic or preventative measures, which in this Example relates to treatment inflammatory side effects of cancer; however, also as described below, uses of antibodies and pharmaceutical compositions are also provided for treatment of infectious disease, sepsis, and/or autoimmune conditions, and/or for inhibiting an undesirable immune activation that follows gene therapy. Those in need of treatment include those already with cancer as well as those in which the cancer is to be prevented. Hence, the mammal to be treated herein may have been diagnosed as having the cancer or may be predisposed or susceptible to the cancer. As used herein the term "treating" refers to preventing, delaying the onset of, curing, reversing, attenuating, alleviating, minimizing, suppressing, halting the deleterious effects or stabilizing of discernible symptoms of the above-described cancerous diseases, disorders or conditions. It also includes managing the cancer as described above. By "manage" it is meant reducing the severity of the disease, reducing the frequency of episodes of the disease, reducing the duration of such episodes, reducing the severity of such episodes, slowing/reducing cancer cell growth or proliferation, slowing progression of at least one symptom, amelioration of at least one measurable physical parameter and the

like. For example, immunostimulatory anti-VISTA antibodies should promote T cell or NK or cytokine immunity against target cells, e.g., cancer, infected or pathogen cells and thereby treat cancer or infectious diseases by depleting the cells involved in the disease condition. Agonistic anti-VISTA antibodies should reduce T cell or NK activity and/or or the secretion of proinflammatory cytokines which are involved in the disease pathology of some immune disease such as autoimmune, inflammatory or allergic conditions and thereby treat or ameliorate the disease pathology and tissue destruction that may be associated with such conditions (e.g., joint destruction associated with rheumatoid arthritis conditions).

[285] "Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cows, etc. Preferably, the mammal is human. Preferably the mammal is a human which is diagnosed with one of the disease, disorder or conditions described hereinabove, or alternatively one who is predisposed to at least one type of cancer.

[286] A "therapeutically effective amount" refers to an amount of agent according to the present invention that is effective to treat a disease or disorder in a mammal. The therapeutic agents of the present invention can be provided to the subject alone, or as part of a pharmaceutical composition where they are mixed with a pharmaceutically acceptable carrier.

[287] An anti-VISTA antibody, a fragment, a conjugate thereof as herein described and/or a pharmaceutical composition comprising same, according to at least some embodiments of the present invention also can be administered in combination therapy, i.e., combined with other potentiating agents and/or other therapies. According to at least some embodiments, the anti-VISTA antibody could be used in combination with any of the known in the art standard of care cancer treatment (as can be found, for example, in http://www.cancer.gov/cancertopics).

[288] For example, the combination therapy can include an anti -VISTA antibody, a fragment, a conjugate thereof and/or a pharmaceutical composition comprising same, combined with at least one other therapeutic or immune modulatory agent, other compounds or immunotherapies, or immuno stimulatory strategy as described herein.

[289] Antagonistic anti-VISTA antibodies may be used in combination with agonistic antibodies targeting immune checkpoints including anti-CTLA4 mAbs, such as ipilimumab, tremelimumab; anti-PD-1 such as nivolumab BMS-936558/ MDX-1106/ONO-4538, AMP224, CT-011, MK-3475, anti-PDL-1 antagonists such as BMS-936559/ MDX-1105, MEDI4736, RG-7446/MPDL3280A; Anti-LAG-3 such as IMP-321), anti-TIM-3, anti-BTLA, anti-B7-H4, anti-B7-H3,; Agonistic antibodies targeting immunostimulatory proteins, including anti-CD40 mAbs such as CP-870,893, lucatumumab, dacetuzumab; anti-CD137 mAbs such as BMS-663513 urelumab, PF-05082566; anti-OX40 mAbs, such as anti-OX40; anti-GITR mAbs such as TRX518; anti-CD27 mAbs, such as CDX-1127; and anti-ICOS mAbs.

[290] Cytokines are molecular messengers that allow the cells of the immune system to communicate with one another to generate a coordinated, robust, but self -limited response to a target antigen. Cytokine-based therapies embody a direct attempt to stimulate the patient's own immune system to reject cancer. The growing interest over the past two decades in harnessing the immune system to eradicate cancer has been accompanied by heightened efforts to characterize cytokines and exploit their vast signaling networks to develop cancer treatments. Cytokines directly stimulate immune effector cells and stromal cells at the tumor site and enhance tumor cell recognition by cytotoxic effector cells. Numerous animal tumor model studies have demonstrated that cytokines have broad anti-tumor activity and this has been translated into a number of cytokine -based approaches for cancer therapy (Lee and Margolin 2011, *Cancers* 3(4):3856-93). A number of cytokines are in preclinical or clinical development as agents potentiating anti-tumor immune responses for cancer immunotherapy, including among others: IL-2, IL-7, IL-12, IL-15, IL-17, IL-18 and IL-21, IL-23, IL-27, GM-CSF, IFNα (interferon α), IFNβ, and IFNγ.

[291] Antagonist anti-VISTA antibodies and pharmaceutical compositions containing may also be administered in conjunction with other compounds or immunotherapies. For example, the combination therapy can include a compound of the present invention combined with at least one other therapeutic or immune modulatory agent, or immuno stimulatory strategy, including, but not limited to, tumor vaccines, adoptive T cell therapy, Treg depletion, antibodies (e.g. bevacizumab, Erbitux), peptides, peptibodies, small molecules, chemotherapeutic agents such as cytotoxic and cytostatic agents (e.g. paclitaxel, cisplatin, vinorelbine, docetaxel, gemcitabine, temozolomide, irinotecan, 5FU, carboplatin), immunological modifiers such as interferons and interleukins, immuno stimulatory antibodies, growth hormones or other cytokines, folic acid, vitamins, minerals, aromatase inhibitors, RNAi, Histone Deacetylase Inhibitors, proteasome inhibitors, and so forth.

[292] According to at least some embodiments, immune cells, preferably T cells can be contacted in vivo or ex vivo with the subject therapeutic agents to modulate immune responses. The T cells contacted with the therapeutic agents can be any cell which expresses the T cell receptor, including α/β and γ/δ T cell receptors. T-cells include all cells which express CD3, including T-cell subsets which also express CD4 and CDS. T-cells include both naive and memory cells and effector cells such as CTL. T-cells also include cells such as Th1, Tel, Th2, Th2, Th3, Thl7, Th22, Treg, and Trl cells. T-cells also include NKT-cells and similar unique classes of the T-cell lineage.

USE OF AGONISTIC ANTI-VISTA ANTIBODIES AND PHARMACEUTICAL COMPOSITIONS CONTAINING FOR TREATMENT OF AUTOIMMUNE DISEASE

[293] According to at least some embodiments, anti-VISTA antibodies, fragments, conjugates thereof or a pharmaceutical composition comprising same, as described herein, which function as VISTA stimulating therapeutic agents, may be used for treating an immune system related disease.

[294] Optionally, the immune system related condition comprises an immune related condition, autoimmune diseases as recited herein, transplant rejection and graft versus host disease and/or for blocking or promoting immune stimulation mediated by VISTA, immune related diseases as recited herein and/or for immunotherapy (promoting or inhibiting immune stimulation).

[295] Optionally the immune condition is selected from autoimmune disease, transplant rejection, inflammatory disease, allergic condition or graft versus host disease. Optionally the treatment is combined with another moiety useful for treating immune related condition.

[296] Thus, treatment of multiple sclerosis using the agents according to at least some embodiments of the present invention may be combined with, for example, any known therapeutic agent or method for treating multiple sclerosis, optionally as described herein.

[297] Thus, treatment of rheumatoid arthritis or other arthritic condition, using the subject agonist antibodies may be combined with, for example, any known therapeutic agent or method for treating rheumatoid arthritis, optionally as described herein.

[298] Thus, treatment of IBD, using the using the subject agonist antibodies may be combined with, for example, any known therapeutic agent or method for treating IBD, optionally as described herein.

[299] Thus, treatment of psoriasis, using the subject agonist antibodies may be combined with, for example, any known therapeutic agent or method for treating psoriasis, optionally as described herein.

[300] Thus, treatment of type 1 diabetes using the subject agonist antibodies may be combined with, for example, any known therapeutic agent or method for treating type 1 diabetes, optionally as described herein.

[301] Thus, treatment of uveitis, using the subject agonist antibodies may be combined with, for example, any known therapeutic agent or method for treating uveitis, optionally as described herein.

[302] Thus, treatment of psoriasis using the subject agonist antibodies may be combined with, for example, any known therapeutic agent or method for treating psoriasis, optionally as described herein.

[303] Thus, treatment of Sjögren's syndrome, using the subject agonist antibodies may be combined with, for example, any known therapeutic agent or method for treating for Sjögren's syndrome, optionally as described herein.

[304] Thus, treatment of systemic lupus erythematosus, using the subject agonist antibodies may be combined with, for example, any known therapeutic agent or method for treating for systemic lupus erythematosus, optionally as described herein.

[305] Thus, treatment of GVHD, using the subject agonist antibodies may be combined with, for example, any known therapeutic agent or method for treating GVHD, optionally as described herein.

[306] Thus, treatment of chronic or acute infection and/or hepatotoxicity associated therewith, e.g., hepatitis, using the subject agonist antibodies may be combined with, for example, any known therapeutic agent or method for treating for chronic or acute infection and/or hepatotoxicity associated therewith, optionally as described herein.

[307] In the above-described therapies preferably a subject with one of the aforementioned or other autoimmune or inflammatory conditions will be administered an immmunoinhibitory anti-VISTA antibody disclosed herein or antigen-binding fragment according to the invention, which antibody mimics or agonizes at least one VISTA- mediated effect on immunity, e.g., it suppresses cytotoxic T cells, or NK activity and/or the production of proinflammatory cytokines which are involved in the disease pathology, thereby preventing or ameliorating the disease symptoms and potentially resulting in prolonged disease remission, e.g., because of the induction of Tregs which elicit T cell tolerance or prolonged immunosuppression.

[308] The therapeutic agents and/or a pharmaceutical composition comprising same, as recited herein, according to at least some embodiments of the invention, may be administered as the sole active ingredient or together with other drugs in immunomodulating regimens or other anti-inflammatory agents e.g. for the treatment or prevention of allo- or xenograft acute or chronic rejection or inflammatory or autoimmune disorders, or to induce tolerance.

USE OF AGONISTIC ANTI-VISTA ANTIBODIES AND PHARMACEUTICAL COMPOSITIONS CONTAINING FOR TREATMENT OF SEPSIS

[309] According to at least some embodiments, VISTA antibodies, fragments, conjugates thereof and/or pharmaceutical compositions as described herein, may be used for treating sepsis. Sepsis is a potentially life-threatening complication of an infection. Sepsis represents a complex clinical syndrome that develops when the initial host response against an infection becomes inappropriately amplified and dysregulated, becoming harmful to the host. The initial hyperinflammatory phase ('cytokine storm') in sepsis is followed by a state of immunosuppression (Hotchkiss et al 2013 *Lancet Infect*. Dis. 13:260-268). This latter phase of impaired immunity, also referred to as 'immunoparalysis', is manifested in failure to clear the primary infection, reactivation of viruses such as HSV and cytomegalovirus, and development of new, secondary infections, often with organisms that are not particularly virulent to the immunocompetent patient. The vast majority of septic patients today survive their initial hyperinflammatory insult only to end up in the intensive care unit with sepsis-induced multi-organ dysfunction over the ensuing days to weeks. Sepsis-induced immunosuppression is increasingly recognized as the overriding immune dysfunction in these vulnerable patients. The impaired pathogen clearance after primary infection and/or

susceptibility to secondary infections contribute to the high rates of morbidity and mortality associated with sepsis.

[310] According to at least some embodiments of the present invention, there is provided use of a combination of the therapeutic agents and/or a pharmaceutical composition comprising same, as recited herein, and a known therapeutic agent effective for treating sepsis.

[311] According to at least some embodiments of the present invention, there is provided use of a combination of the therapeutic agents and/or a pharmaceutical composition comprising same, as recited herein, can be combined with standard of care or novel treatments for sepsis, with therapies that block the cytokine storm in the initial hyperinflammatory phase of sepsis, and/or with therapies that have immunostimulatory effect in order to overcome the sepsis-induced immunosuppression phase.

[312] Combination with standard of care treatments for sepsis, as recommended by the "International Guidelines for Management of Severe Sepsis and Septic Shock" (Dellinger et al 2013 *Intensive Care Med* 39: 165-228), some of which are described below.

1. Broad spectrum antibiotics having activity against all likely pathogens (bacterial and/or fungal - treatment starts when sepsis is diagnosed, but specific pathogen is not identified) - example Cefotaxime (Claforan®), Ticarcillin and clavulanate (Timentin®), Piperacillin and tazobactam (Zosyn®), Imipenem and cilastatin (Primaxin®), Meropenem (Merrem®), Clindamycin (Cleocin), Metronidazole (Flagyl®), Ceftriaxone (Rocephin®), Ciprofloxacin (Cipro®), Cefepime (Maxipime®), Levofloxacin (Levaquin®), Vancomycin or any combination of the listed drugs.
2. Vasopressors: example Norepinephrine, Dopamine, Epinephrine, vasopressin
3. Steroids: example: Hydrocortisone, Dexamethasone, or Fludrocortisone, intravenous or otherwise Inotropic therapy: example Dobutamine for sepsis patients with myocardial dysfunction
4. Recombinant human activated protein C (rhAPC), such as drotrecogin alfa (activated) (DrotAA).
5. β-blockers additionally reduce local and systemic inflammation.
6. Metabolic interventions such as pyruvate, succinate or high dose insulin substitutions.

USE OF ANTI-VISTA ANTIBODIES AND PHARMACEUTICAL COMPOSITIONS CONTAINING FOR REDUCING THE UNDESIRABLE IMMUNE ACTIVATION THAT FOLLOWS GENE OR CELL THERAPY OR TRANSPLANT

[313] As used herein the term "gene therapy" encompasses any type of gene therapy, vector-mediated gene therapy, gene transfer, virus-mediated gene transfer and further encompasses certain cell therapies, e.g., CAR T and CAR NK cell therapies. According to at least some embodiments of the present invention, agonist VISTA antibodies, a fragment, a

conjugate thereof and/or a pharmaceutical compositions as described herein, which target VISTA and have inhibitory activity on immune responses, could be used as therapeutic agents for reducing the undesirable immune activation that follows gene or cell therapy used for treatment of various genetic diseases. Without wishing to be limited by a single hypothesis, such antibodies have VISTA-like inhibitory activity on immune responses and/or enhance VISTA immune inhibitory activity, optionally by inhibition of pathogenic T cells and/or NK cells.

[314] Many gene therapy products for the treatment of genetic diseases are currently in clinical trials. Recent studies document therapeutic success for several genetic diseases using gene therapy vectors. Gene therapy strategies are characterized by 3 critical elements, the gene to be transferred, the target tissue into which the gene will be introduced, and the vector (gene delivery vehicle) used to facilitate entry of the gene to the target tissue. The vast majority of gene therapy clinical trials have exploited viral vectors as very efficient delivery vehicles, including retroviruses, lentiviruses, adenoviruses, adeno-associated viruses, pseudotype viruses and herpes simplex viruses. However, the interactions between the human immune system and all the components of gene therapy vectors seem to represent one of the major limitations to long-lasting therapeutic efficacy. Human studies have shown that the likelihood of a host immune response to the viral vector is high. Such immune responses to the virus or the transgene product itself, resulting in formation of neutralizing antibodies and/or destruction of transduced cells by cytotoxic cells, can greatly interfere with therapeutic efficacy (Seregin and Amalfitano 2010 *Viruses* 2:2013; Mingozzi and High 2013 Blood 122:23; Masat et al 2013 *Discov Med*. 15:379). Therefore, developing strategies to circumvent immune responses and facilitate long-term expression of transgenic therapeutic proteins is one of the main challenges for the success of gene therapy in the clinic.

[315] Factors influencing the immune response against transgenic proteins encoded by viral vectors include route of administration, vector dose, immunogenicity of the transgenic protein, inflammatory status of the host and capsid serotype. These factors are thought to influence immunogenicity by triggering innate immunity, cytokine production, APC maturation, antigen presentation and, ultimately, priming of naive T lymphocytes to functional effectors (Mingozzi and High 2013 *Blood* 122:23). Therefore, the idea to dampen immune activation by interfering with these very mechanisms has logically emerged with the aim to induce a short-term immunosuppression, avoid the early immune priming that follows vector administration and promote long-term tolerance.

[316] As a strategy to inhibit the undesirable immune activation that follows gene therapy, particularly after multiple injections, immunomodulation treatment by targeting of two non-redundant checkpoints of the immune response at the time of vector delivery was tested in animal models. Studies of vector-mediated immune responses upon adenoviral vector instilled into the lung in mice or monkeys showed that transient treatment with an anti-CD40L antibody lead to suppression of adenovirus-induced immune responses;

consequently, the animals could be re-administered with adenovirus vectors. Short treatment with this Ab resulted in long-term effects on immune functions and prolonged inhibition of the adenovirus -specific humoral response well beyond the time when the Ab effects were no longer significant, pointing to the therapeutic potential in blockade of this costimulatory pathway as an immunomodulatory regimen to enable administration of gene transfer vectors (Scaria et al. 1997 *Gene Ther*. 4: 611; Chirmule et al 2000 *J. Virol*. 74: 3345). Other studies showed that co-administration of CTLA4-Ig and an anti-CD40L Ab around the time of primary vector administration decreased immune responses to the vector, prolonged long term adenovirus-mediated gene expression and enabled secondary adenovirus-mediated gene transfer even after the immunosuppressive effects of these agents were no longer present, indicating that it may be possible to obtain persistence as well as secondary adenoviral-mediated gene transfer with transient immunosuppressive therapies (Kay et al 1997 *Proc. Natl. Acad. Sci. U. S. A.* 94:4686). In another study, similar administration of CTLA4-Ig and an anti-CD40L Ab abrogated the formation of neutralizing Abs against the vector, and enabled gene transfer expression, provided the treatment was administered during each gene transfer injection (Lorain et al 2008 *Molecular Therapy* 16:541). Furthermore, administration of CTLA4-Ig to mice, even as single administration, resulted in suppression of immune responses and prolonged transgene expression at early time points (Adriouch et al 2011 *Front. Microbiol*. 2: 199). However, CTLA4-Ig alone was not sufficient to permanently wipe out the immune responses against the transgene product. Combined treatment targeting two immune checkpoints with CTLA4-Ig and PD-L1 or PDL-2 resulted in synergistic improvement of transgene tolerance at later time points, by probably targeting two non-redundant mechanisms of immunomodulation, resulting in long term transgene persistence and expression (Adriouch et al 2011 *Front. Microbiol*. 2: 199).

[317] According to at least some embodiments of the present invention, the subject agonists may be used to overcome the limitation of immune responses to gene therapy, could be used for reducing the undesirable immune activation that follows gene therapy alone or with other actives. Current approaches include exclusion of patients with antibodies to the delivery vector, administration of high vector doses, use of empty capsids to adsorb anti-vector antibodies allowing for subsequent vector transduction, repeated plasma exchange (plasmapheresis) cycles to adsorb immunoglobulins and reduce the anti-vector antibody titer.

[318] Novel approaches attempting to overcome these limitations can be divided into two broad categories: selective modification of the Ad vector itself and pre-emptive immune modulation of the host (Seregin and Amalfitano 2010 *Viruses* 2:2013). The first category comprises several innovative strategies including: (1) Ad-capsid-display of specific inhibitors or ligands; (2) covalent modifications of the entire Ad vector capsid moiety; (3) the use of tissue specific promoters and local administration routes; (4) the use of genome modified Ads; and (5) the development of chimeric or alternative serotype Ads.

[319] The second category of methods includes the use of immunosuppressive drugs or specific compounds to block important immune pathways, which are known to be induced by viral vectors. Immunosuppressive agents have been tested in preclinical studies and shown efficacy in prevention or eradication of immune responses to the transfer vector and transgene product. These include general immunosuppressive agents such as cyclosporine A; cyclophosphamide; FK506; glucocorticoids or steroids such as dexamethasone; TLR9 blockade such as the TLR9 antagonist oligonucleotide ODN-2088; TNF-a blockade with anti-TNF-a antibodies or TNFR-Ig antibody, Erk and other signaling inhibitors such as U0126. In the clinical setting, administration of glucocorticoids has been successfully used to blunt T cell responses directed against the viral capsid upon liver gene transfer of adenovirus-associated virus (AAV) vector expressing human factor IX transgene to severe hemophilia B patients (Nathwani et al 2011 *N. Engl. J. Med*. 365:2357).

[320] In contrast to the previous approaches that utilize drugs that tend to "globally" and non- specifically immunosuppress the host, more selective immunosuppressive approaches have been developed. These include the use of agents which provide blockade of positive co-stimulatory interactions, such as between CD40 and CD154, ICOS and ICOSL, CD28 and CD80 or CD86 (including CTLA4-Ig), NKG2D and NKG2D ligands, LFA-1 and ICAM, LFA-3 and CD2, 4-1BB and 4-1BBL, OX40 and OX40L, GITR and GITRL and agents that stimulate negative costimulatory receptors such as CTLA-4, PD-1, BTLA, LAG-3, TIM-1, TEVI-3, KIRs, and the receptors for B7-H4 and B7-H3. Some of these have been utilized in preclinical or clinical transplantation studies (Pilat et al 2011 *Sem. Immunol*. 23:293).

[321] In the above-described gene or cell therapies or in treating transplant indications preferably a subject who has or is to receive cell or gene therapy or a transplanted tissue or organ will be administered an immmunoinhibitory anti-VISTA antibody disclosed herein or antigen-binding fragment according to the invention, which antibody enhances, agonizes or mimics at least one VISTA-mediated effect on immunity, e.g., its inhibitory effect on cytotoxic T cells or NK activity and/or its inhibitory effect on the production of proinflammatory cytokines, or its stimulatory effect on Tregs thereby preventing or reducing host immune responses against the cell or gene used in therapy or an undesired immune response against the transplanted cells, organ or tissue. Preferably the treatment will elicit prolonged immune tolerance against the transplanted or infused cells, tissue or organ. In some instances, e.g., in the case of transplanted cells, tissues or organs containing immune cells, the immmunoinhibitory anti-VISTA antibody disclosed herein or antigen-binding fragment may be contacted with the cells, tissue or organ prior to infusion or transplant, and/or potentially immune cells of the transplant recipient in order to tolerize the immune cells and potentially prevent an undesired immune response or GVHD immune reaction.

PHARMACEUTICAL COMPOSITIONS

[322] In another aspect, the present invention provides a composition, e.g., a pharmaceutical composition, containing one or a combination of anti-human VISTA

antibodies according to the invention and optionally another immunosuppressive or other active agent. Thus, the present invention features a pharmaceutical composition comprising a therapeutically effective amount of anti-human VISTA antibodies according to at least some embodiments of the present invention. In particular the present invention features a pharmaceutical composition comprising a therapeutically effective [immunosuppressive] amount of at least one agonist anti-human VISTA antibody or antibody fragment according to the present invention

[323] A pharmaceutical composition according to at least some embodiments of the present invention [i.e., in the case of VISTA antagonist antibodies disclosed herein] may be used for the treatment of cancer, wherein the cancer is non-metastatic, invasive or metastatic, and/or for treatment of immune related disorders, autoimmunity, allergy, GVHD, inflammation or hepatotoxicity associated with infectious disorder and/or sepsis [i.e., in the case of VISTA agonist antibodies disclosed herein]. "Treatment" refers to both therapeutic treatment and prophylactic or preventative measures. Those in need of treatment include those already with the disorder as well as those in which the disorder is to be prevented. Hence, the mammal to be treated herein may have been diagnosed as having the disorder or may be predisposed or susceptible to the disorder. "Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cows, etc. Preferably, the mammal is human.

[324] The term "therapeutically effective amount" refers to an amount of agent according to the present invention that is effective to treat a disease or disorder in a mammal. The therapeutic agents of the present invention can be provided to the subject alone or as part of a pharmaceutical composition where they are mixed with a pharmaceutically acceptable carrier. In many instances agonist or antagonist anti-VISTA antibodies according to the invention will be used in combination with other immunotherapeutics or other therapeutic agents useful in treating a specific condition.

[325] A composition is said to be a "pharmaceutically acceptable carrier" if its administration can be tolerated by a recipient patient. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Preferably, the carrier is suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (e.g., by injection or infusion).

[326] Such compositions include sterile water, buffered saline (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength and optionally additives such as detergents and solubilizing agents (e.g., Polysorbate 20, Polysorbate 80), antioxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimersol, benzyl alcohol) and bulking substances (e.g., lactose, mannitol). Non-aqueous solvents or vehicles may also be used as detailed below.

[327] Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions according to at least some embodiments of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. Depending on the route of administration, the active compound, i.e., monoclonal or polyclonal antibodies and antigen-binding fragments and conjugates containing same, and/or alternative scaffolds, that specifically bind any one of VISTA proteins, or bispecific molecule, may be coated in a material to protect the compound from the action of acids and other natural conditions that may inactivate the compound. The pharmaceutical compounds according to at least some embodiments of the invention may include one or more pharmaceutically acceptable salts. A "pharmaceutically acceptable salt" refers to a salt that retains the desired biological activity of the parent compound and does not impart any undesired toxicological effects (see e.g., Berge, S. M., et al. (1977) *J. Pharm. Sci.* 66: 1-19). Examples of such salts include acid addition salts and base addition salts. Acid addition salts include those derived from nontoxic inorganic acids, such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, phosphorous and the like, as well as from nontoxic organic acids such as aliphatic mono-and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, aromatic acids, aliphatic and aromatic sulfonic acids and the like. Base addition salts include those derived from alkaline earth metals, such as sodium, potassium, magnesium, calcium and the like, as well as from nontoxic organic amines, such as N,N'-dibenzylethylenediamine, N-methylglucamine, chloroprocaine, choline, diethanolamine, ethylenediamine, procaine and the like.

[328] A pharmaceutical composition according to at least some embodiments of the invention also may include a pharmaceutically acceptable anti-oxidant. Examples of pharmaceutically acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, a-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[329] These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of presence of microorganisms may be ensured both by sterilization procedures, supra, and by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the

injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[330] Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions according to at least some embodiments of the invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[331] Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin. Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by sterilization microfiltration. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying (lyophilization) that yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[332] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by sterilization microfiltration. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying (lyophilization) that yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[333] A composition of the present invention can be administered via one or more routes of administration using one or more of a variety of methods known in the art. As will

be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. Preferred routes of administration for therapeutic agents according to at least some embodiments of the invention include intravascular delivery (e.g. injection or infusion), intravenous, intramuscular, intradermal, intraperitoneal, subcutaneous, spinal, oral, enteral, rectal, pulmonary (e.g. inhalation), nasal, topical (including transdermal, buccal and sublingual), intravesical, intravitreal, intraperitoneal, vaginal, brain delivery (e.g. intra-cerebroventricular, intracerebral, and convection enhanced diffusion), CNS delivery (e.g. intrathecal, perispinal, and intra-spinal) or parenteral (including subcutaneous, intramuscular, intravenous and intradermal), transmucosal (e.g., sublingual administration), administration or administration via an implant, or other parenteral routes of administration, for example by injection or infusion, or other delivery routes and/or forms of administration known in the art. The phrase "parenteral administration" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion. In a specific embodiment, a protein, a therapeutic agent or a pharmaceutical composition according to at least some embodiments of the present invention can be administered intraperitoneally or intravenously.

[334] Alternatively, an VISTA specific antibody according to the invention can be administered via a non-parenteral route, such as a topical, epidermal or mucosal route of administration, for example, intranasally, orally, vaginally, rectally, sublingually or topically.

[335] The active compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are patented or generally known to those skilled in the art. See, e.g., *Sustained and Controlled Release Drug Delivery Systems*, J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

[336] Therapeutic compositions can be administered with medical devices known in the art. For example, in a preferred embodiment, a therapeutic composition according to at least some embodiments of the invention can be administered with a needles hypodermic injection device, such as the devices disclosed in U.S. Pat. Nos. 5,399,163; 5,383,851; 5,312,335; 5,064,413; 4,941,880; 4,790,824; or 4,596,556. Examples of well-known implants and modules useful in the present invention include: U.S. Pat. No. 4,487,603, which discloses an implantable micro-infusion pump for dispensing medication at a controlled rate; U.S. Pat. No. 4,486,194, which discloses a therapeutic device for administering medicaments through the skin; U.S. Pat. No. 4,447,233, which discloses a medication

infusion pump for delivering medication at a precise infusion rate; U.S. Pat. No. 4,447,224, which discloses a variable flow implantable infusion apparatus for continuous drug delivery; U.S. Pat. No. 4,439,196, which discloses an osmotic drug delivery system having multi-chamber compartments; and U.S. Pat. No. 4,475,196, which discloses an osmotic drug delivery system. These patents are incorporated herein by reference. Many other such implants, delivery systems, and modules are known to those skilled in the art.

[337] In certain embodiments, the anti-VISTA antibodies can be formulated to ensure proper distribution in vivo. For example, the blood-brain barrier (BBB) excludes many highly hydrophilic compounds. To ensure that the therapeutic compounds according to at least some embodiments of the invention cross the BBB (if desired), they can be formulated, for example, in liposomes. For methods of manufacturing liposomes, see, e.g., U.S. Pat. Nos. 4,522,811; 5,374,548; and 5,399,331. The liposomes may comprise one or more moieties which are selectively transported into specific cells or organs, thus enhance targeted drug delivery (see, e.g., V. V. Ranade (1989) *J. Clin. Pharmacol*. 29:685). Exemplary targeting moieties include folate or biotin (see, e.g., U.S. Pat. No. 5,416,016 to Low et al.); mannosides (Umezawa et al., (1988) *Biochem. Biophys. Res. Commun*. 153: 1038); antibodies (P. G. Bloeman et al. (1995) *FEBS Lett*. 357: 140; M. Owais et al. (1995) *Antimicrob. Agents Chemother*. 39: 180); surfactant protein A receptor (Briscoe et al. (1995) *Am. J Physiol*. 1233: 134); pl20 (Schreier et al. (1994) *J. Biol. Chem*. 269:9090); see also K. Keinanen; M. L. Laukkanen (1994) *FEBS Lett*. 346: 123; J. J. Killion; and I. J. Fidler (1994) *Immunomethods* 4:273.

[338] In yet another embodiment, immunoconjugates of the invention can be used to target compounds (e.g., therapeutic agents, labels, cytotoxins, radiotoxins immunosuppressants, etc.) to cells which have VISTA cell surface receptors by linking such compounds to the antibody disclosed herein. Thus, the invention also provides methods for localizing *ex vivo* or *in vivo* cells expressing VISTA (e.g., with a detectable label, such as a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor). Alternatively, the immunoconjugates can be used to kill cells which have VISTA cell surface receptors by targeting cytotoxins or radiotoxins to VISTA antigen.

[339] As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Preferably, the carrier is suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (e.g., by injection or infusion). Depending on the route of administration, the active compound, i.e., soluble polypeptide conjugate containing the ectodomain of the VISTA antigen, antibody, immunoconjugate, alternative scaffolds, and/or bispecific molecule, may be coated in a material to protect the compound from the action of acids and other natural conditions that may inactivate the compound. The pharmaceutical compounds according to at least some embodiments of the present invention may include one or more pharmaceutically acceptable salts. A "pharmaceutically acceptable salt" refers

to a salt that retains the desired biological activity of the parent compound and does not impart any undesired toxicological effects (see e.g., Berge, S. M., et al. (1977) *J. Pharm. Sci.* 66: 1-19). Examples of such salts include acid addition salts and base addition salts. Acid addition salts include those derived from nontoxic inorganic acids, such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, phosphorous and the like, as well as from nontoxic organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, aromatic acids, aliphatic and aromatic sulfonic acids and the like. Base addition salts include those derived from alkaline earth metals, such as sodium, potassium, magnesium, calcium and the like, as well as from nontoxic organic amines, such as N,N'-dibenzylethylenediamine, N-methylglucamine, chloroprocaine, choline, diethanolamine, ethylenediamine, procaine and the like.

[340] A pharmaceutical composition according to at least some embodiments of the present invention also may include a pharmaceutically acceptable anti-oxidant. Examples of pharmaceutically acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, a-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like. Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions according to at least some embodiments of the present invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[341] These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of presence of microorganisms may be ensured both by sterilization procedures, supra, and by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[342] Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions

according to at least some embodiments of the present invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[343] Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin. Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by sterilization microfiltration. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying (lyophilization) that yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[344] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by sterilization microfiltration. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze - drying (lyophilization) that yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[345] The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the subject being treated, and the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the composition which produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 0.01 per cent to about ninety-nine percent of active ingredient, preferably from about 0.1 per cent to about 70 per cent, most preferably from about I per cent to about 30 per cent of active ingredient in combination with a pharmaceutically acceptable carrier.

[346] Dosage regimens are adjusted to provide the optimum desired response (e.g., a therapeutic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms according to at least some embodiments of the present invention are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

[347] For administration of the VISTA antibody disclosed herein, the dosage ranges from about 0.0001 to 100 mg/kg, and more usually 0.01 to 5 mg/kg, of the host body weight. For example dosages can be 0.3 mg/kg body weight, 1 mg/kg body weight, 3 mg/kg body weight, 5 mg/kg body weight or 10 mg/kg body weight or within the range of 1-10 mg/kg. An exemplary treatment regime entails administration once per week, once every two weeks, once every three weeks, once every four weeks, once a month, once every 3 months or once every three to 6 months. Preferred dosage regimens for an antibody disclosed herein according to at least some embodiments of the present invention include 1 mg/kg body weight or 3 mg/kg body weight via intravenous administration, with the antibody disclosed herein being given using one of the following dosing schedules: (i) every four weeks for six dosages, then every three months; (ii) every three weeks; (iii) 3 mg/kg body weight once followed by 1 mg/kg body weight every three weeks.

[348] In some methods, two or more monoclonal antibodies with different binding specificities are administered simultaneously in which case the dosage of each antibody disclosed herein administered falls within the ranges indicated. Antibody disclosed herein is usually administered on multiple occasions. Intervals between single dosages can be, for example, daily, weekly, monthly, every three months or yearly. Intervals can also be irregular as indicated by measuring blood levels of antibody to the target antigen in the patient. In some methods, dosage is adjusted to achieve a plasma antibody concentration of about 1-1000 mug/ml and in some methods about 25-300 microgram /ml.

[349] Alternatively, therapeutic agent can be administered as a sustained release formulation, in which case less frequent administration is required. Dosage and frequency vary depending on the half-life of the therapeutic agent in the patient. In general, human antibodies show the longest half-life, followed by humanized antibodies, chimeric antibodies, and nonhuman antibodies. The half-life for fusion proteins may vary widely. The dosage and frequency of administration can vary depending on whether the treatment is

prophylactic or therapeutic. In prophylactic applications, a relatively low dosage is administered at relatively infrequent intervals over a long period of time. Some patients continue to receive treatment for the rest of their lives. In therapeutic applications, a relatively high dosage at relatively short intervals is sometimes required until progression of the disease is reduced or terminated, and preferably until the patient shows partial or complete amelioration of symptoms of disease. Thereafter, the patient can be administered a prophylactic regime.

[350] Actual dosage levels of the active ingredients in the pharmaceutical compositions of the present invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. The selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[351] Having described the invention the following examples are provided to further illustrate the invention and its inherent advantages.

EXAMPLES

EXAMPLE 1: Use of Assays to Screen for Immunosuppressive Anti-Mouse VISTA Abs

[352] The present inventors developed various assays to screen for putative agonistic anti-mouse VISTA antibodies. As shown in **Figure 1** in vitro and in vivo screening assays were used to identify immunosuppressive anti-VISTA mAbs. In the experiments in **Figure 1A** purified T cells were plated on top of anti-CD3 in the presence of the indicated mAb for 72 hours. Proliferation was measured by H3 incorporation. In the experiments in **Figure 1B** purified DO11.10 T cells were stimulated by ISQ pulsed APCs for 6 days in the presence of the indicated antibody. Proliferation was measured through use of CTV dilution dye. In the experiments in Figure 1C GVHD was induced by transfer of C57BL/6 cells into irradiated BALB/c recipients. Mice were injected I.P. with 200 μg of antibody on day 0, 2 and 4 post transfer and survival was analyzed. In the experiments in Figure 1D mice were treated with 10 mpk of the indicated antibody 3 hours prior to administration of ConA (15 mpk) and IL-2 was analyzed in plasma at 6 by Luminex.

[353] More particularly, in the first assay, $CD4^+$ T cells were isolated and incubated with Ab1, Ab2 or Ab3 before being added to anti-CD3 coated plates. After 3 days in culture, the T cells were pulsed with tritiated thymidine, which is incorporated by proliferating cells.

Notably, both Ab1 and Ab2 induced a significant reduction in the proliferative rate of the T cells, while Ab3 had no effect (**Figure 1**) In a similar assay where transgenic T cells were stimulated with antigen pulsed APCs instead, T cell activation was measured by proliferative dye dilution. Similar to the anti-CD3 assay, Ab1 suppressed antigen-specific T cell proliferation by ~50% (**Figure 1B**). These data indicate that the Ab3 mAb blocks mVISTA function (i.e., enhances immune responses) whereas Ab1 and Ab3 stimulate mVISTA function and down regulate key immune responses.

[354] We also determined whether Ab3 and Ab1 could be distinguished using in vivo animal models, particularly in GVHD and ConA hepatitis models. Mice with GVHD which were treated with a control antibody (Ham Ig) had progressive disease and needed to be euthanized by 4 weeks post graft as expected (**Figure 1C**). Ab3 treated mice were also susceptible to GVHD, and in fact most mice died prior to the control treated group, indicating Ab3 may exacerbate disease. Conversely, all of the Ab1 treated mice showed no obvious symptoms of GVHD and almost all were healthy for at least 40 days. Specifically in these experiments mice with GVHD treated with a control antibody (Ham Ig) had progressive disease and needed to be euthanized by 4 weeks post graft as expected (**Figure 1C**). Ab3 treated mice were also susceptible to GVHD, and in fact most mice died prior to the control treated group, indicating Ab3 may exacerbate disease. Conversely, all of the Ab1 treated mice showed no obvious symptoms of GVHD and almost all were healthy for at least 40 days.

[355] In the ConA model, the inventors tested whether each VISTA antibody would impact the well-characterized T cell cytokine response to ConA. Notably Ab1, but not Ab3, induced decreased plasma cytokine levels of IL-2 (**Figure 1D**). Specifically, in the ConA model, the inventors further tested whether each VISTA antibody would impact the well-characterized T cell cytokine response to ConA. Notably Ab1, but not Ab3, induced decreased plasma cytokine levels of IL-2 (**Figure 1D**).

[356] Accordingly these results demonstrate that both anti-VISTA mAbs (Ab1 and Ab2) are immunosuppressive and it has also been shown that such immunosuppressive anti-mouse VISTA antibodies can be distinguished from inflammatory immunosuppressive anti-mouse VISTA antibodies (Ab3). As shown in **Figure 1** Ab1 is efficacious (immunosuppressive) in multiple inflammatory models including GVHD, NZB/W F1 lupus-like glomerulonephritis, concanavalin A (ConA)-induced hepatitis, collagen antibody induced arthritis (CAIA), and Imiquimod induced psoriasis. In each of these diseases, administration of Ab1 during the progression of disease greatly diminished pathology and/or mortality. Each model listed has a unique requirement on T cells for disease progression. GVHD and ConA are both driven by Th1 T cell responses.

EXAMPLE 2: Identification of Anti-VISTA Abs Which Suppresses Autoimmunity in Different Autoimmune Disease Models

[357] In the experiments in **Figure 2A-F** the effects of different anti-mouse VISTA Abs were again compared in different disease models. In the experiments in **Figure 2A** NZB/W F1 mice were treated 3X/week with either Ab1 or Ham Ig (200 μg) starting at 25 weeks until the end of the experiment. "X" denotes time points where the control treated group had all been sacrificed. In the experiment in **Figure 2B** mice were treated with 200 μg of antibody 3 hours prior to administration of 15 mg/kg (mpk) of ConA and survival was followed for 80 hours. In the experiment in **Figure 2C** mice were treated sequentially with Collagen II mAb followed by LPS and arthritis was measured by measuring for paw swelling. In the experiments Ab1 and Ham-Ig were administered (200 μg) 3X every other day. In the experiment in **Figure 2D** Imiquimod was applied to the ear of mice daily. At day 14, Ab1 or Ham-Ig (200 μg) were administered every other day and ear thickness was measured with calipers. In the experiment in the same **Figure 2E-F** imiquimod was applied to the backs of mice daily. At day 9, mice were euthanized and skin was sectioned & stained for CD3 expression by IHC.

[358] As shown in **Figure 2A-F**, in each of these experimental models, administration of Ab1 during the progression of the particular disease greatly diminished pathology and/or mortality. Each model listed has a unique requirement on T cells for disease progression. GVHD and ConA are both driven by Th1 T cell responses.

[359] Imiquimod induced psoriasis is an IL-17/23 driven disease where T cells are recruited into the dermal layer of the skin. Ab1 drastically reduced the number of $CD3^+$ cells in the dermis (Figure 2E and F), but had no impact on splenic T cell populations (data not shown), indicating that this anti-mouse VISTA Ab preferentially suppressed immunity at the inflammatory lesion.

[360] NZB/W F1 lupus is a multifactorial disease with contributions from B cells, T cells and myeloid cells. In this model, therapeutic administration of Ab1 reduced proteinuria levels indicating decreased damage to the kidneys. Finally, CAIA does not involve adaptive immunity, instead being driven by macrophages and granulocytes. Suppression by anti-VISTA in this model indicates that the antibody may also impact upon the myeloid compartment. As such, suppressive VISTA mAb appear to mediate effects on both the T cell and innate immune compartments.

[361] Therefore, as shown in **Figure 1** and **Figure 2** both monoclonal hamster anti-mouse VISTA Abs Ab1 and AB2 induced a significant reduction in the proliferative rate of the T cells, while Ab3 had no effect (**Figure 1**). In a similar assay where transgenic T cells were stimulated with antigen pulsed APCs, T cell activation was measured by proliferative dye dilution. Similar to the anti-CD3 assay, Ab1 suppressed antigen-specific T cell proliferation by ~50% (**Figure 1B**). These data suggest that Ab1 and Ab2 stimulate VISTA function and thereby down regulate key immune responses.

[362] Particularly, Ab1, a hamster anti-mouse VISTA antibody was efficacious in multiple inflammatory models including GVHD, NZB/W F1 lupus-like glomerulonephritis,

concanavalin A (ConA)-induced hepatitis, collagen antibody induced arthritis (CAIA), and Imiquimod induced psoriasis (Figures 1 and 2). In each of these diseases, administration of Ab1 during the progression of disease greatly diminished pathology and/or mortality. Each model listed has a unique requirement on T cells for disease progression. GVHD and ConA are both driven by Th1 T cell responses. As noted above, Imiquimod induced psoriasis is an IL-17/23 driven disease where T cells are recruited into the dermal layer of the skin. Therefore, suppression by Ab1 in this particular autoimmune model indicates that this antibody may also be affecting the myeloid compartment. Therefore, these immunosuppressive anti-mouse VISTA mAb's appear to mediate effects on both the T cell and innate immune compartments.

EXAMPLE 3: Development of Human VISTA Knock-in mice for Use in Screening for Agonistic Anti-Human VISTA Abs

[363] The previous examples relate to the isolation and characterization of agonistic anti-mouse VISTA Abs. Heretofore an agonistic anti-human VISTA Ab has never been reported in the literature. This is despite the fact that very many antagonistic anti-human VISTA antibodies have been identified by the present Assignee and other groups. Accordingly, prior to this invention it was uncertain whether agonistic anti-human VISTA antibodies would be identified.

[364] Such antibodies would be highly beneficial as currently there is no approved human therapeutics that exploit the natural function of NCR's to suppress the immune response. Although Orencia (CTLA4-Ig) is effective, it only acts by blocking the CD28-B7 interaction and pathway and does not work by stimulating a downregulatory pathway. As illustrated by the potent immunosuppressive effects of 2 different agonistic anti-VISTA mAbs as shown in the examples which follow, the engagement of this pathway may prove to be a revolution in the management of different human autoimmune diseases. Moreover, the immunosuppressive impact of anti-VISTA on both adaptive and innate autoimmune effector mechanisms sets it apart from many other anti-inflammatory agents.

[365] With respect to the foregoing, it was hypothesized that a desirable and necessary reagent in screening for agonistic anti-human VISTA Abs is a human VISTA knock-in mouse. A human VISTA knock-in mouse has been created by the present Assignee ("hV-KI Mouse"). These hV-KI mice express human VISTA in replacement of mouse VISTA. Particularly, as shown in **Figure 3** $CD4^+$ T cells, $CD8^+$ T cells, Tregs ($CD4^+$ $FoxP3^+$), and monocytes, $CD11b^+$, $Ly6C^+$, $Ly6G^-$ were isolated from the lymph nodes of WT and VISTA KI mice, and stained with αVISTA antibodies against mouse or human protein respectively. The expression pattern of the hV-KI is identical to what is seen in WT mice as $CD4^+$ and $CD8^+$ T cells, regulatory T cells and monocytes all express consistent amounts of surface protein between the two strains (see **Figure 3**).

[366] Additionally, hV-KI mice do not develop any signs of inflammatory disease that are observed in VISTA KO mice, indicating that hVISTA is fully functional within the mouse immune system (data not shown). Accordingly, this mouse model may be used in different assays to screen for immunosuppressive mAbs.

EXAMPLE 4: Synthesis Of Putative Agonistic Anti-Human VISTA Antibodies

[367] The sequences of different anti-human VISTA antibodies is contained in **Figure 4**. These antibodies specifically bind to human VISTA, e.g., VSTB49-VSTB116, and possess VISTA antagonist properties, i.e., these antibodies inhibit the suppressive effects of VISTA on immunity when in the IgG1 format, e.g., when the antibody comprises an IgG1 Fc region which is wild-type, i.e., unmodified.

[368] Among the antibodies identified in **Figure 4** is 1E8. This murine anti-human VISTA antibody comprises the variable heavy and light chain polypeptides set forth below and was converted by the inventors into two human chimeric forms. The first chimeric antibody referred to herein as INX800 was obtained by the attachment of human IgG2 heavy and light constant region polypeptides to the 1E8 variable heavy and light chain polypeptides. In this first chimeric antibody none of the amino acid residues within the IgG2 constant regions were modified.

[369] The second chimeric antibody referred to herein as INX801 was similarly obtained by the attachment of human IgG2 heavy and light constant region polypeptides to the 1E8 variable heavy and light chain polypeptides. In this second chimeric antibody the cysteine residue at position 127 within the human IgG2 kappa chain was converted into a serine. Otherwise none of the amino acid residues within the IgG2 constant regions were modified.

IE8 V_H Polypeptide

EVKLLESGGGLVQPGGSLKLSCAASGFDFSRYWMSWVRQAPGKGLEWIGEVYPDSSTINYTPSLKDKFII SRDNAKNTLYLQMIKVRSEDTALYYCARGRGDYWGQGTSVTVSS **(SEQ ID NO:57)**

IE8 V_L Polypeptide

DIQMTQSPASLSASVGETVTITCRASGNIHNYLSWYHQKQGKSPQLLVYNAKTLADGVPSRFSGSGSGT QYSLKINSLQPEDFGSYYCQNFWSTPFTFGSGTKLEIKR. **(SEQ ID NO:58)**

EXAMPLE 5: Evaluation of Putative Agonistic Anti-Human VISTA Antibodies in ConA Animal Model

[370] The effects of both chimeric IgG2 antibodies and control antibodies were compared in a Concavalin A Hepatitis model. In this in vivo model different animals were

predosed with 10 mg/kg of either chimeric IgG2 antibody (INX800 or INX801) or with a control antibody 3 hours prior to Concavalin A administration. 3 hours after antibody administration the mice were then dosed with ConA at 12 mg/kg. These animals and the controls were then bled by cardiac puncture 6 hours after ConA dosing. All of the mice appeared fine, no obvious morbidity or mortality.

[371] The blood was then analyzed for cytokine expression. Particularly, a 32-plex was run using plasma obtained from the collected blood samples using conventional methods and cytokine test kit conventionally used for cytokine analysis. As shown in **Figure 5** the expression of several proinflammatory cytokines was significantly suppressed in the animals administered INX800 or INX801 antibodies compared to the control animals. Particularly, GM-CSF, IL-2, IL-4, IL-6, IL-17 and TNF-α levels were all significantly lower in the INX800 or INX801 treated animals compared to the controls. [Reduced] expression of these cytokines was substantially identical in the INX800 or INX801 treated animals.

[372] Also, the expression of certain chemokines (keratinocyte derived chemokine or "KC") and macrophage inflammatory protein 2 (MIP-2) were substantially increased in the INX800 or INX801 treated animals compared to the controls. Again, the [increased] expression of these proteins was substantially identical in the INX800 or INX801 treated animals. Based on these results both INX800 and INX801 appear to be potent VISTA agonists as they appear to elicit the analogous immunosuppressive effects that VISTA elicits ion the expression of various inflammatory cytokines.

EXAMPLE 6: Evaluation Of Putative Agonistic Anti-Human VISTA Antibodies In Graft Versus Host Disease (GVHD) Animal Model

[373] The effects of the same putative agonistic anti-human VISTA antibodies, INX800 and INX801 were also compared in a graft versus host disease (GVHD) animal model compared to untreated animals or controls treated with irrelevant antibody. In this animal model T cells were adoptively transferred into irradiated hosts and body-weight was measured as a read out of disease. Based on GVHD disease progression all of the Control mice (8/8) had to be euthanized. The results of these animal studies are shown in **Figure 6**. As shown none of the INX800 or INX801 [0/8] treated mice needed to be euthanized as GVHD was considerably depressed as a result of treatment with INX800 or INX801 antibody. Based on these results both INX800 and INX801 appear to be potent VISTA agonists as they appear to potently suppress GVHD immune responses.

EXAMPLE 7: Effects Of Putative Agonistic Anti-Human VISTA Antibodies On CD3-Driven T Cell Immune Responses

[374] The effects of the same agonistic anti-human VISTA antibodies, INX800 and INX801 were also compared as to their potential to suppress CD3-driven T cell immune

response. In these experiments plates were coated with OKT3 (2.5 μg/ml). T cells were the preincubated with antibody for 30 minutes. The antibody treated T cells were then added to the OKT3 coated plates and the T cells cultured on these plates for 72 hours. As a readout of the possible effects of the antibodies on CD3-driven T cell immune responses T cell proliferation was determined using Tritium incorporation methods, a well-accepted method for detecting T cell proliferation. As shown in **Figure 7**, T cell proliferation was considerably reduced in the cultured T cells which were treated with INX800 or INX801 antibodies compared to the control T cell cultures.

EXAMPLE 8: Effects Of Putative Agonistic Anti-Human VISTA Antibodies On Specific T Cell Populations And Total T Cell Numbers

[375] Experiments were also affected in order to compare the possible effects of the same anti-human VISTA antibodies, INX800 and INX801, on the numbers of specific T cells as well as on the total number of T cells. These experiments were conducted in order to assess whether the observed effects of the subject anti-human VISTA antibodies on cytokines and T cells could have been attributable to cell depletion (a non-specific effect) rather than thee antibodies eliciting an immunosuppressive effect based on their promoting specific VISTA-mediated immunosuppressive effects on immunity.

[376] Both agonistic anti-human VISTA antibodies, INX800 and INX801, had no significant effect on the number of specific T cell populations, or on the total number of T cells. Moreover, the results with both the INX800 and INX801 antibodies were substantially the same. The results of exemplary experiments are in **Figure 8**.

[377] Based thereon, the observed agonistic effects of INX800 and INX801 do not appear to be attributable to cell depletion. Rather, both of these antibodies appear to elicit an immunosuppressive effect on T cell activation/proliferation, GVHD immune responses and the expression of proinflammatory cytokines based on their promoting specific VISTA-mediated immunosuppressive effects on immunity.

EXAMPLE 9: Summary of Effects of Different Agonistic Anti-Human VISTA Abs in Different Immune Models

[378] As shown in **Table 1** and **2** below the agonistic or immunosuppressive effects of different anti-human VISTA antibodies was evaluated having the sequences are in **Figure 4**. To date 12 different chimeric anti-human VISTA antibodies have been demonstrated to be immunosuppressive. Some of the results obtained to date are summarized in the Tables. Antibodies in Bin 1 all compete for binding to human VISTA but do not compete for VISTA binding with antibodies in Bin 2. Conversely, the anti-human VISTA antibodies in Bin 2 all compete for binding to human VISTA with each other but not with antibodies in Bin 1.

[379] The antibody in **Table 2** which is marked "inconclusive" elicited different effects, including immunosuppressive effects in the same assay or elicited ambiguous results for other reasons. As shown in **Table 1** and **2** a total of 12 anti-human VISTA antibodies have been isolated which are immunosuppressive in MLR assays or ConA assays and/or other *in vitro* and *in vivo* assays or autoimmune, inflammatory or GVHD disease models and which mimic or agonize the immunosuppressive effects of human VISTA. Based on these results it is expected that other anti-human VISTA antibodies may be obtained by analogous methods including those having the same or different VISTA epitopic specificity.

[380] Also, the experiments in **Figure 9** compare the effects of different anti-human VISTA antibodies in ConA assays and on the expression of select proinflammatory cytokines and inflammation markers, i.e., IL-2, ɣ interferon and IL-12p70.

TABLE 1 (HUMAN OR HUMANIZED ANTI-HUMAN VISTA ANTIBODIES)

mAb ID	Epitope Group	Origin	1st Assay MLR Prolif as IgG1	Kd, M	Status	Suppression as IgG2 In MLR and/or ConA Hep Assay	2nd Assay MLR Prolif. as IgG1)
INX903|VSTB 95	**1**	**HFA Hybr (His)**	**++**	1.26E-10	Tested For immunosuppression	**+**	
INX904|VSTB 103	**1**	**Phage, original**	**-**	6.36E-10	Tested For immunosuppression	**+/-**	yes
INX905|VSTB 53	**1**	**HFA Hybr (Fc)**	**++**	2.64E-11	Tested For immunosuppression	**++**	
INX908|VSTB 92	**1**	**HFA Hybr (Fc)**	**++**	9.34E-11	**Tested For immunosup	**++**	

mAb ID	Epitope Group	Origin	1st Assay MLR Prolifas IgG1	Kd, M	Status	Suppression as IgG2 In MLR and/or ConA Hep Assay	2nd Assay MLR Prolif. as IgG1)
					pression		
INX900|VSTB 50	**2**	**HFA Hybr (Fc)**	**++**	6.32E-10	Tested For immunosuppression	**+/-**	
INX901|VSTB 56	**2**	**HFA Hybr (Fc)**	**+/-**	2.35E-11	Tested For immunosuppression	**++**	yes
INX902|VSTB 63	**2**	**HFA Hybr (Fc)**	**+/-**	8.30E-10	Tested For immunosuppression	**++**	yes
INX906|VSTB 54	**2**	**HFA Hybr (Fc)**	**+/-**	2.53E-11	Tested For immunosuppression	**++**	
INX907|VSTB 66	**2**	**HFA Hybr (Fc)**	**+/-**	8.06E-11	Tested For immunosuppression	**+**	yes
INX909|VSTB 67	**1**	**HFA Hybr (Fc)**	**+/-**	6.29E-11	To be tested		
INX913|VSTB 85	**1**	**HFA Hybr (InterFAD)**	**++**	3.78E-11	To be tested		
INX914|VSTB 97	**1**	**Phage, original**	**+/-**	7.68E-10	To be tested		

mAb ID	Epitope Group	Origin	1st Assay MLR Prolif as IgG1	Kd, M	Status	Suppression as IgG2 In MLR and/or ConA Hep Assay	2nd Assay MLR Prolif. as IgG1)
INX915|VSTB 106	1	Phage, ILM	+/-	1.67E-10	To be tested		
INX916|VSTB 107	1	Phage, ILM	++	8.90E-11	To be tested		
INX917|VSTB 110	1	Phage, ILM	+/-	2.02E-10	To be tested		
INX918|VSTB 113	1	Phage, ILM	++	4.33E-11	To be tested		
INX919|VSTB 115	1	Phage, ILM	+/-	1.45E-10	To be tested		yes
INX910|VSTB 73	2	HFA Hybr (His)	+/-	2.26E-09	To be tested		yes
INX911|VSTB 76	2	HFA Hybr (His)	+/-	1.31E-09	To be tested		
INX912|VSTB 84	2	HFA Hybr (InterFAD)	+	2.03E-09	To be tested		
VSTB100	1	Phage, original	+/-	1.48E-09			
VSTB101	1	Phage, original	+/-	3.18E-09			
VSTB102	1	Phage, original	+/-	2.98E-09			
VSTB104	1	Phage, original	+	6.75E-10			
VSTB105	1	Phage, ILM	+	1.15E-10			
VSTB108	1	Phage, ILM	+	4.94E-10			
VSTB109	1	Phage, ILM	+/-	1.02E-10			
VSTB111	1	Phage, ILM	++	1.71E-10			
VSTB112	1	Phage, ILM	++	1.56E-10			
VSTB114	1	Phage,	++	1.52E-			

mAb ID	Epitope Group	Origin	1st Assay MLR Prolif as IgG1	Kd, M	Status	Suppression as IgG2 In MLR and/or ConA Hep Assay	2nd Assay MLR Prolif. as IgG1)
		ILM		10			
VSTB116	1	Phage, ILM	++	2.13E-10			
VSTB49	1	HFA Hybr (Fc)	+	5.07E-10			
VSTB51	1	HFA Hybr (Fc)	++	1.04E-10			
VSTB59	1	HFA Hybr (Fc)	+	1.06E-10			
VSTB65	1	HFA Hybr (Fc)	++	1.08E-09			
VSTB70	1	HFA Hybr (His)	+/-	2.23E-09			
VSTB81	1	HFA Hybr (InterFAD)	+/-	3.12E-10			
VSTB98	1	Phage, original	+	2.28E-09			
VSTB99	1	Phage, original	+/-	1.54E-09			
VSTB60	2	HFA Hybr (Fc)	+	3.56E-10			
VSTB78	2	HFA Hybr (InterFAD)	++	1.13E-09			
VSTB74	4	HFA Hybr (His)	-	5.62E-10			

TABLE 2 (MURINE ANTI-HUMAN VISTA ANTIBODIES)

Antibody	Bin	Suppressive?	MLR Prolif.	Kd, M

1E8*	1	Yes	++	NT
GG8	1	Yes	++	NT
GA1	2	Inconclusive	_	NT

* Shown to be immunosuppressive in 2 different IgG2 forms.

EXAMPLE 10: Determination Of Epitopes Of Anti-Human VISTA Antibodies By B Cell Epitope Mapping

[381] The epitopic specificity of some putative agonistic anti-human VISTA antibodies was determined using custom peptide arrays using fragments of human VISTA, using proprietary methods [ProArray Ultra™] Essentially, the determination of peptide-antibody binding was performed by incubation of antibody samples with a ProArray Ultra™ peptide microarray, followed by incubation with a fluorescently labeled secondary antibody. After several washing steps the ProArray Ultra™ arrays were dried and scanned using a high-resolution fluorescence microarray scanning.

[382] All peptides (listed below) are synthesized separately, and then bound to the ProArray Ultra™ slide surface using ProImmune's proprietary technology. This optimized process ensures that peptides are presented on the array in such a manner as to closely mimic the properties of the corresponding protein region, circumventing the inherent physiochemical variation of the free peptides themselves and making a compatible, combined peptide and protein array platform. The test analytes (peptides and proteins) are dispensed onto the ProArray Ultra™ slide in discrete spots and appropriate gal-files enable exact alignment of the resulting array features back to the analyte deposited.

[383] Peptide-antibody binding is determined by incubation of antibody samples (provided by the customer) with the ProArray Ultra™ slides, followed by incubation with a fluorescently labeled secondary antibody. After the final incubation and washing steps the microarrays are dried and scanned in a high-resolution microarray scanning system.

[384] After scanning the fluorescently labeled ProArray Ultra™ slides, the scanner records an image which is evaluated using image analysis software – enabling interpretation and quantification of the levels of fluorescent intensities associated with each fluorescent spot on the scanned microarray slide. The peptide microarray was based on an overlapping peptide library synthesized from the human VISTA polypeptide sequence. Based on the sequence 15-mer microarray peptides, overlapping by 12 amino acids, were generated using ProImmune's ProArray Ultra™ technology. Details of the peptides synthesized are listed in TABLE 3 (below). 'Position' refers to the start and end amino acid within the polypeptide sequence from which the peptide was derived. Synthesized peptides were immobilised onto ProArray Ultra™ slides in 24 identical sub-arrays, each comprising test-peptides and control features in sextuplicate spots. The peptides are shown in Table 3 below.

TABLE 3: ProArray Ultra™ Peptide Details

Peptide ID	Position	Sequence
1	1-15	FKVATPYSLY VCPEG **(SEQ ID NO:7)**
2	4-18	ATPYSLYVCP EGQNV **(SEQ ID NO:8)**
3	7-21	YSLYVCPEGQ NVTLT **(SEQ ID NO:9)**
4	10-24	YVCPEGQNV TLTCRL **(SEQ ID NO:10)**
5	13-27	PEGQNVTLTC RLLGP **(SEQ ID NO:11)**
6	16-30	QNVTLTCRLL GPVDK **(SEQ ID NO:12)**
7	19-33	TLTCRLLGPV DKGHD **(SEQ ID NO:13)**
8	22-36	CRLLGPVDKG HDVTF **(SEQ ID NO:14)**
9	25-39	LGPVDKGHD VTFYKT **(SEQ**

		ID NO:15)
10	28-42	VDKGHDVTF YKTWYR **(SEQ ID NO:16)**
11	31-45	GHDVTFYKT WYRSSR **(SEQ ID NO:17)**
12	34-48	VTFYKTWYRS SRGEV **(SEQ ID NO:18)**
13	37-51	YKTWYRSSRG EVQTC **(SEQ ID NO:19)**
14	40-54	WYRSSRGEV QTCSER **(SEQ ID NO:20)**
15	43-57	SSRGEVQTCS ERRPI **(SEQ ID NO:21)**
16	46-60	GEVQTCSERR PIRNL **(SEQ ID NO:22)**
17	49-63	QTCSERRPIR NLTFQ **(SEQ ID NO:23)**

18	52-66	SERRPIRNLTF QDLH **(SEQ ID NO:24)**
19	55-69	RPIRNLTFQD LHLHH **(SEQ ID NO:25)**
20	58-72	RNLTFQDLHL HHGGH **(SEQ ID NO:26)**
21	61-75	TFQDLHLHH GGHQAA **(SEQ ID NO:27)**
22	64-78	DLHLHHGGH QAANTS **(SEQ ID NO:28)**
23	67-81	LHHGGHQAA NTSHDL **(SEQ ID NO:29)**
24	70-84	GGHQAANTS HDLAQR **(SEQ ID NO:30)**
25	73-87	QAANTSHDL AQRHGL **(SEQ ID NO:31)**

26	76-90	NTSHDLAQR HGLESA **(SEQ ID NO:32)**
27	79-93	HDLAQRHGL ESASDH **(SEQ ID NO:33)**
28	82-96	AQRHGLESAS DHHGN **(SEQ ID NO:34)**
29	85-99	HGLESASDH HGNFSI **(SEQ ID NO:35)**
30	88-102	ESASDHHGN FSITMR **(SEQ ID NO:36)**
31	91-105	SDHHGNFSIT MRNLT **(SEQ ID NO:37)**
32	94-108	HGNFSITMR NLTLLD **(SEQ ID NO:38)**
33	97-111	FSITMRNLTL LDSGL **(SEQ ID NO:39)**
34	100-114	TMRNLTLLDS

		GLYCC **(SEQ ID NO:40)**
35	103-117	NLTLLDSGLY CCLVV **(SEQ ID NO:41)**
36	106-120	LLDSGLYCCLV VEIR **(SEQ ID NO:42)**
37	109-123	SGLYCCLVVEI RHHH **(SEQ ID NO:43)**
38	112-126	YCCLVVEIRH HHSEH **(SEQ ID NO:44)**
39	115-129	LVVEIRHHHS EHRVH **(SEQ ID NO:45)**
40	118-132	EIRHHHSEHR VHGAM **(SEQ ID NO:46)**
41	121-135	HHHSEHRVH GAMELQ **(SEQ ID NO:47)**
42	124-138	SEHRVHGAM ELQVQT

		(SEQ ID NO:48)
43	127-141	RVHGAMELQ VQTGKD **(SEQ ID NO:49)**
44	130-144	GAMELQVQT GKDAPS **(SEQ ID NO:50)**
45	133-147	ELQVQTGKD APSNCV **(SEQ ID NO:51)**
46	136-150	VQTGKDAPS NCVVYP **(SEQ ID NO:52)**
47	139-153	GKDAPSNCV VYPSSS **(SEQ ID NO:53)**
48	142-156	APSNCVVYPS SSQDS **(SEQ ID NO:54)**
49	145-159	NCVVYPSSSQ DSENI **(SEQ ID NO:55)**
50	148-162	VYPSSSQDSE NITAA **(SEQ ID**

NO:56)

[385] The results of this epitope analysis with particular anti-human VISTA antibodies are summarized in **Figure 4**.

EXAMPLE 11: Epitope Binning Assay

[386] Additionally the epitopic binding properties of some anti-human VISTA antibodies having sequences shown in **Figure 4** were characterized by placing these antibodies into different epitope "bins" based on their binding characteristics as described below.

[387] Methods: ProteOn XPR36 system (BioRad) was used to perform epitope binning. ProteOn GLC chips (BioRad, Cat#176-5011) were coated with two sets of 6 monoclonal antibodies (mAbs) using the manufacturer instructions for amine-coupling chemistry (BioRad, cat #176-2410). Competing mAbs were pre-incubated in excess (250 nM final concentration) with human VISTA (25 nM final concentration) for 4 hours at room temperature and 6 at a time were run over the chip coated with the panels of coated mAbs with an association time of 4 minutes followed by dissociation for 5 minutes. Following each run, the chips were regenerated with 100 nM phosphoric acid.

[388] The data analysis involved grouping all sensorgrams by ligand and applying an alignment wizard, which automatically performs an X and Y axis alignment, and artifact removal. An Interspot correction was then applied to the data.

[389] A non-competing mAb was defined as having a binding signal the same or > Al signal (binding to human VISTA only). A competing mAb was defined as having binding signal « Al signal {i.e., binding to human VISTA only). For example VSTB49 and VSTB51 complexed with VISTA did not bind to the VSTB85 coated on the chip and therefore were classified as competing for the same binding site on VISTA as VSTB85. The results of this binning analysis with particular anti-human VISTA antibodies are summarized in **Figure 4**.

EXAMPLE 12: Epitope Mapping Of Anti-VISTA Antibodies Using Hydrogen/Deuterium (H D) Exchange Studies

[390] Antibody epitopes of anti-VISTA antibodies may be identified by various methods such as alanine scanning and Hydrogen/Deuterium (H D) Exchange and overlapping peptide arrays as described in the previous Example. Another exemplary means for identifying epitopes of putative agonistic anti-human VISTA antibodies is described below.

[391] To identify the epitopes for VSTB50, 60, 95 and 112 on human VISTA, solution hydrogen/deuterium exchange-mass spectrometry (HDX-MS) was performed using the

corresponding Fabs. For H/D exchange, the procedures used to analyze the Fab perturbation were similar to that described previously (Hamuro et al, *J. Biomol. Techniques* 14:171-182, 2003; Horn et al, Biochemistry 45:8488-8498, 2006) with some modifications. Fabs were prepared from the IgGs with papain digestion and Protein A capture using Pierce Fab Preparation Kit (Thermo Scientific, Cat# 44985). The human VISTA protein sequence contains six N-linked glycosylation sites. To improve the sequence coverage, the protein was deglycosylated with PNGase F. The deglycosylated VISTA protein was incubated in a deuterated water solution for predetermined times resulting in deuterium incorporation at exchangeable hydrogen atoms. The deuterated VISTA protein was in complex with a Fab of VSTB50, VSTB60, VSTB95 or VSTB112 in 46 deuterium oxide (D20) at 4 °C for 30 sec, 2 min, 10 min and 60 min. The exchange reaction was quenched by low pH and the proteins were digested with pepsin. The deuterium levels at the identified peptides were monitored from the mass shift on LC-MS. As a reference control, VISTA protein was processed similarly except that it was not in complex with the Fab molecules. Regions bound to the Fab were inferred to be those sites relatively protected from exchange and, thus, containing a higher fraction of deuterium than the reference VISTA protein. About 94% of the protein could be mapped to specific peptides.

[392] The solution HDX-MS perturbation maps of VISTA with VSTB50 / VSTB60, and VSTB95 / VSTB112 were mapped and two epitope groups were identified. Anti-VISTA VSTB50 recognizes the same epitope as VSTB60 does; VSTB95 binds to another epitope region as VSTB112 does on VISTA. Anti-VISTA VSTB50 and 60 share the same epitope which comprises segments, 103 NLTLLDSGL111 **(SEQ ID NO:59)**, and 136VQTGKDAPSNC146 **(SEQ ID NO:60)** Anti-VISTA VSTB95 and VSTB112 appear to target similar epitopes, comprising segments 27PVDKGHDVTF36**(SEQ ID NO:61)**, and 54RRPIRDLTFQDL65**(SEQ ID NO:62)**. These HDX-MS results provide the peptide level epitopes for exemplary anti-VISTA antibodies having the sequences identified in **Figure 4**. There were no overlapping epitope regions for these two epitope groups. These results are in agreement with the previous competition binning data in that they do not compete with each other. Again the epitope analysis results for various anti-human VISTA antibodies analyzed as described herein is summarized in **Figure 4**.

EXAMPLE 13: Assays for Identifying Agonist Anti-Human VISTA Antibodies

[393] As disclosed herein, we have identified a dozen agonistic anti-human VISTA antibodies and should be in possession of others once further corroborative experiments in the afore-described immune models are conducted or repeated with other antibodies. The antibodies identified in **Figure 4** by "VSTB" designations are fully-human, high-affinity cynomolgus monkey cross-reactive anti-VISTA antibodies (library affinity range 298-24 pM for human and 443-26 pM for cynomolgus monkey) which, based on the successful isolation of numerous agonistic anti-human antibodies as described herein should give rise to the identification of other agonistic anti-human VISTA antibodies, especially others which bind to epitope group 1 or 2. These methods are described below.

FUNCTIONAL SCREENING *IN VITRO*

[394] Direct CD4 mediated: In this approach $CD4^+$ T cells are isolated by negative selection from hV-KI splenocytes. 1x105 T cells will then be incubated with each of the 50 VISTA mAb (20 μg/ml) or an isotype control for 30 minutes on ice. The T cells and antibody will then be placed on anti-CD3 coated 96-well flat-bottom plates and cultured for 72 hours. At the 72-hour time point, tritiated thymidine will be added to the culture for 8 hours to measure proliferation by H3 incorporation. Using this assay, we can screen all 50 mAb in a single experiment in technical triplicates. Each antibody will be tested in three independent experiments to confirm activity. MAb that decrease proliferation to a statistically significant extent in comparison to the isotype control will be identified as "suppressive." All suppressive mAb identified in the initial screen will then be retested in the same assay, to generate a dose-response curve. Each antibody will be tested at half-log dilutions (30 μg/ml→0.01 μg/ml) and IC50 values will be calculated for proliferation. All antibodies that are identified as suppressive in the hV-KI assay will be confirmed on primary human T cells, and ranked by IC50 scores for proliferation.

[395] NHP cross-reactivity assay: In this assay we will screen for functional activity in a relevant tox species, Macaca fascicularis (hereafter referred to as nonhuman primates or "NHPs"), through the identical CD3 mediated proliferation assays described for mouse and human, through use of the CD3 clone SP34 which drives potent T cell proliferation. Whole blood from NHPs will be obtained from World Wide Primates (Florida, USA), and T cells will be isolated through magnetic separation. The T cells will be incubated with antibody and cultured on CD3 coated plates for 72 hours. Proliferation will be measured by tritium incorporation and IC50 scores will be generated for each antibody.

FUNCTIONAL SCREENING USING IN VIVO ANIMAL MODELS

1. TESTING OF VISTA AGONIST ANTIBODIES ACCORDING TO THE INVENTION IN CONCANAVALIN A-INDUCED HEPATITIS ANIMAL MODEL.

[396] Autoimmune hepatitis (AIH) is a chronic inflammatory disease of the liver, characterized by the loss of self-tolerance leading to B and T cell responses against the liver. The ConA model represents the best-characterized system for understanding the pathogenesis of AIH. ConA is a lectin that binds to specific sugar moieties, which are enriched in the liver. The modification of these sugar residues by ConA results in rapid $CD4^+$ T cell activation through interaction with modified MHC structures expressed by liver macrophages. An intense, but transient, cytokine production occurs with most canonical T cell cytokines (IL-2, IL-3, IFNγ and TNFα) reaching peak plasma levels within 4-6 hours. Notably, ConA induced inflammation can be blocked by depleting CD4+ T cells. The ConA model with hV-KI mice may be used to confirm suppressive activity of agonistic anti-VISTA mAbs according to the invention. Mice are weighed and treated with 10 mpk of anti-VISTA antibody or the appropriate isotype control 3 hours prior to injection with 15 mpk of ConA. The anti-VISTA mAbs are administered I.P. while ConA is injected via the tail-vein in these

mice. At the 6-hour time-point post ConA administration, the mice are euthanized and blood is collected. The plasma fraction is then be analyzed for plasma cytokines by a multiplex assay for 32 cytokines. Each antibody is tested two times in independent experiments to confirm activity. For each cytokine in the 32-plex, a one-way ANOVA will be performed, with a Dunnett's post-test to compare each anti-VISTA antibody to the isotype control. The tested anti-VISTA mAb is ranked based upon efficacy of cytokine suppression (how much was the cytokine suppressed) and variability (how consistent is the suppression within each experiment and between experiments). Additional emphasis is placed on mAb that suppress cytokines that are canonically associated with T cell activation.

[397] As disclosed in a related PCT application filed on even date and *supra*, several anti-human VISTA antibodies according to the invention were screened in the ConA model and were efficacious (immunosuppressive) therein, i.e., they suppressed ConA-induced cytokine production and promoted survival and in particular suppressed the expression of cytokines involved in T cell activation including IL-2. Particularly, the inventors tested INX800, INX801, and INX903 and INX904 as well as agonist anti-murine VISTA antibodies and all were efficacious (immunosuppressive) in the ConA hepatitis model. Therefore, agonist anti-human VISTA antibodies according to the invention should be useful in treating/preventing inflammation and hepatotoxicity associated with some chronic and acute infectious conditions such as hepatitis.

2. TESTING OF VISTA AGONIST ANTIBODIES ACCORDING TO THE INVENTION IN GRAFT VERSUS HOST DISEASE ANIMAL MODELS

[398] GVHD is a systemic disease mediated by adoptive transfer of allogeneic T cells into an irradiated host. There are five major steps that are critical in the pathogenesis of GVHD; 1) Damage to the host, most commonly in the form of the irradiation event that precedes the T cell transfer; 2) Activation of the allogeneic T cells by both host and donor APCs; 3) Expansion of the T cells in the lymph nodes and spleen; 4) Trafficking into peripheral sites such as the skin, gut, liver and lung; and 5) Damage to the host driven by T cells and also recruited myeloid cells. In certain models, such as F1→Parental strain, a chronic GVHD occurs that is a suitable model for lupus as the mice develop anti-nuclear mAb and immune complex mediated glomerular nephritis. Of note, genetic deletion of VISTA from the donor T cells results in a more aggressive form of GHVD than seen in mice receiving WT T cells.

[399] This assay may be used to identify and rank agonism of agonistic anti-human VISTA candidates. Also this assay may be used to confirm that agonist antibodies according to the invention may be used to treat or prevent GVHD. In this model BALB/c mice are lethally irradiated and given allogeneic bone marrow and splenic T cells from hV-KI mice to induce GVHD; with one group not receiving T cells as a negative control. Mice receiving the allogeneic T cells are split into the control Ig group and the treatment groups. Up to four unique VISTA mAb will be used in a single experiment, with eight mice per group, and two

replicate experiments will be conducted. 10 mpk or another dose of antibody is administered at the time of T cell transfer, as well as at days 2 and 4 post transfer. The body weight of each mouse will be tracked, and any mouse that loses more than 20% of its initial starting bodyweight will be sacrificed. Kaplan Meier curves are generated for each experiment with a log-rank statistical test comparing each anti-VISTA antibody to the control. Should all four VISTA mAb fully protect against GVHD, then dose response assays will be run in the GVHD model with groups being treated with 10, 3, 1 and 0.3 mpk of antibody. LD50 values will be calculated for each antibody.

[400] As disclosed in a related application filed on even date and *supra* a number of agonist anti-human VISTA antibodies according to the invention were evaluated in this animal model. These tested antibodies all were efficacious (immunosuppressive) in this model, i.e., they reduced the symptoms of the disease, slowed disease progression, reduced disease-associated weight loss and promoted survival. Particularly, each of INX800, INX801, INX901, INX902, INX903 and INX904 were evaluated and were demonstrated to alleviate or prevent disease symptoms in this animal model. Also, it was determined using the A and B forms of INX901 that either the A or B form were equally effective in the GVHD animal model.

3. TESTING OF VISTA AGONIST ANTIBODIES ACCORDING TO THE INVENTION IN AN ANIMAL MODEL OF INFLAMMATORY BOWEL DISEASE.

[401] Inflammatory bowel diseases (IBD), Crohn's disease and ulcerative colitis result from incompletely defined and complex interactions between host immune responses, genetic susceptibility, environmental factors, and the enteric luminal contents. Recent genome-wide association studies report associations between immune cell regulatory genes and IBD susceptibility. Both innate and adaptive immune cell intrinsic genes are represented in these studies, indicating a central role for these cell populations in IBD pathogenesis. There currently exist more than 50 animal models of human IBD. While no one model perfectly phenocopies human IBD, many are useful for studying various aspects of human disease, including disease onset and progression and the wound-healing response.

[402] In one well established IBD model intestinal inflammation is initiated with syngeneic splenic $CD4^+$ $CD45RB^{hi}$ T cell adoptive transfer into T and B cell deficient recipient mice. The CD4+ CD45RBhi T cell population contains mainly naive T cells primed for activation that are capable of inducing chronic small bowel and colonic inflammation. This method allows the researcher to modify key experimental variables, including both innate and adaptive immune cell populations, to answer biologically relevant questions relating to disease pathogenesis. Additionally, this method provides precise initiation of disease onset and a well-characterized experimental time course permitting the kinetic study of clinical features of disease progression in mice. Intestinal inflammation induced by this method shares many features with human IBD, including chronic large and small bowel transmural inflammation, pathogenesis driven by cytokines such as TNF and IL-12, and systemic

symptoms such as wasting. Thus, it is an ideal model system for studying the pathogenesis of human IBD.

[403] As disclosed in a related PCT application filed on even date an agonistic anti-human VISTA antibody according to the invention (INX901) was tested and shown to be efficacious in this IBD model. Particularly this agonist antibody was demonstrated to suppress cytokine levels and to effectively prevent or inhibit (i) colitis related weight loss, (ii) weight loss associated with colitis progression, (iii) colon shortening, (iv) the recruitment of inflammatory infiltrates to the colon and (v) the development of colitis. Therefore, agonist VISTA antibodies according to the invention may be used in the treatment of IBD and related inflammatory and intestinal conditions.

4. TESTING OF VISTA AGONIST ANTIBODIES ACCORDING TO THE INVENTION IN LUPUS ANIMAL MODELS.

[404] Lupus is an autoimmune or inflammatory condition with symptoms including kidney inflammation, increased proteinuria, and splenomegaly. There are 4 types of lupus of which Systemic Lupus Erythematosus or ("SLE") is the most common form. This disease can be mild or severe and can affect major organ systems. Lupus is an autoimmune condition of unknown cause that may result in inflammation of the kidneys—called lupus nephritis—which can affect the body's ability to filter waste from the blood, and or if severe may result in kidney damage requiring dialysis or kidney transplant. Also SLE may result in an increase in blood pressure in the lungs—called pulmonary hypertension—which can cause difficulty breathing. Further SLE may cause Inflammation of the nervous system and brain which can cause memory problems, confusion, headaches, and strokes. Further SLE may result in inflammation in the brain's blood vessels which can cause high fevers, seizures, and behavioral changes. Also SLE may result in hardening of the arteries or coronary artery disease—the buildup of deposits on coronary artery walls—can lead to a heart attack.

[405] As disclosed in a related PCT application filed on even date agonistic anti-human VISTA antibodies according to the invention (INX903, INX901, INX901-A and INX901-B) and anti-murine VISTA antibodies were tested and shown to be efficacious in different lupus models including the MRL/lpr lupus model, the NZBWF-1 lupus model and the B6D2F model. The B6D2F model is a murine model wherein SLE is induced by the transfer of human VISTA knock-in DDE1 CD8 depleted splenocytes (donor) into a B6D2F1 host (recipient) In this model, donor CD4 T cell polyclonal activation drives cognate host B cell activation, expansion, and their production of autoantibodies leading to renal disease. Lupus-like features of B6 CD8 depleted transferred to B6D2F1 model include: (1) Immune complex glomerulonephritis; (2) anti-nuclear abs; (3) anti-dsDNA abs; and (4) anti-RBC abs (Coombs positivity). Additionally, this model meets sex-based differences in renal disease severity.

[406] In 3 different lupus models agonistic anti-human and murine VISTA antibodies were demonstrated to be efficacious and to reduce the incidence of lupus disease

development, disease progression, reduce proteinuria levels, inhibit nephritis and kidney damage, reduce T cell activation and accumulation, reduce B cell activation and accumulation, and to inhibit autoantibody production. Particularly, INX903, INX901, INX901-A and INX901-B were shown to (i) reduce T cell proliferation and activation, (ii) reduce cognate B cell activation (MHCII expression) and accumulation, reduce splenomegaly, reduce anti-dsDNA IgG auto-antibody production and to reduce type I interferon signature. Also these immunosuppressive effects were not impacted by whether the human IgG2 constant region of the antibody was in the A or B form. Therefore, agonist VISTA antibodies according to the invention may be used in the treatment of lupus and related inflammatory and autoimmune conditions.

5. TESTING OF VISTA AGONIST ANTIBODIES IN A PSORIASIS ANIMAL MODEL

Imiquimod (IMQD) induced Psoriasis Model

[407] The ability of anti-VISTA antibodies to treat psoriasis was evaluated using the Imiquimod (IMQD) induced Psoriasis Model. Imiquimod (IMQD) is a commercially available cream containing TLR7/8 agonists that is widely used for dermatological conditions such as viral infections and melanoma. Application of IMQD to the skin over multiple days results in thickening of the epidermis via proliferation of the keratinocytes. Additionally, an immunological infiltration into the dermis layer occurs, with populations of both T cells and myeloid cells. Recurrent administration of IMQD creates a skin lesion similar to what is observed in patients with Psoriasis. IL-17 and IL-23 are thought to be the major cytokines involved in the immune response to IMQD.

[408] As disclosed in a related PCT application filed on even date an agonistic anti-VISTA antibody was tested and shown to be efficacious in this psoriasis model. Particularly, this antibody reduced the number of $CD3^+$ T cells infiltrating Imiquimod treated skin. Based on the observed results VISTA agonist antibodies may be used in the treatment or prevention of psoriasis and other T cell mediated autoimmune or inflammatory skin conditions.

6. TESTING OF VISTA AGONIST ANTIBODIES IN ARTHRITIS ANIMAL MODEL

[409] The immunosuppressive effects of anti-VISTA antibodies to treat arthritis may be tested in different animal models. As disclosed in a related PCT application filed on even date agonistic anti-murine and anti-human VISTA antibodies were tested and shown to be efficacious in a well-accepted arthritis model, i.e., the Collagen induced arthritis or CIA Model. INX800, INX901, INX902 and INX903 as well as a hamster anti-murine anti-VISTA antibodies were all tested in this arthritis model. Disease development was assessed by measuring inflammation swelling in the affected joints over time. Clinical scoring was accomplished by awarding a score of 1 for each swollen digit, a score of 5 for a swollen

footpad and a score of 5 for a swollen wrist or ankle (Charles River Labs scoring system), which added together give a maximal score of 60 for each animal.

[410] As shown in this PCT application each of these antibodies decreased the arthritis disease and INX901 and INX902 significantly decreased disease scope. Based on these results anti-human VISTA agonist antibodies may be used in the treatment or prevention of rheumatoid arthritis and other inflammatory or autoimmune conditions.

EXAMPLE 14: Evaluation of the role of the human IgG2 backbone on α-human VISTA antibody INX901 agonist/immune-suppressive activity in different *in vitro* and *in vivo* models

[411] Antibodies on a native human IgG2 backbone exist as a mixture of isoforms caused by disulfide bond shuffling among cysteines present in the heavy chain hinge, CH1, and light chain (Zhang, A., (2015), "Conformational difference in human IgG2 disulfide isoforms revealed by hydrogen/deuterium exchange mass spectrometry", *Biochemistry*, 54(10), 1956-1962; **Figure 10**). These isoforms were assessed by RP-HPLC (**Figure 10**), based on methods developed by Dillon et al., "Optimization of a reversed-phase high-performance liquid chromatography/mass spectrometry method for characterizing recombinant antibody heterogeneity and stability", J Chromatography A, 1120(1), 112-120. The optimized method used a shallower and higher organic mobile phase B content relative to that in Dillon (id). Separate A and B forms enriched from INX901 were prepared closely following the conditions reported in Dillon (id) but combined with a buffer exchange back into DPBS and an endotoxin removal procedure employed subsequent to the enrichment reactions (**Figure 11**).

[412] In the course of preparing these experiments it was observed that reversion of the A-enriched form occurs more quickly than expected, and at lower residual redox reagent concentrations than expected. Utilization of a fast-spin, size-exclusion based desalting procedure was therefore employed, which appeared to largely prevent this reversion. As shown in panel (**A**) in **Figure 10** disulfide shuffling leads to isoforms A and B, along with the transition for A/B (reproduced from Zhang, A. et al., 2015). (**B**) Isoforms are distinguishable by RP-HPLC (figure from Zhang, A. et al., 2015). (**C**) Observed RP-HPLC chromatogram for INX901.

[413] The inventors optimized RP-HPLC Method for detecting IgG2 isoforms is described below. In **Figure 11**: (**Black line, top**) the chromatogram shows a dominant left-most peak defining the B-form. (**Red line, bottom**) Chromatogram shows a dominant right peak defining the A-form.

Optimized RP-HPLC Methods for Isoform Detection

Mobile Phase A Preparation (0.1% v/v TFA in water):

1. Measured 1.0 L Milli-Q water in a 1.0 L graduated cylinder
2. Added 1.0 mL of TFA to the 1 L of water using a 1 mL glass Hamilton syringe
3. Transferred the solution to a 1 L bottle, mixed well.
4. Expiry is 2 weeks after preparation

Mobile Phase B Preparation (70% v/v IPA, 20% v/v ACN, 9.9% v/v water, 0.1% v/v TFA):

1. Measured 700 mL IPA into a 1.0 L graduated cylinder
2. Measured 200 mL ACN into a 250 mL graduated cylinder and transferred to the 1.0 L graduated cylinder containing the 700 mL IPA
3. Added Milli-Q water to the 1.0 L graduated cylinder containing the 700 mL IPA and 200 mL ACN until the liquid reached to 1.0 L mark
4. Added 1.0 mL of TFA to the 1 L of water using a 1 mL glass Hamilton syringe
5. Transferred the solution to a 1 L bottle, mixed well.
6. Expiry is 2 weeks after preparation

RP-HPLC Chromatography Conditions

1. Column A (large bore): Zorbax 300SB-C8, 5µm, 2.1x150mm, <<OR>>
2. Column B (narrow bore): Zorbax 300SB-C8, 3.5µm, 1x50mm
3. Mobile Phase A: 0.1% v/v TFA in water
4. Mobile Phase B: 70% v/v IPA, 20% v/v ACN, 9.9% v/v water, 0.1% v/v TFA
5. Flow rate: 0.5 mL/min for Column A or 0.25 mL/min for Column B
6. Column compartment: 75.0 ±1.0 °C
7. Detection: 214 nm
8. RP-HPLC mobile phase gradient (Table below)

Time (min)	Mobile Phase B%
0	15
2	26
34	36
35	75
36	15
40	15

INX901 Disulfide Isoform Enrichment Methods

B-form Enrichment

1. Into endotoxin free non-pyrogenic tube, add:
   2.1 mL of INX901 (5.66 mg/mL)
   792.6 µL 1 M Tris pH 8.0

495.4 µL endo-free water
396.3 additional endo-free water
237.8 µL of 100 mM Cysteine
39.6 µL of 100 mM Cystamine

2. Finger vortex (lightly), then place capped at 2-8°C for 24hr
3. Soaked Pall microsep spin-concentrator in 0.3M NaOH 2 hr at RT, then rinsed 3X with 10X DPBS, then 3X with endo-free water. Air dried in BSC before use
4. Followed vendor's instructions for regenerating 0.5 mL endotoxin removal column, using the 0.2N NaOH/ 95% ethanol (2 hrs at RT) option for step 3; used 1 X DPBS as final equilibration buffer
5. Concentrated ~4,020 µL of reaction (from Step 2) in a separate PALL microsep (as prepared above).
6. Concentrated at 2,500 X G for 35 min to less 0.4 mL (≥10X) then re-diluted with 4 mL 1X DPBS, repeated 2 additional times
7. Concentrated at 2,500 X G for 15 min to below 2 mL, then added back 1X DPBS to 2 mL
8. Added all 2 mL of buffer exchanged sample to the regenerated, spun dried, bottom capped endotoxin removal column, capped the top tightly, inverted, placed at room temp- inverted 3 more times every ~20 minutes, then spun out the sample into non-pyrogenic tube (1 min at 500 X G, as per Vendor's instructions), placed at 2-8°C

A-form Enrichment

1. Into endotoxin free non-pyrogenic tube, add:
   1750 µL INX901 (6.2 mg/mL)
   370 µL endo-free water
   700 µL 1M Tris pH8.0
   435 µL 8M GdCl
   210 µL 0.1 M Cysteine HCl (made fresh from 1 M stock)
   35 µL 0.1 M Cystamine -2HCl (made fresh from 1 M stock)
   (Final volume 3500 µL)
2. Finger vortex (lightly), then place capped at 2-8°C for 24hr
3. Prepared #7- 2 mL Zeba spin columns (Thermo P/N 89890) as per vendor's instructions, equilibrating into 1 X Dulbecco's Phosphate Buffered Saline (DPBS).
4. Loaded 500 µL of the above reaction mixture onto each of the #7, and spun 2 minutes at 1000 X G (also as per vendor's instructions), collecting into clean pyrogen free tubes.
5. Placed in de-pyrogenated PALL microsep, spun total of 1 hour, 10 minutes, concentrated to approximately 1.7 mL at approximately 5 mg/mL
6. Added all ~ 1.7 mL above to one 0.5 mL endotoxin removal spin column (Thermo P/N 88274) prepared as per Vendor's instructions (including overnight in 0.2 M NaOH at room tempo), equilibrated into 1 X DPBS. Left at room temp approximately 1 hr, then placed at 4°C for approximately another 1 hr, in both cases inverting the capped tube about every 15 minutes.
7. Recovered prep by spinning 500 X G for 1 minute (also as per vendor's instructions).
8. Recovered volume: approximately 1.3 mL at 4.61 mg/ mL (all concentrations based on the NanoDrop's built-in IgG extinction coefficient of 0.73)

IgG2 A- and B-locked Variants

[414] Specific substitutions to the amino acid sequence of IgG2 are capable of preventing disulfide shuffling, and depending on the mutation will result in a locked conformation that is either A-like or B-like (Martinez, et al., (2008). "Disulfide connectivity of human immunoglobulin G2 structural isoforms", *Biochemistry*, 47(28), 7496-7508; Allen, et al., (2009), "Interchain disulfide bonding in human IgG2 antibodies probed by site-directed mutagenesis", *Biochemistry*, 48(17), 3755-3766.

[415] The inventors therefore designed INX901 and INX908 variants with either the C233S (A-locked) or C127S (B-locked) mutation (Eu numbering) to match the IgG2 variants used by White et al., (2015), "Conformation of the human immunoglobulin G2 hinge imparts superagonistic properties to immunostimulatory anticancer antibodies", *Cancer Cell*, 27(1), 138-148. Constant heavy chain sequences are listed below.

IgG2 C233S (A-locked)
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCSVECPPCPAPPVAGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFR
VVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN
QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGK **(SEQ ID NO:63)**

IgG2 C127S (B-locked)
ASTKGPSVFPLAPSSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFR
VVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN
QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGK **(SEQ ID NO:64)**

Silent Fc Variants

[416] The inventors designed INX901 and INX908 variants with a silent Fc region by introducing the following point mutations on an IgG1 backbone: L234A/L235A/G237A/P238A/H268A/A330S/P331S (McCarthy et al., (2015) US Patent Application 14/818864. Washington, DC: U.S. In one type of variant (INX901Si and INX908Si), the CH1/hinge region of the heavy constant region is native IgG1, which does not support the disulfide shuffling of a native IgG2 (**Figure 12,** middle). In a second type of variant (INX901HSi and INX908HSi), the CH1/hinge region is native IgG2, which does support disulfide shuffling (White, A. L. et al., 2015) (**Figure 12**, bottom). Constant heavy chain sequences for both types of variants are listed below.

IgG1 with silent Fc (INX901Si and INX908Si)

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGA
SSVFLFPPKPKDTLMISRTPEVTCVVVDVSAEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPSSIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK **(SEQ ID NO:65)**

IgG2 CH1/hinge + IgG1 silent Fc (INX901HSi and INX908HSi)
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPEAAGASSV
FLFPPKPKDTLMISRTPEVTCVVVDVSAEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKALPSSIEKTISKAKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPGK **(SEQ ID NO:66)**

[417] The experiments in **Figure 12** compare the immune properties of INX901 Fc-silent variants with respect to disulfide shuffling. (**Top**) INX901 on an IgG2 backbone exhibits an expected mixture of A, A/B, and B isoforms. (**Middle**) INX901Si on a silent IgG1 backbone exists as a single isoform. (**Bottom**) INX901HSi possesses an IgG1 silent Fc region with a CH1/hinge from IgG2, which enables disulfide shuffling equivalent to native IgG2. These results indicate that FcR binding appears to affect the agonist properties of the inventive antibodies.

EXAMPLE 15: Function of INX901 and INX908 in various Ig backbones to determine requirement of hinge and Fc regions

[418] We conducted experiments to assess the functional requirements of the CH1/hinge and Fc regions of the heavy chain of the anti-human VISTA antibodies, INX901 and INX908. In their original state, both molecules are on native human IgG2 backbones, and are therefore mixtures of conformationally distinct isoforms resulting disulfide shuffling. The high cell density mixed lymphocyte reaction (MLR) was chosen for these studies as previous data indicates that this assay provides a robust read out of functionality for both INX901 and INX908. The following modifications of INX901 and/or INX908 were made to investigate whether specific isoforms are responsible for function: biochemical skewing to either the A or B isoform, genetic modifications to "lock" the conformation into the A or B form, and chimeric molecules where the Fc was silenced and the CH1/hinge region came from either IgG1, in which disulfide shuffling does not occur, or IgG2, which allows for native disulfide shuffling.

[419] The results of the assay indicate that INX901 and INX908 retain function regardless of whether in the A form, B form, or the mixture of forms that characterizes a native IgG2. Additionally, both INX901 and INX908 require an active Fc region for functionality.

[420] The MLR is a standard immunological assay that depends upon MHC class I and II mismatching to drive an allogeneic T cell response. Peripheral blood mononuclear cells are isolated from two mismatched individuals, incubated together and as a result of these mismatches, proliferation and cytokine production occurs. High cell density conditions (HCD), meaning cultures with $>1x10^7$ cells/ml, have previously been reported to elucidate agonistic functions of antibodies in vitro. Our previous data indicates that both INX901 and INX908 can suppress the expression of TNFα under HCD conditions in the MLR.

[421] The HCD MLR assay was used to assess the function of INX901 and INX908 following either genetic or biochemical modifications with respect to IgG2 disulfide isoforms and/or Fc silencing of each antibody. Prior to running the MLR, each antibody was confirmed to bind recombinant VISTA via ELISA. INX901 was sent to Elion, LLC (Louisville, CO) where it was modified by redox to either be predominantly A form (INX901 A skew) or B form (INX901 B skew). Skewing was confirmed by RP-HPLC as described in the prior example. (**Figure 11**). Each antibody, as well as the parental INX901, was diluted in a dose response in the HCD MLR and cytokine production was measured by Luminex. Previous data has indicated that TNFα and/or IL-2 are robust readouts for antibody function of the parental INX901 antibody. In two separate MLRs, both TNFα and IL-2 were reduced by INX901 parental, INX901 A skew and INX901 B skew compared to the IgG2 control (**Figure 13**).

[422] To confirm the data from **Figure 13**, additional variants of INX901 were made with mutations to generate locked variants in either the A form or the B form. Additionally, chimeric versions of INX901 were made with fully silent Fc regions to test the function of the Fc domain. INX901 Si is a fully silent IgG1 antibody. INX901 HSi has a fully silent IgG1 Fc, but also possesses an IgG2 CH1/hinge region that enables disulfide shuffling that is indistinguishable from a native IgG2 . Prior to running the MLR, each antibody was confirmed to bind recombinant VISTA via ELISA. Confirming the data from the biochemical skewing, both the A lock and B locked versions of INX901 were able to reduce the production of both IL-2 and TNFα (**Figure 14**). In contrast, both the Si and HSi versions of INX901 were unable to reduce production of IL-2 and TNFα (**Figure 14**).

[423] To confirm the data from **Figure 14**, identical mutations were made to the INX908 antibody to generate locked variants in either the A form or the B form. Additionally, chimeric versions of INX908 were made with fully silent Fc regions to test the function of the Fc domain. INX908 Si is a fully silent IgG1 antibody. INX908 HSi has a fully silent IgG1 Fc but contains the IgG2 CH1/hinge region. Prior to running the MLR, each antibody was confirmed to bind recombinant VISTA via ELISA. Confirming the data with the INX901 variants, both the A lock and B locked versions of INX908 were able to reduce the production of both IL-2 and TNFα (**Figure 15**). In contrast, both the Si and HSi versions of INX908 were unable to reduce production of IL-2 and TNFα (**Figure 15**).

EXAMPLE 15: Discontinuous Epitope Mapping of Agonist Antibodies using PEPPSCAN

methods

[424] Pepscan uses peptide arrays to determine both linear and discontinuous epitopes. This methodology is an accepted method used by many researchers and companies to ascertain antibody epitopes. **Figure 16** schematically describes the Pepscan® technology used to identify linear and discontinuous epitopes bound by various agonist anti-human VISTA antibodies according to the invention.

THE PRINCIPLES OF CLIPS TECHNOLOGY

[425] CLIPS technology structurally fixes peptides into defined three-dimensional structures. This results in functional mimics of even the most complex binding sites. CLIPS technology is now routinely used to shape peptide libraries into single, double or triple looped structures as well as sheet- and helix-like folds. The CLIPS reaction takes place between bromo groups of the CLIPS scaffold and thiol sidechains of cysteines. The reaction is fast and specific under mild conditions. Using this elegant chemistry, native protein sequences are transformed into CLIPS constructs with a range of structures.

COMBINATORIAL CLIPS LIBRARY SCREENING IN DETAIL

[426] CLIPS library screening starts with the conversion of the target protein into a library of up to 10,000 overlapping peptide constructs, using a combinatorial matrix design. On a solid carrier, a matrix of linear peptides is synthesized, which are subsequently shaped into spatially defined CLIPS constructs. Constructs representing both parts of the discontinuous epitope in the correct conformation bind the antibody with high affinity, which is detected and quantified. Constructs presenting the incomplete epitope bind the antibody with lower affinity, whereas constructs not containing the epitope do not bind at all. Affinity information is used in iterative screens to define the sequence and conformation of epitopes in detail. The results of this epitope analysis are summarized below.

ANTIBODIES INX901, INX902, INX904, INX906, INX907, INX908

[427] When tested under moderate stringency conditions antibodies INX901, INX902, INX904, INX906, INX907, INX908 strongly bound linear and conformational epitope mimics. Bound peptides contain core sequences $_{48}$NVTLTCRLLGPV$_{60}$ **(SEQ ID NO:67)**, $_{79}$EVQTCSERRPIR$_{90}$**(SEQ ID NO:68)**, $_{123}$SDHHGNFS$_{130}$ **(SEQ ID NO:69)**and $_{153}$HHHSEH$_{158}$ **(SEQ ID NO:70)**, where peptide stretch $_{79}$EVQTCSERRPIR$_{90}$ **(SEQ ID NO:68)**is the dominant part of the epitope.

[428] Additional analysis of data recorded with linear epitope mimics allowed us to identify residues that are important for binding for INX 904, INX906, INX907 and INX908, as double Ala mutants on certain positions notably decreased signal intensities. In particular, replacement of residues CR within $_{48}$NVTLTCRLLGPV$_{60}$ **(SEQ ID NO:71)**affects binding of INX906, INX907 and INX908. Also the replacement of residues TC within $_{79}$EVQTCSERRPIR$_{90}$ **(SEQ ID NO:68)** notably affects binding of INX904 and INX907.

ANTIBODY INX800

[429] When tested under moderate stringency conditions antibody INX800 did not detectably bind linear and simple constrained epitope mimics, but showed detectable binding with discontinuous epitope mimics. Analysis of data obtained with discontinuous epitope mimics suggest that antibody INX800 recognizes a discontinuous epitope with core sequences $_{53}$TCRLLGPVDKG$_{63}$**(SEQ ID NO:72)**, 101HGGHQAA$_{107}$**(SEQ ID NO:73)**, $_{121}$SASDHHGNFS$_{130}$ **(SEQ ID NO:74)** and $_{153}$HHHSEHRVHGAM$_{164}$ **(SEQ ID NO:75)**, where sequence $_{153}$HHHSEHRVHGAM$_{164}$ **(SEQ ID NO:76)**represents the dominant recognition site.

ANTIBODIES INX803 AND INX804

[430] When tested under high stringency conditions antibodies INX803 and INX804 did not bind any peptide present on the array. When tested under moderate stringency conditions both antibodies bound discontinuous epitope mimics. Cumulative analysis of binding profiles suggests that both antibodies similarly recognize peptide stretches $_{52}$LTCRLLGPV$_{60}$ **(SEQ ID NO:77)**, $_{79}$EVQTCSERRPIR$_{90}$ **(SEQ ID NO:78)**, $_{98}$HLHHGGHQAA$_{107}$**(SEQ ID NO:79)**, $_{123}$SDHHGNFS$_{130}$**(SEQ ID NO:80)**, $_{153}$HHHSEHRVHGAM$_{164}$**(SEQ ID NO:81)**, where region $_{52}$LTCRLLGPV$_{60}$ **(SEQ ID NO:77)** is the dominant recognition site.

ANTIBODY INX900

[431] When tested under high stringency conditions antibody INX900 very weakly bound linear epitope mimics with core sequence $_{79}$EVQTCSERRPIR$_{90}$ **(SEQ ID NO:68)**. Notably higher binding was observed with discontinuous epitope mimics, which in addition to sequence $_{79}$EVQTCSERRPIR$_{90}$ **(SEQ ID NO:68)**contain core sequences $_{56}$LLGPVDKGHDVTFYK$_{70}$**(SEQ ID NO:82)**, $_{113}$LAQRHGLESASDHHG$_{127}$**(SEQ ID NO:83)**, $_{153}$HHHSEHRVHGAM$_{164}$**(SEQ ID NO:84)**.

ANTIBODY INX903

[432] When tested under high stringency conditions antibody INX903 did not bind linear epitope mimics, but weakly bound conformational epitope mimics. Analysis of recorded intensity profiles suggests that the antibody recognizes a discontinuous epitope composed of core sequences $_{79}$EVQTCSERR$_{87}$**(SEQ ID NO:85)**, $_{93}$TFQDLHLHHGGHQAA$_{107}$**(SEQ ID NO:86)**, $_{146}$CLVVEIRHHHSEH$_{158}$**(SEQ ID NO:87)**, where sequence $_{79}$EVQTCSERR$_{87}$ **(SEQ ID NO:85)** is the core of the epitope.

ANTIBODY INX905

[433] When tested under high stringency conditions antibody INX905 bound linear peptides with core sequence $_{79}$EVQTCSERRP$_{88}$**(SEQ ID NO:88)**. Data acquired with double Ala mutants indicate that motif RR within $_{79}$EVQTCSERRP$_{88}$ **(SEQ ID NO:88)** is critical for the recognition. Intensity profiles recorded with discontinuous epitope mimics suggest that addition of peptide sequences $_{53}$TCRLLGPVDKG$_{63}$ **(SEQ ID NO:89)**, $_{123}$SDHHG$_{127}$ **(SEQ ID**

NO:90) and $_{153}$HHHSEHRVHGAM$_{164}$ **(SEQ ID NO:91)** augments binding of the antibody. **Figure 17** shows that most agonist anti-human VISTA antibodies bind to the same core sequence. **Figure 18** also summarizes the epitope results. **Figure 19** shows the epitopes bound by exemplary agonist anti-human VISTA antibodies according to the invention and identifies important residues involved in binding.

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SEQUENCE LISTING

SEQ ID NO:1: Homo sapiens VISTA (Alternate names: B7-H5; B7H5; DD1alpha; GI24; PP2135; SISP1) AMINO ACID SEQUENCE

1 mgvptaleag swrwgsllfa lflaaslgpv aafkvatpys lyvcpegqnv tltcrllgpv
61 dkghdvtfyk twyrssrgev qtcserrpir nltfqdlhlh hgghqaants hdlaqrhgle
121 sasdhhgnfs itmrnltlld sglycclvve irhhhsehrv hgamelqvqt gkdapsncvv
181 ypsssqdsen itaaalatga civgilclpl illlvykqrq aasnrraqel vrmdsniqgi
241 enpgfeaspp aqgipeakvr hplsyvaqrq psesgrhlls epstplsppg pgdvffpsld
301 pvpdspnfev i

SEQ ID NO:2: Mus musculus VISTA AMINO ACID SEQUENCE

1 mgvpavpeas sprwgtllla iflaasrglv aafkvttpys lyvcpegqna tltcrilgpv
61 skghdvtiyk twylssrgev qmckehrpir nftlqhlqhh gshlkanash dqpqkhglel
121 asdhhgnfsi tlrnvtprds glycclviel knhhpeqrfy gsmelqvqag kgsgstcmas
181 neqdsdsita aalatgaciv gilclplill lvykqrqvas hrraqelvrm dsntqgienp
241 gfettppfqg mpeaktrppl syvaqrqpse sgryllsdps tplsppgpgd vffpsldpvp
301 dspnseai

SEQ ID NO:3: Mus musculus VISTA AMINO ACID SEQUENCE

1 mgvpavpeas sprwgtllla iflaasrglv aafkvttpys lyvcpegqna tltcrilgpv
61 skghdvtiyk twylssrgev qmckehrpir nftlqhlqhh gshlkanash dqpqkhglel
121 asdhhgnfsi tlrnvtprds glycclviel knhhpeqrfy gsmelqvqag kgsgstcmas
181 neqdsdsita aalatgaciv gilclplill lvykqrqvas hrraqelvrm dssntqgien
241 pgfettppfq gmpeaktrpp lsyvaqrqps esgryllsdp stplsppgpg dvffpsldpv
301 pdspnseai

SEQ ID NO:4: Homo sapiens VISTA (Alternate names: B7-H5; B7H5; DD1alpha; GI24; PP2135; SISP1) NUCLEIC ACID SEQUENCE

1 gggggcgggt gcctggagca cggcgctggg gccgcccgca gcgctcactc gctcgcactc
61 agtcgcggga ggcttccccg cgccggccgc gtcccgcccg ctccccggca ccagaagttc
121 ctctgcgcgt ccgacggcga catgggcgtc cccacggccc tggaggccgg cagctggcgc
181 tggggatccc tgctcttcgc tctcttcctg gctgcgtccc taggtccggt ggcagccttc
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421 ttccaggacc ttcacctgca ccatggaggc caccaggctg ccaacaccag ccacgacctg
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541 cgcaacctga ccctgctgga tagcggcctc tactgctgcc tggtggtgga gatcaggcac
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1201 gatactgtga catcccagaa gcccagcccc tcaacccctc tggatgctac atggggatgc
1261 tggacggctc agcccctgtt ccaaggattt tggggtgctg agattctccc ctagagacct
1321 gaaattcacc agctacagat gccaaatgac ttacatctta agaagtctca gaacgtccag
1381 cccttcagca gctctcgttc tgagacatga gccttgggat gtggcagcat cagtgggaca
1441 agatggacac tgggccaccc tcccaggcac cagacacagg gcacggtgga gagacttctc
1501 ccccgtggcc gccttggctc ccccgttttg cccgaggctg ctcttctgtc agacttcctc
1561 tttgtaccac agtggctctg gggccaggcc tgcctgccca ctggccatcg ccaccttccc
1621 cagctgcctc ctaccagcag tttctctgaa gatctgtcaa caggttaagt caatctgggg
1681 cttccactgc ctgcattcca gtccccagag cttggtggtc ccgaaacggg aagtacatat
1741 tggggcatgg tggcctccgt gagcaaatgg tgtcttgggc aatctgaggc caggacagat
1801 gttgccccac ccactggaga tggtgctgag ggaggtgggt ggggccttct gggaaggtga
1861 gtggagaggg gcacctgccc cccgccctcc ccatccccta ctcccactgc tcagcgcggg
1921 ccattgcaag ggtgccacac aatgtcttgt ccaccctggg acacttctga gtatgaagcg
1981 ggatgctatt aaaaactaca tggggaaaca ggtgcaaacc ctggagatgg attgtaagag
2041 ccagtttaaa tctgcactct gctgctcctc ccccaccccc accttccact ccatacaatc
2101 tgggcctggt ggagtcttcg cttcagagcc attcggccag gtgcgggtga tgttcccatc
2161 tcctgcttgt gggcatgccc tggctttgtt tttatacaca taggcaaggt gagtcctctg
2221 tggaattgtg attgaaggat tttaaagcag gggaggagag taggggggcat ctctgtacac
2281 tctgggggta aaacagggaa ggcagtgcct gagcatgggg acaggtgagg tggggctggg
2341 cagacccccт gtagcgttta gcaggatggg ggccccaggt actgtggaga gcatagtcca
2401 gcctgggcat ttgtctccta gcagcctaca ctggctctgc tgagctgggc ctgggtgctg
2461 aaagccagga tttggggcta ggcgggaaga tgttcgccca attgcttggg gggttggggg
2521 gatggaaaag gggagcacct ctaggctgcc tggcagcagt gagccctggg cctgtggcta
2581 cagccaggga accccacctg gacacatggc cctgcttcta agccccccag ttaggcccaa
2641 aggaatggtc cactgagggc ctcctgctct gcctgggctg ggccaggggc tttgaggaga
2701 gggtaaacat aggcccggag atggggctga cacctcgagt ggccagaata tgcccaaacc
2761 ccggcttctc ccttgtccct aggcagaggg gggtcccttc ttttgttccc tctggtcacc
2821 acaatgcttg atgccagctg ccataggaag agggtgctgg ctggccatgg tggcacacac
2881 ctgtcctccc agcactttgc agggctgagg tggaaggacc gcttaagccc aggtgttcaa
2941 ggctgctgtg agctgtgttc gagccactac actccagcct ggggacggag caaaactttg
3001 cctcaaaaca aattttaaaa agaaagaaag aaggaaagag ggtatgtttt tcacaattca
3061 tgggggcctg catggcagga gtggggacag gacacctgct gttcctggag tcgaaggaca
3121 agcccacagc ccagattccg gttctcccaa ctcaggaaga gcatgccctg ccctctgggg

3181 aggctggcct ggccccagcc ctcagctgct gaccttgagg cagagacaac ttctaagaat
3241 ttggctgcca gaccccaggc ctggctgctg ctgtgtggag agggaggcgg cccgcagcag
3301 aacagccacc gcacttcctc ctcagcttcc tctggtgcgg ccctgccctc tcttctctgg
3361 acccttttac aactgaacgc atctgggctt cgtggtttcc tgttttcagc gaaatttact
3421 ctgagctccc agttccatct tcatccatgg ccacaggccc tgcctacaac gcactaggga
3481 cgtccctccc tgctgctgct ggggaggggc aggctgctgg agccgccctc tgagttgccc
3541 gggatggtag tgcctctgat gccagccctg gtggctgtgg gctggggtgc atgggagagc
3601 tgggtgcgag aacatggcgc ctccaggggg cgggaggagc actaggggct ggggcaggag
3661 gctcctggag cgctggattc gtggcacagt ctgaggccct gagagggaaa tccatgcttt
3721 taagaactaa ttcattgtta ggagatcaat caggaattag gggccatctt acctatctcc
3781 tgacattcac agtttaatag agacttcctg cctttattcc ctcccaggga gaggctgaag
3841 gaatggaatt gaaagcacca tttggagggt tttgctgaca cagcggggac tgctcagcac
3901 tccctaaaaa cacaccatgg aggccactgg tgactgctgg tgggcaggct ggccctgcct
3961 gggggagtcc gtggcgatgg gcgctggggt ggaggtgcag gagccccagg acctgctttt
4021 caaaagactt ctgcctgacc agagctccca ctacatgcag tggcccaggg cagaggggct
4081 gatacatggc ctttttcagg gggtgctcct cgcggggtgg acttgggagt gtgcagtggg
4141 acagggggct gcaggggtcc tgccaccacc gagcaccaac ttggcccctg gggtcctgcc
4201 tcatgaatga ggccttcccc agggctggcc tgactgtgct gggggctggg ttaacgtttt
4261 ctcagggaac cacaatgcac gaaagaggaa ctggggttgc taaccaggat gctgggaaca
4321 aaggcctctt gaagcccagc cacagcccag ctgagcatga ggcccagccc atagacggca
4381 caggccacct ggcccattcc ctgggcattc cctgctttgc attgctgctt ctcttcaccc
4441 catggaggct atgtcaccct aactatcctg gaatgtgttg agagggattc tgaatgatca
4501 atatagcttg gtgagacagt gccgagatag atagccatgt ctgccttggg cacgggagag
4561 ggaagtggca gcatgcatgc tgtttcttgg ccttttctgt tagaatactt ggtgctttcc
4621 aacacacttt cacatgtgtt gtaacttgtt tgatccaccc ccttccctga aaatcctggg
4681 aggttttatt gctgccattt aacacagagg gcaatagagg ttctgaaagg tctgtgtctt
4741 gtcaaaacaa gtaaacggtg gaactacgac taaa
//

SEQ ID NO:5: Homo sapiens VISTA (Alternate names: B7-H5; B7H5; DD1alpha; GI24; PP2135; SISP1) CODING NUCLEIC ACID SEQUENCE

1 ctcgccgcgc tgagccgcct cgggacggag ccatgcggcg ctgggcctgg gccgcggtcg
61 tggtcccccc cgggccgcag ctcgtgctcc tcgggggcgt cggggcccgg cgggaggcac
121 agaggacgca gcagcctggc cagcgcgcag atccccccaa cgccaccgcc agcgcgtcct
181 cccgcgaggg gctgcccgag gcccccaagc catcccaggc ctcaggacct gagttctccg
241 acgcccacat gacatggctg aactttgtcc ggcggccgga cgacggcgcc ttaaggaagc
301 ggtgcggaag cagggacaag aagccgcggg atctcttcgg tcccccagga cctccaggtg
361 cagaagtgac cgcggagact ctgcttcacg agtttcagga gctgctgaaa gaggccacgg
421 agcgccggtt ctcagggctt ctggacccgc tgctgcccca gggggcgggc ctgcggctgg
481 tgggcgaggc ctttcactgc cggctgcagg gtccccgccg ggtggacaag cggacgctgg
541 tggagctgca tggtttccag gctcctgctg cccaaggtgc cttcctgcga ggctccggtc
601 tgagcctggc ctcgggtcgg ttcacggccc ccgtgtccgg catcttccag ttctctgcca
661 gtctgcacgt ggaccacagt gagctgcagg gcaaggcccg gctgcgggcc cgggacgtgg
721 tgtgtgttct catctgtatt gagtccctgt gccagcgcca cacgtgcctg gaggccgtct

781 caggcctgga gagcaacagc agggtcttca cgctacaggt gcaggggctg ctgcagctgc
841 aggctggaca gtacgcttct gtgtttgtgg acaatggctc cggggccgtc ctcaccatcc
901 aggcgggctc cagcttctcc gggctgctcc tgggcacgtg agggcgccca gggggggctgg
961 cgaggagctg ccgccggatc ccggggaccc tcctactgat gcccgtggtc accacaataa
1021 agagccctcc accctcaaaa aaaaaaaaaa aaaaa
//

SEQ ID NO:6: Mus musculus VISTA CODING NUCLEIC ACID SEQUENCE

1 ctcgccgcgc tgagccgcct cgggacggag ccatgcggcg ctgggcctgg gccgcggtcg
61 tggtcccccct cgggccgcag ctcgtgctcc tcgggggcgt cggggcccgg cgggaggcac
121 agaggacgca gcagcctggc cagcgcgcag atccccccaa cgccaccgcc agcgcgtcct
181 cccgcgaggg gctgcccgag gcccccaagc catcccaggc ctcaggacct gagttctccg
241 acgcccacat gacatggctg aactttgtcc ggcggccgga cgacggcgcc ttaaggaagc
301 ggtgcggaag cagggacaag aagccgcggg atctcttcgg tcccccagga cctccaggtg
361 cagaagtgac cgcggagact ctgcttcacg agtttcagga gctgctgaaa gaggccacgg
421 agcgccggtt ctcagggctt ctggacccgc tgctgcccca gggggcgggc ctgcggctgg
481 tgggcgaggc ctttcactgc cggctgcagg gtccccgccg ggtggacaag cggacgctgg
541 tggagctgca tggtttccag gctcctgctg cccaaggtgc cttcctgcga ggctccggtc
601 tgagcctggc ctcgggtcgg ttcacggccc ccgtgtccgg catcttccag ttctctgcca
661 gtctgcacgt ggaccacagt gagctgcagg gcaaggcccg gctgcgggcc cgggacgtgg
721 tgtgtgttct catctgtatt gagtccctgt gccagcgcca cacgtgcctg gaggccgtct
781 caggcctgga gagcaacagc agggtcttca cgctacaggt gcaggggctg ctgcagctgc
841 aggctggaca gtacgcttct gtgtttgtgg acaatggctc cggggccgtc ctcaccatcc
901 aggcgggctc cagcttctcc gggctgctcc tgggcacgtg agggcgccca gggggggctgg
961 cgaggagctg ccgccggatc ccggggaccc tcctactgat gcccgtggtc accacaataa
1021 agagccctcc accctcaaaa aaaaaaaaaa aaaaa
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CLAIMS

1. An isolated antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to human V-domain Ig Suppressor of T cell Activation (human VISTA), wherein the antibody or antibody fragment agonizes or promotes one or more of the effects of VISTA on immunity.
2. The isolated antibody of claim 1, which comprises a human IgG2 constant or human IgG2 Fc region.
3. The isolated antibody of claim 2, wherein the human IgG2 constant or Fc region binds to Fc gamma receptors including human CD32A.
4. The isolated antibody of claim 2, wherein the IgG2 constant or Fc region comprises native human IgG2 binding to Fc gamma receptors.
5. The isolated antibody of claim 4 wherein said FcγRs include one or more of hFcγRI(CD64), FcγRIIA or hFcγRIIB, (CD32 or CD32A) and FcγRIIIA (CD16A) or FcγRIIIB (CD16B).
6. The isolated antibody or antibody fragment of any one of claims 1-5 which competes with or binds to a VISTA epitope which includes or overlaps with the epitope bound by any of the anti-human VISTA antibodies having the sequences of **Figure 4**.
7. The isolated antibody or antibody fragment of any one of claims 1-6 which binds or interacts with one of more residues of an epitope comprising residues of LLDSGLYCCLVVEIRHHHSEHRVH.
8. The isolated antibody or antibody fragment of any one of claims 1-6 which binds or interacts with one of more residues of an epitope comprising one or more residues of $_{79}$EVQTCSERRPIR$_{90}$, $_{48}$NVTLTCRLLGPV$_{60}$, $_{153}$HHHSEHRVHGAM$_{164}$, $_{52}$LTCRLLGPV$_{60}$, $_{56}$LLGPVDKGHDVTFYK$_{70}$, $_{113}$LAQRHGLESASDHHG$_{127}$, $_{153}$HHHSEHRVHGAM$_{164}$, $_{93}$TFQDLHLHHGGHQAA$_{107}$, $_{146}$CLVVEIRHHHSEH158, $_{53}$TCRLLGPVDKG$_{63}$, $_{123}$SDHHG$_{127}$ and/or $_{153}$HHHSEHRVHGAM$_{164}$.
9. The isolated antibody or antibody fragment of any one of claims 1-6 which binds or interacts with one of more residues of an epitope comprising one or more residues of $_{79}$EVQTCSERRPIR$_{90}$.
10. The agonist anti-human VISTA antibody or antibody fragment of any one of Claims 1-9 which promotes or enhances at least one effect of human VISTA on immunity, e.g. its suppressive effect on any one or more of T cell immunity, activation of monocytes, induction of T-cell proliferation; induction or suppression of cytokine expression, increased survival of monocytes, induction of antibody-dependent cell-mediated cytotoxicity (ADCC) in cells-expressing VISTA; and induction of antibody-dependent cellular phagocytosis (ADCP) in cells-expressing VISTA.
11. An isolated agonistic or antagonistic anti-human VISTA antibody or antibody fragment thereof comprising an antigen binding region that specifically binds to

human VISTA, wherein the antibody or antibody fragment comprises variable heavy and light sequences having the identical CDR polypeptides as any one of the anti-human VISTA antibodies having the CDR and variable heavy and light polypeptides shown in Figure 4, with the proviso that if said antibody or fragment comprises an antagonist anti-human VISTA antibody or antibody fragment then the antibody or antibody fragment does not comprise the same CDRs as any one of VSTB112, VSTB116, VSTB95, VSTB50, VSTB53 or VSTB60.

12. The isolated antibody or antibody fragment of Claim 11, which comprises the same CDRs as an antibody selected from VSTB49-VSTB116, with the proviso that if said antibody or fragment comprises an antagonist anti-human VISTA antibody or fragment then the antibody or antibody fragment does not comprise the same CDRs as any one of VSTB112, VSTB116, VSTB95, VSTB50, VSTB53 or VSTB60.
13. The isolated antibody or antibody fragment of Claim 11 or 12, which comprises a variable heavy and/or variable light polypeptide having at least 90% sequence identity to those of an anti-human VISTA antibody selected from any one of VSTB49-VSTB116, wherein the variable heavy and light polypeptide sequences thereof are shown in Figure 4, with the proviso that if said antibody or fragment comprises an antagonist anti-human VISTA antibody or fragment then the antibody or antibody fragment does not comprise the same CDRs as any one of VSTB112, VSTB116, VSTB95, VSTB50, VSTB53 or VSTB60.
14. The isolated antibody or antibody fragment of Claim 11 or 12, which comprises a variable heavy and/or variable light polypeptide having at least 95% sequence identity to those of an anti-human VISTA antibody selected from any one of VSTB49-VSTB116, wherein the variable heavy and light polypeptide sequences thereof are shown in Figure 4, with the proviso that if said antibody or fragment comprises an antagonist anti-human VISTA antibody or antibody fragment then the antibody or antibody fragment does not comprise the same CDRs as any one of VSTB112, VSTB116, VSTB95, VSTB50, VSTB53 or VSTB60.
15. The isolated antibody or antibody fragment of Claim 11 or 12, which comprises a variable heavy and/or variable light polypeptide having at least 96-99% sequence identity to those of an anti-human VISTA antibody selected from any one of VSTB49-VSTB116, wherein the variable heavy and light polypeptide sequences thereof are shown in Figure 4, with the proviso that if said antibody or fragment comprises an antagonist anti-human VISTA antibody or antibody fragment then the antibody or antibody fragment does not comprise the same CDRs as any one of VSTB112, VSTB116, VSTB95, VSTB50, VSTB53 or VSTB60.
16. The isolated antibody or antibody fragment of Claim 11 or 12, which comprises a variable heavy and/or variable light polypeptide identical to those of an anti-human VISTA antibody selected from one of VSTB49-VSTB116, wherein the variable heavy and light polypeptide sequences thereof are shown in **Figure 4**, with the proviso that if said antibody or fragment comprises an antagonist anti-human VISTA antibody or

antibody fragment then the antibody or antibody fragment does not comprise the same CDRs as any one of VSTB112, VSTB116, VSTB95, VSTB50, VSTB53 or VSTB60.

17. The isolated antibody or antibody fragment of any one of the foregoing Claims which antagonizes or blocks at least one effect of human VISTA on immunity.
18. The isolated antibody or antibody fragment of any one of the foregoing Claims which agonizes or blocks at least one effect of human VISTA on immunity.
19. The isolated antibody or antibody fragment of any one of the foregoing Claims which comprises a human constant domain.
20. The isolated antibody or antibody fragment of any one of the foregoing Claims which comprises a human constant domain selected from IgG1, IgG2, IgG3 and IgG4, which optionally is modified, e.g., by deletion, substitution or addition mutations or any combination of the foregoing.
21. The antibody or antibody fragment of any one of the foregoing Claims wherein the antibody fragment comprises or is a Fab, $F(ab')_2$, or scFv antibody fragment.
22. An antagonistic anti-human VISTA antibody or antibody fragment according to any of the foregoing claims which blocks or suppresses at least one of the effects of human VISTA on immunity, e.g., selected from its suppressive effect on T cell immunity, activation of monocytes, or T-cell proliferation; induction or suppression of cytokine expression, increased survival of monocytes, suppression of antibody-dependent cell-mediated cytotoxicity (ADCC) of cells-expressing VISTA; and suppression of antibody-dependent cellular phagocytosis (ADCP) of cells-expressing VISTA.
23. An agonistic anti-human VISTA antibody or antibody fragment according to any of the foregoing claims which promotes or enhances at least one of the effects of human VISTA on immunity, e.g., selected from its suppressive effect T cell immunity, activation of monocytes, suppression of T-cell proliferation; induction or suppression of cytokine expression, increased survival of monocytes, suppression of antibody-dependent cell-mediated cytotoxicity (ADCC) in cells-expressing VISTA; and suppression of antibody-dependent cellular phagocytosis (ADCP) of cells-expressing VISTA.
24. The agonist anti-human VISTA antibody or antibody fragment of Claim 23, which comprises a human IgG2 constant or Fc region.
25. The agonist anti-human VISTA antibody or antibody fragment of Claim 23 or 24 promotes or enhances the suppressive effect of human VISTA on immunity, e.g. its effect on any one or more of T cell immunity, activation of monocytes, T-cell proliferation; cytokine expression, survival of monocytes, antibody-dependent cell-mediated cytotoxicity (ADCC) in cells-expressing VISTA; and antibody-dependent cellular phagocytosis (ADCP) in cells-expressing VISTA.
26. The agonist anti-human VISTA antibody or antibody fragment of any one of Claim 23-25, which inhibits T cell immunity and/or proinflammatory cytokine expression.

27. The agonist antibody or antibody fragment of any of the foregoing claims which is a human, humanized or chimeric antibody that comprises a human Fc region, e.g., human IgG1, IgG2, IgG3 and IgG4 or a chimera of any of the foregoing.
28. The agonist antibody of any of any of the foregoing claims which is chimeric, human or humanized.
29. The antibody of any of the foregoing claims which comprises a human IgG2 constant domain or Fc region which potentially may be mutated.
30. The agonist antibody of any of any of the foregoing claims which comprises a human IgG2 constant domain or fragment thereof or an hIgG1, hIgG3, hIgG4, IgA, IgD, IgE, or IgM, wherein the entire or substantially the entire hinge and CH1 domains of said antibody and optionally the entire or substantially the entire light chain constant region have been replaced with the corresponding entire or substantially the entire light chain, and the hinge and C_{H1} domains ("H2 regions" or "H2 domains") of hIgG2.
31. The agonist antibody of any of any of the foregoing claims which (i) comprises an IgG2 Fc region wherein either or both of the heavy chain cysteine residue at position 127 and the light chain cysteine residue at position 214 (wherein numbering is according to Kabat) are deleted or changed to a different amino acid residue, resulting in an increase in the agonistic properties of the resultant modified antibody relative to an antibody wherein these residues are unchanged, (ii) the cysteine residue at position 214 in the H2 region of said antibody is mutated or substituted with another amino acid and/or one or more of the cysteine residues at positions 127, 232 or 233 of the heavy chain are deleted or substituted with another amino acid, (iii) it comprises a human IgG2 constant domain wherein at least one cysteine residue is deleted or changed to another amino acid, (iv) it competes with or binds to the same epitope on human VISTA as VSTB95 (variable heavy and light sequences shown in **Figure 4**).
32. The antibody or antibody fragments of any one of the foregoing claims which:

(i) comprises the V_H CDRs of SEQ ID NO:100, 101 and 102 and the V_L CDRs of SEQ ID NO:103, 104 and 105;
(ii) comprises the V_H CDRs of SEQ ID NO:110, 111 and 112 and the V_L CDRs of SEQ ID NO:113, 114 and 115;
(iii) comprises the V_H CDRs of SEQ ID NO:120, 121 and 122 and the V_L CDRs of SEQ ID NO:123, 124 and 125;
(iv) comprises the V_H CDRs of SEQ ID NO:130, 131 and 132 and the V_L CDRs of SEQ ID NO:133, 134 and 135;
(v) comprises the V_H CDRs of SEQ ID NO:140, 141 and 142 and the V_L CDRs of SEQ ID NO:143, 144 and 145;
(vi) comprises the V_H CDRs of SEQ ID NO:150, 151 and 152 and the V_L CDRs of SEQ ID NO:153, 154 and 155;

(vii) comprises the V_H CDRs of SEQ ID NO:160, 161 and 162 and the V_L CDRs of SEQ ID NO:163, 164 and 165;

(viii) comprises the V_H CDRs of SEQ ID NO:170, 171 and 172 and the V_L CDRs of SEQ ID NO:173, 174 and 175;

(ix) comprises the V_H CDRs of SEQ ID NO:180, 181 and 182 and the V_L CDRs of SEQ ID NO:183, 184 and 185;

(x) comprises the V_H CDRs of SEQ ID NO:190, 191 and 192 and the V_L CDRs of SEQ ID NO:193, 194 and 195;

(xi) comprises the V_H CDRs of SEQ ID NO:200, 201 and 202 and the V_L CDRs of SEQ ID NO:203, 204 and 205;

(xii) comprises the V_H CDRs of SEQ ID NO:210, 211 and 212 and the V_L CDRs of SEQ ID NO:213, 214 and 215;

(xiii) comprises the V_H CDRs of SEQ ID NO:220, 221 and 222 and the V_L CDRs of SEQ ID NO:223, 224 and 225;

(xiv) comprises the V_H CDRs of SEQ ID NO:230, 231 and 232 and the V_L CDRs of SEQ ID NO:233, 234 and 235;

(xv) comprises the V_H CDRs of SEQ ID NO:240, 241 and 242 and the V_L CDRs of SEQ ID NO:243, 244 and 245;

(xvi) comprises the V_H CDRs of SEQ ID NO:250, 251 and 252 and the V_L CDRs of SEQ ID NO:253, 254 and 255;

(xvii) comprises the VH CDRs of SEQ ID NO:260, 261 and 262 and the V_L CDRs of SEQ ID NO:263, 264 and 265;

(xviii) comprises the V_H CDRs of SEQ ID NO:270, 271 and 272 and the V_L CDRs of SEQ ID NO:273, 274 and 275;

(xix) comprises the V_H CDRs of SEQ ID NO:280, 281 and 282 and the V_L CDRs of SEQ ID NO:283, 284 and 285;

(xx) comprises the V_H CDRs of SEQ ID NO:290, 291 and 292 and the V_L CDRs of SEQ ID NO:293, 294 and 295;

(xxi) comprises the V_H CDRs of SEQ ID NO:300, 301 and 302 and the V_L CDRs of SEQ ID NO:303, 304 and 305;

(xxii) comprises the V_H CDRs of SEQ ID NO:310, 311 and 312 and the V_L CDRs of SEQ ID NO:313, 314 and 315;

(xxiii) comprises the V_H CDRs of SEQ ID NO:320, 321 and 322 and the V_L CDRs of SEQ ID NO:323, 324 and 325;

(xxiv) comprises the V_H CDRs of SEQ ID NO:330, 331 and 332 and the V_L CDRs of SEQ ID NO:333, 334 and 335;

(xxv) comprises the V_H CDRs of SEQ ID NO:340, 341 and 342 and the V_L CDRs of SEQ ID NO:343, 344 and 345;

(xxvi) comprises the V_H CDRs of SEQ ID NO:350, 351 and 352 and the V_L CDRs of SEQ ID NO:353, 354 and 355;

(xxvii) comprises the V_H CDRs of SEQ ID NO:360, 361 and 362 and the V_L CDRs of SEQ ID NO:363, 364 and 365;

(xxviii) comprises the V_H CDRs of SEQ ID NO:370, 371 and 372 and the V_L CDRs of SEQ ID NO:373, 374 and 375;

(xxix) comprises the V_H CDRs of SEQ ID NO:380, 381 and 382 and the V_L CDRs of SEQ ID NO:383, 384 and 385;

(xxx) comprises the V_H CDRs of SEQ ID NO:390, 391 and 392 and the V_L CDRs of SEQ ID NO:393, 394 and 395;

(xxxi) comprises the V_H CDRs of SEQ ID NO:400, 401 and 402 and the V_L CDRs of SEQ ID NO:403, 404 and 405;

(xxxii) comprises the V_H CDRs of SEQ ID NO:410, 411 and 412 and the V_L CDRs of SEQ ID NO:413, 414 and 415;

(xxxiii) comprises the V_H CDRs of SEQ ID NO:420, 421 and 422 and the V_L CDRs of SEQ ID NO:423, 424 and 425;

(xxxiv) comprises the V_H CDRs of SEQ ID NO:430, 431 and 432 and the V_L CDRs of SEQ ID NO:433, 434 and 435;

(xxxv) comprises the V_H CDRs of SEQ ID NO:440, 441 and 442 and the V_L CDRs of SEQ ID NO:443, 444 and 445;

(xxxvi) comprises the V_H CDRs of SEQ ID NO:450, 451 and 452 and the V_L CDRs of SEQ ID NO:453, 454 and 455;

(xxxvii) comprises the V_H CDRs of SEQ ID NO:460, 461 and 462 and the V_L CDRs of SEQ ID NO:463, 464 and 465;

(xxxviii) comprises the V_H CDRs of SEQ ID NO:470, 471 and 472 and the V_L CDRs of SEQ ID NO:473, 474 and 475;

(xxxix) comprises the V_H CDRs of SEQ ID NO:480, 481 and 482 and the V_L CDRs of SEQ ID NO:483, 484 and 485;

(xl) comprises the V_H CDRs of SEQ ID NO:490, 491 and 492 and the VL CDR polypeptides of SEQ ID NO:493, 494 and 495;

(xli) comprises the V_H CDRs of SEQ ID NO:500, 501 and 502 and the VL CDR polypeptides of SEQ ID NO:503, 504 and 505;

(xlii) comprises the V_H CDRs of SEQ ID NO:510, 511 and 512 and the VL CDR polypeptides of SEQ ID NO:513, 514 and 515;

(xliii) comprises the V_H CDRs of SEQ ID NO:520, 521 and 522 and the VL CDR polypeptides of SEQ ID NO:523, 524 and 525;

(xliv) comprises the V_H CDRs of SEQ ID NO:530, 531 and 532 and the VL CDR polypeptides of SEQ ID NO:533, 534 and 535;

(xlv) comprises the V_H CDRs of SEQ ID NO:540, 541 and 542 and the VL CDR polypeptides of SEQ ID NO:543, 544 and 545;

(xlvi) comprises the V_H CDRs of SEQ ID NO:550, 551 and 552 and the VL CDR polypeptides of SEQ ID NO:553, 554 and 555;

(xlvii) comprises the V_H CDRs of SEQ ID NO:560, 561 and 562 and the V_L CDRs of SEQ ID NO:563, 564 and 565;

(xlviii) comprises the V_H CDRs of SEQ ID NO:570, 571 and 572 and the V_L CDRs of SEQ ID NO:573, 574 and 575;

(xlix) comprises the V_H CDRs of SEQ ID NO:580, 581 and 582 and the V_L CDRs of SEQ ID NO:583, 584 and 585;

(l) comprises the V_H CDRs of SEQ ID NO:590, 591 and 592 and the V_L CDRs of SEQ ID NO:593, 594 and 595;

(li) comprises the V_H CDRs of SEQ ID NO:600, 601 and 602 and the V_L CDRs of SEQ ID NO:603, 604 and 605;

(lii) comprises the V_H CDRs of SEQ ID NO:610, 611 and 612 and the V_L CDRs of SEQ ID NO:613, 614 and 615;

(liii) comprises the V_H CDRs of SEQ ID NO:620, 621 and 622 and the V_L CDRs of SEQ ID NO:623, 624 and 625;

(liv) comprises the V_H CDRs of SEQ ID NO:630, 631 and 632 and the V_L CDRs of SEQ ID NO:633, 634 and 635;

(lv) comprises the V_H CDRs of SEQ ID NO:640, 641 and 642 and the V_L CDRs of SEQ ID NO:643, 644 and 645;

(lvi) comprises the V_H CDRs of SEQ ID NO:650, 651 and 652 and the V_L CDRs of SEQ ID NO:653, 654 and 655;

(lvii) comprises the V_H CDRs of SEQ ID NO:660, 661 and 662 and the V_L CDRs of SEQ ID NO:663, 664 and 665;

(lviii) comprises the V_H CDRs of SEQ ID NO:670, 671 and 672 and the V_L CDRs of SEQ ID NO:673, 674 and 675;

(lix) comprises the V_H CDRs of SEQ ID NO:680, 681 and 682 and the V_L CDRs of SEQ ID NO:683, 684 and 685;

(lx) comprises the V_H CDRs of SEQ ID NO:690, 691 and 692 and the V_L CDRs of SEQ ID NO:693, 694 and 695;

(lxi) comprises the V_H CDRs of SEQ ID NO:700, 701 and 702 and the V_L CDRs of SEQ ID NO:703, 704 and 705;

(lxii) comprises the V_H CDRs of SEQ ID NO:710, 711 and 712 and the V_L CDRs of SEQ ID NO:713, 714 and 715;

(lxiii) comprises the V_H CDRs of SEQ ID NO:720, 721 and 722 and the V_L CDRs of SEQ ID NO:723, 724 and 725;

(lxiv) comprises the V_H CDRs of SEQ ID NO:730, 731 and 732 and the V_L CDRs of SEQ ID NO:733, 734 and 735;

(lxv) comprises the V_H CDRs of SEQ ID NO:740, 741 and 742 and the V_L CDRs of SEQ ID NO:743, 744 and 745;

(lxvi) comprises the V_H CDRs of SEQ ID NO:750, 751 and 752 and the V_L CDRs of SEQ ID NO:753, 754 and 755;

(lxvii) comprises the V_H CDRs of SEQ ID NO:760, 761 and 762 and the V_L CDRs of SEQ ID NO:763, 764 and 765;

(lxviii) comprises the V_H CDRs of SEQ ID NO:770, 771 and 772 and the V_L CDRs of SEQ ID NO:773, 774 and 775;

(lxix) comprises the V_H CDRs of SEQ ID NO:780, 781 and 782 and the V_L CDRs of SEQ ID NO:783, 784 and 785;

(lxx) comprises the V_H CDRs of SEQ ID NO:790, 791 and 792 and the V_L CDRs of SEQ ID NO:793, 794 and 795;

(lxxi) comprises the V_H CDRs of SEQ ID NO:800, 801 and 802 and the V_L CDRs of SEQ ID NO:803, 804 and 805;

(lxxii) comprises the V_H CDRs of SEQ ID NO:810, 811 and 812 and the V_L CDRs of SEQ ID NO: 813, 814 and 815.

33. The antibody or antibody fragments of any one of the foregoing claims which:

(i) comprises the V_H polypeptide of SEQ ID NO:106 and the V_L polypeptide of SEQ ID NO:108;

(ii) comprises the V_H polypeptide of SEQ ID NO:116 and the V_L polypeptide of SEQ ID NO:118;

(iii) comprises the V_H polypeptide of SEQ ID NO:126 and the V_L polypeptide of SEQ ID NO:128;

(iv) comprises the V_H polypeptide of SEQ ID NO:136 and the V_L polypeptide f SEQ ID NO:138;

(v) comprises the V_H polypeptide of SEQ ID NO:146 and the V_L polypeptide of SEQ ID NO:148;

(vi) comprises the V_H polypeptide of SEQ ID NO:156 and the V_L polypeptide of SEQ ID NO:158;

(vii) comprises the V_H polypeptide of SEQ ID NO:166 and the V_L polypeptide of SEQ ID NO:168;

(viii) comprises the V_H polypeptide of SEQ ID NO:176 and the V_L polypeptide of SEQ ID NO:178;

(ix) comprises the V_H polypeptide of SEQ ID NO:186 and the V_L polypeptide of SEQ ID NO:188;

(x) comprises the V_H polypeptide of SEQ ID NO:196 and the V_L polypeptide of SEQ ID NO:198;

(xi) comprises the V_H polypeptide of SEQ ID NO:206 and the V_L polypeptide of SEQ ID NO:208;

(xii) comprises the V_H polypeptide of SEQ ID NO:216 and the V_L polypeptide of SEQ ID NO:218;

(xiii) comprises the V_H polypeptide of SEQ ID NO:226 and the V_L polypeptide of SEQ ID NO:228;

(xiv) comprises the V_H polypeptide of SEQ ID NO:236 and the V_L polypeptide of SEQ ID NO:238;

(xv) comprises the V_H polypeptide of SEQ ID NO:246 and the V_L polypeptide of SEQ ID NO:248;

(xvi) comprises the V_H polypeptide of SEQ ID NO:256 and the V_L polypeptide of SEQ ID NO:258;

(xvii) comprises the V_H polypeptide of SEQ ID NO:266 and the V_L polypeptide of SEQ ID NO:268;

(xviii) comprises the V_H polypeptide of SEQ ID NO:276 and the VL polypeptide of SEQ ID NO:278;

(xix) comprises the V_H polypeptide of SEQ ID NO:286 and the V_L polypeptide of SEQ ID NO:288;

(xx) comprises the V_H polypeptide of SEQ ID NO:296 and the V_L polypeptide of SEQ ID NO:298;

(xxi) comprises the V_H polypeptide of SEQ ID NO:306 and the V_L polypeptide of SEQ ID NO:308;

(xxii) comprises the V_H polypeptide of SEQ ID NO:316 and the V_L polypeptide of SEQ ID NO:318;

(xxiii) comprises the V_H polypeptide of SEQ ID NO:326 and the V_L polypeptide of SEQ ID NO:328;

(xxiv) comprises the V_H polypeptide of SEQ ID NO:336 and the V_L polypeptide of SEQ ID NO:338;

(xxv) comprises the V_H polypeptide of SEQ ID NO:346 and the V_L polypeptide of SEQ ID NO:348;

(xxvi) comprises the V_H polypeptide of SEQ ID NO:356 and the V_L polypeptide of SEQ ID NO:358;

(xxvii) comprises the V_H polypeptide of SEQ ID NO:366 and the V_L polypeptide of SEQ ID NO:368;

(xxviii) comprises the V_H polypeptide of SEQ ID NO:376 and the V_L polypeptide of SEQ ID NO:378;

(xxix) comprises the V_H polypeptide of SEQ ID NO:386 and the V_L polypeptide of SEQ ID NO:388;

(xxx) comprises the V_H polypeptide of SEQ ID NO:396 and the V_L polypeptide of SEQ ID NO:398;

(xxxi) comprises the V_H polypeptide of SEQ ID NO:406 and the V_L polypeptide of SEQ ID NO:408;

(xxxii) comprises the V_H polypeptide of SEQ ID NO:416 and the V_L polypeptide of SEQ ID NO:418;

(xxxiii) comprises the V_H polypeptide of SEQ ID NO:426 and the V_L polypeptide of SEQ ID NO:428;

(xxxiv) comprises the V_H polypeptide of SEQ ID NO:436 and the V_L polypeptide of SEQ ID NO:438;

(xxxv) comprises the V_H polypeptide of SEQ ID NO:446 and the V_L polypeptide of SEQ ID NO:448;

(xxxvi) comprises the V_H polypeptide of SEQ ID NO:456 and the V_L polypeptide of SEQ ID NO:458;

(xxxvii) comprises the V_H polypeptide of SEQ ID NO:466 and the V_L polypeptide of SEQ ID NO:468;

(xxxviii) comprises the V_H polypeptide of SEQ ID NO:476 and the V_L polypeptide of SEQ ID NO:478;

(xxxix) comprises the V_H polypeptide of SEQ ID NO:486 and the V_L polypeptide of SEQ ID NO:488;

(xl) comprises the V_H polypeptide of SEQ ID NO:496 and the V_L polypeptide of SEQ ID NO:498;

(xli) comprises the V_H polypeptide of SEQ ID NO:506 and the V_L polypeptide of SEQ ID NO:508;

(xlii) comprises the V_H polypeptide of SEQ ID NO:516 and the V_L polypeptide of SEQ ID NO:518;

(xliii) comprises the V_H polypeptide of SEQ ID NO:526 and the V_L polypeptide of SEQ ID NO:528;

(xliv) comprises the V_H polypeptide of SEQ ID NO:536 and the V_L polypeptide of SEQ ID NO:533, 534 and 535;

(xlv) comprises the V_H polypeptide of SEQ ID NO:546 and the V_L polypeptide of SEQ ID NO:548;

(xlvi) comprises the V_H polypeptide of SEQ ID NO:556 and the V_L polypeptide of SEQ ID NO:558;

(xlvii) comprises the V_H polypeptide of SEQ ID NO:566 and the V_L polypeptide of SEQ ID NO:568;

(xlviii) comprises the V_H polypeptide of SEQ ID NO:576 and the V_L polypeptide of SEQ ID NO:578;

(xlix) comprises the V_H polypeptide of SEQ ID NO:586 and the V_L polypeptide of SEQ ID NO:588;

(l) comprises the V_H polypeptide of SEQ ID NO:596 and the V_L polypeptide of SEQ ID NO:598;

(li) comprises the V_H polypeptide of SEQ ID NO:606 and the V_L polypeptide of SEQ ID NO:608;

(lii) comprises the V_H polypeptide of SEQ ID NO:616 and the V_L polypeptide of SEQ ID NO:618;

(liii) comprises the V_H polypeptide of SEQ ID NO:626 and the V_L polypeptide of SEQ ID NO:628;

(liv) comprises the V_H polypeptide of SEQ ID NO:636 and the V_L polypeptide of SEQ ID NO:638;

(lv) comprises the V_H polypeptide of SEQ ID NO:646 and the V_L polypeptide of SEQ ID NO:648;

(lvi) comprises the V_H polypeptide of SEQ ID NO:656 and the V_L polypeptide of SEQ ID NO:658;

(lvii) comprises the V_H polypeptide of SEQ ID NO:666 and the V_L polypeptide of SEQ ID NO:668;

(lviii) comprises the V_H polypeptide of SEQ ID NO:676 and the V_L polypeptide of SEQ ID NO:678;

(lix) comprises the V_H polypeptide of SEQ ID NO:686 and the V_L polypeptide of SEQ ID NO:688;

(lx) comprises the V_H polypeptide of SEQ ID NO:696 and the V_L polypeptide of SEQ ID NO:698;

(lxi) comprises the V_H polypeptide of SEQ ID NO:706 and the V_L polypeptide of SEQ ID NO:708;

(lxii) comprises the V_H polypeptide of SEQ ID NO:716 and the V_L polypeptide of SEQ ID NO:718;

(lxiii) comprises the V_H polypeptide of SEQ ID NO:726 and the V_L polypeptide of SEQ ID NO:728;

(lxiv) comprises the V_H polypeptide of SEQ ID NO:736 and the V_L polypeptide of SEQ ID NO:738;

(lxv) comprises the V_H polypeptide of SEQ ID NO:746 and the V_L polypeptide of SEQ ID NO:748;

(lxvi) comprises the V_H polypeptide of SEQ ID NO:756 and the V_L polypeptide of SEQ ID NO:758;

(lxvii) comprises the V_H polypeptide of SEQ ID NO:766 and the V_L polypeptide of SEQ ID NO:768;

(lxviii) comprises the V_H polypeptide of SEQ ID NO:776 and the V_L polypeptide of SEQ ID NO:778;

(lxix) comprises the V_H polypeptide of SEQ ID NO:786 and the V_L polypeptide of SEQ ID NO:788;

(lxx) comprises the V_H polypeptide of SEQ ID NO:796 and the V_L polypeptide of SEQ ID NO:798;

(lxxi) comprises the V_H polypeptide of SEQ ID NO:806 and the V_L polypeptide of SEQ ID NO:808; and

(lxxii) comprises the V_H polypeptide of SEQ ID NO:816 and the V_L polypeptide of SEQ ID NO: 818.

34. The antibody of Claim 32 or 33, which comprises a human IgG2 constant domain wherein optionally at least one cysteine residue is deleted or changed to another amino acid.
35. An agonistic anti-human VISTA antibody or antibody fragment according to any of the foregoing claims which mediates any one or combination of at least one of the following immmunoinhibitory effects: (i) decreases immune response, (ii) decreases T cell activation, (iii) decreases cytotoxic T cell activity, (iv) decreases natural killer (NK) cell activity, (v) decreases T-cell activity, (vi) decreases pro-inflammatory cytokine secretion, (vii) decreases IL-2 secretion; (viii) decreases interferon-γ production, (ix) decreases Th1 response, (x) decreases Th2 response, (xi) increases cell number and/or activity of regulatory T cells, (xii) increases regulatory cell activity and/or one or more of myeloid derived suppressor cells (MDSCs), iMCs, mesenchymal stromal cells, TIE2-expressing monocytes, (xiii) increases regulatory cell activity and/or the activity of one or more of myeloid derived suppressor cells (MDSCs), iMCs, mesenchymal stromal cells, TIE2-expressing monocytes, (xiii) increases M2 macrophages, (xiv) increases M2 macrophage activity, (xv) increases N2 neutrophils, (xvi) increases N2 neutrophils activity, (xvii) increases inhibition of T cell activation, (xviii) increases inhibition of CTL activation, (xix) increases inhibition of NK cell activation, (xx) increases T cell exhaustion, (xxi) decreases T cell response, (xxii) decreases activity of cytotoxic cells, (xxiii) reduces antigen-specific memory responses, (xxiv) inhibits apoptosis or lysis of cells, (xxv) decreases cytotoxic or cytostatic effect on cells, (xxvi) reduces direct killing of cells, (xxvii) decreases Thl7 activity, and/or (xxviii) reduces complement dependent cytotoxicity and/or antibody dependent cell-mediated cytotoxicity, with the proviso that said anti-VISTA antibody or antigen-binding fragment may elicit an opposite effect to one or more of (i)-(xxviii) and optionally is used to treat autoimmunity, allergy, inflammation, transplant or sepsis.
36. A pharmaceutical or diagnostic composition comprising at least one antagonistic or agonistic antibody or antibody fragment according to any of the above claims.
37. A method of treatment and/or diagnosis, or use of a composition containing at least one antagonistic antibody or antibody fragment according to any of the foregoing claims for diagnostic or therapeutic use, which method or use comprises the administration to a subject in need thereof at least one dosage or composition comprising a therapeutically or diagnostically effective amount of at least one at least one antagonistic antibody or antibody fragment according to any of the foregoing claims or composition containing according to any of the above claims.
38. The method of claim 37 which is for the treatment of cancer or an infectious disorder.
39. The method of claim 38, wherein the cancer is a blood cancer or solid tumor, e.g., one surrounded by a tumor stroma comprising myeloid cells, T-cells, or a combination of myeloid cells and T-cells.

40. The method of claim 38, which is for the treatment of cancer selected from leukemia, lymphoma, myelodysplastic syndrome or myeloma, lung cancer or a combination thereof.
41. The method of claim 40, wherein the leukemia comprises acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myeloid (myelogenous) leukemia (AML), chronic myelogenous leukemia (CML); hairy cell leukemia, T-cell prolymphocytic leukemia, large granular lymphocytic leukemia, or adult T-cell leukemia.
42. A method of treatment and/or diagnosis, or use of a composition containing at least one agonistic antibody or antibody fragment according to any of the foregoing claims for diagnostic or therapeutic use, which method or use comprises the administration to a subject in need thereof at least one dosage or composition comprising a therapeutically or diagnostically effective amount of at least one at least one agonistic antibody or antibody fragment according to any of the foregoing claims or composition containing according to any of the above claims.
43. A method or use of any agonistic antibody or antibody fragment according to any of the foregoing claims, for effecting in vitro and/or in vivo any one or combination of at least one of the following immmunoinhibitory effects: (i) decreases immune response, (ii) decreases T cell activation, (iii) decreases cytotoxic T cell activity, (iv) decreases natural killer (NK) cell activity, (v) decreases T-cell activity, (vi) decreases pro-inflammatory cytokine secretion, (vii) decreases IL-2 secretion; (viii) decreases interferon-γ production, (ix) decreases Th1 response, (x) decreases Th2 response, (xi) increases cell number and/or activity of regulatory T cells, (xii) increases regulatory cell activity and/or one or more of myeloid derived suppressor cells (MDSCs), iMCs, mesenchymal stromal cells, TIE2-expressing monocytes, (xiii) increases regulatory cell activity and/or the activity of one or more of myeloid derived suppressor cells (MDSCs), iMCs, mesenchymal stromal cells, TIE2-expressing monocytes, (xiii) increases M2 macrophages, (xiv) increases M2 macrophage activity, (xv) increases N2 neutrophils, (xvi) increases N2 neutrophils activity, (xvii) increases inhibition of T cell activation, (xviii) increases inhibition of CTL activation, (xix) increases inhibition of NK cell activation, (xx) increases T cell exhaustion, (xxi) decreases T cell response, (xxii) decreases activity of cytotoxic cells, (xxiii) reduces antigen-specific memory responses, (xxiv) inhibits apoptosis or lysis of cells, (xxv) decreases cytotoxic or cytostatic effect on cells, (xxvi) reduces direct killing of cells, (xxvii) decreases Thl7 activity, and/or (xxviii) reduces complement dependent cytotoxicity and/or antibody dependent cell-mediated cytotoxicity, with the proviso that said anti-VISTA antibody or antigen-binding fragment may elicit an opposite effect to one or more of (i)-(xxviii) and optionally is used to treatr autoimmunity, allergy, inflammation, transplant or sepsis.
44. The method or use of any of claims 37-43, which is used in the treatment or prevention of allergy, autoimmunity, transplant, gene therapy, inflammation, cancer,

GVHD or sepsis, or to treat or prevent inflammatory, autoimmune, or allergic side effects associated with any of the foregoing therewith in a human subject.

45. An anti-VISTA antibody or antigen-binding fragment or composition, or method or use according to any of the foregoing claims, further comprising another immunomodulatory antibody or fusion protein which is selected from immmunoinhibitory antibodies or fusion proteins targeting one or more of CTLA4, PD-1, PDL-1, LAG-3, TIM-3, BTLA, B7-H4, B7-H3, VISTA, and/or agonistic antibodies or fusion protein targeting one or more of CD40, CD137, OX40, GITR, CD27, CD28 or ICOS.
46. The method or use of any of the foregoing claims, which includes assaying VISTA protein by the individual's cells or in bodily fluids prior, concurrent and/or after treatment.
47. The method or use of any of the foregoing claims which includes assaying VISTA levels on hematopoietic cells.
48. The method or use of any of the foregoing claims which includes assaying VISTA levels on hematopoietic cells selected from any one or more of myeloid lineage cells and/or a lymphocytes, monocyte or a neutrophils, T cells, B cells, a natural killer (NK) cells or a natural killer T (NKT) cells.
49. The method or use of any of the foregoing claims wherein the agonist anti-human VISTA antibody or fragment comprises the same CDRs as an antibody selected from VSTB49-VSTB116 and a human IgG2 Fc region which optionally may be mutated.
50. The method or use of claim 49 wherein the IgG2 constant or Fc region retains native FcR binding and/or the ability to bind CD32A.
51. The antibody, composition, method or use of any of the foregoing claims wherein the anti-human VISTA antibody or fragment comprises an affinity or K_D for human VISTA which is 50M or less as determined by surface plasmon resonance at 37° C.
52. The antibody, composition, method or use of any of the foregoing claims wherein the anti-human VISTA antibody or fragment comprises an affinity or K_D for human VISTA which is 1nM or less as determined by surface plasmon resonance at 37° C.

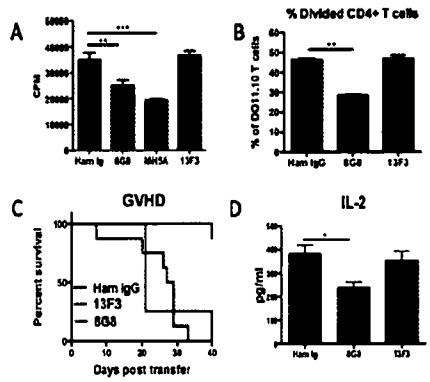


Figure 1. *In vitro* and *in vivo* screening assays can be used to identify suppressive VISTA mAb.
A) Purified T cells were plated on top of anti-CD3 in the presence of the indicated mAb for 72 hours. Proliferation was measured by H^3 incorporation.
B) Purified DO11.10 T cells were stimulated by ISQ pulsed APCs for 6 days in the presence of the indicated antibody. Proliferation was measured through use of CTV dilution dye.
C) GVHD was induced by transfer of C57BL/6 cells into irradiated BALB/c recipients. Mice were injected I.P. with 200 µg of antibody on day 0, 2 and 4 post transfer and survival was analyzed.
D) Mice were treated with 10 mpk of the indicated antibody 3 hours prior to administration of ConA (15 mpk) and IL-2 was analyzed in plasma at 6 by Luminex

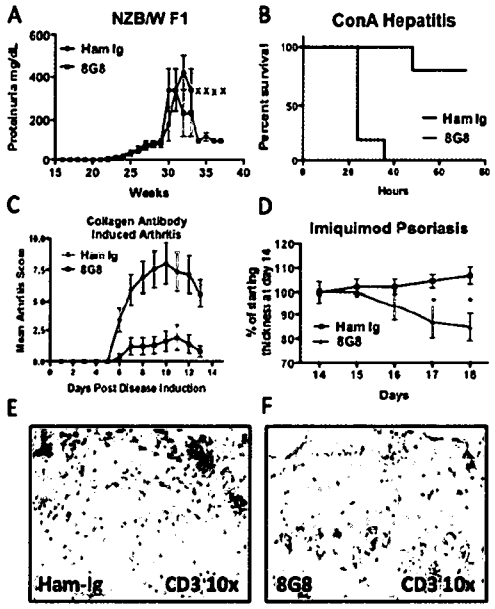


Figure 2. VISTA suppresses multiple models of autoimmune disease. A) NZB/W F1 mice were treated 3X/week with either 8G8 or Ham Ig (200 μg) starting at 25 weeks until the end of the experiment. "X" denotes time points where the control treated group had all been sacrificed. B) Mice were treated with 200 μg of antibody 3 hours prior to administration of 15 mg/kg (mpk) of ConA and survival was followed for 80 hours. C) Mice were treated sequentially with Collagen II mAb followed by LPS and arthritis was measured by measuring for paw swelling. 8G8 and Ham-Ig were administered (200 μg) 3X every other day. D) Imiquimod was applied to the ear of mice daily., At day 14, 8G8 or Ham-Ig (200 μg) were administered every other day and ear thickness was measured with calipers. E, F) Imiquimod was applied to the backs of mice daily. At day 9, mice were euthanized and skin was sectioned & stained for CD3 expression by IHC.

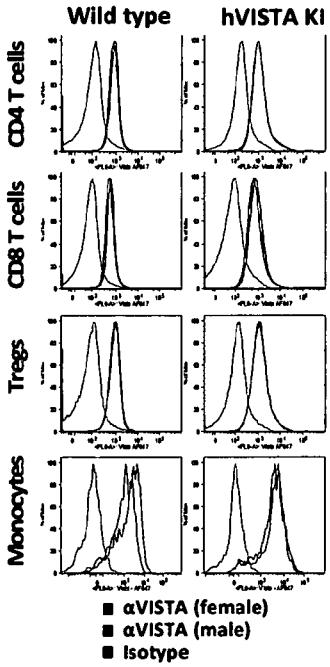


Figure 3. Expression of VISTA in WT and hV-KI mice. CD4+ T cells, CD8+ T cells, Tregs (CD4+ FoxP3+), and monocytes, CD11b+, Ly6C+, Ly6G- were isolated from the lymph nodes of WT and VISTA KI mice, and stained with αVISTA antibodies against mouse or human protein respectively.

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
GA1	Mouse IgG1/kappa	LLDSGLYCC LVVEIRHHH SEHRVH	GYTLTDYN (SEQ ID NO:100)	INLNYAIT (SEQ ID NO:101)	ARGGYRYTY YAMDY (SEQ ID NO:102)	ENIYSN (SEQ ID NO:103)	AAT (SEQ ID NO:104)	QHFWGTP RT (SEQ ID NO:105)	EVQLQQFGAELVKPG ASVKISCKASGYTLTD YNMDWVKQSHGKSL EWIGHINLNYAITTYN QKFKGKATLTVDKSSS TAYMELRSLTSEDTAV YYCARGGYRYTYYAM DYWGQGTSVTVSS (SEQ ID NO:106)	AKTTPPSVYPLAPGSAAQT NSMVTLGCLVKGYFPEPVT VTWNSGSLSSGVHTFPAVL QSDLYTLSSSVTVPSSTWPS ETVTCNVAHPASSTKVDKK IVPRDCGCKPCICTVPEVSS VFIFPPKPKDVLTITLTPKVT CVVVDISKDDPEVQFSWFV DDVEVHTAQTQPREEQFN STFRSVSELPIMHQDWLN GKEFKCRVNSAAFPAPIEKT ISKTKLNPKS (SEQ ID NO:107)	DIQMTQSPASLSVS VGETVTITCRASENI YSNLAWYQQKQGK SPQLLVYAATNLAD GVPSRFSGSGSGTQ YSLKINSLQSEDFGS YYCQHFWGTPRTFG GGTKLEIK (SEQ ID NO:108)	RADAAPTVSI FPPSSEQLTSG GASVVCFLNN FYPKDINVKW KIDGSERQNG VLNSWTDQD SKDSTYSMSS TLTLTKDEYER HNSYTCEATH KTSTSPIVKSF NRNEC (SEQ ID NO:109)
GA1-IgG2	Human IgG2/kappa	LLDSGLYCC LVVEIRHHH SEHRVH	GYTLTDYN (SEQ ID NO:110)	INLNYAIT (SEQ ID NO:111)	ARGGYRYTY YAMDY (SEQ ID NO:112)	ENIYSN (SEQ ID NO:113)	AAT (SEQ ID NO:114)	QHFWGTP RT (SEQ ID NO:115)	EVQLQQFGAELVKPG ASVKISCKASGYTLTD YNMDWVKQSHGKSL EWIGHINLNYAITTYN QKFKGKATLTVDKSSS TAYMELRSLTSEDTAV YYCARGGYRYTYYAM DYWGQGTSVTVSS (SEQ ID NO:116)	ASTKGPSVFPLAPCSRSTSE STAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSNFGT QTYTCNVDHKPSNTKVDK TVERKCCVECPPCPAPPVA GPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVQF NWYVDGVEVHNAKTKPR EEQFNSTFRVVSVLTVVHQ DWLNGKEYKCKVSNKGLP APIEKTISKTKGQPREPQVY TLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQ PENNYKTTPPMLDSDGSFF LYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLS LSPGK (SEQ ID NO:117)	DIQMTQSPASLSVS VGETVTITCRASENI YSNLAWYQQKQGK SPQLLVYAATNLAD GVPSRFSGSGSGTQ YSLKINSLQSEDFGS YYCQHFWGTPRTFG GGTKLEIK (SEQ ID NO:118)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:119)
GG8	Mouse IgG1/?	LLDSGLYCC LVVEIRHHH SEHRVH; GHDVTFYK TWYRSSRG EVQTC	GYSFTGYT (SEQ ID NO:120)	INPYNGGI (SEQ ID NO:121)	ARRTLLRPYF FDY (SEQ ID NO:122)	QSVSTSTFSY (SEQ ID NO:123)	YAS (SEQ ID NO:124)	QHSWEIPY T (SEQ ID NO:125)	EVQLQQSGPELVKPG TSMKISCKASGYSFTG YTMNWVRQSHGKNL EWIGLINPYNGGINYN QKFKARATLTVDKSSS TAYMELLSLTSEDSAV YYCARRTLLRPYFFDY WGQGTTLTVSS (SEQ ID NO:126)	EVQLQQSGPELVKPGTSM KISCKASGYSFTGYTMNW VRQSHGKNLEWIGLINPYN GGINYNQKFKARATLTVDK SSSTAYMELLSLTSEDSAVY YCARRTLLRPYFFDYWGQG TTLTVSS (SEQ ID NO:127)	DIVLTQSPASLAVSL GQRATISCRASQSV STSTFSYMHWYQQ KPGQPPKLLIKYASN LESGVPARFSGSGS GTDFTLNIHPVEEED TATYYCQHSWEIPY TFGGGTKLEIK (SEQ ID NO:128)	DIVLTQSPAS LAVSLGQRATI SCRASQSVST STFSYMHWY QQKPGQPPK LLIKYASNLES GVPARFSGSG SGTDFTLNIHP VEEEDTATYY CQHSWEIPYT FGGGTKLEIK (SEQ ID NO:129)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
GG8-IgG2	Human IgG2/kappa	LLDSGLYCC LVVEIRHHH SEHRVH; GHDVTFYK TWYRSSRG EVQTC	GYSFTGYT (SEQ ID NO:130)	INPYNGGI (SEQ ID NO:131)	ARRTLLRPYF FDY (SEQ ID NO:132)	QSVSTSTFSY (SEQ ID NO:133)	YAS (SEQ ID NO:134)	QHSWEIPY T (SEQ ID NO:135)	EVQLQQSGPELVKPG TSMKISCKASGYSFTG YTMNWVRQSHGKNL EWIGLINPYNGGINYN QKFKARATLTVDKSSS TAYMELLSLTSEDSAV YYCARRTLLRPYFFDY WGQGTTLTVSS (SEQ ID NO:136)	ASTKGPSVFPLAPCSRSTSE STAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSNFGT QTYTCNVDHKPSNTKVDK TVERKCCVECPPCPAPPVA GPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVQF NWYVDGVEVHNAKTKPR EEQFNSTFRVVSVLTVVHQ DWLNGKEYKCKVSNKGLP APIEKTISKTKGQPREPQVY TLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQ PENNYKTTPPMLDSDGSFF LYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLS LSPGK (SEQ ID NO:137)	DIVLTQSPASLAVSL GQRATISCRASQSV STSTFSYMHWYQQ KPGQPPKLLIKYASN LESGVPARFSGSGS GTDFTLNIHPVEEED TATYYCQHSWEIPY TFGGGTKLEIK (SEQ ID NO:138)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:139)
IE8	Mouse IgG1/?	LLDSGLYCC LVVEIR	GFDFSRYW (SEQ ID NO:140)	VYPDSSTI (SEQ ID NO:141)	ARGRGDY (SEQ ID NO:142)	GNIHNY (SEQ ID NO:143)	NAK (SEQ ID NO:144)	QNFWSTPF T (SEQ ID NO:145)	EVKLLESGGGLVQPG GSLKLSCAASGFDFSR YWMSWVRQAPGKG LEWIGEVYPDSSTINY TPSLKDKFIISRDNAK NTLYLQMIKVRSEDTA LYYCARGRGDYWGQ GTSVTVSS (SEQ ID NO:146)	ASTKGPSVFPLAPCSRSTSE STAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSNFGT QTYTCNVDHKPSNTKVDK TVERKCCVECPPCPAPPVA GPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVQF NWYVDGVEVHNAKTKPR EEQFNSTFRVVSVLTVVHQ DWLNGKEYKCKVSNKGLP APIEKTISKTKGQPREPQVY TLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQ PENNYKTTPPMLDSDGSFF LYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLS LSPGK (SEQ ID NO:147)	DIQMTQSPASLSAS VGETVTITCRASGNI HNYLSWYHQKQGK SPQLLVYNAKTLAD GVPSRFSGSGSGTQ YSLKINSLQPEDFGS YYCQNFWSTPFTFG SGTKLEIK (SEQ ID NO:148)	RTVAAPSVFI FPPSDEQLKS GTASVVCLLN NFYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:149)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
IE8-IgG2	Human IgG2/kappa	LLDSGLYCC LVVEIR	GFDFSRYW (SEQ ID NO:150)	VYPDSSTI (SEQ ID NO:151)	ARGRGDY (SEQ ID NO:152)	GNIHNY (SEQ ID NO:153)	NAK (SEQ ID NO:154)	QNFWSTPF T (SEQ ID NO:155)	EVKLLESGGGLVQPG GSLKLSCAASGFDFSR YWMSWVRQAPGKG LEWIGEVYPDSSTINY TPSLKDKFIISRDNAK NTLYLQMIKVRSEDTA LYYCARGRGDYWGQ GTSVTVSS (SEQ ID NO:156)	ASTKGPSVFPLAPCSRSTSE STAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSNFGT QTYTCNVDHKPSNTKVDK TVERKCCVECPPCPAPPVA GPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVQF NWYVDGVEVHNAKTKPR EEQFNSTFRVVSVLTVVHQ DWLNGKEYKCKVSNKGLP APIEKTISKTKGQPREPQVY TLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQ PENNYKTTPPMLDSDGSFF LYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLS LSPGK (SEQ ID NO:157)	DIQMTQSPASLSAS VGETVTITCRASGNI HNYLSWYHQKQGK SPQLLVYNAKTLAD GVPSRFSGSGSGTQ YSLKINSLQPEDFGS YYCQNFWSTPFTFG SGTKLEIK (SEQ ID NO:158)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:159)
IE8-IgG2-C127S	Human mutated IgG2/kappa	LLDSGLYCC LVVEIR	GFDFSRYW (SEQ ID NO:160)	VYPDSSTI (SEQ ID NO:161)	ARGRGDY (SEQ ID NO:162)	GNIHNY (SEQ ID NO:163)	NAK (SEQ ID NO:164)	QNFWSTPF T (SEQ ID NO:165)	EVKLLESGGGLVQPG GSLKLSCAASGFDFSR YWMSWVRQAPGKG LEWIGEVYPDSSTINY TPSLKDKFIISRDNAK NTLYLQMIKVRSEDTA LYYCARGRGDYWGQ GTSVTVSS (SEQ ID NO:166)	ASTKGPSVFPLAPSSRSTSE STAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSNFGT QTYTCNVDHKPSNTKVDK TVERKCCVECPPCPAPPVA GPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVQF NWYVDGVEVHNAKTKPR EEQFNSTFRVVSVLTVVHQ DWLNGKEYKCKVSNKGLP APIEKTISKTKGQPREPQVY TLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQ PENNYKTTPPMLDSDGSFF LYSKLTVDKSRWQQGNVF SCSVMHEALHNHYTQKSLS LSPGK (SEQ ID NO:167)	DIQMTQSPASLSAS VGETVTITCRASGNI HNYLSWYHQKQGK SPQLLVYNAKTLAD GVPSRFSGSGSGTQ YSLKINSLQPEDFGS YYCQNFWSTPFTFG SGTKLEIK (SEQ ID NO:168)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:169)

WO 2017/181109 PCT/US2017/027765

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB100	Human IgG1/kappa	Group 1	GYSFTSYW (SEQ ID NO:170)	IYPGDSDT (SEQ ID NO:171)	ARDVSSFYGY SPMFDY (SEQ ID NO:172)	QSVSSY (SEQ ID NO:173)	DAS (SEQ ID NO:174)	QQRSNWP LT (SEQ ID NO:175)	EVQLVQSGAEVKKPG ESLKISCKGSGYSFTSY WIGWVRQMPGKGLE WMGIIYPGDSDTRYS PSFQGQVTISADKSIS TAYLQWSSLKASDTA MYYCARDVSSFYGYS PMFDYWGQGTLVTV SS (SEQ ID NO:176)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK ((SEQ ID NO:177)	EIVLTQSPATLSLSPG ERATLSCRASQSVSS YLAWYQQKPGQAP RLLIYDASNRATGIP ARFSGSGSGTDFTLT ISSLEPEDFAVYYCQ QRSNWPLTFGQGT KVEIK (SEQ ID NO:178)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:179)
VSTB101	Human IgG1/kappa	VSTB101 Group 1	GYSFTSYW (SEQ ID NO:180)	IYPGDSDT (SEQ ID NO:181)	ARDAHSFYG YSALLDY (SEQ ID NO:182)	QSVSSSY (SEQ ID NO:183)	GAS (SEQ ID NO:184)	QQYGSSPL T (SEQ ID NO:185)	EVQLVQSGAEVKKPG ESLKISCKGSGYSFTSY WIGWVRQMPGKGLE WMGIIYPGDSDTRYS PSFQGQVTISADKSIS TAYLQWSSLKASDTA MYYCARDAHSFYGYS ALLDYWGQGTLVTVS S (SEQ ID NO:186)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:187)	EIVLTQSPGTLSLSPG ERATLSCRASQSVSS SYLAWYQQKPGQA PRLLIYGASSRATGIP DRFSGSGSGTDFTLT ISRLEPEDFAVYYCQ QYGSSPLTFGQGTK VEIK (SEQ ID NO:188)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:189)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB102	Human IgG1/kappa	Group 1	GYSFTSYW (SEQ ID NO:190)	IYPGDSDT (SEQ ID NO:191)	ARDSYSFYGH TPVLDY (SEQ ID NO:192)	QSVSSSY (SEQ ID NO:193)	GAS (SEQ ID NO:194)	QQYGSSPL T (SEQ ID NO:195)	EVQLVQSGAEVKKPG ESLKISCKGSGYSFTSY WIGWVRQMPGKGLE WMGIIYPGDSDTRYS PSFQGQVTISADKSIS TAYLQWSSLKASDTA MYYCARDSYSFYGHT PVLDYWGQGTLVTVS S (SEQ ID NO:196)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:197)	EIVLTQSPGTLSLSPG ERATLSCRASQSVSS SYLAWYQQKPGQA PRLLIYGASSRATGIP DRFSGSGSGTDFTLT ISRLEPEDFAVYYCQ QYGSSPLTFGQGTK VEIK (SEQ ID NO:198)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:199)
VSTB103 INX904	Human IgG1/kappa	VSTB101 Group 1	GYSFTSYW (SEQ ID NO:200)	IYPGDSDT (SEQ ID NO:201)	ARDDALYGG YYLDY (SEQ ID NO:202)	QSVLYSSNNK NY (SEQ ID NO:203)	WAS (SEQ ID NO:204)	QQYYSTPLT (SEQ ID NO:205)	EVQLVQSGAEVKKPG ESLKISCKGSGYSFTSY WIGWVRQMPGKGLE WMGIIYPGDSDTRYS PSFQGQVTISADKSIS TAYLQWSSLKASDTA MYYCARDDALYGGYY LDYWGQGTLVTVSS (SEQ ID NO:206)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:207)	DIVMTQSPDSLAVS LGERATINCKSSQSV LYSSNNKNYLAWYQ QKPGQPPKLLIYWA STRESGVPDRFSGS GSGTDFTLTISSLQA EDVAVYYCQQYYST PLTFGQGTKVEIK ((SEQ ID NO:208)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:209)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB104	Human IgG1/kappa	Group 1	GYSFTSYW (SEQ ID NO:210)	IYPGDSDT (SEQ ID NO:211)	ARDANSFYS AASIFDY (SEQ ID NO:212)	QSVLYSSNNK NY (SEQ ID NO:213)	WAS (SEQ ID NO:214)	QQYYSTPLT (SEQ ID NO:215)	EVQLVQSGAEVKKPG ESLKISCKGSGYSFTSY WIGWVRQMPGKGLE WMGIIYPGDSDTRYS PSFQGQVTISADKSIS TAYLQWSSLKASDTA MYYCARDANSFYSAA SIIFDYWGQGTLVTVS S (SEQ ID NO:216)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:217)	DIVMTQSPDSLAVS LGERATINCKSSQSV LYSSNNKNYLAWYQ QKPGQPPKLLIYWA STRESGVPDRFSGS GSGTDFTLTISSLQA EDVAVYYCQQYYST PLTFGQGTKVEIK (SEQ ID NO:218)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:219)
VSTB105	Human IgG1/kappa	Group 1	GGTFSSYA (SEQ ID NO:220)	IIPIFGTA (SEQ ID NO:221)	ARSSYGWSY EFDY (SEQ ID NO:222)	QSIATN (SEQ ID NO:223)	AAS (SEQ ID NO:224)	QQNDDRPI T (SEQ ID NO:225)	QVQLVQSGAEVKKPG SSVKVSCKASGGTFSS YAISWVRQAPGQGLE WMGGIIPIFGTANYA QKFQGRVTITADESTS TAYMELSSLRSEDTAV YYCARSSYGWSYEFD YWGQGTLVTVSS (SEQ ID NO:226)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK ((SEQ ID NO:227)	DIQMTQSPSSLSAS VGDRVTITCRASQSI ATNLNWYQQKPGK APKLLIYAASSLQSG VPSRFSGSGSGTDFT LTISSLQPEDFATYYC QQNDDRPITFGQGT KVEIK (SEQ ID NO:228)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:229)

WO 2017/181109 PCT/US2017/027765

2022252828 14 Oct 2022

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB106 INX915	Human IgG1/kappa	Group 1	GGTFSSYA (SEQ ID NO:230)	IIPIFGTA (SEQ ID NO:231)	ARSSYGWSY EFDY (SEQ ID NO:232)	QSRTD ((SEQ ID NO:233)	SAS (SEQ ID NO:234)	QQNERTPIT (SEQ ID NO:235)	QVQLVQSGAEVKKPG SSVKVSCKASGGTFSS YAISWVRQAPGQGLE WMGGIIPIFGTANYA QKFQGRVTITADESTS TAYMELSSLRSEDTAV YYCARSSYGWSYEFD YWGQGTLVTVSS (SEQ ID NO:236)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:237)	DKQMTQSPSSLSAS VGDRVTITCRASQSI RTDLNWYQQKPGK APKLLIYSASSLQSG VPSRFSGSGSGTDFT LTISSLQPEDFATYYC QQNERTPITFGQGT KVEIK (SEQ ID NO:238)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:239)
VSTB107 INX916	Human IgG1/kappa	Group 1	GGTFSSYA (SEQ ID NO:240)	IIPIFGTA (SEQ ID NO:241)	ARSSYGWSY EFDY (SEQ ID NO:242)	QSINND (SEQ ID NO:243)	AAS (SEQ ID NO:244)	QQNRATPI T (SEQ ID NO:245)	QVQLVQSGAEVKKPG SSVKVSCKASGGTFSS YAISWVRQAPGQGLE WMGGIIPIFGTANYA QKFQGRVTITADESTS TAYMELSSLRSEDTAV YYCARSSYGWSYEFD YWGQGTLVTVSS (SEQ ID NO:246)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:247)	DKQMTQSPSSLSAS VGDRVTITCRASQSI NNDLNWYQQKPGK APKLLIYAASSLQSG VPSRFSGSGSGTDFT LTISSLQPEDFATYYC QQNRATPITFGQGT KVEIK (SEQ ID NO:248)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:249)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB108	Human IgG1/kappa	Group 1	GGTFSSYA (SEQ ID NO:250)	IIPIFGTA (SEQ ID NO:251)	ARNTFGWSG ELDY (SEQ ID NO:252)	QSISNR (SEQ ID NO:253)	SAS (SEQ ID NO:254)	QQNHDNPI T (SEQ ID NO:255)	QVQLVQSGAEVKKPG SSVKVSCKASGGTFSS YAISWVRQAPGQGLE WMGGIIPIFGTANYA QKFQGRVTITADESTS TAYMELSSLRSEDTAV YYCARNTFGWSGELD YWGQGTLVTVSS (SEQ ID NO:256)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:257)	DIQMTQSPSSLSAS VGDRVTITCRASQSI SNRLNWYQQKPGK APKLLIYSASSLQSG VPSRFSGSGSGTDFT LTISSLQPEDFATYYC QQNHDNPITFGQG TKVEIK (SEQ ID NO:258)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:259)
VSTB109	Human IgG1/kappa	Group 1	GGTFSSYA (SEQ ID NO:260)	IIPIFGTA (SEQ ID NO:261)	ARSSYGWSY EFDY (SEQ ID NO:262)	QSIATY (SEQ ID NO:263)	AAS (SEQ ID NO:264)	QQNHNRPI T (SEQ ID NO:265)	QVQLVQSGAEVKKPG SSVKVSCKASGGTFSS YAISWVRQAPGQGLE WMGGIIPIFGTANYA QKFQGRVTITADESTS TAYMELSSLRSEDTAV YYCARSSYGWSYEFD YWGQGTLVTVSS (SEQ ID NO:266)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:267)	DIQMTQSPSSLSAS VGDRVTITCRASQSI ATYLNWYQQKPGK APKLLIYAASSLQSG VPSRFSGSGSGTDFT LTISSLQPEDFATYYC QQNHNRPITFGQGT KVEIK (SEQ ID NO:268)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:269)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB110 INX917	Human IgG1/kappa	Group 1	GGTFSSYA (SEQ ID NO:270)	IIPIFGTA (SEQ ID NO:271)	ARHSIGWVA ELDY (SEQ ID NO:272)	QSINTD (SEQ ID NO:273)	AAS (SEQ ID NO:274)	QQGASDPI T (SEQ ID NO:275)	QVQLVQSGAEVKKPG SSVKVSCKASGGTFSS YAISWVRQAPGQGLE WMGGIIPIFGTANYA QKFQGRVTITADESTS TAYMELSSLRSEDTAV YYCARHSIGWVAELD YWGQGTLVTVSS (SEQ ID NO:276)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:277)	DIQMTQSPSSLSAS VGDRVTITCRASQSI NTDLNWYQQKPGK APKLLIYAASSLQSG VPSRFSGSGSGTDFT LTISSLQPEDFATYYC QQGASDPITFGQGT KVEIK (SEQ ID NO:278)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:279)
VSTB111	Human IgG1/kappa	Group 1	GGTFSSYA (SEQ ID NO:280)	IIPIFGTA (SEQ ID NO:281)	ARSSYGWSY EFDY (SEQ ID NO:282)	QSINTD (SEQ ID NO:283)	AAS (SEQ ID NO:284)	QQNRGSPI T (SEQ ID NO:285)	QVQLVQSGAEVKKPG SSVKVSCKASGGTFSS YAISWVRQAPGQGLE WMGGIIPIFGTANYA QKFQGRVTITADESTS TAYMELSSLRSEDTAV YYCARSSYGWSYEFD YWGQGTLVTVSS (SEQ ID NO:286)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:287)	DIQMTQSPSSLSAS VGDRVTITCRASQSI NTDLNWYQQKPGK APKLLIYAASSLQSG VPSRFSGSGSGTDFT LTISSLQPEDFATYYC QQNRGSPITFGQGT KVEIK (SEQ ID NO:288)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:289)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB113 INX918	Human IgG1/kappa	Group 1	GGTFSSYA (SEQ ID NO:290)	IIPIFGTA (SEQ ID NO:291)	ARHSIGWVA ELDY (SEQ ID NO:292)	QSIATD (SEQ ID NO:293)	AAS (SEQ ID NO:294)	QQAHWYP LT (SEQ ID NO:295)	QVQLVQSGAEVKKPG SSVKVSCKASGGTFSS YAISWVRQAPGQGLE WMGGIIPIFGTANYA QKFQGRVTITADESTS TAYMELSSLRSEDTAV YYCARHSIGWVAELD YWGQGTLVTVSS (SEQ ID NO:296)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:297)	DIQMTQSPSSLSAS VGDRVTITCRASQSI ATDLNWYQQKPGK APKLLIYAASSLQSG VPSRFSGSGSGTDFT LTISSLQPEDFATYYC QQAHWYPLTFGQG TKVEIK (SEQ ID NO:298)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:299)
VSTB114	Human IgG1/kappa	Group 1	GGTFSSYA (SEQ ID NO:300)	IIPIFGTA (SEQ ID NO:301)	ARHSIGWVA ELDY (SEQ ID NO:302)	QSIATS (SEQ ID NO:303)	YAS (SEQ ID NO:304)	QQGAYYPL T (SEQ ID NO:305)	QVQLVQSGAEVKKPG SSVKVSCKASGGTFSS YAISWVRQAPGQGLE WMGGIIPIFGTANYA QKFQGRVTITADESTS TAYMELSSLRSEDTAV YYCARHSIGWVAELD YWGQGTLVTVSS (SEQ ID NO:306)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:307)	DIQMTQSPSSLSAS VGDRVTITCRASQSI ATSLNWYQQKPGK APKLLIYYASSLQSG VPSRFSGSGSGTDFT LTISSLQPEDFATYYC QQGAYYPLTFGQGT KVEIK (SEQ ID NO:308)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:309)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB115 INX919	Human IgG1/kappa	Group 1	GGTFSSYA (SEQ ID NO:310)	IIPIFGTA (SEQ ID NO:311)	ARSSYGWSY EFDY (SEQ ID NO:312)	QSIRTY (SEQ ID NO:313)	AAS (SEQ ID NO:314)	QQAYSNPI T (SEQ ID NO:315)	QVQLVQSGAEVKKPG SSVKVSCKASGGTFSS YAISWVRQAPGQGLE WMGGIIPIFGTANYA QKFQGRVTITADESTS TAYMELSSLRSEDTAV YYCARSSYGWSYEFD YWGQGTLVTVSS (SEQ ID NO:316)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:317)	DIQMTQSPSSLSAS VGDRVTITCRASQSI RTYLNWYQQKPGK APKLLIYAASSLQSG VPSRFSGSGSGTDFT LTISSLQPEDFATYYC QQAYSNPITFGQGT KVEIK (SEQ ID NO:318)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:319)
VSTB116	Human IgG1/kappa	Group 1	GGTFSSYA (SEQ ID NO:320)	IIPIFGTA (SEQ ID NO:321)	ARSSYGWSY EFDY (SEQ ID NO:322)	QSINTN (SEQ ID NO:323)	AAS (SEQ ID NO:324)	QQARDTPI T (SEQ ID NO:325)	QVQLVQSGAEVKKPG SSVKVSCKASGGTFSS YAISWVRQAPGQGLE WMGGIIPIFGTANYA QKFQGRVTITADESTS TAYMELSSLRSEDTAV YYCARSSYGWSYEFD YWGQGTLVTVSS (SEQ ID NO:326)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:327)	DIQMTQSPSSLSAS VGDRVTITCRASQSI NTNLNWYQQKPGK APKLLIYAASSLQSG VPSRFSGSGSGTDFT LTISSLQPEDFATYYC QQARDTPITFGQGT KVEIK (SEQ ID NO:328)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:329)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB49	Human IgG1/kappa	Group 1	GYTFPSHT (SEQ ID NO:330)	IYPFIDST (SEQ ID NO:331)	ARGIRGYTMDY (SEQ ID NO:332)	ESVDNYGLSF (SEQ ID NO:333)	GAS (SEQ ID NO:334)	QQSKEVPYT (SEQ ID NO:335)	QVQLVQSGAEVKKPGASVKVSCKASGYTFPSHTIHWVRQAPGQRLEWMGSIYPFIDSTIYNQKFKDRVTITRDTSASTAYMELSSLRSEDTAVYYCARGIRGYTMDYWGQGTLVTVSS (SEQ ID NO:336)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:337)	DVVMTQSPLSLPVTLGQPASISCRASESVDNYGLSFMNWFQQRPGQSPRRLIYGASNQGSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCQQSKEVPYTFGQGTKLEIK (SEQ ID NO:338)	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:339)
VSTB50 INX500	Human IgG1/kappa	NLTLLDSGL and VQTGKDAP SNC Group 2	GYTFTNYG (SEQ ID NO:340)	INPYTGEP (SEQ ID NO:341)	AREGYGNYIFPY (SEQ ID NO:342)	ESVDTYANSL (SEQ ID NO:343)	RAS (SEQ ID NO:344)	QQTNEDPRT (SEQ ID NO:345)	QVQLVQSGSELKKPGASVKVSCKASGYTFTNYGLNWVRQAPGQGLEWMGWINPYTGEPTYADDFKGRFVFSLDTSVSTAYLQICSLKAEDTAVYYCAREGYGNYIFPYWGQGTLVTVSS (SEQ ID NO:346)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:347)	DIVMTQTPLSLSVTPGQPASISCRASESVDTYANSLMHWYLQKPGQPPQLLIYRASNLESGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCQQTNEDPRTFGQGTKLEIK (SEQ ID NO:348)	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:349)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB51	Human IgG1/kappa	Group 1	GFTFSSYT (SEQ ID NO:350)	ISNSGSYT (SEQ ID NO:351)	ARDTVLSPFDY (SEQ ID NO:352)	SSISY (SEQ ID NO:353)	DTS (SEQ ID NO:354)	HQRSSFT (SEQ ID NO:355)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYTMSWVRQAPGKGLEWVATISNSGSYTYYLDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDTVLSPFDYWGQGTTVTVSS (SEQ ID NO:356)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:357)	EIVLTQSPDFQSVTPKEKVTITCSATSSISYMHWYQQKPDQSPKLLIKDTSELASGVPSRFSGSGSGTDFTLTINSLEAEDAATYYCHQRSSFTFGQGTKLEIK (SEQ ID NO:358)	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:359)
VSTB52	Human IgG1/kappa		GGTFSNYW (SEQ ID NO:360)	IYPGGGFT (SEQ ID NO:361)	ARYYRSDEDYSMDF (SEQ ID NO:362)	QSLLYSNGKTY (SEQ ID NO:363)	LVS (SEQ ID NO:364)	VQATHFPQT (SEQ ID NO:365)	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSNYWIGWVRQAPGQGLEWMGEIYPGGGFTHYNEKFKGRVTITADESTSTAYMELSSLRSEDTAVYYCARYYRSDEDYSMDFWGQGTLVTVSS (SEQ ID NO:366)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:367)	DVVMTQSPLSLPVTLGQPASISCKSSQSLLYSNGKTYLNWFQQRPGQSPRRLIYLVSKLDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCVQATHFPQTFGQGTKLEIK (SEQ ID NO:368)	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:369)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB53 INX905	Human IgG1/kappa	Group 1	GYTFTHYT (SEQ ID NO:370)	IIPSSGYS (SEQ ID NO:371)	ARGAYDDYY DYYAMDY (SEQ ID NO:372)	QTIVHSNGN TY (SEQ ID NO:373)	KVS (SEQ ID NO:374)	FQASHVPW T (SEQ ID NO:375)	QVQLVQSGAEVKKPG ASVKVSCKASGYTFTH YTIHWVRQAPGQGLE WMGYIIPSSGYSEYN QKFKDRVTMTRDTST STVYMELSSLRSEDTA VYYCARGAYDDYYDY YAMDYWGQGTLVTV SS (SEQ ID NO:376)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:377)	DIVMTQSPLSLPVTP GEPASISCRSSQTIV HSNGNTYLEWYLQK PGQSPQLLIYKVSNR FSGVPDRFSGSGSG TDFTLKISRVEAEDV GVYYCFQASHVPW TFGQGTKLEIK (SEQ ID NO:378)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:379)
VSTB54 INX906	Human IgG1/kappa	Group 2	GYNIKDTY (SEQ ID NO:380)	IDPTHGYV (SEQ ID NO:381)	ARDRFDPYW FLDV (SEQ ID NO:382)	ESVEYYGTSL (SEQ ID NO:383)	DAF (SEQ ID NO:384)	QQSRKVP WT (SEQ ID NO:385)	QVQLVQSGAEVKKPG ASVKVSCKASGYNIKD TYMHWVRQAPGQG LEWMGRIDPTHGYVI YDPKFQGRVTMTRDT STSTVYMELSSLRSED TAVYYCARDRFDPYW FLDVWGQGTLVTVSS (SEQ ID NO:386)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:387)	DIVMTQTPLSLSVTP GQPASISCRASESVE YYGTSLMQWYLQK PGQSPQLLIYDAFN VESGVPDRFSGSGS GTDFTLKISRVEAED VGVYYCQQSRKVP WTFGQGTKLEIK (SEQ ID NO:388)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:389)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB55	Human IgG1/kappa		GYSIASDYV (SEQ ID NO:390)	ISYSGST (SEQ ID NO:391)	ARITTVVPTG SYYGVDF (SEQ ID NO:392)	SSVNF (SEQ ID NO:393)	DTS (SEQ ID NO:394)	QQWSNYP FT (SEQ ID NO:395)	QVQLQESGPGLVKPS ETLSLTCAVSGYSIASD YVWNWIRQPPGKGL EWIGYISYSGSTSNNP SLNSRVTISVDTSKNQ FSLKLSSVTAADTAVY YCARITTVVPTGSYYG VDFWGQGTTVTVSS (SEQ ID NO:396)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:397)	EIVLTQSPDFQSVTP KEKVTITCSGSSSVN FMYWYQQKPDQSP KLLIKDTSNLASGVP SRFSGSGSGTDFTLTI NSLEAEDAATYYCQ QWSNYPFTFGQGT KLEIK (SEQ ID NO:398)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:399)
VSTB56 IN0901	Human IgG1/kappa	Group 2	GYTFTSYW (SEQ ID NO:400)	IIPNTLHT (SEQ ID NO:401)	ARLDGDYDY ALDY (SEQ ID NO:402)	ESVEYYGTSF (SEQ ID NO:403)	TAS (SEQ ID NO:404)	QQSRKVPY T (SEQ ID NO:405)	QVQLVQSGAEVKKPG ASVKVSCKASGYTFTS YWLHWVRQAPGQG LEWMGYIIPNTLHTD YNQKFKDRVTMTRD TSTSTVYMELSSLRSE DTAVYYCARLDGDYD YALDYWGQGTLVTVS S (SEQ ID NO:406)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:407)	DIVMTQTPLSLSVTP GQPASISCRASESVE YYGTSFMQWYLQK PGQPPQLLIYTASNV ESGVPDRFSGSGSG TDFTLKISRVEAEDV GVYYCQQSRKVPYT FGQGTKLEIK (SEQ ID NO:408)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:409)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB57	Human IgG1/kappa		GFTFSTYA (SEQ ID NO:410)	ISSGGSDT (SEQ ID NO:411)	ARPTYYGIFS YFDY (SEQ ID NO:412)	SSVSY (SEQ ID NO:413)	STS (SEQ ID NO:414)	HQWRTYPT (SEQ ID NO:415)	EVQLVESGGGLVQPG GSLRLSCAASGFTFSTY AMSWVRQAPGKGLE WVATISSGGSDTYYP DTVKGRFTISRDNAK NSLYLQMNSLRAEDT AVYYCARPTYYGIFSY FDYWGQGTLVTVSS (SEQ ID NO:416)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:417)	DIQLTQSPSFLSASV GDRVTITCSASSSVS YMHWYQQKPGKA PKLLIYSTSNLASGVP SRFSGSGSGTEFTLTI SSLQPEDFATYYCH QWRTYPTFGQGTKL EIK(SEQ ID NO:418)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:419)
VSTB58	Human IgG1/kappa		GFSLT NYG (SEQ ID NO:420)	IWRGG NT (SEQ ID NO:421)	ARSMV SYTVDY (SEQ ID NO:422)	SSVSY (SEQ ID NO:423)	DTS (SEQ ID NO:424)	QQWS SYPPT (SEQ ID NO:425)	QVQLQESGPGLVKPS ETLSLTCTVSGFSLTNY GVHWIRQPPGKGLE WIGVIWRGGNTDYN AAFMSRVTISVDTSK NQFSLKLSSVTAADTA VYYCARSMVSYTVDY WGQGTLVTVSS (SEQ ID NO:426)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:427)	EIVLTQSPDFQSVTP KEKVTITCSASSSVSY MHWYQQKPDQSP KLLIKDTSNLASGVP SRFSGSGSGTDFTLTI NSLEAEDAATYYCQ QWSSYPPTFGQGTK LEIK (SEQ ID NO:428)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:429)

2022252828 14 Oct 2022

FIGURE 4

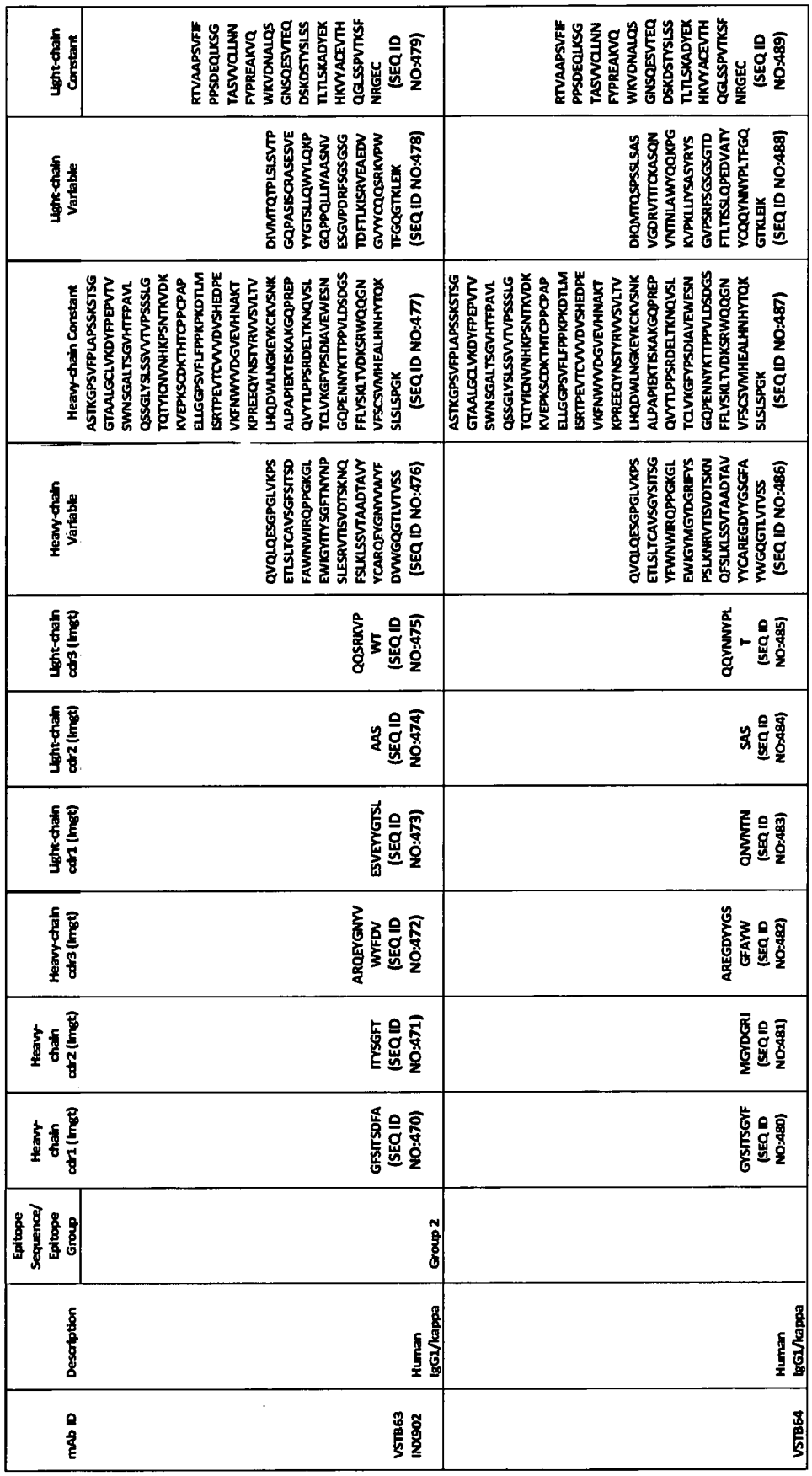
mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB59	Human IgG1/kappa	Group 1	GYTFTDYW (SEQ ID NO:430)	IETSLNYP (SEQ ID NO:431)	ARWGIYGNP WFAY (SEQ ID NO:432)	ESVDSYVNSF (SEQ ID NO:433)	RAS (SEQ ID NO:434)	QQSNEDPY T (SEQ ID NO:435)	QVQLVQSGAEVKKPG ASVKVSCKASGYTFTD YWMHWVRQAPGQ GLEWMGAIETSLNYP SYNQKFKGRVTMTRD TSTSTVYMELSSLRSE DTAVYYCARWGIYGN PWFAYWGRGTLVTV SS (SEQ ID NO:436)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:437)	DIVMTQTPLSLSVTP GQPASISCRASESVD SYVNSFVHWYLQKP GQPPQLLIYRASNLE SGVPDRFSGSGSGT DFTLKISRVEAEDVG VYYCQQSNEDPYTF GQGTKLEIK (SEQ ID NO:438)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:439)
VSTB60 Group 2	Human IgG1/kappa	NLTLLDSGL and VQTGKDAP SNC Group 2	GYTFTNYG (SEQ ID NO:440)	INTYTGES (SEQ ID NO:441)	ARDYYGIYVS AY (SEQ ID NO:442)	ESVDNYANS F (SEQ ID NO:443)	RAS (SEQ ID NO:444)	QQSHEDPY T (SEQ ID NO:445)	QVQLVQSGSELKKPG ASVKVSCKASGYTFTN YGMTWVRQAPGQG LEWMGWINTYTGES TYADDFKGRFVFSLDT SVSTAYLQICSLKAEDT AVYYCARDYYGIYVSA YWGQGTLVTVSS (SEQ ID NO:446)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:447)	DIVMTQTPLSLSVTP GQPASISCRASESVD NYANSFMHWYLQK PGQSPQLLIYRASNL ESGVPDRFSGSGSGG TDFTLKISRVEAEDV GVYYCQQSHEDPYT FGQGTKLEIK (SEQ ID NO:448)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:449)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB61	Human IgG1/kappa		GYTFTSHW (SEQ ID NO:450)	INPRDGRT (SEQ ID NO:451)	ARGDFHYGD YFWYFDV (SEQ ID NO:452)	QNVHGA (SEQ ID NO:453)	MAS (SEQ ID NO:454)	LQHWNYLT (SEQ ID NO:455)	QVQLVQSGAEVKKPG ASVKVSCKASGYTFTS HWMHWVRQAPGQ GLEWMGEINPRDGR TNYNEKFKTRVTMTR DTSTSTVYMELSSLRS EDTAVYYCARGDFHY GDYFWYFDVWGQGT LVTVSS (SEQ ID NO:456)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:457)	DIQMTQSPSSLSAS VGDRVTITCKASQN VHGAVAWYQQKP GKVPKLLIYMASNR PTGVPSRFSGSGSG TDFTLTISSLQPEDV ATYYCLQHWNYLTF GQGTKLEIK (SEQ ID NO:458)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:459)
VSTB62	Human IgG1/kappa		GYTFTHYW (SEQ ID NO:460)	IYPGDGDT (SEQ ID NO:461)	ARRDYDYGD Y (SEQ ID NO:462)	SSVSH (SEQ ID NO:463)	LTS (SEQ ID NO:464)	QQYQTYPP T (SEQ ID NO:465)	QVQLVQSGAEVKKPG ASVKVSCKASGYTFTH YWIQWVRQAPGQGL EWMGAIYPGDGDTR YTQKFKGRVTMTRDT STSTVYMELSSLRSED TAVYYCARRDYDYGD YWGQGTTVTVSS (SEQ ID NO:466)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:467)	EIVLTQSPDFQSVTP KEKVTITCSASSSVS HMYWYQQKPDQS PKLLIKLTSNLASGVP SRFSGSGSGTDFTLTI NSLEAEDAATYYCQ QYQTYPPTFGQGTR LEIK (SEQ ID NO:468)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:469)

2022252828 14 Oct 2022

FIGURE 4



mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB63 IN0902	Human IgG1/kappa	Group 2	GFSITSDFA (SEQ ID NO:470)	ITYSGFT (SEQ ID NO:471)	ARQEYGNVV WYFDV (SEQ ID NO:472)	ESVEYYGTSL (SEQ ID NO:473)	AAS (SEQ ID NO:474)	QQSRKVP WT (SEQ ID NO:475)	QVQLQESGPGLVKPS ETLSLTCAVSGFSITSD FAWNWIRQPPGKGL EWIGYITYSGFTNYNP SLESRVTISVDTSKNQ FSLKLSSVTAADTAVY YCARQEYGNVVWYF DVWGQGTLVTVSS (SEQ ID NO:476)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:477)	DIVMTQTPLSLSVTP GQPASISCRASESVE YYGTSLLQWYLQKP GQPPQLLIYAASNV ESGVPDRFSGSGSG TDFTLKISRVEAEDV GVYYCQQSRKVPW TFGQGTKLEIK (SEQ ID NO:478)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:479)
VSTB64	Human IgG1/kappa		GYSITSGYF (SEQ ID NO:480)	MGYDGRI (SEQ ID NO:481)	AREGDYYGS GFAYW (SEQ ID NO:482)	QNVNTN (SEQ ID NO:483)	SAS (SEQ ID NO:484)	QQYNNYPL T (SEQ ID NO:485)	QVQLQESGPGLVKPS ETLSLTCAVSGYSITSG YFWNWIRQPPGKGL EWIGYMGYDGRIFYS PSLKNRVTISVDTSKN QFSLKLSSVTAADTAV YYCAREGDYYGSGFA YWGQGTLVTVSS (SEQ ID NO:486)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:487)	DIQMTQSPSSLSAS VGDRVTITCKASQN VNTNLAWYQQKPG KVPKLLIYSASYRYS GVPSRFSGSGSGTD FTLTISSLQPEDVATY YCQQYNNYPLTFGQ GTKLEIK (SEQ ID NO:488)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:489)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB65	Human IgG1/kappa	Group 1	GYTFTSYW (SEQ ID NO:490)	INPSNGLT (SEQ ID NO:491)	ARSYDYDGD YYAMDY (SEQ ID NO:492)	QSIVHSNGN TY (SEQ ID NO:493)	KVS (SEQ ID NO:494)	FQASHVPW T (SEQ ID NO:495)	QVQLVQSGAEVKKPG ASVKVSCKASGYTFTS YWIHWVRQAPGQGL EWMGEINPSNGLTNY NEKFRNRVTMTRDTS TSTVYMELSSLRSEDT AVYYCARSYDYDGDY YAMDYWGQGTLVTV SS (SEQ ID NO:496)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:497)	DIVMTQSPLSLPVTP GEPASISCRSTQSIV HSNGNTYLEWYLQK PGQSPQLLIYKVSNR FSGVPDRFSGSGSG TDFTLKISRVEAEDV GVYYCFQASHVPW TFGQGTKLEIK (SEQ ID NO:498)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:499)
VSTB66 INX907	Human IgG1/kappa	Group 2	GYPFTGYF (SEQ ID NO:500)	INPYNGGT (SEQ ID NO:501)	ARWTFDGLF MDY (SEQ ID NO:502)	ENVDKYGISF (SEQ ID NO:503)	ATS (SEQ ID NO:504)	QQSKEDPY T (SEQ ID NO:505)	QVQLVQSGAEVKKPG ASVKVSCKASGYPFTG YFMHWVRQAPGQG LEWMGRINPYNGGT VYNQNFNDRVTMTR DTSTSTVYMELSSLRS EDTAVYYCARWTFDG LFMDYWGQGTTVTV SS (SEQ ID NO:506)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:507)	DVVMTQSPLSLPVT LGQPASISCRASENV DKYGISFMNWFQQ RPGQSPRRLIYATSN QGSGVPDRFSGSGS GTDFTLKISRVEAED VGVYYCQQSKEDPY TFGQGTKLEIK (SEQ ID NO:508)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:509)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB67 INX909	Human IgG1/kappa	Group 1	DYIFSSYW (SEQ ID NO:510)	IFPGSGGT (SEQ ID NO:511)	ARAMYDYD MYVFDS (SEQ ID NO:512)	QDISSY (SEQ ID NO:513)	YTS (SEQ ID NO:514)	QHVMTLP WT (SEQ ID NO:515)	QVQLVQSGAEVKKPG ASVKVSCKASDYIFSS YWIQWVRQAPGQGL EWMGEIFPGSGGTNY NEKFKGRVTMTRDTS TSTVYMELSSLRSEDT AVYYCARAMYDYDM YYFDSWGQGTTVTVS S (SEQ ID NO:516)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:517)	DIQMTQSPSSLSAS VGDRVTITCRASQDI SSYLNWYQQKPGK VPKLLIYYTSRLHSG VPSRFSGSGSGTDFT LTISSLQPEDVATYY CQHVNTLPWTFGQ GTKLEIK (SEQ ID NO:518)	RTVAAPSVFIF PPSDEQLKSGT ASVVCLLNNFY PREAKVQWK VDNALQSGNS QESVTEQDSK DSTYSLSSTLTL SKADYEKHKV YACEVTHQGL SSPVTKSFNRG EC (SEQ ID NO:519)
VSTB68	Human IgG1/kappa		GYTFTDYT (SEQ ID NO:520)	INPYNGG T (SEQ ID NO:521)	ARHYGNYN WYFDV (SEQ ID NO:522)	QYVNTA (SEQ ID NO:523)	SAS (SEQ ID NO:524)	QQHFTTPI T (SEQ ID NO:525)	QVQLVQSGAEVKKPG ASVKVSCKASGYTFTD YTMNWVRQAPGQRL EWMGLINPYNGGTT YNQKFKGRVTITRDTS ASTAYMELSSLRSEDT AVYYCARHYGNYNW YFDVWGQGTTVTVSS (SEQ ID NO:526)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:527)	DIQLTQSPSFLSASV GDRVTITCKASQYV NTAVAWYQQKPGK APKLLIYSASYRYTG VPSRFSGSGSGTEFT LTISSLQPEDFATYYC QQHFTTPITFGQGT KLEIK (SEQ ID NO:528)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:529)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (imgt)	Heavy-chain cdr2 (imgt)	Heavy-chain cdr3 (imgt)	Light-chain cdr1 (imgt)	Light-chain cdr2 (imgt)	Light-chain cdr3 (imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB69	Human IgG1/kappa	Group 1	GYTFTNY G (SEQ ID NO:530)	INTYTGEP (SEQ ID NO:531)	ARNYGNVV AY (SEQ ID NO:532)	QDINSY (SEQ ID NO:533)	RAN (SEQ ID NO:534)	LQYDEFPL T (SEQ ID NO:535)	QVQLVQSGSELKKPG ASVKVSCKASGYTFTN YGMNWVRQAPGQG LEWMGWINTYTGEP TYADDFKGRFVFSLDT SVSTAYLQICSLKAEDT AVYYCARNYGNVVAY WGQGTTVTVSS (SEQ ID NO:536)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:537)	DIQMTQSPSSLSAS VGDRVTITCKASQDI NSYLSWFQQKPGK APKSLIYRANRLVDG VPSRFSGSGSGTDFT LTISSLQPEDFATYYC LQYDEFPLTFGQGT RLEIK (SEQ ID NO:538)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:539)
VSTB70	Human IgG1/kappa	Group 1	GYTFSNYW (SEQ ID NO:540)	ILPGSGNV (SEQ ID NO:541)	ATPPHYYGY DYYDVNY (SEQ ID NO:542)	QSLLDSDGKT Y (SEQ ID NO:543)	LVS (SEQ ID NO:544)	WQGTHFP QT (SEQ ID NO:545)	EVQLVQSGAEVKKPG ATVKISCKVSGYTFSN YWIEWVQQAPGKGL EWMGEILPGSGNVH YNEKFKGRVTITADTS TDTAYMELSSLRSEDT AVYYCATPPHYYGYD YYDVNYWGQGTLVT VSS (SEQ ID NO:546)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:547)	DVVMTQSPLSLPVT LGQPASISCKSSQSL LDSDGKTYLNWFQ QRPGQSPRRLIYLVS ELDSGVPDRFSGSG SGTDFTLKISRVEAE DVGVYYCWQGTHF PQTFGQGTKLEIK (SEQ ID NO:548)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:549)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB71	Human IgG1/kappa		GYVFSRSW (SEQ ID NO:550)	IYPGDGDT (SEQ ID NO:551)	ARRWFL (SEQ ID NO:552)	QSLLNSGDQ KSY (SEQ ID NO:553)	GAS (SEQ ID NO:554)	QNDHSYPL T (SEQ ID NO:555)	QVQLVQSGAEVKKPG SSVKVSCKASGYVFSR SWINWVRQAPGQGL EWMGRIYPGDGDTN YNGKFKGRVTITADES TSTAYMELSSLRSEDT AVYYCARRWFLWGQ GTLVTVSS (SEQ ID NO:556)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:557)	DIVMTQSPDSLAVS LGERATINCKSSQSL LNSGDQKSYLAWY QQKPGQPPKLLIYG ASTRESGVPDRFSGS GSGTDFTLTISSLQA EDVAVYYCQNDHSY PLTFGQGTKLEIK (SEQ ID NO:558)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:559)
VSTB72	Human IgG1/kappa		GFTFSSYA (SEQ ID NO:560)	ISSGGSHT (SEQ ID NO:561)	ARRGNLYDG PY (SEQ ID NO:562)	SSVSH (SEQ ID NO:563)	DTS (SEQ ID NO:564)	QQWNFYP FT (SEQ ID NO:565)	EVQLVESGGGLVQPG GSLRLSCAASGFTFSSY AMSWVRQAPGKGLE WVAEISSGGSHTYYP DTVTGRFTISRDNAK NSLYLQMNSLRAEDT AVYYCARRGNLYDGP YWGQGTLVTVSS (SEQ ID NO:566)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:567)	EIVLTQSPATLSLSPG ERATLSCSASSSVSH MYWYQQKPGQAP RLLIYDTSKLASGIPA RFSGSGSGTDFTLTIS SLEPEDFAVYYCQQ WNFYPFTFGQGTKL EIK (SEQ ID NO:568)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:569)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (imgt)	Heavy-chain cdr2 (imgt)	Heavy-chain cdr3 (imgt)	Light-chain cdr1 (imgt)	Light-chain cdr2 (imgt)	Light-chain cdr3 (imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB73 INX910	Human IgG1/kappa	Group 2	GYTFTDYV (SEQ ID NO:570)	IYPGSGNT (SEQ ID NO:571)	ARVLVSVMDY (SEQ ID NO:572)	SSINY (SEQ ID NO:573)	DTS (SEQ ID NO:574)	HQRSSYPWT (SEQ ID NO:575)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYVVISWVRQAPGQGLEWMGEIYPGSGNTYYYEKFKGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARVLVSVMDYWGQGTLVTVSS (SEQ ID NO:576)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:577)	EIVLTQSPDFQSVTPKEKVTITCSASSSINYITWYQQKPDQSPKLLIKDTSKLASGVPSRFSGSGSGTDFTLTINSLEAEDAATYYCHQRSSYPWTFGQGTRLEIK (SEQ ID NO:578)	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:579)
VSTB74	Human IgG1/kappa Group 4	Group 4	GYIFTDYN (SEQ ID NO:580)	INPKYDST (SEQ ID NO:581)	AADGSSAMDY (SEQ ID NO:582)	QSLLNSGHQKNY (SEQ ID NO:583)	GAS (SEQ ID NO:584)	QNDHRYPLT (SEQ ID NO:585)	QMQLVQSGPEVKKPGTSVKVSCKASGYIFTDYNIDWVRQARGQRLEWIGDINPKYDSTRYNQKFKGRVTITRDMSTSTAYMELSSLRSEDTAVYYCAADGSSAMDYWGQGTTVTVSS (SEQ ID NO:586)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:587)	DIVMTQSPDSLAVSLGERATINCKSSQSLLNSGHQKNYLAWYQQKPGQPPKLLIYGASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQNDHRYPLTFGQGTKLEIK (SEQ ID NO:588)	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:589)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB75	Human IgG1/kappa		GFNIKDYY (SEQ ID NO:590)	IDPENGNT (SEQ ID NO:591)	ARDYGYFDY W (SEQ ID NO:592)	SSVIY (SEQ ID NO:593)	STS (SEQ ID NO:594)	QQRSSYPH T (SEQ ID NO:595)	QVQLVQSGAEVKKPG SSVKVSCKASGFNIKD YYIHWVRQAPGQGLE WMGWIDPENGNTIY DPKFQGRVTITADEST STAYMELSSLRSEDTA VYYCARDYGYFDYW GQGTLVTVSS (SEQ ID NO:596)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:597)	DVVMTQSPAFLSVT PGEKVTITCSAGSSV IYMYWYQQKPDQA PKLLIKSTSNLASGVP SRFSGSGSGTDFTFT ISSLEAEDAATYYCQ QRSSYPHTFGQGTK LEIK (SEQ ID NO:598)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:599)
VSTB76 INX911	Human IgG1/kappa	Group 2	GYTFTDYW (SEQ ID NO:600)	IYPSHSYT (SEQ ID NO:601)	ARGGYRYPY YAMDY (SEQ ID NO:602)	ENIYGA (SEQ ID NO:603)	GAT (SEQ ID NO:604)	QNVLSTPYT (SEQ ID NO:605)	QVQLVQSGAEVKKPG ASVKVSCKASGYTFTD YWINWVRQAPGQGL EWMGNIYPSHSYTNY NQEFKDRVTMTRDTS TSTVYMELSSLRSEDT AVYYCARGGYRYPYY AMDYWGQGTTVTVS S (SEQ ID NO:606)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:607)	AIQLTQSPSSLSASV GDRVTITCGASENIY GALNWYQQKPGKA PKLLIYGATNLADGV PSRFSGSGSGTDFTL TISSLQPEDFATYYC QNVLSTPYTFGQGT KLEIK (SEQ ID NO:608)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:609)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB78	Human IgG1/kappa	Group 2	GYTFTNYW (SEQ ID NO:610)	INPSSGYT (SEQ ID NO:611)	ARDGGSVLFGY (SEQ ID NO:612)	QSLLNSGIRKNY (SEQ ID NO:613)	SAS (SEQ ID NO:614)	KQSYNLYT (SEQ ID NO:615)	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWMHWVRQAPGQGLEWMGYINPSSGYTEYNQKFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDGGSVLFGYWGQGTTVTVSS (SEQ ID NO:616)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:617)	DIVMTQSPDSLAVSLGERATINCKSSQSLLNSGIRKNYLAWYQQKPGQPPKLLIYSASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCKQSYNLYTFGQGTKLEIK (SEQ ID NO:618)	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:619)
VSTB79	Human IgG1/kappa		AYSITSDYA (SEQ ID NO:620)	ITYSGST (SEQ ID NO:621)	ARSFGY (SEQ ID NO:622)	QSIGTS (SEQ ID NO:623)	YAS (SEQ ID NO:624)	QQJNSWPTT (SEQ ID NO:625)	QVQLQESGPGLVKPSETLSLTCAVSAYSITSDYAWNWIRQPPGKGLEWIGYITYSGSTRYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARSFGYWGQGTTVTVSS (SEQ ID NO:626)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:627)	EIVMTQSPATLSVSPGERATLSCRASQSIGTSIHWYQQKPGQAPRLLIYYASESISGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQJNSWPTTFGQGTKLEIK (SEQ ID NO:628)	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:629)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB80	Human IgG1/kappa		GFNIKDYY (SEQ ID NO:630)	IDPENGDT (SEQ ID NO:631)	ARDMGSSYVY (SEQ ID NO:632)	SSVIY (SEQ ID NO:633)	STS (SEQ ID NO:634)	QQRSSYPFT (SEQ ID NO:635)	QVQLVQSGAEVKKPGASVKVSCKASGFNIKDYYMHWVRQAPGQGLEWMGWIDPENGDTEYAPKFQDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDMGSSYVYWGRGTLVTVSS (SEQ ID NO:636)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:637)	DVVMTQSPAFLSVTPGEKVTITCSASSSVIYMHWYQQKPDQAPKLLIKSTSNLASGVPSRFSGSGSGTDFTFTISSLEAEDAATYYCQQRSSYPFTFGQGTKLEIK (SEQ ID NO:638)	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:639)
VSTB81	Human IgG1/kappa	Group 1	GFSLSTSGMG (SEQ ID NO:640)	IYWDDDK (SEQ ID NO:641)	ARRPDYFGSSYVD (SEQ ID NO:642)	ESVDTYGNSF (SEQ ID NO:643)	LAS (SEQ ID NO:644)	QQNNEDPWT (SEQ ID NO:645)	QVTLKESGPALVKPTQTLTLTCTFSGFSLSTSGMGVSWIRQPPGKALEWLAHIYWDDDKRYNPSLKSRLTISKDTSKNQVVLTMTNMDPVDTATYYCARRPDYFGSSYVDVWGQGTTVTVSS (SEQ ID NO:646)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:647)	DIVMTQTPLSLSVTPGQPASISCRASESVDTYGNSFMHWYLQKPGQPPQLLIYLASNLDFGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCQQNNEDPWTFGQGTKLEIK (SEQ ID NO:648)	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:649)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB82	Human IgG1/kappa		GYSITSDYA (SEQ ID NO:650)	ITYSGST (SEQ ID NO:651)	ARSHYGSTY WYFDV (SEQ ID NO:652)	ESVEYYGTSL (SEQ ID NO:653)	AAS (SEQ ID NO:654)	QQTRKVP WT (SEQ ID NO:6565)	QVQLQESGPGLVKPS ETLSLTCAVSGYSITSD YAWNWIRQPPGKGL EWIGFITYSGSTNYNP SLKSRVTISVDTSKNQ FSLKLSSVTAADTAVY YCARSHYGSTYWYFD VWGQGTTVTVSS (SEQ ID NO:656)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:657)	DIVMTQTPLSLSVTP GQPASISCRASESVE YYGTSLMQWYLQK PGQSPQLLIYAASN VESGVPDRFSGSGS GTDFTLKISRVEAED VGVYYCQQTRKVP WTFGQGTRLEIK (SEQ ID NO:658)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:659)
VSTB83	Human IgG1/kappa		GYTFTSYD (SEQ ID NO:660)	IYPGDGYT (SEQ ID NO:661)	ARWGYGSYA MDY (SEQ ID NO:662)	QSLVHSNGN TY (SEQ ID NO:664)	KVS (SEQ ID NO:664)	SQSTHVPP T (SEQ ID NO:665)	QVQLVQSGAEVKKPG ASVKVSCKASGYTFTS YDINWVRQAPGQGL EWMGWIYPGDGYTE YNEKFRGRVTMTRDT STSTVYMELSSLRSED TAVYYCARWGYGSYA MDYWGQGTLVTVSS (SEQ ID NO:666)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:667)	DIVMTQSPLSLPVTP GEPASISCRSSQSLV HSNGNTYLHWYLQ KPGQSPQLLIYKVSN RFSGVPDRFSGSGS GTDFTLKISRVEAED VGVYYCSQSTHVPP TFGQGTKLEIK (SEQ ID NO:668)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:669)

WO 2017/181109 PCT/US2017/027765

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB84 INX912	Human IgG1/kappa	Group 2	GYTFTSYW (SEQ ID NO:670)	INPSTGYP (SEQ ID NO:671)	ARSYYDYDG GAWFAY (SEQ ID NO:672)	ESVEYYGTSL (SEQ ID NO:673)	AAS (SEQ ID NO:674)	QQSRKVPS T (SEQ ID NO:675)	QVQLVQSGAEVKKPG ASVKVSCKASGYTFTS YWMHWVRQAPGQ GLEWMGYINPSTGYP GYNQKFKDRVTMTR DTSTSTVYMELSSLRS EDTAVYYCARSYYDY DGGAWFAYWGQGT TVTVSS (SEQ ID NO:676)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:677)	DIVMTQTPLSLSVTP GQPASISCRASESVE YYGTSLMQWYLQK PGQPPQLLIYAASN VESGVPDRFSGSGS GTDFTLKISRVEAED VGVYYCQQSRKVPS TFGQGTKLEIK (SEQ ID NO:678)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:679)
VSTB85 INX913	Human IgG1/kappa	Group 1	GYTFTDYA (SEQ ID NO:680)	IDTYYGNT (SEQ ID NO:681)	ARGGGIDALD Y (SEQ ID NO:682)	QSVSND (SEQ ID NO:683)	YAS (SEQ ID NO:684)	QQGYTSLR T (SEQ ID NO:685)	QVQLVQSGAEVKKPG ASVKVSCKASGYTFTD YAMHWVRQAPGQG LEWMGVIDTYYGNT NYNQKFKGRVTMTR DTSISTAYMELSRLRS DDTAVYYCARGGGID ALDYWGQGTTVTVSS (SEQ ID NO:686)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:687)	DKQMTQSPSSLSAS VGDRVTITCKASQS VSNDVVWYQQKPG KAPKLLIYYASNRYI GVPSRFSGSGSGTD FTFTISSLQPEDIAT YYQQGYTSLRTFGQ GTKLEIK (SEQ ID NO:688)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:689)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB87	Human IgG1/kappa		GYSITSGYS (SEQ ID NO:690)	IHYIGIT (SEQ ID NO:691)	AREDYDYDG VFAY (SEQ ID NO:692)	QSISNN (SEQ ID NO:693)	YAS (SEQ ID NO:694)	QQSNSWP HT (SEQ ID NO:695)	QVQLQESGPGLVKPS ETLSLTCAVSGYSITSG YSWHWIRQPPGKGL EWIGYIHYIGITNNNP SLKSRVTISVDTSKNQ FSLKLSSVTAADTAVY YCAREDYDYDGVFAY WGQGTLVTVSS (SEQ ID NO:696)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:697)	EIVLTQSPATLSLSPG ERATLSCRASQSISN NLHWYQQKPGQAP RLLIYYASQSISGIPA RFSGSGSGTDFTLTIS SLEPEDFAVYYCQQ SNSWPHTFGQGTKL EIK (SEQ ID NO:698)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:699)
VSTB88	Human IgG1/kappa		GFSLTNYD (SEQ ID NO:700)	IWTGGGT (SEQ ID NO:701)	AREGLLLPLY (SEQ ID NO:702)	QNVGTN (SEQ ID NO:703)	SAS (SEQ ID NO:704)	QQYNSYPL T (SEQ ID NO:705)	QVQLQESGPGLVKPS ETLSLTCTVSGFSLTNY DISWIRQPPGKGLEW IGVIWTGGGTNYNSA FMSRVTISVDTSKNQF SLKLSSVTAADTAVYY CAREGLLLPLYWGQG TLVTVSS (SEQ ID NO:706)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:707)	DIQMTQSPSSLSAS VGDRVTITCKASQN VGTNVAWYQQKPG KVPKLLIYSASYRYS GVPSRFSGSGSGTD FTLTISSLQPEDVATY YCQQYNSYPLTFGQ GTKLEIK (SEQ ID NO:708)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:709)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB89	Human IgG1/kappa		GYTFTNFG (SEQ ID NO:710)	INTYTGEP (SEQ ID NO:711)	ARGAYYYGS RVWFAY (SEQ ID NO:712)	QNLVHSNGN TY (SEQ ID NO:713)	KVS (SEQ ID NO:714)	SQSSHVPYT (SEQ ID NO:715)	QVQLVQSGSELKKPG ASVKVSCKASGYTFTN FGMNWVRQAPGQG LEWMGWINTYTGEP TYADDFKGRFVFSLDT SVSTAYLQICSLKAEDT AVYYCARGAYYYGSR VWFAYWGQGTLVTV SS (SEQ ID NO:716)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:717)	DIVMTQSPLSLPVTP GEPASISCTSSQNLV HSNGNTYLHWYLQ KPGQSPQLLIYKVSN RFSGVPDRFSGSGS GTDFTLKISRVEAED VGVYYCSQSSHVPY TFGQGTKLEIK (SEQ ID NO:718)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:719)
VSTB90	Human IgG1/kappa		GFSLTSSG (SEQ ID NO:720)	IWSGGNT (SEQ ID NO:721)	AREDYDYDW YFDV (SEQ ID NO:722)	ESVEYYGTSL (SEQ ID NO:723)	AAS (SEQ ID NO:724)	QQSRKVP WT (SEQ ID NO:725)	QVQLQESGPGLVKPS ETLSLTCTVSGFSLTSS GVHWIRQPPGKGLE WIGVIWSGGNTDYN AAFISRVTISVDTSKN QFSLKLSSVTAADTAV YYCAREDYDYDWYFD VWGQGTTVTVSS (SEQ ID NO:726)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:727)	DIVMTQTPLSLSVTP GQPASISCRASESVE YYGTSLMQWYLQK PGQPPQLLIYAASN VKSGVPDRFSGSGS GTDFTLKISRVEAED VGVYYCQQSRKVP WTFGQGTKLEIK (SEQ ID NO:728)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:729)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB91	Human IgG1/kappa		GYTFA NFW (SEQ ID NO:730)	IFPGNS DT (SEQ ID NO:731)	ARELTG TYYFDY (SEQ ID NO:732)	SSVSY (SEQ ID NO:733)	SSS (SEQ ID NO:734)	HQWS GHFT (SEQ ID NO:735)	QVQLVQSGAEVKKPG ASVKVSCKASGYTFA NFWMHWVRQAPGQ GLEWMGAIFPGNSDT GYNQKFKGRVTMTR DTSTSTVYMELSSLRS EDTAVYYCARELTGTY YFDYWGQGTLVTVSS (SEQ ID NO:736)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:737)	EIVLTQSPATLSLSPG ERATLSCSATSSVSY MHWYQQKPGQAP RLLIYSSSNLASGIPA RFSGSGSGTDFTLTIS SLEPEDFAVYYCHQ WSGHFTFGQGTKLE IK (SEQ ID NO:738)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:739)
VSTB92 IN0908	Human IgG1/kappa	Group 1	GYTFANYL (SEQ ID NO:740)	IYPGGGFI (SEQ ID NO:741)	ARRFDYGGY FFDY (SEQ ID NO:742)	QSIVHSNGNI Y (SEQ ID NO:743)	KVS (SEQ ID NO:744)	FQGSHVP WT (SEQ ID NO:745)	QVQLVQSGAEVKKPG ASVKVSCKASGYTFA NYLIGWVRQAPGQRL EWMGDIYPGGGFSY NEKFKGRVTITRDTSA STAYMELSSLRSEDTA VYYCARRFDYGGYFF DYWGQGTLVTVSS (SEQ ID NO:746)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:747)	DIVMTQSPLSLPVTP GEPASISCRSSQSIV HSNGNIYLEWYLQK PGQSPQLLIYKVSNR FSGVPDRFSGSGSG TDFTLKISRVEAEDV GVYYCFQGSHVPW TFGQGTKLEIK (SEQ ID NO:748)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:749)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB93	Human IgG1/kappa		GFSITNYD (SEQ ID NO:750)	IWTGGGT (SEQ ID NO:751)	ARDRSPYFGY DY (SEQ ID NO:752)	QSLVHSNGN TY (SEQ ID NO:753)	KVS (SEQ ID NO:754)	SQSTHVPW T (SEQ ID NO:755)	QVQLQESGPGLVKPS ETLSLTCTVSGFSITNY DISWIRQPPGKGLEW IGVIWTGGGTNYNSA FMSRVTISVDTSKNQF SLKLSSVTAADTAVYY CARDRSPYFGYDYWG QGTTVTVSS (SEQ ID NO:756)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:757)	DIVMTQTPLSLSVTP GQPASISCRSSQSLV HSNGNTYLHWYLQ KPGQSPQLLIYKVSN RFSGVPDRFSGSGS GTDFTLKISRVEAED VGVYYCSQSTHVP WTFGQGTKLEIK (SEQ ID NO:758)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:759)
VSTB94	Human IgG1/kappa		GYSITSDYA (SEQ ID NO:760)	MIMYSGSA (SEQ ID NO:761)	ARFDHYYGR FDY (SEQ ID NO:762)	SSVSY (SEQ ID NO:763)	EIS (SEQ ID NO:764)	QQWNYPLF T (SEQ ID NO:765)	QVQLQESGPGLVKPS ETLSLTCAVSGYSITSD YAWTWIRQPPGKGL EWIGYIMMYSGSASY NPSLKGRVTISVDTSK NQFSLKLSSVTAADTA VYYCARFDHYYGRFD YWGQGTTVTVSS (SEQ ID NO:766)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:767)	AIQLTQSPSSLSASV GDRVTITCSASSSVS YIHWYQQKPGKAP KLLIYEISKLASGVPS RFSGSGSGTDFTLTIS SLQPEDFATYYCQQ WNYPLFTFGQGTKL EIK (SEQ ID NO:768)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:769)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB95 INX903	Human IgG1/kappa	PVDKGHDV TF and RRPIRDLTF QDL Group 1	GFTFRNYG (SEQ ID NO:770)	IISGGSYT (SEQ ID NO:771)	ARIYDHDGD YYAMDY (SEQ ID NO:772)	QSIVHSNGN TY (SEQ ID NO:773)	KVS (SEQ ID NO:774)	FQGSHVP WT (SEQ ID NO:775)	EVQLVESGGGLVQPG GSLRLSCAASGFTFRN YGMSWVRQAPGKGL EWVASIISGGSYTYYP DSVKGRFTISRDNAK NSLYLQMNSLRAEDT AVYYCARIYDHDGDY YAMDYWGQGTTVTV SS (SEQ ID NO:776)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:777)	DIVMTQSPLSLPVTP GEPASISCRSSQSIV HSNGNTYLEWYLQK PGQSPQLLIYKVSNR FSGVPDRFSGSGSG TDFTLKISRVEAEDV GVYYCFQGSHVPW TFGQGTKLEIK (SEQ ID NO:778)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:779)
VSTB96	Human IgG1/kappa		(SEQ ID NO:780)	(SEQ ID NO:781)	(SEQ ID NO:782)	(SEQ ID NO:783)	(SEQ ID NO:784)	(SEQ ID NO:785)	QVQLVQSGAEVKKPG SSVKVSCKASGYTFTS YDINWVRQAPGQGL EWMGRIYPGDGSTKY NEKFKGRVTITADKST STAYMELSSLRSEDTA VYYCAREGITPFAYW GQGTTVTVSS (SEQ ID NO:786)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:787)	AIQLTQSPSSLSASV GDRVTITCRASKSIS KYLAWYQQKPGKA PKLLIYSGSTLQSGV PSRFSGSGSGTDFTL TISSLQPEDFATYYC QQHNEYPWTFGQG TKLEIK (SEQ ID NO:788)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:789)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB97 INX914	Human IgG1/kappa	Group 1	GGTFSSYA (SEQ ID NO:790)	IIPIFGTA (SEQ ID NO:791)	ARSSYGWSY EFDY (SEQ ID NO:792)	QSISSY (SEQ ID NO:793)	AAS (SEQ ID NO:794)	QQSYSTPLT (SEQ ID NO:795)	QVQLVQSGAEVKKPG SSVKVSCKASGGTFSS YAISWVRQAPGQGLE WMGGIIPIFGTANYA QKFQGRVTITADESTS TAYMELSSLRSEDTAV YYCARSSYGWSYEFD YWGQGTLVTVSS (SEQ ID NO:796)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:797)	DIQMTQSPSSLSAS VGDRVTITCRASQSI SSYLNWYQQKPGK APKLLIYAASSLQSG VPSRFSGSGSGTDFT LTISSLQPEDFATYYC QQSYSTPLTFGQGT KVEIK (SEQ ID NO:798)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:799)
VSTB98	Human IgG1/kappa	Group 1	GGTFSSYA (SEQ ID NO:800)	IIPIFGTA (SEQ ID NO:801)	ARSTVGWSY EFDY (SEQ ID NO:802)	QSISSY (SEQ ID NO:803)	AAS (SEQ ID NO:804)	QQSYSTPLT (SEQ ID NO:805)	QVQLVQSGAEVKKPG SSVKVSCKASGGTFSS YAISWVRQAPGQGLE WMGGIIPIFGTANYA QKFQGRVTITADESTS TAYMELSSLRSEDTAV YYCARSTVGWSYEFD YWGQGTLVTVSS (SEQ ID NO:806)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:807)	DIQMTQSPSSLSAS VGDRVTITCRASQSI SSYLNWYQQKPGK APKLLIYAASSLQSG VPSRFSGSGSGTDFT LTISSLQPEDFATYYC QQSYSTPLTFGQGT KVEIK (SEQ ID NO:808)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:809)

FIGURE 4

mAb ID	Description	Epitope Sequence/ Epitope Group	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB99	Human IgG1/kappa	Group 1	GGTFSSYA (SEQ ID NO:810)	IIPIFGTA (SEQ ID NO:811)	ARHVLGWVL ELDY (SEQ ID NO:812)	QSISSV (SEQ ID NO:813)	AAS (SEQ ID NO:814)	QQSYSTPLT (SEQ ID NO:815)	QVQLVQSGAEVKKPG SSVKVSCKASGGTFSS YAISWVRQAPGQGLE WMGGIIPIFGTANYA QKFQGRVTITADESTS TAYMELSSLRSEDTAV YYCARHVLGWVLELD YWGQGTLVTVSS (SEQ ID NO:816)	ASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVL QSSGLYSLSSVVTVPSSSLG TQTYICNVNHKPSNTKVDK KVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREP QVYTLPPSRDELTKNQVSL TCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGS FFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO:817)	DIQMTQSPSSLSAS VGDRVTITCRASQSI SSYLNWYQQKPGK APKLLIYAASSLQSG VPSRFSGSGSGTDFT LTISSLQPEDFATYYC QQSYSTPLTFGQGT KVEIK (SEQ ID NO:818)	RTVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQ WKVDNALQS GNSQESVTEQ DSKDSTYSLSS TLTLSKADYEK HKVYACEVTH QGLSSPVTKSF NRGEC (SEQ ID NO:819)

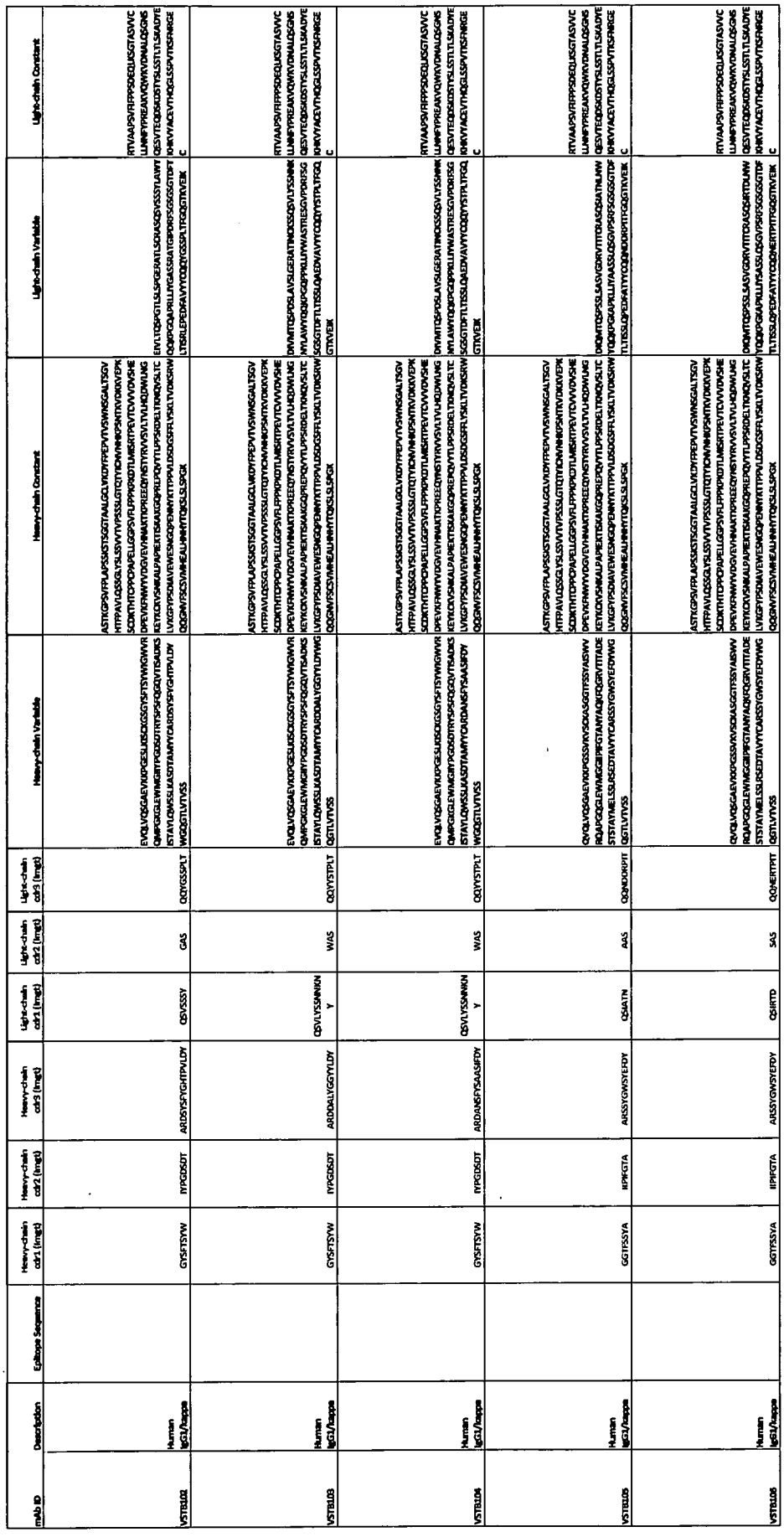
FIGURE 4

mAb ID	Description	Epitope Sequence	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
GA1	Mouse IgG1/kappa	LLDSGLYCCLVVEIRHHH SEHRVH	GYTLTDYN	INLNYAIT	ARGGYRYTYYAMDY	ENIYSN	AAT	QHFWGTPRT	EVQLQQSGAELVKPGASVKISCKASGYTLTDYNMDWV KQSHGKSLEWIGHINLNYAITTYNQKFKGKATLTVDKS SSTAYMELRSLTSEDTAVYYCARGGYRYTYYAMDYW GQGTSVTVSS	AKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPEPVTVTWNSGSLSSG VHTFPAVLQSDLYTLSSSVTVPSSTWPSETVTCNVAHPASSTKVDKKIVP RDCGCKPCICTVPEVSSVFIFPPKPKDVLTITLTPKVTCVVVDISKDDPEVQ FSWFVDDVEVHTAQTQPREEQFNSTFRSVSELPIMHQDWLNGKEFKCR VNSAAFPAPIEKTISKTKGRPKS	DIQMTQSPASLSVSVGETVTITCRASENIYSNLAWY QQKQGKSPQLLVYAATNLADGVPSRFSGSGSGTQ YSLKINSLQSEDFGSYYCQHFWGTPRTFGGGTKLEI K	RADAAPTVSIFPPSSEQLTSGGASVVC FLNNFYPKDINVKWKIDGSERQNGVL NSWTDQDSKDSTYSMSSTLTLTKDEY ERHNSYTCEATHKTSTSPIVKSFNRNE C
GA1-IgG2	Human IgG2/kappa	LLDSGLYCCLVVEIRHHH SEHRVH	GYTLTDYN	INLNYAIT	ARGGYRYTYYAMDY	ENIYSN	AAT	QHFWGTPRT	EVQLQQSGAELVKPGASVKISCKASGYTLTDYNMDWV KQSHGKSLEWIGHINLNYAITTYNQKFKGKATLTVDKS SSTAYMELRSLTSEDTAVYYCARGGYRYTYYAMDYW GQGTSVTVSS	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVER KCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKE YKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPASLSVSVGETVTITCRASENIYSNLAWY QQKQGKSPQLLVYAATNLADGVPSRFSGSGSGTQ YSLKINSLQSEDFGSYYCQHFWGTPRTFGGGTKLEI K	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
GG8	Mouse IgG1/?	LLDSGLYCCLVVEIRHHH SEHRVH; GHDVTFYKTWYRSSRG EVQTC	GYSFTGYT	INPYNGGI	ARRTLLRPYFFDY	QSVSTSTFSY	YAS	QHSWEIPYT	EVQLQQSGPELVKPGTSMKISCKASGYSFTGYTMNWV RQSHGKNLEWIGLINPYNGGINYNQKFKARATLTVDK SSSTAYMELLSLTSEDSAVYYCARRTLLRPYFFDYWGQ GTTLTVSS		DIVLTQSPASLAVSLGQRATISCRASQSVSTSTFSY MHWYQQKPGQPPKLLIKYASNLESGVPARFSGSG SGTDFTLNIHPVEEEDTATYYCQHSWEIPYTFGGGT KLEIK	
GG8-IgG2	Human IgG2/kappa	LLDSGLYCCLVVEIRHHH SEHRVH; GHDVTFYKTWYRSSRG EVQTC	GYSFTGYT	INPYNGGI	ARRTLLRPYFFDY	QSVSTSTFSY	YAS	QHSWEIPYT	EVQLQQSGPELVKPGTSMKISCKASGYSFTGYTMNWV RQSHGKNLEWIGLINPYNGGINYNQKFKARATLTVDK SSSTAYMELLSLTSEDSAVYYCARRTLLRPYFFDYWGQ GTTLTVSS	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVER KCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKE YKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIVLTQSPASLAVSLGQRATISCRASQSVSTSTFSY MHWYQQKPGQPPKLLIKYASNLESGVPARFSGSG SGTDFTLNIHPVEEEDTATYYCQHSWEIPYTFGGGT KLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C

FIGURE 4

mAb ID	Description	Epitope Sequence	Heavy-chain cdr1 (kmgt)	Heavy-chain cdr2 (kmgt)	Heavy-chain cdr3 (kmgt)	Light-chain cdr1 (kmgt)	Light-chain cdr2 (kmgt)	Light-chain cdr3 (kmgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
IE8	Mouse IgG1/κ	LLDSGLYCDLVVEIR	GFDFSRYW	VYPDSST	ARGRGDY	GMHHVY	NAK	QNFWSTPFT	EVKLLESGGGLVQPGGSLKLSCAASGFDFSRYWMSWV RQAPGKGLEWIGEVYPDSSTINYTPSLKDKFIISRDNAK NTLYLQMSKVRSEDTALYYCARGRGDYWGQGTSVTVS S	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVER KCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKE YKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPASLSASVGETVTITCRASGNIHNYLSW YHQKQGKSPQLLVYNAKTLADGVPSRFSGSGSGT QYSLKINSLQPEDFGSYYCQHFWSTPFTFGSGTKLEI K	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
IE8-IgG2	Human IgG2/kappa	LLDSGLYCDLVVEIR	GFDFSRYW	VYPDSST1	ARGRGDY	GMHHVY	NAK	QNFWSTPFT	EVKLLESGGGLVQPGGSLKLSCAASGFDFSRYWMSWV RQAPGKGLEWIGEVYPDSSTINYTPSLKDKFIISRDNAK NTLYLQMSKVRSEDTALYYCARGRGDYWGQGTSVTVS S	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVER KCCVEPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKE YKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPASLSASVGETVTITCRASGNIHNYLSW YHQKQGKSPQLLVYNAKTLADGVPSRFSGSGSGT QYSLKINSLQPEDFGSYYCQHFWSTPFTFGSGTKLEI K	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
IE8-IgG2-C127S	Human mutated IgG2/kappa	LLDSGLYCDLVVEIR	GFDFSRYW	VYPDSST1	ARGRGDY	GMHHVY	NAK	QNFWSTPFT	EVKLLESGGGLVQPGGSLKLSCAASGFDFSRYWMSWV RQAPGKGLEWIGEVYPDSSTINYTPSLKDKFIISRDNAK NTLYLQMSKVRSEDTALYYCARGRGDYWGQGTSVTVS S	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPASLSASVGETVTITCRASGNIHNYLSW YHQKQGKSPQLLVYNAKTLADGVPSRFSGSGSGT QYSLKINSLQPEDFGSYYCQHFWSTPFTFGSGTKLEI K	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB1100	Human IgG1/kappa		GYSFTSYW	IYPGDSDT	ARDVSSFYGYSPNFDY	QSVSSY	DAS	QQDHSNWPLT	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVR QMPGKGLEWMGIIYPGDSDTRYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARDVSSFYGYSPNFDY WGQGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	QDIQSKNWPLT WGQGTLVTVSS	QDIQSKNWPLT WGQGTLVTVSS	GAS	QQYGSSPLT	EVKLLESGGGLVQPGGSLKLSCAASGFDFSRYWMSWV RQAPGKGLEWIGEVYPDSSTINYTPSLKDKFIISRDNAK NTLYLQMSKVRSEDTALYYCARGRGDYWGQGTSVTVS S	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVER KCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKE YKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPASLSASVGETVTITCRASGNIHNYLSW YHQKQGKSPQLLVYNAKTLADGVPSRFSGSGSGT QYSLKINSLQPEDFGSYYCQHFWSTPFTFGSGTKLEI K	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB1101	Human IgG1/kappa		GYSFTSYW	IYPGDSDT	ARDAVSFYGYSALLDY	QSVSSSY	GAS	QQYGSSPLT	EVKLLESGGGLVQPGGSLKLSCAASGFDFSRYWMSWV RQAPGKGLEWIGEVYPDSSTINYTPSLKDKFIISRDNAK NTLYLQMSSLRASDTAMYYCARDAVSFYGYSALLDY WGQGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	QDIQSKNWPLT WGQGTLVTVSS	QDIQSKNWPLT WGQGTLVTVSS	GAS	QQYGSSPLT	EVKLLESGGGLVQPGGSLKLSCAASGFDFSRYWMSWV RQAPGKGLEWIGEVYPDSSTINYTPSLKDKFIISRDNAK NTLYLQMSKVRSEDTALYYCARGRGDYWGQGTSVTVS S	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVER KCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKE YKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPASLSASVGETVTITCRASGNIHNYLSW YHQKQGKSPQLLVYNAKTLADGVPSRFSGSGSGT QYSLKINSLQPEDFGSYYCQHFWSTPFTFGSGTKLEI K	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C

FIGURE 4

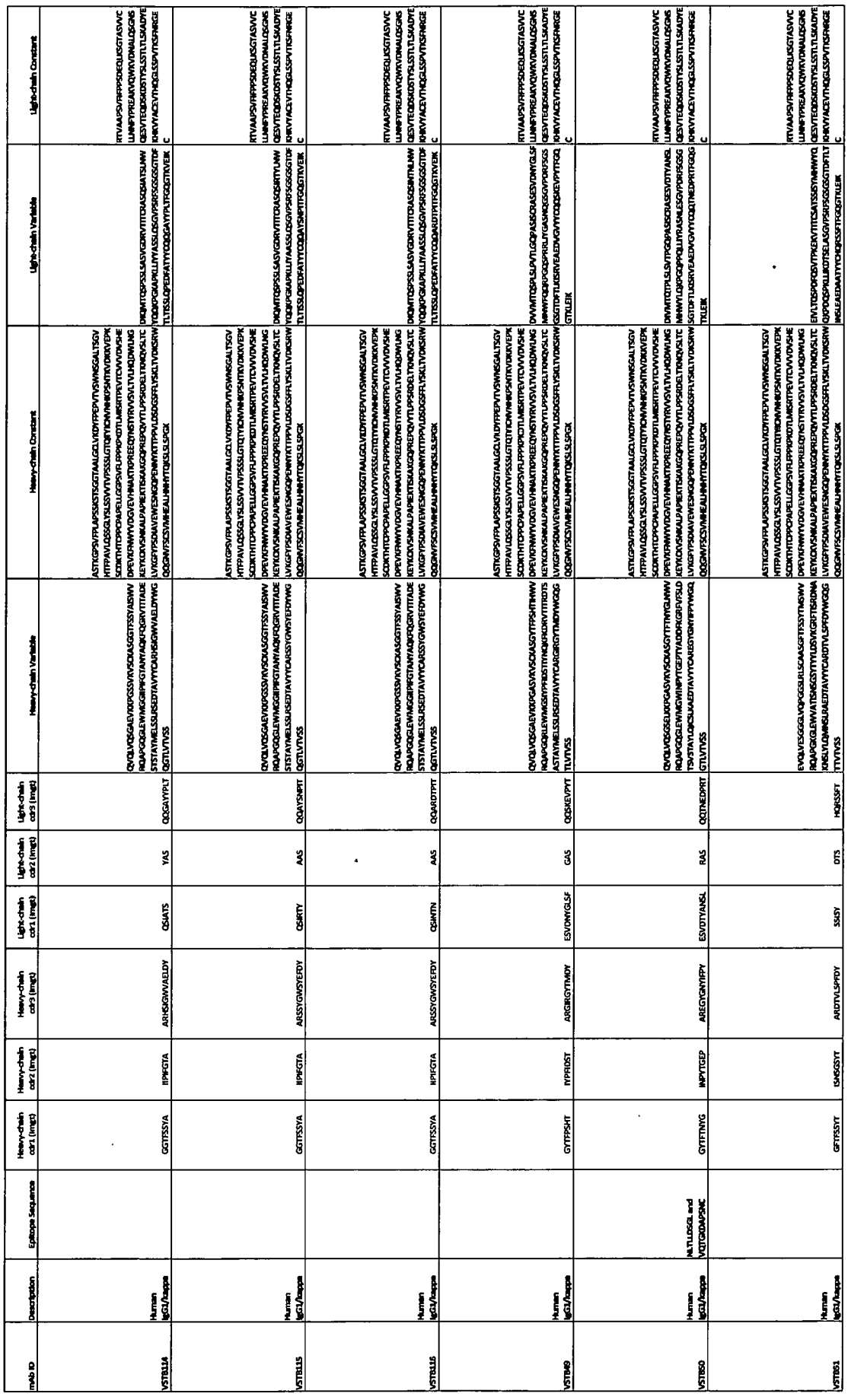


mAb ID	Description	Epitope Sequence	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB102	Human IgG1/kappa		GYSFTSYW	IYPGDSDT	ARDSYSFVGHTPVLDY	QSVSSSY	GAS	QQYGSSPLT	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVR QMPGKGLEWMGIIYPGDSDTRYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARDSYSFVGHTPVLDY WGQGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNK NYLAWYQQKPGQPPKLLIYWASTRESGVPDRFSG SGSGTDFTLTISSLQAEDVAVYYCQQYYSTPLTFGQ GTKVEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB103	Human IgG1/kappa		GYSFTSYW	IYPGDSDT	ARDDALYGGYYLDY	QSVLYSSNNKN Y	WAS	QQYYSTPLT	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVR QMPGKGLEWMGIIYPGDSDTRYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARDDALYGGYYLDYWG QGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNK NYLAWYQQKPGQPPKLLIYWASTRESGVPDRFSG SGSGTDFTLTISSLQAEDVAVYYCQQYYSTPLTFGQ GTKVEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB104	Human IgG1/kappa		GYSFTSYW	IYPGDSDT	ARDANSFYSAASFDY	QSVLYSSNNKN Y	WAS	QQYYSTPLT	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVR QMPGKGLEWMGIIYPGDSDTRYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARDANSFYSAASFDY WGQGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNK NYLAWYQQKPGQPPKLLIYWASTRESGVPDRFSG SGSGTDFTLTISSLQAEDVAVYYCQQYYSTPLTFGQ GTKVEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB105	Human IgG1/kappa		GGTFSSYA	IIPIFGTA	ARSSYGWSYEFDY	QSIATN	AAS	QQSNDDRPIT	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARSSYGWSYEFDYWG QGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPSSLSASVGDRVTITCRASQSIRDYLNW YQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDF TLTISSLQPEDFATYYCQQSNDDRPITFGQGTKVEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB106	Human IgG1/kappa		GGTFSSYA	IIPIFGTA	ARSSYGWSYEFDY	QSIRTD	SAS	QQHEIRTPIT	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARSSYGWSYEFDYWG QGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPSSLSASVGDRVTITCRASQSIRDYLNW YQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDF TLTISSLQPEDFATYYCQQSNDDRPITFGQGTKVEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C

FIGURE 4

mAb ID	Description	Epitope Sequence	Heavy-chain cdr1 (kmgt)	Heavy-chain cdr2 (kmgt)	Heavy-chain cdr3 (kmgt)	Light-chain cdr1 (kmgt)	Light-chain cdr2 (kmgt)	Light-chain cdr3 (kmgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTR107	Human IgG1/kappa		GGTFSSYA	IIPIFGTA	ARSSYGMSYEDY	QSMWND	AAS	QQNRATPPIT	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARSSYGMSYEDYWG QGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPSSLSASVGDRVTITCRASQSINNYLNW YQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDF TLTISSLQPEDFATYYCQQNRATPPITFGQGTRVEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTR108	Human IgG1/kappa		GGTFSSYA	IIPIFGTA	ARNTFGWSGELDY	QSRNR	SAS	QQNHNDPIT	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARNTFGWSGELDYWG QGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPSSLSASVGDRVTITCRASQSINNYLNW YQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDF TLTISSLQPEDFATYYCQQNHNDPITFGQGTRVEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTR109	Human IgG1/kappa		GGTFSSYA	IIPIFGTA	ARSSYGWSYEDY	QSIATY	AAS	QQHHNRPIT	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARSSYGWSYEDYWG QGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPSSLSASVGDRVTITCRASQSINTDLNW YQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDF TLTISSLQPEDFATYYCQQSHTTPQGTRVEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTR110	Human IgG1/kappa		GGTFSSYA	IIPIFGTA	ARHSAGWVAELDY	QSNTD	AAS	QQGASDPIT	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARHSAGWVAELDYWG QGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPSSLSASVGDRVTITCRASQSINTDLNW YQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDF TLTISSLQPEDFATYYCQQASDPITFGQGTRVEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTR111	Human IgG1/kappa		GGTFSSYA	IIPIFGTA	ARSSYGWSYEDY	QSNTD	AAS	QQNRGSPIT	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARSSYGWSYEDYWG QGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPSSLSASVGDRVTITCRASQSINTDLNW YQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDF TLTISSLQPEDFATYYCQQNRGSPITFGQGTRVEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTR113	Human IgG1/kappa		GGTFSSYA	IIPIFGTA	ARHSAGWVAELDY	QSIATD	AAS	QQAHWYPLIT	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARHSAGWVAELDYWG QGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPSSLSASVGDRVTITCRASQSIATDLNW YQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDF TLTISSLQPEDFATYYCQQAHWYPLITFGQGTRVEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C

FIGURE 4



mAb ID	Description	Epitope Sequence	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB114	Human IgG1/kappa		GGTFSSYA	IIPIFGTA	ARHSAGWVAELDY	QSIATS	YAS	QQGAYYPLT	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARHSAGWVAELDYWG QGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARHSAGWVAELDYWG QGTLVTVSS	DIQMTQSPSSLSASVGDRVTITCRASQSIATSLNWY QQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDF TLTISSLQPEDFATYYCQQGAYYPLTFGQGTKVEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB115	Human IgG1/kappa		GGTFSSYA	IIPIFGTA	ARSSYGWSYEDY	QSIKTY	AAS	QQAYSNPT	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARSSYGWSYEDYWG QGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARSSYGWSYEDYWG QGTLVTVSS	DIQMTQSPSSLSASVGDRVTITCRASQSIATSLNWY QQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDF TLTISSLQPEDFATYYCQQSYSNPTFGQGTKVEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB89	Human IgG1/kappa		GYTFPSHT	IYPRDST	ARGRIGYYMDY	ESVDNYGLSF	GAS	QQSKEVPYT	QVQLVQSGAEVKKPGASVKVSCKASGYTFPSHTMHW RQAPGQRLEWMGSIYPRDSTYTQKFRDRVTITRDTS ASTAYMELSSLRSEDTAVYYCARGRIGYYMDYWGQG TLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DVVMTQSPLSLPVTLGQPASISCRSSQSLVHSDGNTYLSF LHWFQQRPGQSPRRLIYGASNQGSGVPDRFSGS GSGTDFTLKISRVEAEDVGVYYCQQSKEVPYTFGQ GTKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB50	Human IgG1/kappa	NLTLDSGL and VQTGRGAPSMC	GYTFTNYG	INPYTGEP	AREGYGNYFPY	ESVDTYANSL	RAS	QQTNEDPRT	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KETKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIVMTQTPLSLSVTPGQPASISCRASQSLVDTYANSL HWYLQKPGQSPQLLIYRASNLESGVPDRFSGSG TDFTLKISRVEAEDVGVYYCQQTNEDPRTFGQG TKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB51	Human IgG1/kappa		GFTFSSYT	ISNSGSYT	ARDTVLSFFDY	SSISY	DTS	HQRSSFT	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYTMSWV RQAPGKGLEWVATISNSGSYTYYLDSVKGRFTISRDNA KNSLYLQMNSLRAEDTAVYYCARDTVLSFFDYWGQG TTVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	EIVLTQSPDFQSVTPKEKVTITCSASQSISSYMHWYQQ KPDQSPKLLIKGTSNLASGVPSRFSGSGSGTDFTLT INSLEAEDAATYYCHQSSSFTFGQGTKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C

FIGURE 4

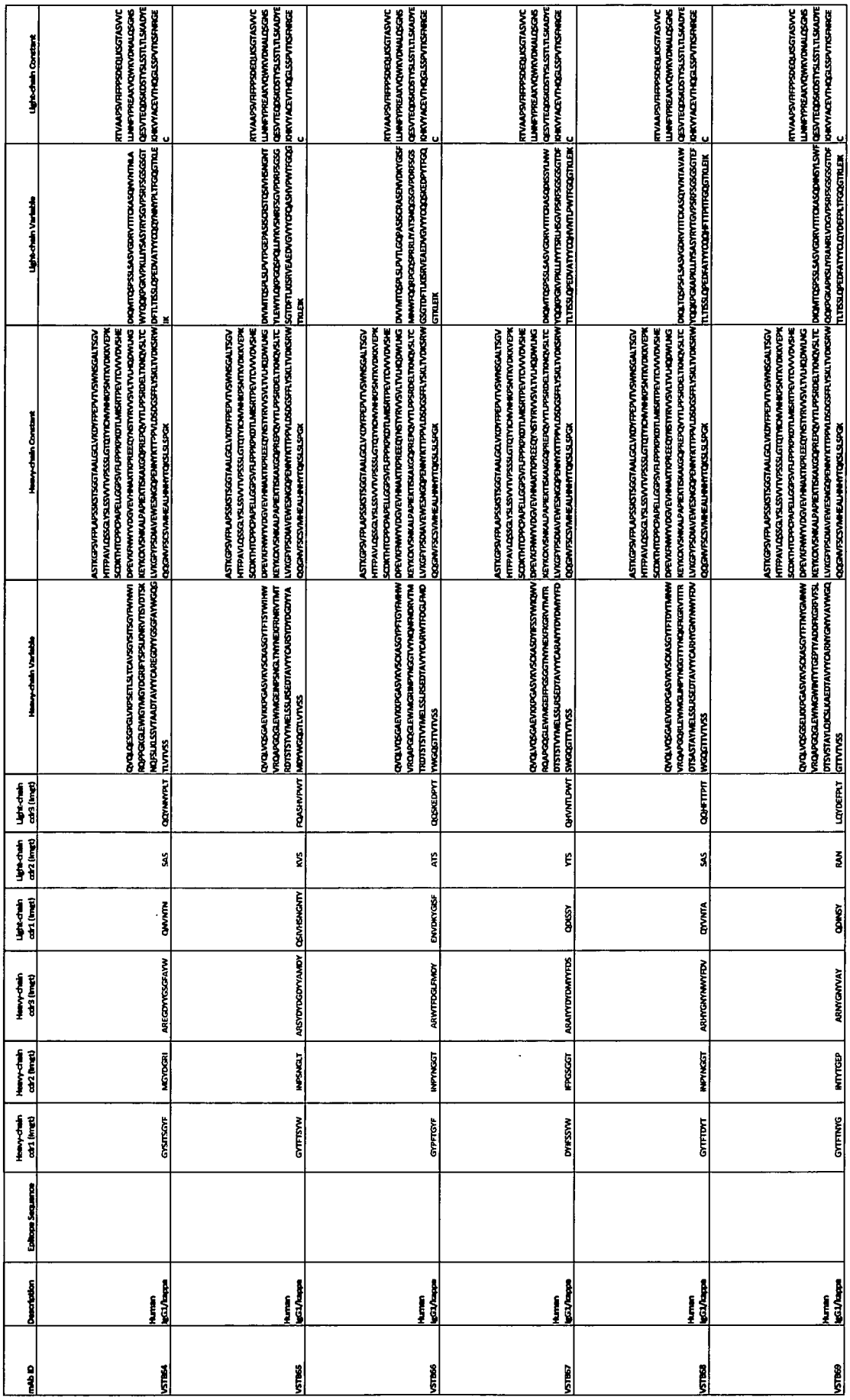
mAb ID	Description	Epitope Sequence	Heavy-chain cdr1 (kmgt)	Heavy-chain cdr2 (kmgt)	Heavy-chain cdr3 (kmgt)	Light-chain cdr1 (kmgt)	Light-chain cdr2 (kmgt)	Light-chain cdr3 (kmgt)	Heavy-chain Constant	Heavy-chain Variable	Light-chain Variable	Light-chain Constant
VSTB52	Human IgG1/kappa		GGTFSNYW	IYPGGGFT	ARYYRSDDVSMDF	QSLLYSNGKTY	LVS	VQATHFPQT	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSNYWIGW DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG VRQAPGQGLEWMGEIYPGGGFTHYNEKFKGRVTITA KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC DESTSTAYMELSSLRSEDTAVYYCARYYRSDDVSMDFW LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW WGQGTLVTVSS QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	QVVMTQSPLSLPVTLGQPASISCRSSQSLVYSNGKT YLNWFQQRPGQSPRRLLIYKVSNRDSGVPDRFSGSG SGTDFTLKISRVEAEDVGVYYCQQATHFPQTFGQG TKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB53	Human IgG1/kappa		GYTFTHYT	IIPSSGYS	ARGAYDDYDYDYAMDY	QTIDHSNGNTY	KVS	FQASHVPWT	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	QVQLVQSGAEVKKPGASVKVSCKASGYTFTHYTMHWV RQAPGQGLEWMGIIPSSGYSEYNQKFKDRVTMTRD TSTSTVYMELSSLRSEDTAVYYCARGAYDDYDYDYAM DYWGQGTLVTVSS	DVVMTQSPLSLPVTPGEPASISCRSSQSLVYSNGNT YLEWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSG SGTDFTLKISRVEAEDVGVYYCFQASHVPWTFGQG TKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB54	Human IgG1/kappa		GYNWGDTY	IDPTHGYV	AADWRDPWYFDV	ESVEYYGTSL	DAF	QQSRKVPWT	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	QVQLVQSGAEVKKPGASVKVSCKASGYTMIDYTMHWV VRQAPGQGLEWMGRIDPTHGYVDPKFQGRVTMT RDTSTSTVYMELSSLRSEDTAVYYCARDRFDPWYFDV WGQGTLVTVSS	EIVLTQSPGTLSLSPGERATLSCRASESVEYYGTSL MQWYQQKPGQPPKLLIYDAFNVESGVPDRFSGSG SGTDFTLKISRVEAEDVGVYYCQQSRKVPWTFGQ GTKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB55	Human IgG1/kappa		GYSFASDYV	ISYSGST	ARITTVVPTGSYYGVDF	SSVNF	DTS	QQWSNYPPT	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	QVQLQESGPGLVKPSETLSLTCAVSGYSIASGYVWNWI RQPPGKGLEWIGYISYSGSTSWNPSLNSRVTISIDTSKN QFSLKLSSVTAADTAVYYCARITTVVPTGSYYGVDFWG QGTTVTVSS	EIVLTQSPDFQSVTPKEKVTITCSQSSSVNFMYWY QQKPDQSPKLLIKDTSNLASGVPSRFSGSGSGTDFT LTINSLEAEDAATYYCQQWSNYPPTFGQGTKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB56	Human IgG1/kappa		GYTFTSYW	IIPNTGHT	ARLDGDYDYALDY	ESVEYYGTSF	TAS	QQSRKVPYT	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	QVQLMQSGPGLVKPSQTLSLTCTVSGFSLTGYGVNWV RQPPGKGLEWLGMIWGDGSTDYNSALKSRLSISKDNS KSQVFLKMNSLQTDDTARYYCARDRGLRFYFDYWG QGTTLTVSS	DIQLTQSPSFLSASVGDRVTITCSASSSVSYMHWY QQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTEFTL TISSLQPEDFATYYCHQWRTYPFTFGQGTKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB57	Human IgG1/kappa		GFTFSTYA	ISSGGSDT	ARFTYYGIFSYFDW	SSVSY	STS	HQWRTYPFT	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	EVQLVESGGGLVQPGGSLRLSCAASGFTISTYAMSWV RQAPGKGLEWVATISSGGSDTYYPDTVKGRFTISRDN AKNSLYLQMNSLRAEDTAVYYCARFTYYGIFSYFDW GQGTLVTVSS	DIQLTQSPSFLSASVGDRVTITCSASSSVSYMHWY QQKPGKAPKLLIYSTSNLASGVPSRFSGSGSGTEFTL TISSLQPEDFATYYCHQWRTYPFTFGQGTKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C

FIGURE 4

mAb ID	Description	Epitope Sequence	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB58	Human IgG1/kappa		GFSLTNYG	IWRGGNT	ARSMVSYTVDY	SSVSY	DTS	QQWSSYPPT	QVQLQESGPGLVKPSETLSLTCTVSGFSLTNYGVHWIR QPPGKGLEWIGVIWRGGNTDYNAAFMSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARSMVSYTVDYWGQG TLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	EIVLTQSPDFQSVTPKEKVTITCSASSSVSYMHWY QQKPDQSPKLLIKDTSNLASGVPSRFSGSGSGTDFT LTINSLEAEDAATYYCQQWSSYPPTFGQGTKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB59	Human IgG1/kappa		GYTFTDYW	IETSLNYP	ARWGIYGNPWFAY	ESVDSYVNSF	RAS	QQSNEDPYT	QVQLVQSGAEVIKKPGASVKVSCKASGYTFTDYWMH WVRQAPGQGLEWMGAIETSLNYPSYNQKFRGRVTIM TRDTSTSTVYMELSSLRSEDTAVYYCARWGIYGNPWF AYWGRGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIVMTQTPLSLSVTPGQPASISCRASESVDSYVNSF VHWYLQKPGQPPQLLIYRASNLESGVPDRFSGSGS GTDFTLKISRVEAEDVGVYYCQQSNEDPYTFGQGT KLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB60	Human IgG1/kappa	NLTLLDSGL and VQTGKDAPSNC	GYTFTNYG	INTYTGES	ARDYYGIYVSAY	ESVDNYANSF	RAS	QQSHEDPYT	QVQLVQSGSELKKPGASVKVSCKASGYTFTNYGMTW VRQAPGQGLEWMGWINTYTGESTYADDFKGRFVFSL DTSVSTAYLQICSLKAEDTAVYYCARDYYGIYVSAYWG QGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIVMTQTPLSLSVTPGQPASISCRASESVDNYANSF MHWYLQKPGQSPQLLIYRASNLESGVPDRFSGSGS GTDFTLKISRVEAEDVGVYYCQQSHEDPYTFGQGT KLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB61	Human IgG1/kappa		GYTFTSHW	INPRLDGRT	ARGDFHYGDYFWYFDV	QNVHGA	MAS	LQHWNYLT	QVQLVQSGAEVIKKPGASVKVSCKASGYTFTSHWMH WVRQAPGQGLEWMGEINPRLDGRTNYNEKFKTRVTM TRDTSTSTVYMELSSLRSEDTAVYYCARGDFHYGDYF WYFDVWGQGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPSSLSASVGDRVTITCKASQNVHGAVA WYQQKPGKVPKLLIYMASNRPTGVPSRFSGSGSG TDFTLTISSLQPEDVATYYCLQHWNYLTFGQGTKLE IK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB62	Human IgG1/kappa		GYTFTHYW	IYPGDGDT	ARRDYDYGDY	SSVSH	LTS	QQYQTYPPT	QVQLVQSGAEVIKKPGASVKVSCKASGYTFTHYWIQW VRQAPGQGLEWMGAIYPGDGDTRYTQKFKGRVTMT RDTSTSTVYMELSSLRSEDTAVYYCARRDYDYGDYWG QGTTVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	EIVLTQSPDFQSVTPKEKVTITCSASSSVSYMHWY QQKPDQSPKLLIKLTSNLASGVPSRFSGSGSGTDFT LTINSLEAEDAATYYCQQYQTYPPTFGQGTRLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB63	Human IgG1/kappa		GFSITSDFA	ITYSGFT	ARQEYGNYVWYFDV	ESVEYYGTSL	AAS	QQSRKVPWT	QVQLQESGPGLVKPSETLSLTCAVSGFSITSDFAWNWI RQPPGKGLEWIGYITYSGFTNYNPSLESRVTISVDTSKN QFSLKLSSVTAADTAVYYCARQEYGNYVWYFDVWGQ GTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIVMTQTPLSLSVTPGQPASISCRASESVEYYGTSLL QWYLQKPGQPPQLLIYAASNVESGVPDRFSGSGS GTDFTLKISRVEAEDVGVYYCQQSRKVPWTFGQG TKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C

WO 2017/181109 PCT/US2017/027765

FIGURE 4

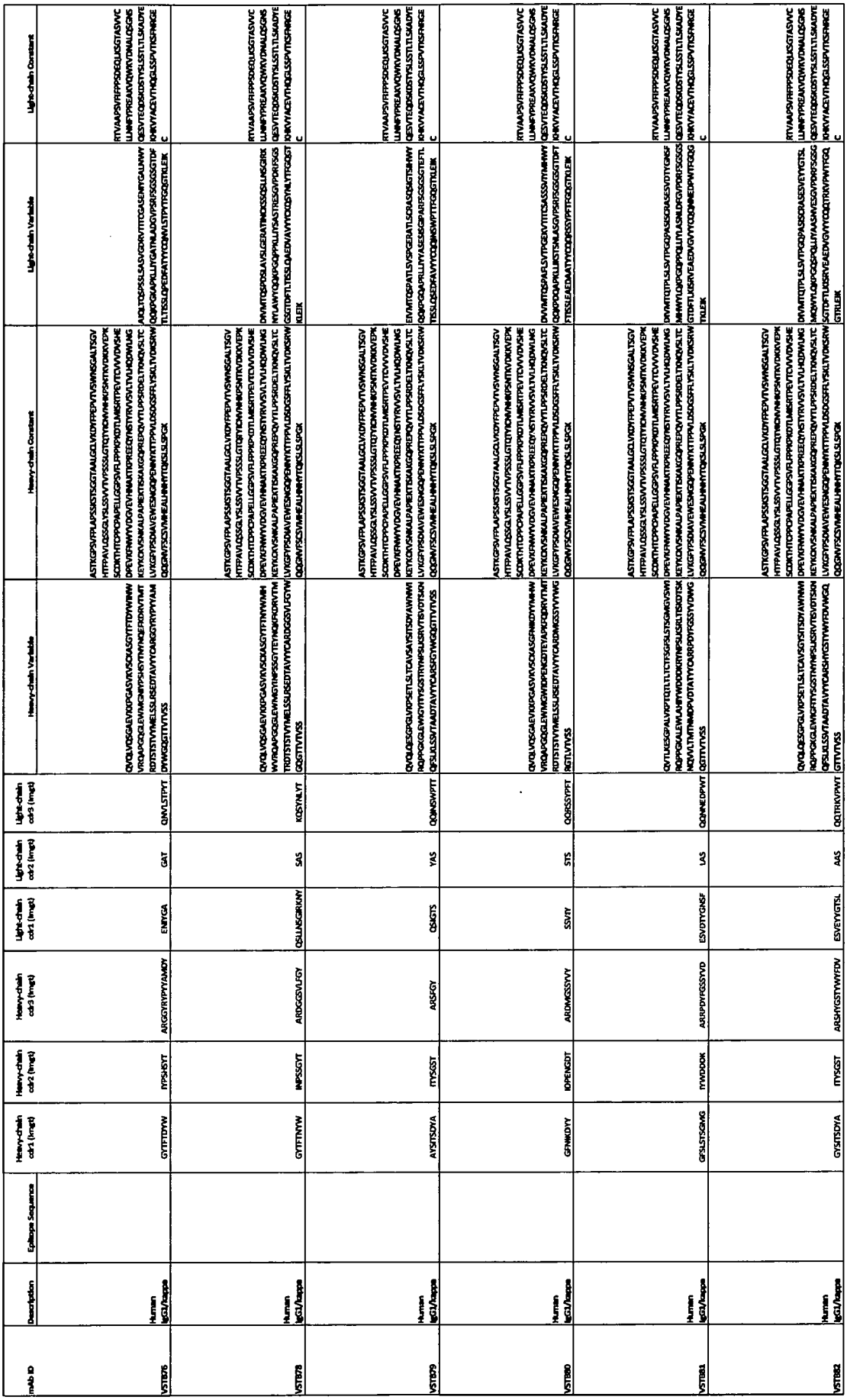


mAb ID	Description	Epitope Sequence	Heavy-chain cdr1 (kmgt)	Heavy-chain cdr2 (kmgt)	Heavy-chain cdr3 (kmgt)	Light-chain cdr1 (kmgt)	Light-chain cdr2 (kmgt)	Light-chain cdr3 (kmgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB64	Human IgG1/kappa		GYSITSGYF	MDYDGRI	AREGDVYGSGFAYW	QNVNTN	SAS	QQYNNYPLT	QVQLQESGPGLVKPSETLSLTCAVSGYSITSGYFWNWI RQPPGKGLEWIGYMGYDGRIFYSPSLKSRVTISYDTSK NQFSLKLSSVTAADTAVYYCAREGDVYGSGFAYWGQG TLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPSSLSASVGDRVTITCKASQNVNTNLA WYQQKPGKVPKLLIYSASYRYSGVPSRFSGSGSGT DFTLTISSLQPEDVATYYCQQYNNYPLTFGQGTKLE IK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB65	Human IgG1/kappa		GYTFTSYW	INPSNGLT	ARSDYDGDYYAMDY	QSVVSNGNTYY	KVS	FQASHVPWT	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWIHW VRQAPGQGLEWMGEINPSNGLTNYNEKFKNRVTMT RDTSTSTVYMELSSLRSEDTAVYYCARSDYDGDYYA MDYWGQGTTVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIVMTQSPLSLPVTPGEPASISCRSSQSLVHSNGNTY LHWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSG QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB66	Human IgG1/kappa		GYTFTGYF	INPYNGGT	ARWTFDGLFMDY	ENVDKYGDSF	ATS	QQSKEDPYT	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYFMHW VRQAPGQGLEWMGWINPYNGGTVYNQNFRGRVTM TRDTSTSTVYMELSSLRSEDTAVYYCARWTFDGLFMD YWGQGTTVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPSSLSASVGDRVTITCRASQDVSTAVAW YQQKPGKAPKLLISASYRYTGVPSRFSGSGSGTDF TLTISSLQPEDFATYYCQQHYSTPPTFGQGTKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB67	Human IgG1/kappa		DYFSSYW	IFPGSGGT	ARAMYYDYDMMYFDS	QDISSY	YTS	QHVNTLPWT	QVQLVQSGAEVKKPGASVKVSCKASGYSFSSYWIQWV RQAPGQGLEWMGEIFPGSGGTNYNEKFKGRVTMTR DTSTSTVYMELSSLRSEDTAVYYCARAMYYDYDMMYFD WGQGTTVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMVTQSPSSLSASVGDRVTITCRASQNIYSYLN WYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDF TLTISSLQPEDVATYYCQQSYSTPLTFGQGTRLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB68	Human IgG1/kappa		GYTFTDYT	INPYNGGT	ARAMYDYDMMYFDV	QDVNTA	SAS	QQHFTTPIT	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYTMHWV RQAPGQRLEWMGWINPYNGGTAYAQKFQGRVTITR DTSATTAYMELSSLRSEDTAVYYCARAMYDYDMMYFDV WGQGTTVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQLTQSPSFLSASVGDRVTITCKASQDVSTAVAW YQQKPGKAPKLLIYSASTRYTGVPSRFSGSGSGTEF TLTISSLQPEDFATYYCQQDYSTPPTFGQGTKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB69	Human IgG1/kappa		GYTFTNYG	INTYTGEP	ARNYGNYVAY	QDINSY	RAN	LQYDEFPLT	QVQLVQSGGEVVQPGASVKVSCKASGYTFTNYGMNWV VRQAPGQGLEWMGWINTYTGEPTYADDFRGRFVFSL DTSVSTAYLQICSLKAEDTAVYYCARNYGNYVAYWGQ GTTVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPSSLSASVGDRVTITCKASQDINSYLSWF QQKPGKAPKSLIYRAMRLVDGVPSRFSGSGSGTDF TLTISSLQPEDFATYYCLQYDEFPLTFGQGTRLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C

FIGURE 4

mAb ID	Description	Epitope Sequence	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB70	Human IgG1/kappa		GYTFSAYYW	IIJPGSGNV	ATPPMYYGYDYYDVNY	QSLLDSDGKTY	LVS	WQGTHFPQT	EVQLVQSGAEVKKPGATVKISCKVSGYTFSNYWIEWVV QQAPGKGLEWMAGEILPGSGNVVYNEKFKGRVTITADT STDTAYMELSSLRSEDTAVYYCATPPMYYGYDYYDVNY WGQGTLVTVSS	DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQ KEYKCKVSNKALPAPEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C.
VSTB71	Human IgG1/kappa		GVVFSRSW	IYPGDGDT	ARRWFL	QSLLNSGDQKS Y	GAS	QNDHSYPLT	QVQLVQSGAEVKKPGSSVKVSCKASGYVFSRSWMNWV VRQAPGQGLEWMGRIYPGDGDTNYNGKFKGRVTITA DESTSTAYMELSSLRSEDTAVYYCARRWFLNWGQGTLV TVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DVVMTQSPDSLAVSLGERATINCKSSQSLLNSGDQ KSYLAWYQQKPGQPPKLLIYGASTRESGVPDRFSG QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C.	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C.
VSTB72	Human IgG1/kappa		GFTFSSYA	ISSGGSHT	ARRGMLYDGPY	SSVSH	DTS	QQWNPYPFT	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWV RQAPGKGLEWVAEISSGGSHTYYPDTVTGRFTISRDNA KNSLYLQMNSLRAEDTAVYYCARRGMLYDGPYWGQG TLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	EIVLTQSPATLSLSPGERATLSCASSSVSHMNWYQQ KPGQAPRLLIYDTSKLASGIPARFSGSGSGTDFTLTI SSLEPEDFAVYYCQQWNPYPFTFGQGTKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C.
VSTB73	Human IgG1/kappa		GYTFTDYV	IYPGSGNT	ARVLVSVMDY	SSINY	DTS	HQRSSYPWT	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYVISWV RQAPGQGLEWMGEIYPGSGNTYYEDKGRVTMTTDT TSTSTVYMELSSLRSEDTAVYYCARVLVSVMDYWGQG TLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	EIVLTQSPDRQSVTTKEDVTTICSASSNNTTMVYQQ KPDQSPKLLIKDTSKLASGVPSRFSGSGSGTDFTLTI NSLEAEDAATYYCHQQSSYPWTTFGQGTRLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C.
VSTB74	Human IgG1/kappa		GYIFTDYN	INPNYDST	AADGSSAMDY	QSLLHSGHQUN Y	GAS	QHDHRYPLT	QMQLVQSGPEVKKPGTSVKVSCKASGYIFTDYNMHWVV QAPGQRLEWMGWINPNYDSTRYSQKFQGRVTITRDM STSTAYMELSSLRSEDTAVYYCATRDAAADGSSAMDYWGQG TLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIVMTQSPDSLAVSLGERATINCKSSQSLLNSGAQ NQKNYLAWYQQKPGQPPKLLIYGASTRESGVPDRFSG QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C.	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C.
VSTB75	Human IgG1/kappa		GFNIKDYY	IDPENGNT	ARDYGYDYVM	SSVIY	STS	QQRSSYPHT	QVQLVQSGAEVKKPGSSVKVSCKASGFNIKDYYIHWVV RQAPGQGLEWMGDPENGNTVDPKFQGRVTITAD ESTSTAYMELSSLRSEDTAVYYCARDYGYDYVMDQGT LVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DVVMTQSPAFLSVTPGEKVTITCKASQSVVTAVVWYQ QKPDQAPELLIKSTSRLASGVPSRFSGSGSGTDFTLTI NSLEAEDAATYYCQQPDQDAPELLIKSTSRLASGVPSRFSGSGSGTDFT /TSSLEADDAATYYCQQPDQDAPELLIKSTSRLASGVPSRFSGSGSGTDFT LVTVSS	QQHPDQDAPELLIKSTSRLASGVPSRFSGSGSGTDFT LVTVSS	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C.

FIGURE 4



mAb ID	Description	Epitope Sequence	Heavy-chain cdr1 (kmgt)	Heavy-chain cdr2 (kmgt)	Heavy-chain cdr3 (kmgt)	Light-chain cdr1 (kmgt)	Light-chain cdr2 (kmgt)	Light-chain cdr3 (kmgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB75	Human IgG1/kappa		GYTFTDYW	IYPGHSYT	ARGGVRYPYYAMDY	ENIYGA	GAT	QMVLSTPYT	QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYWIHW VRQAPGQGLEWMGMIYPGHSYTNYNQKFKDRVTMT RDTSTSTVYMELSSLRSEDTAVYYCARGGVRYPYYAM DYWGQGTTVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIVMTQSPDSLAVSLGERATINCKSSQSLLNSGNQK NYLAWYQQKPGQPPKLLIYSASTRESGVPDRFSGS GSGTDFTLTISSLQAEDVAVYYCQQDYNLYTFGQGT KLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB78	Human IgG1/kappa		GYTFTNYW	INPSSGYT	ARDGGSVLFGY	QSLLNSGNQKNY	SAS	KQSYNLYT	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWMH WVRQAPGQGLEWMGTINPSSGYTEYNQKFRDRVTM TRDTSTSTVYMELSSLRSEDTAVYYCARDGGSVLFGY WGQGTTVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DVVMTQSPLSLPVTLGQPASISCRSSQSLVHSDGN TYLSWFQQRPGQSPRRLIYKVSNRDSGVPDRFSGS GSGTDFTLKISRVEAEDVGVYYCMQGTHWPPTFGQG TKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB79	Human IgG1/kappa		AYSITSDYA	ITYSGST	ARSFGY	QSIGTS	YAS	QQHNSWPFT	QVQLQESGPGLVKPSETLSLTCAVSAYSITSDYAWNWIR RQPPGKGLEWMGYITYSGSTRYNPSLKSRVTISIDTSKN RQFSLKLSSVTAADTAVYYCARSFGYWGQGTTVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIVLTQSPASLAVSLGQRATISCRASESVDSFGNSFMH WYQQKPGQPPKLLIYAASNQGSGVPARFSGSGSRTDFTL TISSLQAEDVATYYCQQSKEVPWTFGQGTKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB80	Human IgG1/kappa		GFNIKDYY	IDPENGDT	ARDMGSSYVY	SSVTY	STS	QQRSSYPFT	QVQLVQSGAEVKKPGASVKVSCKASGFNIKDYYMHW VRQAPGQGLEWMGWIDPENGDTEYAPKFQGRVTMT RDTSTSTVYMELSSLRSEDTAVYYCARDMGSSYVYWG RGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DVVMTQSPASLSVTPGERVTITCSASSSVNYMHWW QQKPGQAPRLLIYSTSNLASGVPSRFSGSGSGTDFT LTISSLEAEDAATYYCQQRSSYPFTFGQGTKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB81	Human IgG1/kappa		GFSLSTSGVG	IYWDDDK	ARRPDYFGSSYYD	ESVDTYGNSF	LAS	QQHNEDPWT	QVTLKESGPALVKPTQTLTLTCTFSGFSLSTSGVGVSWI RQPPGKALEWLAHIYWDDDKRYNPSLKSRLTISKDTSK NQVVLTMTNMDPVDTATYYCARRPDYFGSSYYDWG QGTTVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIVMTQTPLSLSVTPGQPASISCRSSQSLVHSNGN TYLHWYLQKPGQSPQLLIYTVSNRFSGVPDRFSGSG SGTDFTLKISRVEAEDVGVYYCSQSTHVPPTFGQG TKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB82	Human IgG1/kappa		GYSITSDYA	ITYSGST	ARSHYGSTYWYFDV	ESVEYYGTSL	AAS	QQTRKVPWT	QVQLQESGPGLVKPSETLSLTCAVSGYSITSDYAWNWIR RQPPGKGLEWMGFITYSGSTRYNPSLKSRVTISVDTSKN QFSLKLSSVTAADTAVYYCARSHYGSTYWYFDVWGQ GTTVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIVMTQTPLSLSVTPGQPASISCRASESVEYYGTSL MQWYLQKPGQSPQLLIYAASNVESGVPDRFSGSG SGTDFTLKISRVEAEDVGVYYCQQTRKVPWTFGQ GTKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C

FIGURE 4

mAb ID	Description	Epitope Sequence	Heavy-chain cdr1 (imgt)	Heavy-chain cdr2 (imgt)	Heavy-chain cdr3 (imgt)	Light-chain cdr1 (imgt)	Light-chain cdr2 (imgt)	Light-chain cdr3 (imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB83	Human IgG1/kappa		GYTFTSYD	IYPGDGYT	ARWGYGSYAMDY	QSLVHSNGNTY	KVS	SQSTHVPPT	QVQLVQSGAEVIKPGASVKVSCKASGYTFTSYDINWV RQAPGQGLEWMGWIYPGDGYTEYNEKFRGRVTMTR DTSTSTVYMELSSLRSEDTAVYYCARWGYGSYAMDY WGQGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIVMTQSPLSLPVTPGEPASISCRSSQSLVHSNGNT YLHWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSG GTDFTLKISRVEAEDVGVYYCSQSTHVPPTFGQGT KLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB84	Human IgG1/kappa		GYTFTSYW	INPSTGYP	ARSYYDYDGGAWFAY	ESVEYYGTSL	AAS	QQSRKVPST	QVQLVQSGAEVIKPGASVKVSCKASGYTFTSYWMIH WVRQAPGQGLEWMGYINPSTGYPGYNQKFKDRVTIM TRDTSTSTVYMELSSLRSEDTAVYYCARSYYDYDGGA WFAYWGQGTTVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIVMTQTPLSLSVTPGQPASISCRASESVEYYGTSL MIQWYLQKPGQSPQLLIYAASNVESGVPDRFSGSG SGTDFTLKISRVEAEDVGVYYCQQSRKVPSTFGQG TKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB85	Human IgG1/kappa		GYTFTDYA	IOTYYGNT	ARGGGDALDY	QSVSND	YAS	QQGYTSLRT	QVQLVQSGAEVIKKPGASVKVSCKASGYTFTDYAMHW VRQAPGQGLEWMGVIDTYYGNTNYNQKFKGRVTMT RDTSISTAYMELSRLRSDDTAVYYCARGGGDALDYWG QGTTVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPSSLSASVGDRVTITCKASQSVSNDVV WYQQKPGKAPKLLIYYASNRYIGVPSRFSGSGSGT DFTFTISSLQPEDIATYYCQQGYTSLRTFGQGTKLEI K	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB87	Human IgG1/kappa		GYSITSGYS	IHYIGIT	AREDYDYDGVFAY	QSISNN	YAS	QQSNSWPHT	QVQLQESGPGLVKPSETLSLTCAVSGYSITSGYSWHWI RQPPGKGLEWIGYIHYIGITNNNPSLKSRVTISVDTSKN QFSLKLSSVTAADTAVYYCAREDYDYDGVFAYWGQGT LVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	EIVLTQSPATLSLSPGERATLSCRASQSISNNLHWY QQKPGQAPRLLIYYASQSISGIPARFSGSGSGTDFTL TISSLEPEDFAVYYCQQSNSWPHTFGQGTKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB88	Human IgG1/kappa		GFSLTNYD	IWTGGGT	AREGLLLPLY	QNVGTN	SAS	QQYNSYPLT	QVQLQESGPGLVKPSETLSLTCTVSGFSLTNYDISWIRQ PPGKGLEWIGVIWTGGGTNYNSAFMSRVTISVDTSKN QFSLKLSSVTAADTAVYYCAREGLLLPLYWGQGTLVTV SS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPSSLSASVGDRVTITCKASQNVGTNVA WYQQKPGKVPKLLIYSASYRYSGVPSRFSGSGSGT DFTLTISSLQPEDVATYYCQQYNSYPLTFGQGTKLEI K	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB89	Human IgG1/kappa		GYTFTNFG	INTYTGEP	ARGAYYYGSRVVWFAY	QNLVHSNGNTY	KVS	SQSSHVPYT	QVQLVQSGSELIKKPGASVKVSCKASGYTFTNFGMNW VRQAPGQGLEWMGWINTYTGEPTYADDFKGRFVFSL DTSVSTAYLQICSLKAEDTAVYYCARGAYYYGSRVVWFA YWGQGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIVMTQSPLSLPVTPGEPASISCTSSQNLVHSNGNT YLHWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSG SGTDFTLKISRVEAEDVGVYYCSQSSHVPYTFGQGT KLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C

WO 2017/181109 PCT/US2017/027765

FIGURE 4

mAb ID	Description	Epitope Sequence	Heavy-chain cdr1 (kmgt)	Heavy-chain cdr2 (kmgt)	Heavy-chain cdr3 (kmgt)	Light-chain cdr1 (kmgt)	Light-chain cdr2 (kmgt)	Light-chain cdr3 (kmgt)	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB90	Human IgG1/kappa		GFSLTSSG	IWSGGNT	ARSDYDYDWYFDV	ESVEYGTSL	AAS	QQSHKVPWT	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIVMTQTPLSLSVTPGQPASISCRASESVEYGTSLLNWFPQRAGQSPQRLLIYAASNVQSGVPDRFSGSG SGTDFTLKISRVEAEDVGVYYCQQSHKVPWTFGQGTKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB91	Human IgG1/kappa		GYTFANFW	IFPGNSDT	ARELTGYFDY	SSVSY	SSS	HQWSGHPT	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIVMTQSPLSLPVTPGEPASISCRSSQSIVHSNGNTYLEWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSG SGTDFTLKISRVEAEDVGVYYCFQGSHVPWTFGQGTKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB92	Human IgG1/kappa		GYTFANYL	IYPGSGFI	ARRFDYGGYFDV	QSIVHSNGNTY	KVS	FQGSHVPWT	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIVMTQTPLSLSVTPGQPASISCKSSQSLVHSNGNTYLNWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSG SGTDFTLKISRVEAEDVGVYYCSQSTHVPWTFGQGTKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB93	Human IgG1/kappa		GFSITNYD	IWTGGGT	ARDRSPYFDY	QSLVHSNGNTY	KVS	SQSTHVPWT	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIVMTQTPLSLSVTPGQPASISCRSSQSLVHSNGNTYLHWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSG SGTQFTLKISRVEAEDVGVYYCSQSTHVPWTFGGGTKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB94	Human IgG1/kappa		GYSITSDYA	KMAYSGDA	ARFDHYYGRFDY	SSVSY	EIS	QQWNYPLPT	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	AIQLTQSPSSLSASVGDRVTITCSASSSVSYMNWYQ QTPGKAPKRLITDTSKLASGVPSRFSGSGSGTDFTLTI SSLQPEDFATYYCQQWNYPLPTFGQGTKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB95	Human IgG1/kappa	PVDKGHDVTF and RRPREDLTFQDL	GFTFRNYG	IISGGSYT	ARIYDHDGDYYAMDY	QSNVHSNGNTY	KVS	FQGSHVPWT	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIVMTQSPLSLPVTPGEPASISCRSSQSIVHSNGNTYLEWYLQKPGQSPQLLIYKVSNRFSGVPDRFSGSG SGTDFTLKISRVEAEDVGVYYCFQGSHVPWTFGQGTKLEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C

FIGURE 4

mAb ID	Description	Epitope Sequence	Heavy-chain cdr1 (Imgt)	Heavy-chain cdr2 (Imgt)	Heavy-chain cdr3 (Imgt)	Light-chain cdr1 (Imgt)	Light-chain cdr2 (Imgt)	Light-chain cdr3 (Imgt)	Heavy-chain Variable	Heavy-chain Constant	Light-chain Variable	Light-chain Constant
VSTB95	Human IgG1/kappa		GYTFTSYD	IYPGDGST	AREGTPFAY	KSISKY	SGS	QQHNEYPWT	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYDINWV RQAPGQGLEWVAGIIYPGDGSTIYNEKFKGRVTITAD KSTSTAYMELSSLRSEDTAVYYCAREGTPFAYWGQGT TVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWY QQLPGTAPKLLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYC AAWDDSLNGPVFGGGTKLTVL	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB97	Human IgG1/kappa		GGTFSSYA	IIPIFGTA	ARSSYGMSYEFDY	QSISSY	AAS	QQSYSTPLT	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARSSYGMSYEFDYWG QGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWY QQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFT LTISSLQPEDFATYYCQQSYSTPLTFGQGTKVEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB98	Human IgG1/kappa		GGTFSSYA	IIPIFGTA	ARSTVGMSYEFDY	QSISSY	AAS	QQSYSTPLT	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARSTVGMSYEFDYWG QGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWY QQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFT LTISSLQPEDFATYYCQQSYSTPLTFGQGTKVEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C
VSTB99	Human IgG1/kappa		GGTFSSYA	IIPIFGTA	ARAVLGMWVLELDY	QSISSY	AAS	QQSYSTPLT	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWV RQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARAVLGMWVLELDYWG QGTLVTVSS	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWY QQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFT LTISSLQPEDFATYYCQQSYSTPLTFGQGTKVEIK	RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYE KHKVYACEVTHQGLSSPVTKSFNRGE C

FIGURE 5

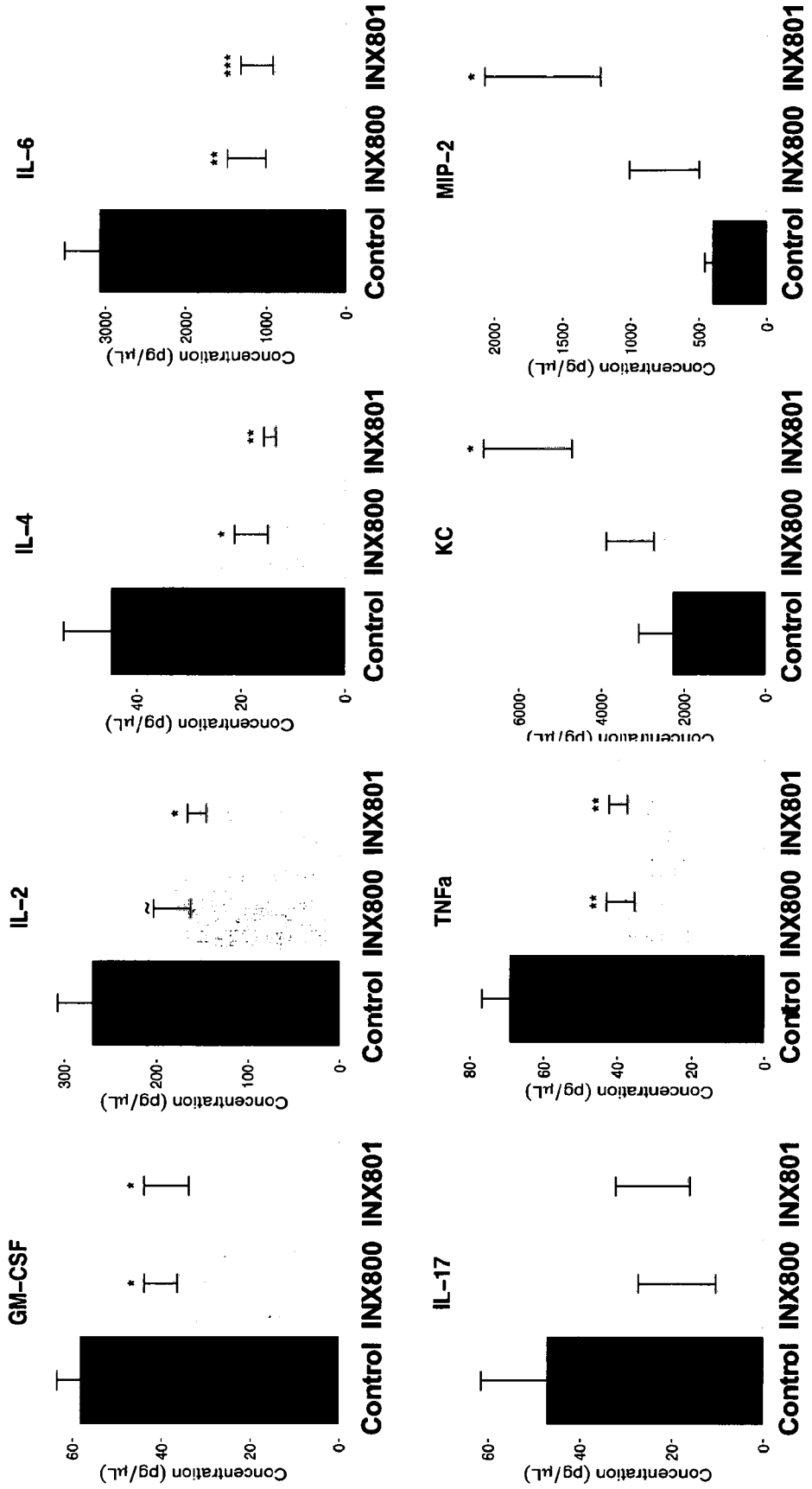


FIGURE 6:

Effects Of Agonist Anti-Human VISTA Abs In A GVHD Animal Model.

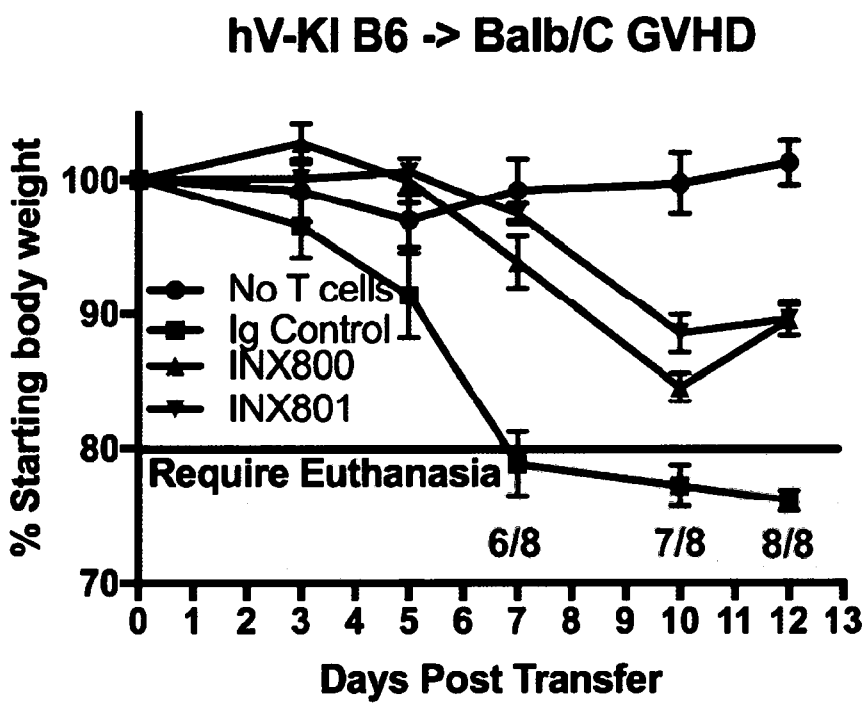


FIGURE 7
Agonist VISTA Antibodies SuppressCD3 driven T cell response

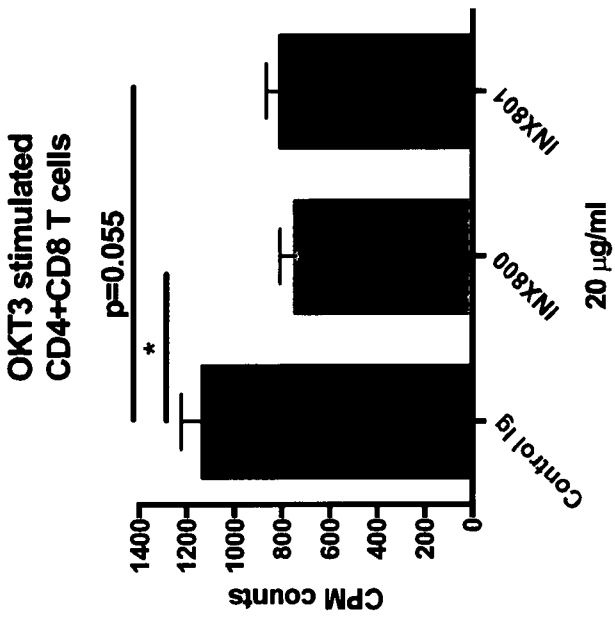


FIGURE 8

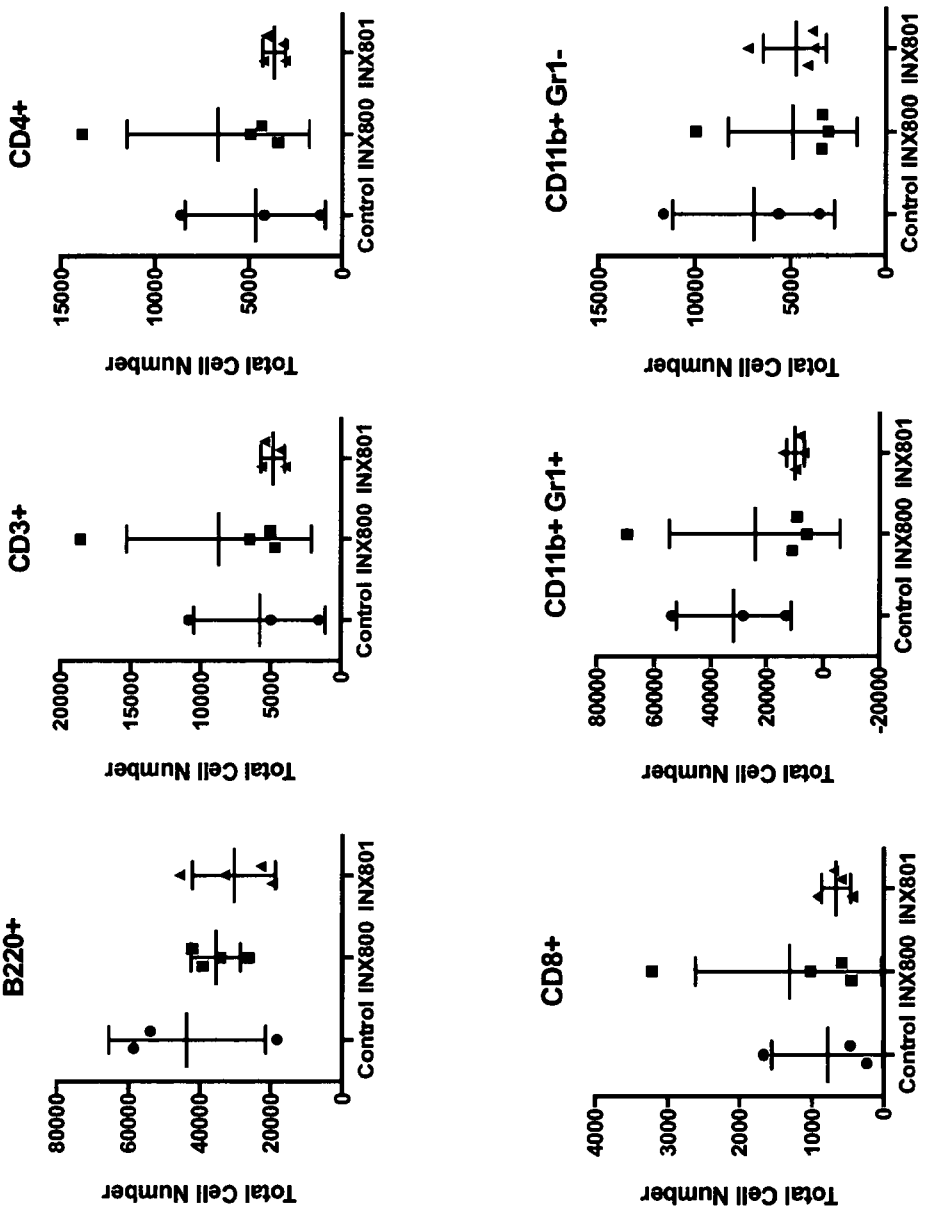
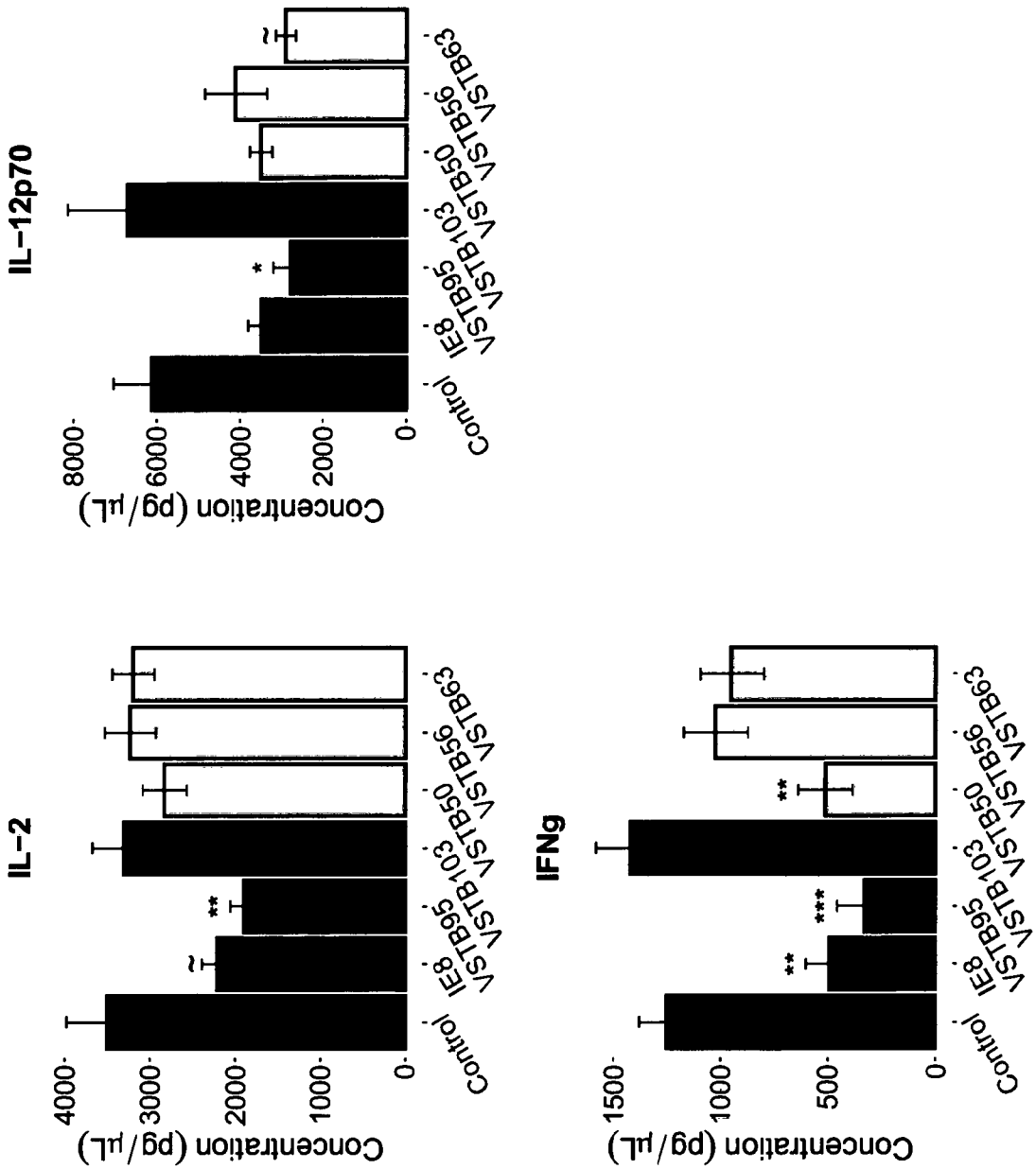


FIGURE 9: Effects of VISTA Abs in ConA Assay and on Select Proinflammatory Cytokines and Markers



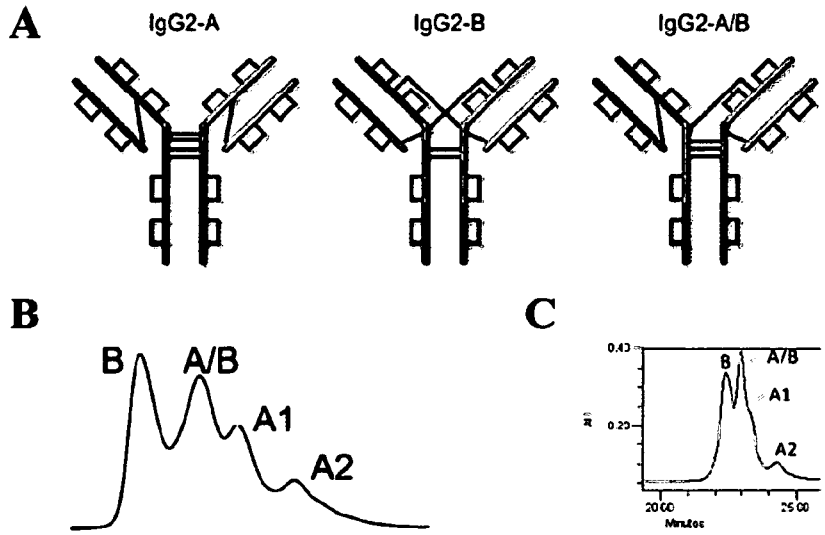


Figure 10: IgG2 Isoforms. (**A**) Disulfide shuffling leads to isoforms A and B, along with the transition for A/B (figure from Zhang, A. *et al.*, 2015). (**B**) Isoforms are distinguishable by RP-HPLC (figure from Zhang, A. *et al.*, 2015). (**C**) Observed RP-HPLC chromatogram for INX901.

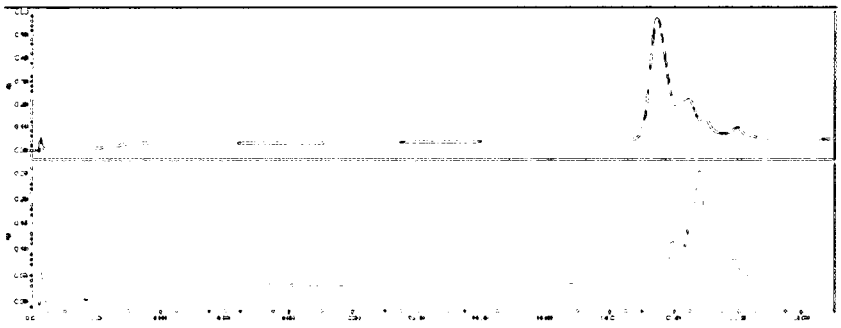


Figure 11: Chemical enrichment of IgG2 A or B isoforms. (Black line, top) Chromatogram shows a dominant left-most peak defining the B-form. (Red line, bottom) Chromatogram shows a dominant right peak defining the A-form.

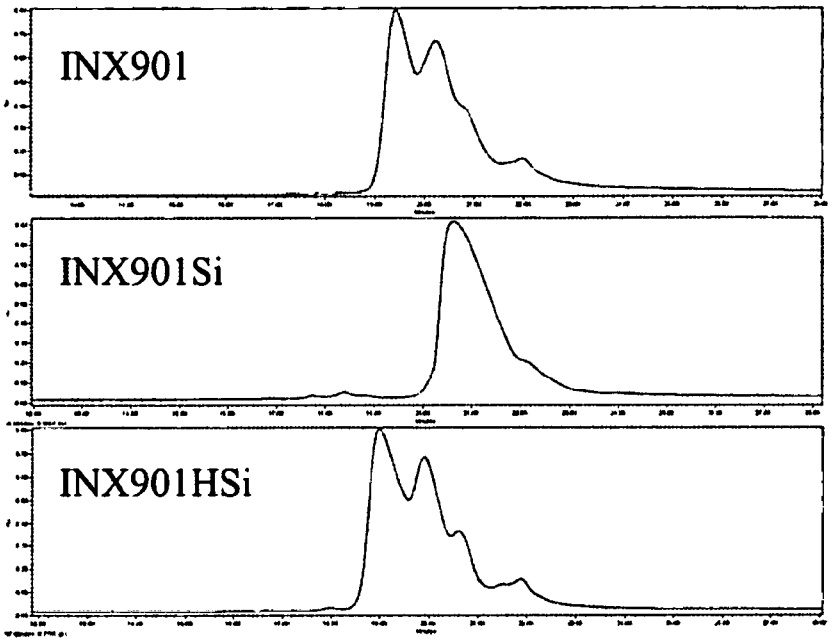


Figure 12: Comparison of INX901 Fc-silent variants with respect to disulfide shuffling. **(Top)** INX901 on an IgG2 backbone exhibits an expected mixture of A, A/B, and B isoforms. (Middle) INX901Si on a silent IgG1 backbone exists as a single isoform. **(Bottom)** INX901HSi possesses an IgG1 silent Fc region with a CH1/hinge from IgG2, which enables disulfide shuffling equivalent to native IgG2.

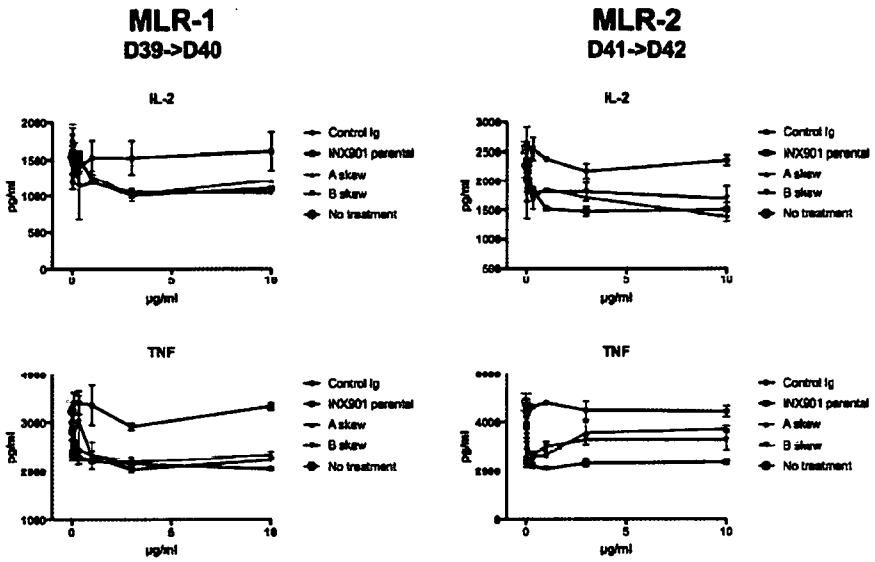


Figure 13. Biochemically skewed INX901 forms can still reduce cytokine production in the MLR.

Supernatants from two separate MLRs were analyzed for cytokine production at the 72-hour time point by Luminex analysis. INX901 parental, A skew and B skew all reduced the production of TNFα and IL-2 in a dose dependent fashion.

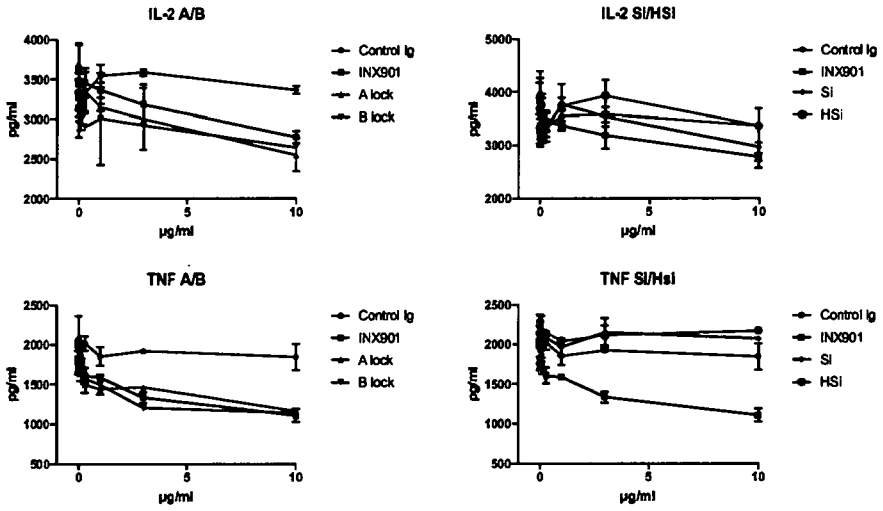


Figure 14. Genetically locked INX901 forms can still reduce cytokine production in the MLR, but Fc silent variants cannot. Supernatants from each MLR were analyzed for cytokine production at the 72-hour time point by Luminex analysis. INX901 parental, A lock and B lock all reduced the production of TNFα and IL-2 in a dose dependent fashion. The Si and HSi variants, which contain mutations to silence the Fc domain, did not consistently suppress cytokine production.

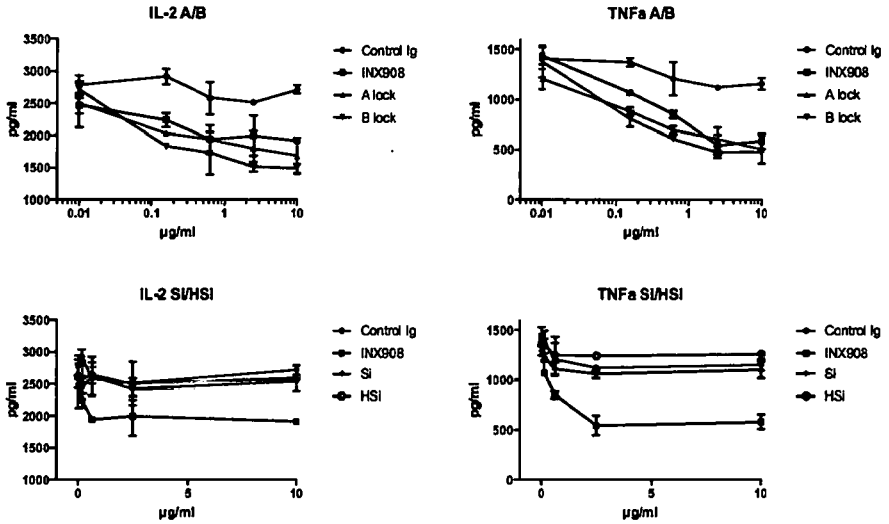


Figure 15. Genetically locked INX908 forms can still reduce cytokine production in the MLR, but Fc silent variants cannot. Supernatants from each MLR were analyzed for cytokine production at the 72-hour time point by Luminex analysis. INX908 parental, A lock and B lock all reduced the production of TNFα and IL-2 in a dose dependent fashion. The Si and HSi variants, which contain mutations to silence the Fc domain, did not consistently suppress cytokine production.

2022252828 14 Oct 2022

FIG 16

Pepscan uses peptide arrays to determine both linear and discontinuous epitopes

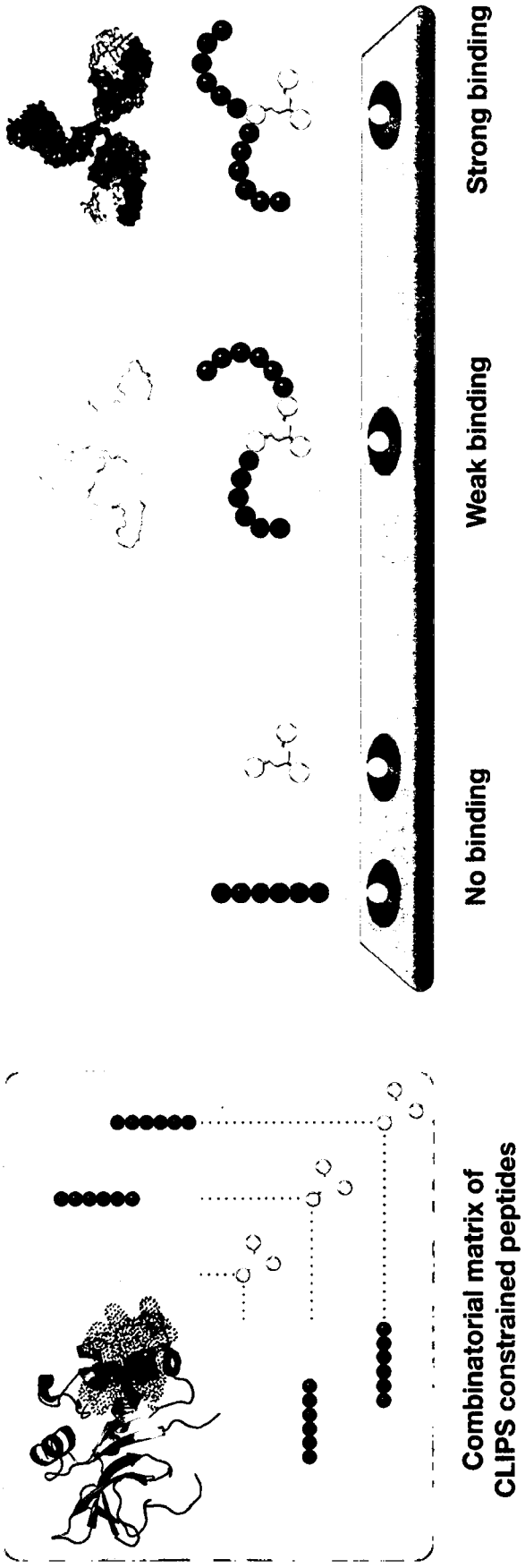
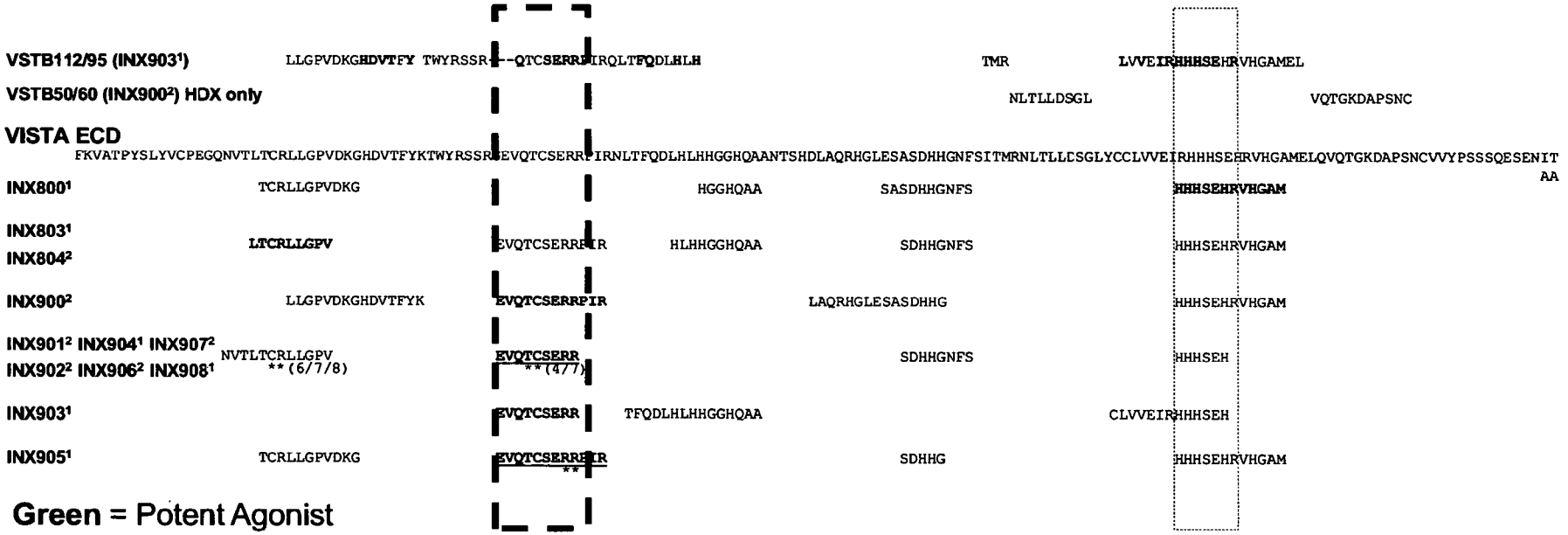


FIG 17 All suppressive INX abs bind same core seq

HDX/Crystal Results (Above ECD Sequence)

Bold indicates crystal support



Green = Potent Agonist

Red = Stability Issues (not potent)

[1/2] = Competitive Binding Bin

Pepscan Results (Below ECD Sequence)

Bold indicates dominantly recognized core sequences

Underlined indicates strong linear epitope recognition

*Important residues

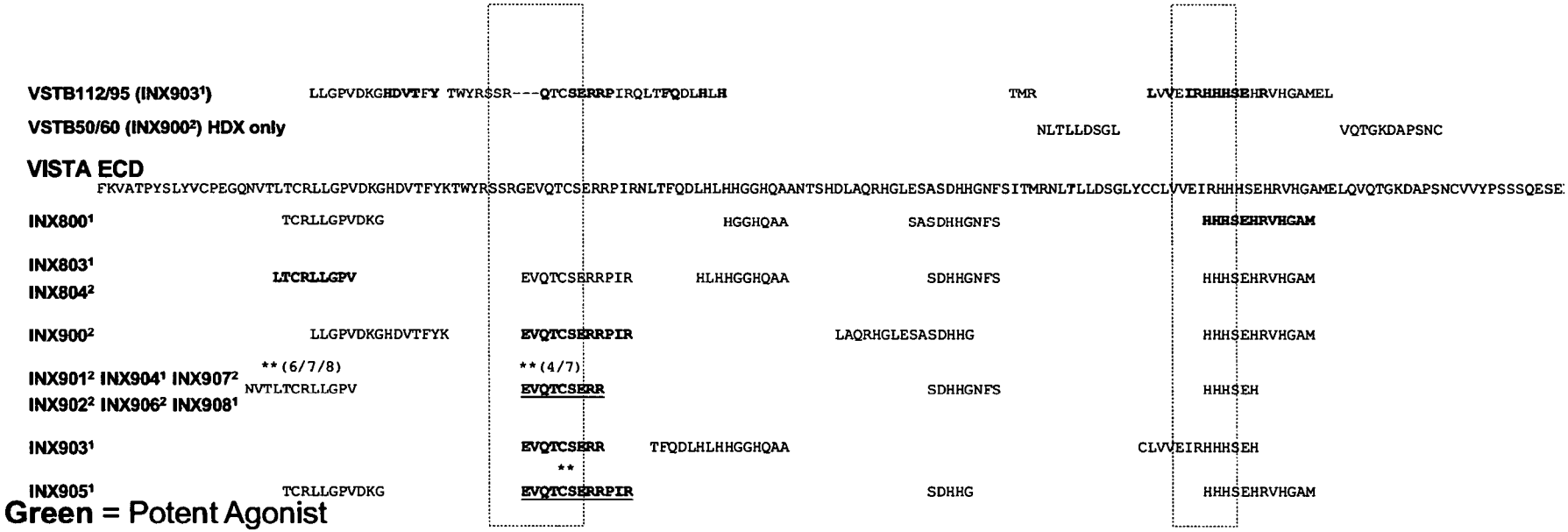
FIG 18: Epitope Mapping Summary

	mGVHD	NSG	MLR	CAIA	Epitope EQVT?
INX800	+/-	-		-	no
INX803	+				yes
INX804	+				yes
INX900	-	-	-	+	yes
INX901	+	+	+	+	yes
INX902	+	+	+	+	yes
INX903	+	+	+	+	yes
INX904	-	-			yes
INX905		+	+		yes
INX906	+	+	+	+	yes
INX907		-			yes
INX908	+	+	+	+	yes

FIG 19: VISTA Epitopes

HDX/Crystal Results

Bold indicates crystal support



Green = Potent Agonist

Red = Stability Issues (not potent)

[1/2] = Competitive Binding Bin

Pepscan Results

Bold indicates dominantly recognized core sequences

Underlined indicates strong linear epitope recognition

*Important residues

WO 2017/181109 PCT/US2017/027765