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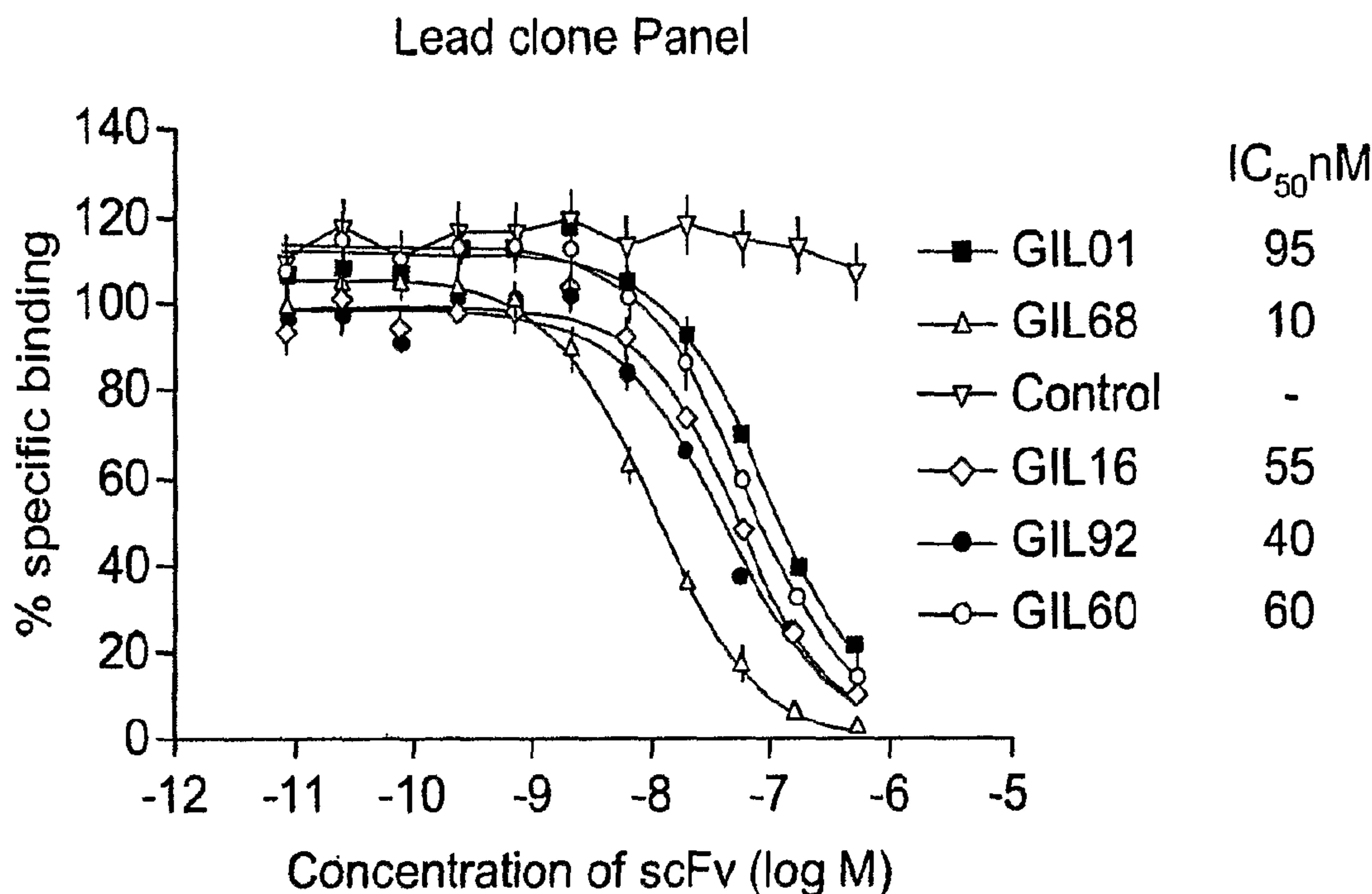
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(54) Titre : ANTICORPS DIRIGES CONTRE L'IL-22 HUMAINE ET LEURS UTILISATIONS

(54) Title: ANTIBODIES AGAINST HUMAN IL-22 AND USES THEREFOR



(57) Abrégé/Abstract:

The present application provides human antibodies and antigen binding fragments thereof that specifically bind to the human interleukin-22 (IL-22). The antibodies can act as antagonists of IL-22 activity, thereby modulating immune responses in general, and those mediated by IL-22 in particular. The disclosed compositions and methods may be used for example, in diagnosing, treating or preventing inflammatory disorders, autoimmune diseases, allergies, septic shock, infectious disorders, transplant rejection, cancer, and other immune system disorders.

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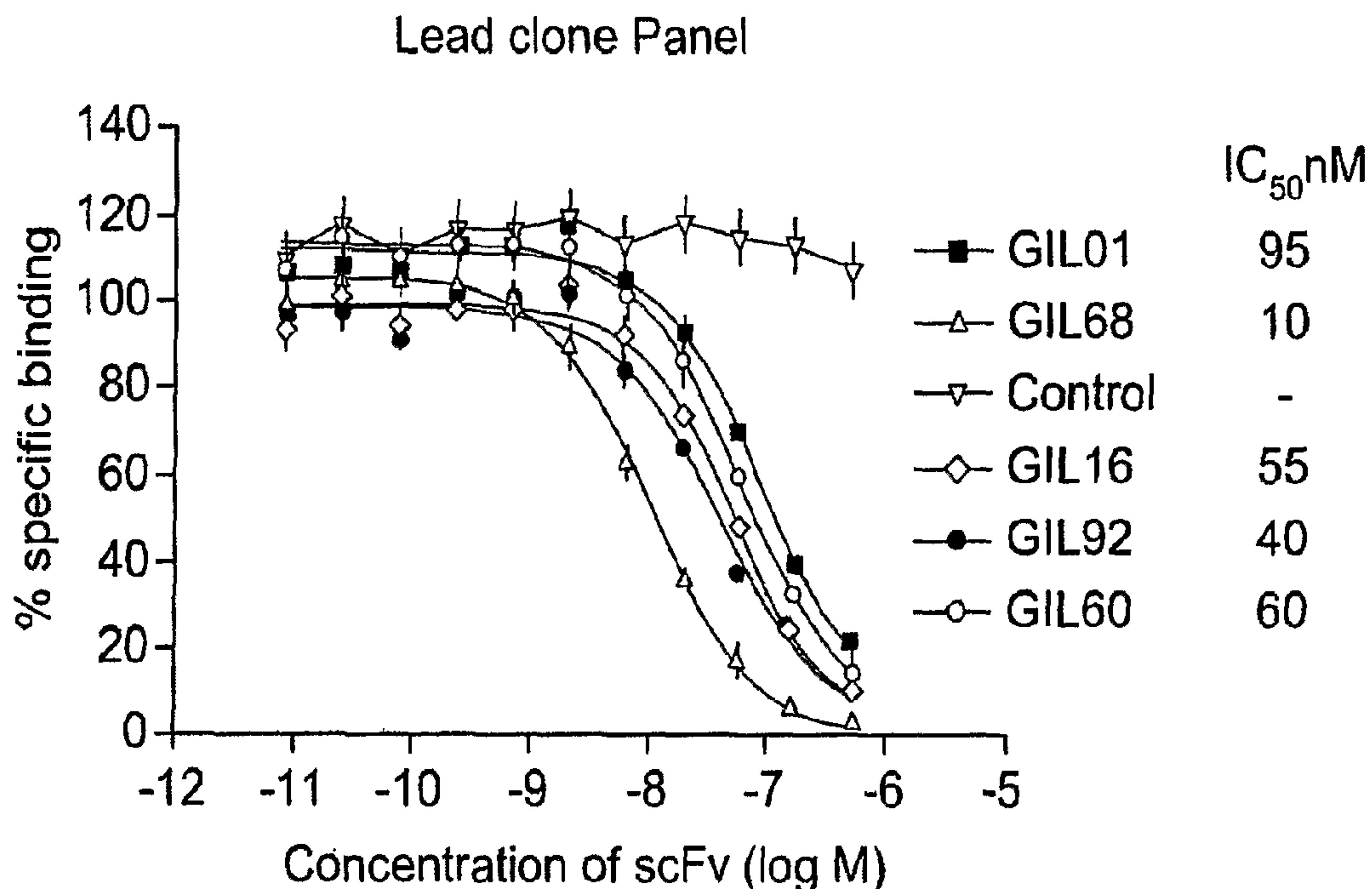
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(54) Title: ANTIBODIES AGAINST HUMAN IL-22 AND USES THEREFOR



(57) Abstract: The present application provides human antibodies and antigen binding fragments thereof that specifically bind to the human interleukin-22 (IL-22). The antibodies can act as antagonists of IL-22 activity, thereby modulating immune responses in general, and those mediated by IL-22 in particular. The disclosed compositions and methods may be used for example, in diagnosing, treating or preventing inflammatory disorders, autoimmune diseases, allergies, septic shock, infectious disorders, transplant rejection, cancer, and other immune system disorders.

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JUMBO APPLICATIONS / PATENTS

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ANTIBODIES AGAINST HUMAN IL-22 AND USES THEREFOR
CROSS REFERENCE TO RELATED APPLICATIONS

TECHNICAL FIELD

[0001] This invention relates to antibodies, e.g., human antibodies, and antigen-binding fragments thereof that bind interleukin-22 (IL-22), in particular, human IL-22, and their use in regulating IL-22-associated activities. The antibodies disclosed herein are useful in diagnosing, preventing, and/or treating IL-22 associated disorders, e.g., autoimmune disorders, including arthritis.

BACKGROUND OF THE INVENTION

[0002] Antigens initiate immune responses and activate the two largest populations of lymphocytes: T cells and B cells. After encountering antigen, T cells proliferate and differentiate into effector cells, while B cells proliferate and differentiate into antibody-secreting plasma cells. These effector cells secrete and/or respond to cytokines, which are small proteins (< about 30 kDa) secreted by lymphocytes and other cell types.

[0003] Interleukin-22 (IL-22) is a class II cytokine that shows sequence homology to IL-10. Its expression is up-regulated in T cells by IL-9 or ConA (Dumoutier L. et al. (2000) *Proc Natl Acad Sci USA* 97(18):10144-9). Further studies have shown that expression of IL-22 mRNA is induced *in vivo* in response to LPS administration, and that IL-22 modulates parameters indicative of an acute phase response (Dumoutier L. et al. (2000); Pittman D. et al. (2001) *Genes and Immunity* 2:172). In addition, IL-22 enhances the expression of antimicrobial peptides associated with host defense, including β -defensin, S100A7, S100A8, and S100A. Wolk et al., *Immunity*, 21:241-54 (2004); Boniface et al., *J. Immunol.* 174:3695-3702 (2005); Liang et al., *J. Exp. Med.*, 203(10):2271-79 (2006). Taken together, these observations indicate that IL-22 plays a role in inflammation (Kotenko S.V. (2002) *Cytokine & Growth Factor Reviews* 13(3):223-40).

[0004] IL-22 is believed to bind to a receptor complex consisting of IL-22R and IL-10R2, two members of the type II cytokine receptor family (CRF2) (Xie M.H. et al. (2000) *J Biol Chem* 275(40):31335-9; Kotenko S.V. et al. (2001) *J Biol Chem* 276(4):2725-32). Both chains of the IL-22 receptor are expressed constitutively in a number of organs. Epithelial cell lines derived from these organs are responsive

to IL-22 *in vitro* (Kotenko S.V. (2002) *Cytokine & Growth Factor Reviews* 13(3):223-40). IL-22 induces activation of the JAK/STAT3 and ERK pathways, as well as intermediates of other MAPK pathways (Dumoutier L. et al. (2000) *supra*; Xie M.H. et al. (2000) *supra*; Dumoutier L. et al. (2000) *J Immunol* 164(4):1814-9; Kotenko S.V. et al. (2001) *J Biol Chem* 276(4):2725-32; Lejeune, D. et al. (2002) *J Biol Chem* 277(37):33676-82).

[0005]CRF2 members are receptors for IFN α/β , IFN γ , coagulation factor VIIa, IL-10 and the IL-10 related proteins IL-19, IL-20, IL-22, IL-24, IL-26, as well as the recently identified IFN-like cytokines, IL-28 and IL-29 (Kotenko S.V. (2002) *Cytokine & Growth Factor Reviews* 13(3):223-40; Kotenko, S.V. et al. (2000) *Oncogene* 19(21):2557-65; Sheppard, P. et al. (2003) *Nature Immunology* 4(1):63-8; Kotenko, S.V. et al. (2003) *Nature Immunology* 4(1):69-77). In addition to these membrane receptors, the CRF2 family also includes a soluble protein, IL-22 binding protein (IL-22BP), which is specific for IL-22 and blocks its activity (Dumoutier, L. et al. (2001) *J Immunol* 166(12):7090-5; Kotenko, S.V. et al. (2001) *J Immunol* 166(12):7096-103; Xu, W. et al. (2001) *Proc Natl Acad Sci USA* 98(17):9511-6; Gruenberg, B.H. et al. (2001) *Genes & Immunity* 2(6):329-34; Wei C-C et al. (2003) *Genes & Immunity* 4:204-211). While the IL-22 receptor complex is unique for IL-22, each chain (i.e., IL-22R and IL-10R2) is shared with other CRF2 members to define functional receptors for other cytokines, including IL-20, IL-24 (IL-22R/IL-20R2), IL-28, IL-29 (IFN- λ R1/IL-10R2) and IL-10 (IL-10R1/IL-10R2) (Dumoutier, L. et al. (2001) *J. Immunol.* 167(7):3545-9; Wang, M. et al. (2002) *J Biol Chem* 277(9):7341-7; Parrish-Novak, J. et al. (2002) *J Biol Chem* 277(49):47517-23; Kotenko, S.V. et al. (1997) *EMBO J.* 16(19):5894-903; Spencer, S.D. et al. (1998) *J Exp Med* 187(4):571-8).

[0006]Both chains of the CRF2-composed receptor are necessary for signal transduction. One chain of the composed receptor has been historically defined as a ligand binding chain (e.g., IFN γ R1) based on its high affinity for the cytokine. The other chain (e.g., IFN γ R2) has been characterized as a helper or accessory chain, and shows minimal affinity for the cytokine alone (Kotenko, S.V. et al. (2000) *Oncogene* 19(21):2557-65). For IL-22, IL-22R is the high affinity receptor subunit with IL-10R2 subsequently binding to the IL-22/IL-22R complex (Li, J. et al. (2004)

Int. Immunopharmacol. 4(5):673-708; Logsdon, N. J. et al. (2002) *J. Interferon Cytokine Res* 22(11):1099-1112).

SUMMARY OF THE INVENTION

[0007] The present application provides, at least in part, IL-22 binding agents such as antibodies and antigen-binding fragments thereof that bind to interleukin-22 ("IL-22"), in particular, human IL-22, with high affinity and specificity. The antibodies and antigen-binding fragments thereof of the present invention are also referred to herein as "anti-IL-22 antibodies" and "fragments thereof," respectively. In one embodiment, the antibody or fragment thereof reduces, inhibits, or antagonizes IL-22 activity. Such antibodies can be used to regulate immune responses or IL-22-associated disorders by antagonizing IL-22 activity. In other embodiments, the anti-IL-22 antibody can be used diagnostically, or as a targeting antibody to deliver a therapeutic or a cytotoxic agent to an IL-22-expressing cell. Thus, the anti-IL-22 antibodies of the invention are useful in diagnosing, treating, and/or preventing IL-22-associated disorders, e.g., autoimmune disorders, e.g., arthritis (including rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, psoriatic arthritis, lupus-associated arthritis or ankylosing spondylitis), scleroderma, systemic lupus erythematosus, HIV, Sjogren's syndrome, vasculitis, multiple sclerosis, autoimmune thyroiditis, dermatitis (including atopic dermatitis and eczematous dermatitis), myasthenia gravis, inflammatory bowel disease (IBD), Crohn's disease, colitis, diabetes mellitus (type I); inflammatory conditions of, e.g., the skin (e.g., psoriasis), cardiovascular system (e.g., atherosclerosis), nervous system (e.g., Alzheimer's disease), liver (e.g., hepatitis), kidney (e.g., nephritis) and pancreas (e.g., pancreatitis); cardiovascular disorders, e.g., cholesterol metabolic disorders, oxygen free radical injury, ischemia; disorders associated with wound healing; respiratory disorders, e.g., asthma and COPD (e.g., cystic fibrosis); acute inflammatory conditions (e.g., endotoxemia, sepsis and septicaemia, toxic shock syndrome and infectious disease); transplant rejection and allergy. In one embodiment, the IL-22-associated disorder is, an arthritic disorder, e.g., a disorder chosen from one or more of rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, psoriatic arthritis, or ankylosing spondylitis; a respiratory disorder (e.g., asthma, chronic obstructive pulmonary disease (COPD)); or an inflammatory condition of, e.g., the skin (e.g., psoriasis), cardiovascular system (e.g.,

atherosclerosis), nervous system (e.g., Alzheimer's disease), liver (e.g., hepatitis), kidney (e.g., nephritis), pancreas (e.g., pancreatitis), and gastrointestinal organs, e.g., colitis, Crohn's disease and IBD.

[0008]Accordingly, in one aspect, the invention features an isolated antibody that binds to IL-22, in particular, human IL-22. In certain embodiments, the anti-IL-22 antibody may have at least one of the following characteristics: (1) it is a monoclonal or single specificity antibody; (2) it is a human antibody; (3) it is an *in vitro* generated antibody; (4) it is an *in vivo* generated antibody (e.g., transgenic mouse system); (5) it binds to IL-22 with an association constant of at least 10^{12} M^{-1} ; (6) it binds to IL-22 with an association constant of at least 10^{11} M^{-1} ; (7) it binds to IL-22 with an association constant of at least 10^{10} M^{-1} ; (8) it binds to IL-22 with an association constant of at least 10^9 M^{-1} ; (9) it binds to IL-22 with an association constant of at least 10^6 M^{-1} ; (10) it binds to IL-22 with a dissociation constant of 500 nM or less; (11) it binds to IL-22 with a dissociation constant of 10 nM or less; (12) it binds to IL-22 with a dissociation constant of 150 pM or less; (13) it binds to IL-22 with a dissociation constant of 60 pM or less; (14) it inhibits binding of IL-22 to IL-22R or a receptor complex of IL-22R and IL-10R2 with an IC_{50} of 10 nM or less; (15) it blocks IL-22 mediated proliferation of IL-22 receptor engineered BaF3 cells with an IC_{50} of 1 nM or less in one embodiment, with an IC_{50} of 150 pM or less in another embodiment, with an IC_{50} of 100 pM or less in another embodiment, and with an IC_{50} of 10 pM or less in another embodiment; and (16) it blocks IL-22 mediated GRO α secretion from HT29 cells with an IC_{50} of 1 nM or less in one embodiment, with an IC_{50} of 150 pM or less in another embodiment, and with an IC_{50} of 10 pM or less in another embodiment. IL-22 mediated BaF3 cell proliferation and IL-22 mediated GRO α secretion from HT29 cells can be measured as described in the examples.

[0009]Nonlimiting illustrative embodiments of the antibodies of the invention are referred to herein as "GIL01," "GIL16," "GIL45," "GIL60," "GIL68," "GIL92," "097D09," "062A09," "062G05," "087B03," "367D04," "368D04," "166B06," "166G05," "375G06," "376B10," "354A08," "355B06," "355E04," and "356A11." These antibodies can be germlined or non-germlined. In another embodiment, the antibody is chosen from 356A11, 354A08, 087B03, and 368D04. The antibodies of the invention may specifically bind to the same IL-22 epitope or a similar epitope

(e.g., an overlapping epitope) that GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 097D09, 062A09, 062G05, 087B03, 367D04, 368D04, 166B06, 166G05, 375G06, 376B10, 354A08, 355B06, 355E04, or 356A11 binds to. In other embodiments, the antibodies specifically bind to a fragment of an IL-22, e.g., a fragment of at least 10, 20, 50, 75, 100, 150, or 200 amino acids contiguous to the amino acid sequence set forth in SEQ ID NO:1, or a sequence that is at least 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical thereto. In other embodiments, the antibody competitively inhibits the binding of at least one of GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 097D09, 062A09, 062G05, 087B03, 367D04, 368D04, 166B06, 166G05, 375G06, 376B10, 354A08, 355B06, 355E04, or 356A11 to its target epitope.

[0010] In one embodiment, the antibody of the present invention includes a V_H domain, V_L domain, or combination thereof, of the F_v fragment of GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 097D09, 062A09, 062G05, 087B03, 367D04, 368D04, 166B06, 166G05, 375G06, 376B10, 354A08, 355B06, 355E04, or 356A11. For example, the antibody includes a V_H and/or a V_L domain having amino acid sequence as set forth in Tables 1 and 7 (SEQ ID NO:5, 23, 41, 59, 77, 95, 113, 131, 149, 167, 185, 203, 221, 239, 257, 275, 293, 311, 329, 347, 365, 383, 401, 419, 437, 455, 473, 491, 509, 527, 545, 563, 581, 599, or 617 for V_H and SEQ ID NO:6, 24, 42, 60, 78, 96, 114, 132, 150, 168, 186, 204, 222, 240, 258, 276, 294, 312, 330, 348, 366, 384, 402, 420, 438, 456, 474, 492, 510, 528, 546, 564, 582, 600, or 618 for V_L), or a sequence substantially identical thereto (e.g., a sequence at least about 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical thereto, or which differs by no more than 1, 2, 5, 10 or 15 amino acid residues from SEQ ID NO:5, 6, 23, 24, 41, 42, 59, 60, 77, 78, 95, 96, 113, 114, 131, 132, 149, 150, 167, 168, 185, 186, 203, 204, 221, 222, 239, 240, 257, 258, 275, 276, 293, 294, 311, 312, 329, 330, 347, 348, 365, 366, 383, 384, 401, 402, 419, 420, 437, 438, 455, 456, 473, 474, 491, 492, 509, 510, 527, 528, 545, 546, 563, 564, 581, 582, 599, 600, 617, or 618).

[0011] In another embodiment, the antibody of the present invention includes a V_H domain, V_L domain, or combination thereof, of the F_v fragment of an antibody chosen from 356A11, 354A08, 087B03, and 368D04. In this embodiment, the antibody, or antigen-binding fragment thereof, comprises:

[0012] a V_H domain comprising the amino acid sequence set out in SEQ ID NO:167 or 491 and/or a V_L domain comprising the amino acid sequence set out in SEQ ID NO:168 or 492 (087B03);

[0013] a V_H domain comprising the amino acid sequence set out in SEQ ID NO:293 or 545 and/or a V_L domain having the amino acid sequence set out in SEQ ID NO:294 or 546 (354A08);

[0014] a V_H domain comprising the amino acid sequence set out in SEQ ID NO:203 or 617 and/or a V_L domain comprising the amino acid sequence set out in SEQ ID NO:204 or 618 (368D04); or

[0015] a V_H domain comprising the amino acid sequence set out in SEQ ID NO:347 or 599 and/or a V_L domain comprising the amino acid sequence set out in SEQ ID NO:348 or 600 (356A11).

[0016] In another embodiment, the antibody includes a V_H and/or V_L domain encoded by a nucleic acid having a nucleotide sequence as set forth in Tables 1 and 7 (SEQ ID NO:14, 32, 50, 68, 86, 104, 122, 140, 158, 176, 194, 212, 230, 248, 266, 284, 302, 320, 338, 356, 374, 392, 410, 428, 446, 464, 482, 500, 518, 536, 554, 572, 590, 608, or 626 for V_H and SEQ ID NO:15, 33, 51, 69, 87, 105, 123, 141, 159, 177, 195, 213, 231, 249, 267, 285, 303, 321, 339, 357, 375, 393, 411, 429, 447, 465, 483, 501, 519, 537, 555, 573, 591, 609, or 627 for V_L), or a sequence substantially identical thereto (e.g., a sequence at least about 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical thereto, or which differs by no more than 1, 2, 3, 6, 15, 30 or 45 nucleotides from SEQ ID NO: 14, 15, 32, 33, 50, 51, 68, 69, 86, 87, 104, 105, 122, 123, 140, 141, 158, 159, 176, 177, 194, 195, 212, 213, 230, 231, 248, 249, 266, 267, 284, 285, 302, 303, 320, 321, 338, 339, 356, 357, 374, 375, 392, 393, 410, 411, 428, 429, 446, 447, 464, 465, 482, 483, 500, 501, 518, 519, 536, 537, 554, 555, 572, 573, 590, 591, 608, 609, 626, or 627).

[0017] In other embodiments, the antibody includes an Fv domain having an amino acid sequence as set forth in Tables 1 and 7 (SEQ ID NO:7, 25, 43, 61, 79, 97, 115, 133, 151, 169, 187, 205, 223, 241, 259, 277, 295, 313, 331, 349, 367, 385, 403, 421, 439, 457, 475, 493, 511, 529, 547, 565, 583, 601, or 619), or a sequence substantially identical thereto (e.g., a sequence at least about 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical thereto, or which differs by no more than 1, 2, 5, 10, 15, 20, 30 or 35 amino acid residues from SEQ ID NO:7, 25, 43,

61, 79, 97, 115, 133, 151, 169, 187, 205, 223, 241, 259, 277, 295, 313, 331, 349, 367, 385, 403, 421, 439, 457, 475, 493, 511, 529, 547, 565, 583, 601, or 619). In another embodiment, the antibody of the present invention includes an Fv domain of an antibody chosen from 356A11 (SEQ ID NO:349 or 601), 354A08 (SEQ ID NO:295 or 547), 087B03 (SEQ ID NO:169 or 493), and 368D04 (SEQ ID NO:205 or 619). In another embodiment, the antibody includes an Fv domain encoded by a nucleic acid having a nucleotide sequence as set forth in Tables 1 and 7 (SEQ ID NO:16, 34, 52, 70, 88, 106, 124, 142, 160, 178, 196, 214, 232, 250, 268, 286, 304, 322, 340, 358, 376, 394, 412, 430, 448, 466, 484, 502, 520, 538, 556, 574, 592, 610, or 628), or a sequence substantially identical thereto (e.g., a sequence at least about 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical thereto, or which differs by no more than 1, 2, 3, 6, 15, 30, 45, 60, 90 or 105 nucleotides from SEQ ID NO: 16, 34, 52, 70, 88, 106, 124, 142, 160, 178, 196, 214, 232, 250, 268, 286, 304, 322, 340, 358, 376, 394, 412, 430, 448, 466, 484, 502, 520, 538, 556, 574, 592, 610, or 628). In yet other embodiments, the antibody comprises at least one complementarity determining region (CDR) of these V_H and V_L domains. For example, the antibody can include one, two, or three CDR's of the V_H domain having an amino acid sequence as set forth in or included within the sequences in Tables 1 and 7 (SEQ ID NO:5, 7, 8, 9, 10, 23, 25, 26, 27, 28, 41, 43, 44, 45, 46, 59, 61, 62, 63, 64, 77, 79, 80, 81, 82, 95, 97, 98, 99, 100, 113, 115, 116, 117, 118, 131, 133, 134, 135, 136, 149, 151, 152, 153, 154, 167, 169, 170, 171, 172, 185, 187, 188, 189, 190, 203, 205, 206, 207, 208, 221, 223, 224, 225, 226, 239, 241, 242, 243, 244, 257, 259, 260, 261, 262, 275, 277, 278, 279, 280, 293, 295, 296, 297, 298, 311, 313, 314, 315, 316, 329, 331, 332, 333, 334, 347, 349, 350, 351, 352, 365, 367, 368, 369, 370, 383, 385, 386, 387, 388, 401, 403, 404, 405, 406, 419, 421, 422, 423, 424, 437, 439, 440, 441, 442, 455, 457, 458, 459, 460, 473, 475, 476, 477, 478, 491, 493, 494, 495, 496, 509, 511, 512, 513, 514, 527, 529, 530, 531, 532, 545, 547, 548, 549, 550, 563, 565, 566, 567, 568, 581, 583, 584, 585, 586, 599, 601, 602, 603, 604, 617, 619, 620, 621, or 622), or a sequence substantially homologous thereto (e.g., a sequence at least about 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical thereto). In another embodiment, the antibody of the present invention includes one, two, or three CDR's of the V_H domain of an antibody chosen from 356A11, 354A08, 087B03, and 368D04. In this

embodiment, the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region comprising:

[0018]a) SEQ ID NO:170 or 494; b) SEQ ID NO: 171 or 495; and/or c) SEQ ID NO: 172 or 496 (087B03);

[0019]a) SEQ ID NO:296 or 548; b) SEQ ID NO:297 or 549; and/or c) SEQ ID NO:298 or 550 (354A08);

[0020]a) SEQ ID NO:206 or 620; b) SEQ ID NO:207 or 621; and/or c) SEQ ID NO:208 or 622 (368D04); or

[0021]a) SEQ ID NO:350 or 602; b) SEQ ID NO:351 or 603; and/or c) SEQ ID NO:352 or 604 (356A11).

[0022]In another embodiment, the antibody can include one, two, or three CDR's of the V_L domain having an amino acid sequence as set forth in or included within the sequences in Tables 1 and 7 (SEQ ID NO:6, 7, 11, 12, 13, 24, 25, 29, 30, 31, 42, 43, 47, 48, 49, 60, 61, 65, 66, 67, 78, 79, 83, 84, 85, 96, 97, 101, 102, 103, 114, 115, 119, 120, 121, 132, 133, 137, 138, 139, 150, 151, 155, 156, 157, 168, 169, 173, 174, 175, 186, 187, 191, 192, 193, 204, 205, 209, 210, 211, 222, 223, 227, 228, 229, 240, 241, 245, 246, 247, 258, 259, 263, 264, 265, 276, 277, 281, 282, 283, 294, 295, 299, 300, 301, 312, 313, 317, 318, 319, 330, 331, 335, 336, 337, 348, 349, 353, 354, 355, 366, 367, 371, 372, 373, 384, 385, 389, 390, 391, 402, 403, 407, 408, 409, 420, 421, 425, 426, 427, 438, 439, 443, 444, 445, 456, 457, 461, 462, 463, 474, 475, 479, 480, 481, 492, 493, 497, 498, 499, 510, 511, 515, 516, 517, 528, 529, 533, 534, 535, 546, 547, 551, 552, 553, 564, 565, 569, 570, 571, 582, 583, 587, 588, 589, 600, 601, 605, 606, 607, 618, 619, 623, 624, or 625), or a sequence substantially identical thereto (e.g., a sequence at least about 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical thereto). In another embodiment, the antibody of the present invention includes one, two, or three CDR's of the V_L domain of an antibody chosen from 356A11, 354A08, 087B03, and 368D04. In this embodiment, the antibody, or antigen-binding fragment thereof, comprises a light chain variable region comprising:

[0023]a) SEQ ID NO:173 or 497; b) SEQ ID NO: 174 or 498; and/or c) SEQ ID NO:175 or 499 (087B03);

[0024]a) SEQ ID NO:299 or 551; b) SEQ ID NO:300 or 552; and/or c) SEQ ID NO:301 or 553 (354A08);

[0025]a) SEQ ID NO:209 or 623; b) SEQ ID NO:210 or 624; and/or c) SEQ ID NO:211 or 625 (368D04); or

[0026]a) SEQ ID NO:353 or 605; b) SEQ ID NO:354 or 606; and/or c) SEQ ID NO:355 or 607 (356A11).

[0027]In a still further embodiment, the antibody comprises an H3 fragment of the V_H domain of GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 097D09, 062A09, 062G05, 087B03, 367D04, 368D04, 166B06, 166G05, 375G06, 376B10, 354A08, 355B06, 355E04, or 356A11, e.g., an H3 fragment having the amino acid sequence as set forth in Tables 1 and 7 (SEQ ID NO:10, 28, 46, 64, 82, 100, 118, 136, 154, 172, 190, 208, 226, 244, 262, 280, 298, 316, 334, 352, 370, 388, 406, 424, 442, 460, 478, 496, 514, 532, 550, 568, 586, 604, or 622), or a sequence substantially identical thereto (e.g., a sequence at least about 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identical thereto).

[0028]The antibody of the invention can be full-length (e.g., include at least one complete heavy chain and at least one complete light chain) or can include only an antigen-binding fragment (e.g., a Fab, F(ab')₂, Fv, a single chain Fv fragment, a Fd fragment, or a dAb fragment). The antibody can include a constant region, or a portion thereof, chosen from any of: the kappa, lambda, alpha, gamma, delta, epsilon and mu constant region genes. For example, heavy chain constant regions of the various isotypes can be used, including: IgG₁, IgG₂, IgG₃, IgG₄, IgM, IgA₁, IgA₂, IgD, and IgE. The light chain constant region can be chosen from kappa or lambda. The antibody may be an IgG, or it may also be IgG_{1κ} or IgG_{1γ}.

[0029] The anti-IL-22 antibody described herein can be derivatized or linked to another functional molecule (such as another peptide or protein (e.g., a Fab fragment)). For example, an antibody of the invention can be functionally linked (e.g., by chemical coupling, genetic fusion, non-covalent association or otherwise) to at least one other molecular entity, such as another antibody (e.g., a bispecific or a multispecific antibody), toxin, radioisotope, cytotoxic or cytostatic agent, among others.

[0030]In another aspect, the invention features a pharmaceutical composition containing at least one anti-IL-22 antibody and a pharmaceutically acceptable carrier. The pharmaceutical composition can further include a

combination of at least one anti-IL-22 antibody and at least one therapeutic agent (e.g., cytokine and growth factor inhibitors, immunosuppressants, anti-inflammatory agents, metabolic inhibitors, enzyme inhibitors, cytotoxic agents, cytostatic agents, or combinations thereof, as described in more detail herein). Combinations of the anti-IL-22 antibody and a therapeutic agent are also within the scope of the invention. The compositions and combinations of the invention can be used to regulate IL-22-associated inflammatory conditions, e.g., by modulating IL-22 signaling through its receptors located on epithelial cells of a variety of tissues, including, but not limited to, those of the pancreas, skin, lung, gut, liver, kidney, salivary gland, and vascular endothelia, in addition to potentially activated and tissue localized immune cells.

[0031] In another aspect, the invention features a method of treating a subject with an IL-22-associated disorder. The method includes administering to the subject an anti-IL-22 antibody in an amount sufficient to inhibit at least one IL-22 activity of immune cells, thereby treating the IL-22-associated disorder.

[0032] The anti-IL-22 antibody can be administered to the subject, alone or in combination, with other therapeutic agents as described herein. The subject may be a mammal, e.g. human. For example, the method can be used to treat a subject with an IL-22-associated disorder such as autoimmune disorders, e.g., arthritis (including rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, psoriatic arthritis, lupus-associated arthritis or ankylosing spondylitis), scleroderma, systemic lupus erythematosus, HIV, Sjogren's syndrome, vasculitis, multiple sclerosis, autoimmune thyroiditis, dermatitis (including atopic dermatitis and eczematous dermatitis), myasthenia gravis, inflammatory bowel disease (IBD), Crohn's disease, colitis, diabetes mellitus (type I); inflammatory conditions of, e.g., the skin (e.g., psoriasis), cardiovascular system (e.g., atherosclerosis), nervous system (e.g., Alzheimer's disease), liver (e.g., hepatitis), kidney (e.g., nephritis) and pancreas (e.g., pancreatitis); cardiovascular disorders, e.g., cholesterol metabolic disorders, oxygen free radical injury, ischemia; disorders associated with wound healing; respiratory disorders, e.g., asthma and COPD (e.g., cystic fibrosis); acute inflammatory conditions (e.g., endotoxemia, sepsis and septicaemia, toxic shock syndrome and infectious disease); transplant rejection and allergy. In one embodiment, the IL-22-associated disorder is, an arthritic disorder, e.g., a disorder

chosen from one or more of rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, psoriatic arthritis, or ankylosing spondylitis; a respiratory disorder (e.g., asthma, chronic obstructive pulmonary disease (COPD)); or an inflammatory condition of, e.g., the skin (e.g., psoriasis), cardiovascular system (e.g., atherosclerosis), nervous system (e.g., Alzheimer's disease), liver (e.g., hepatitis), kidney (e.g., nephritis), pancreas (e.g., pancreatitis), and gastrointestinal organs, e.g., colitis, Crohn's disease and IBD.

[0033] In another aspect, the invention features a method of decreasing, inhibiting or reducing an acute phase response in a subject. The method includes administering to the subject an IL-22 binding agent, e.g., an IL-22 antagonist, (e.g., an anti-IL-22 antibody or fragment thereof as described herein), in an amount sufficient to decrease, inhibit or reduce the acute phase response in the subject. In one embodiment, the subject is a mammal, e.g., a human suffering from an IL-22-associated disorder, including, e.g., respiratory disorders, inflammatory disorders and autoimmune disorders. In one embodiment, the IL-22 binding agent is administered locally, e.g., topically, subcutaneously, or other administrations that are not in the general circulation.

[0034] In another aspect, an IL-22 binding agent can be used to alter the type of immune response and/or increase the efficacy of a vaccine formulation used to immunize a subject. For example, an anti-IL-22 antibody of the present invention can be administered before, during and/or after an immunization to increase vaccine efficacy. In one embodiment, the vaccine formulation contains one or more IL-22 antagonists and an antigen, i.e., an immunogen, including, for example, viral, bacterial, or tumor antigens. In another embodiment, the IL-22 antagonist and the immunogen are administered separately, e.g., within one hour, three hours, one day or two days of each other.

[0035] In another aspect, the invention provides a method for detecting the presence of IL-22 in a sample *in vitro*. Samples may include biological samples such as serum, plasma, tissue and biopsy. The subject method can be used to diagnose a disorder, such as an IL-22-associated disorder as described herein. The method includes: (1) contacting the sample or a control sample with an anti-IL-22 antibody, and (2) detecting formation of a complex between the anti-IL-22 antibody and the sample or the control sample, wherein a statistically significant

change in the formation of the complex in the sample relative to a control sample, is indicative of the presence of the IL-22 in the sample.

[0036] In another aspect, the invention provides a method for detecting the presence of IL-22 *in vivo* (e.g., *in vivo* imaging in a subject). The method can be used to diagnose a disorder, e.g., an IL-22-associated disorder as described herein. The method includes: (1) administering an anti-IL-22 antibody to a subject or a control subject under conditions that allow binding of the antibody to IL-22, and (2) detecting formation of a complex between the antibody and IL-22, wherein a statistically significant change in the formation of the complex in the subject relative to a control, e.g., a control subject, is indicative of the presence of IL-22.

[0037] The antibody may be directly or indirectly labeled with a detectable substance to facilitate detection of the bound or unbound antibody. Suitable detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials and radioactive materials.

[0038] In another aspect, the invention provides a method for delivering or targeting an agent, e.g., a therapeutic or a cytotoxic agent, to an IL-22-expressing cell *in vivo*. The method includes administering an anti-IL-22 antibody to a subject under conditions that allow binding of the antibody to IL-22. The antibody may be coupled to a second therapeutic moiety, such as a toxin.

[0039] The disclosure provides nucleic acid sequences from the V_H and V_L domains of GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 097D09, 062A09, 062G05, 087B03, 367D04, 368D04, 166B06, 166G05, 375G06, 376B10, 354A08, 355B06, 355E04, and 356A11. Also provided are nucleic acid sequences that comprise at least one CDR from GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 097D09, 062A09, 062G05, 087B03, 367D04, 368D04, 166B06, 166G05, 375G06, 376B10, 354A08, 355B06, 355E04, and 356A11. The disclosure also provides vectors and host cells comprising such nucleic acids.

[0040] The disclosure further provides methods of producing new V_H and V_L domains and functional antibodies comprising all or a portion of such domains derived from the V_H or V_L domains of GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 097D09, 062A09, 062G05, 087B03, 367D04, 368D04, 166B06, 166G05, 375G06, 376B10, 354A08, 355B06, 355E04, or 356A11.

[0041] Additional aspects of the disclosure will be set forth in part in the description, and in part will be obvious from the description, or may be learned by practicing the invention. The invention is set forth and particularly pointed out in the claims, and the disclosure should not be construed as limiting the scope of the claims. The following detailed description includes exemplary representations of various embodiments of the invention, which are not restrictive of the invention as claimed. The accompanying figures constitute a part of this specification and, together with the description, serve only to illustrate embodiments and not limit the invention.

BRIEF DESCRIPTION OF THE FIGURES

[0042] Figure 1. Potency of parent anti-IL-22 scFv clones in the IL-22 receptor complex assay: bio.IL-22 binding IL-22 receptor complex DELFIA competition assay.

[0043] Figure 2. Profiling of lead scFv clones in IL-22 receptor complex assay: bio.IL-22 binding IL-22 receptor complex DELFIA competition assay. (A) GIL 1 derived. (B) GIL 16 derived. (C) GIL 16, GIL 60, and GIL 68 derived. (D) GIL 60 derived. (E) GIL 68 derived. (F) GIL 68 derived. (G) GIL 92 derived.

[0044] Figure 3. IgG potency in GROa cell based assays. Optimized GIL-IgGs in huIL-22 GROa assay. (A) Germlined IgG. (B) Non-germlined IgG.

[0045] Figure 4. Cross species reactivity of IL-22 antibodies by ELISA. Optimized GIL-IgGs specifically bind to IL-22. (A) Germlined IgG. (B) Non-germlined IgG.

[0046] Figure 5. Amino acid and nucleotide sequences of human IL-22. The nucleotide sequence of human IL-22 is SEQ ID NO:2 and includes a poly (A) tail. The disclosed nucleotide sequence includes an open reading frame and the amino acid sequence of full-length IL-22 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:1. The amino acid sequence of mature IL-22 corresponds to about amino acids 34-179 of SEQ ID NO:1.

[0047] Figure 6. Amino acid and nucleotide sequences of mouse IL-22.

[0048] Figure 7. Amino acid and nucleotide sequences of non-germlined GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 097D09, 062A09, 062G05, 087B03, 367D04, 368D04, 166B06, 166G05, 375G06, 376B10, 354A08, 355B06, 355E04,

and 356A11, including V_H and V_L domains, and CDRs (H1, H2, H3, L1, L2, and L3).

[0049]Figure 8. Amino acid and nucleotide sequences of germlined GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 062A09, 087B03, 166B06, 166G05, 354A08, 355B06, 355E04, 356A11, and 368D04, including V_H and V_L domains, and CDRs (H1, H2, H3, L1, L2, and L3).

[0050]Figure 9. Amino acid and nucleotide sequences of scFv's for non-germlined GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 097D09, 062A09, 062G05, 087B03, 367D04, 368D04, 166B06, 166G05, 375G06, 376B10, 354A08, 355B06, 355E04, and 356A11, with CDRs underlined (H1, H2, H3, L1, L2, and L3).

[0051]Figure 10. Amino acid and nucleotide sequences of scFv's for germlined GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 062A09, 087B03, 166B06, 166G05, 354A08, 355B06, 355E04, 356A11, and 368D04 with CDRs underlined (H1, H2, H3, L1, L2, and L3).

DETAILED DESCRIPTION

I. Definitions

[0052]In order that the present invention may be more readily understood, certain terms are first defined. Additional definitions are set forth throughout the detailed description.

[0053]The term “**antibody**” refers to an immunoglobulin or fragment thereof, and encompasses any polypeptide comprising an antigen-binding fragment or an antigen-binding domain. The term includes but is not limited to polyclonal, monoclonal, monospecific, polyspecific, non-specific, humanized, human, single-chain, chimeric, synthetic, recombinant, hybrid, mutated, grafted, and *in vitro* generated antibodies. Unless preceded by the word “intact”, the term “antibody” includes antibody fragments such as Fab, F(ab')₂, Fv, scFv, Fd, dAb, and other antibody fragments that retain antigen-binding function. Typically, such fragments would comprise an antigen-binding domain.

[0054]The terms “**antigen-binding domain**” and “**antigen-binding fragment**” refer to a part of an antibody molecule that comprises amino acids responsible for the specific binding between antibody and antigen. The part of the antigen that is specifically recognized and bound by the antibody is referred to as the “epitope.” An antigen-binding domain may comprise an antibody light chain

variable region (V_L) and an antibody heavy chain variable region (V_H); however, it does not have to comprise both. Fd fragments, for example, have two V_H regions and often retain some antigen-binding function of the intact antigen-binding domain. Examples of antigen-binding fragments of an antibody include (1) a Fab fragment, a monovalent fragment having the V_L , V_H , C_L and C_{H1} domains; (2) a $F(ab')_2$ fragment, a bivalent fragment having two Fab fragments linked by a disulfide bridge at the hinge region; (3) a Fd fragment having the two V_H and C_{H1} domains; (4) a Fv fragment having the V_L and V_H domains of a single arm of an antibody, (5) a dAb fragment (Ward et al., (1989) *Nature* 341:544-546), which has a V_H domain; (6) an isolated complementarity determining region (CDR), and (7) a single chain Fv (scFv). 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; and Huston et al. (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883). These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are evaluated for function in the same manner as are intact antibodies.

[0055]The term “**effective amount**” refers to a dosage or amount that is sufficient to regulate IL-22 activity to ameliorate clinical symptoms or achieve a desired biological outcome, e.g., decreased T cell and/or B cell activity, suppression of autoimmunity, suppression of transplant rejection, etc.

[0056]The term “**human antibody**” includes antibodies having variable and constant regions corresponding substantially to human germline immunoglobulin sequences known in the art, including, for example, those described by Kabat et al. (See Kabat, et al. (1991) *Sequences of Proteins of Immunological Interest*, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). The human 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, and in particular, CDR3. The human antibody can have at least one, two, three, four, five, or more positions replaced with an

amino acid residue that is not encoded by the human germline immunoglobulin sequence.

[0057] The phrase “**inhibit**” or “**antagonize**” IL-22 activity and its cognates refer to a reduction, inhibition, or otherwise diminution of at least one activity of IL-22 due to binding an anti-IL-22 antibody, wherein the reduction is relative to the activity of IL-22 in the absence of the same antibody. The activity can be measured using any technique known in the art, including, for example, as described in Examples 7 and 9. Inhibition or antagonism does not necessarily indicate a total elimination of the IL-22 polypeptide biological activity. A reduction in activity may be about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or more.

[0058] The term “**interleukin-22**” or “**IL-22**” refers to a class II cytokine (which may be mammalian) capable of binding to IL-22R and/or a receptor complex of IL-22R and IL-10R2, and has at least one of the following features: (1) an amino acid sequence of a naturally occurring mammalian IL-22 polypeptide (full length or mature form) or a fragment thereof, e.g., an amino acid sequence shown as SEQ ID NO:1 (human) or SEQ ID NO:3 (murine) or a fragment thereof; (2) an amino acid sequence substantially identical to, e.g., at least 85%, 90%, 95%, 96%, 97%, 98%, 99% identical to, an amino acid sequence shown as SEQ ID NO:1 or amino acids 34-179 thereof (human) or SEQ ID NO:3 (murine) or a fragment thereof; (3) an amino acid sequence which is encoded by a naturally occurring mammalian IL-22 nucleotide sequence or a fragment thereof (e.g., SEQ ID NO:2 or nucleotides 71 to 610 (human) or SEQ ID NO:4 (murine) or a fragment thereof); (4) an amino acid sequence encoded by a nucleotide sequence which is substantially identical to, e.g., at least 85%, 90%, 95%, 96%, 97%, 98%, 99% identical to, a nucleotide sequence shown as SEQ ID NO:2 or nucleotides 71 to 610 thereof (human) or SEQ ID NO:4 (murine) or a fragment thereof; (5) an amino acid sequence encoded by a nucleotide sequence degenerate to a naturally occurring IL-22 nucleotide sequence or a fragment thereof, e.g., SEQ ID NO:2 (human) or SEQ ID NO:4 (murine) or a fragment thereof; or (6) a nucleotide sequence that hybridizes to one of the foregoing nucleotide sequences under stringent conditions, e.g., highly stringent conditions. The IL-22 may bind to IL-22R and/or a receptor complex of IL-22R and IL-10R2 of mammalian origin, e.g., human or mouse.

[0059]The nucleotide sequence and the predicted amino acid sequence of human IL-22 are shown in SEQ ID NO:2 and SEQ ID NO:1, respectively. The amino acid sequence of mature human IL-22 corresponds to amino acids 34-179 of SEQ ID NO:1. Analysis of recombinant human IL-22 reveals many structural domains. (Nagem et al. (2002) Structure, 10:1051-62; U.S. Patent Application No. US 2002/0187512 A1).

[0060]The term “**IL-22 activity**” refers to at least one cellular process initiated or interrupted as a result of IL-22 binding to a receptor complex consisting of IL-22R and IL-10R2 on the cell. IL-22 activities include at least one of, but are not limited to: (1) binding IL-22R or a receptor complex of IL-22R and IL-10R2 (e.g., human IL-22R with or without human IL-10R2); (2) associating with signal transduction molecules (e.g., JAK-1); (3) stimulating phosphorylation of STAT proteins (e.g., STAT5, STAT3, or combination thereof); (4) activating STAT proteins; and (5) modulating (e.g., increasing or decreasing) proliferation, differentiation, effector cell function, cytolytic activity, cytokine secretion, survival, or combinations thereof, of epithelial cells, fibroblasts, or immune cells. Epithelial cells include, but are not limited to, cells of the skin, gut, liver, and kidney, as well as endothelial cells. Fibroblasts include, but are not limited to, synovial fibroblasts. Immune cells may include CD8+ and CD4+ T cells, NK cells, B cells, macrophages, and megakaryocytes. IL-22 activity can be determined *in vitro*, for example, using the IL-22 receptor inhibition assay as described in Examples 2 and 6, the GRO α secretion assay in Example 9, or the BAF3 proliferation assay of Example 7. IL-22 activity can also be determined *in vivo*, for example, by scoring progression of an immune response or disorder as described in Example 13.

[0061]As used herein, “***in vitro* generated antibody**” refers to an antibody where all or part of the variable region (e.g., at least one CDR) is generated in a non-immune cell selection (e.g., an *in vitro* phage display, protein chip or any other method in which candidate sequences can be tested for their ability to bind to an antigen). This term excludes sequences generated by genomic rearrangement in an immune cell.

[0062]The term “**isolated**” refers to a molecule that is substantially free of its natural environment. For instance, an isolated protein is substantially free of cellular material or other proteins from the cell or tissue source from which it was

derived. The term also refers to preparations where the isolated protein is sufficiently pure for pharmaceutical compositions; or at least 70-80% (w/w) pure; or at least 80-90% (w/w) pure; or at least 90-95% pure; or at least 95%, 96%, 97%, 98%, 99%, or 100% (w/w) pure.

[0063] The phrase “**percent identical**” or “**percent identity**” refers to the similarity between at least two different sequences. This percent identity can be determined by standard alignment algorithms, for example, the Basic Local Alignment Tool (BLAST) described by Altschul et al. ((1990) J. Mol. Biol., 215: 403-410); the algorithm of Needleman et al. ((1970) J. Mol. Biol., 48: 444-453); or the algorithm of Meyers et al. ((1988) Comput. Appl. Biosci., 4: 11-17). A set of parameters may be the Blosum 62 scoring matrix with a gap penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5. The percent identity between two amino acid or nucleotide sequences can also be determined using the algorithm of E. Meyers and W. Miller ((1989) CABIOS, 4:11-17) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. The percent identity is usually calculated by comparing sequences of similar length.

[0064] The term “**repertoire**” refers to at least one nucleotide sequence derived wholly or partially from at least one sequence encoding at least one immunoglobulin. The sequence(s) may be generated by rearrangement *in vivo* of the V, D, and J segments of heavy chains, and the V and J segments of light chains. Alternatively, the sequence(s) can be generated from a cell in response to which rearrangement occurs, e.g., *in vitro* stimulation. Alternatively, part or all of the sequence(s) may be obtained by DNA splicing, nucleotide synthesis, mutagenesis, and other methods, see, e.g., U.S. Patent 5,565,332. A repertoire may include only one sequence or may include a plurality of sequences, including ones in a genetically diverse collection.

[0065] The terms “**specific binding**” or “**specifically binds**” refers to two molecules forming a complex that is relatively stable under physiologic conditions. Specific binding is characterized by a high affinity and a low to moderate capacity as distinguished from nonspecific binding which usually has a low affinity with a moderate to high capacity. Typically, binding is considered specific when the association constant K_A is higher than $10^6 M^{-1}$. If necessary, nonspecific binding

can be reduced without substantially affecting specific binding by varying the binding conditions. The appropriate binding conditions, such as concentration of antibodies, ionic strength of the solution, temperature, time allowed for binding, concentration of a blocking agent (e.g., serum albumin, milk casein), etc., may be optimized by a skilled artisan using routine techniques. Illustrative conditions are set forth in Example 3, but other conditions known to the person of ordinary skill in the art fall within the scope of this invention.

[0066]As used herein, the term “**stringent**” describes conditions for hybridization and washing. Stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. Aqueous and nonaqueous methods are described in that reference and either can be used. One example of stringent hybridization conditions is hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by at least one wash in 0.2X SSC, 0.1% SDS at 50°C. A second example of stringent hybridization conditions is hybridization in 6X SSC at about 45°C, followed by at least one wash in 0.2X SSC, 0.1% SDS at 55°C. Another example of stringent hybridization conditions is hybridization in 6X SSC at about 45°C, followed by at least one wash in 0.2X SSC, 0.1% SDS at 60°C. A further example of stringent hybridization conditions is hybridization in 6X SSC at about 45°C, followed by at least one wash in 0.2X SSC, 0.1% SDS at 65°C. High stringent conditions include hybridization in 0.5M sodium phosphate, 7% SDS at 65°C, followed by at least one wash at 0.2X SSC, 1% SDS at 65°C.

[0067]The phrase “**substantially as set out**,” “**substantially identical**” or “**substantially homologous**” means that the relevant amino acid or nucleotide sequence (e.g., CDR(s), V_H, or V_L domain) will be identical to or have insubstantial differences (through conserved amino acid substitutions) in comparison to the sequences which are set out. Insubstantial differences include minor amino acid changes, such as 1 or 2 substitutions in a 5 amino acid sequence of a specified region. In the case of antibodies, the second antibody has the same specificity and has at least 50% of the affinity of the first antibody.

[0068]Sequences substantially identical or homologous (e.g., at least about 85% sequence identity) to the sequences disclosed herein are also part of this application. In some embodiment, the sequence identity can be about 85%, 90%,

95%, 96%, 97%, 98%, 99% or higher. Alternatively, substantial identity or homology exists when the nucleic acid segments will hybridize under selective hybridization conditions (e.g., highly stringent hybridization conditions), to the complement of the strand. The nucleic acids may be present in whole cells, in a cell lysate, or in a partially purified or substantially pure form.

[0069]The term “**therapeutic agent**” is a substance that treats or assists in treating a medical disorder. Therapeutic agents may include, but are not limited to, substances that modulate immune cells or immune responses in a manner that complements the IL-22 activity of anti-IL-22 antibodies. Non-limiting examples and uses of therapeutic agents are described herein.

[0070]As used herein, a “**therapeutically effective amount**” of an anti-IL-22 antibody refers to an amount of an antibody which is effective, upon single or multiple dose administration to a subject (such as a human patient) at treating, preventing, curing, delaying, reducing the severity of, and/or ameliorating at least one symptom of a disorder or recurring disorder, or prolonging the survival of the subject beyond that expected in the absence of such treatment.

[0071]The term “**treatment**” refers to a therapeutic or preventative measure. The treatment may be administered to a subject having a medical disorder or who ultimately may acquire the disorder, in order to prevent, cure, delay, reduce the severity of, and/or ameliorate one or more symptoms of a disorder or recurring disorder, or in order to prolong the survival of a subject beyond that expected in the absence of such treatment.

II. Anti-IL-22 Antibodies

[0072]The disclosure provides novel anti-IL-22 antibodies that comprise novel antigen-binding fragments.

[0073]Numerous methods known to those skilled in the art are available for obtaining antibodies or antigen-binding fragments thereof. For example, antibodies can be produced using recombinant DNA methods (U.S. Patent 4,816,567). Monoclonal antibodies may also be produced by generation of hybridomas (see e.g., Kohler and Milstein (1975) *Nature*, 256: 495-499) in accordance with known methods. Hybridomas formed in this manner are then screened using standard methods, such as enzyme-linked immunosorbent assay (ELISA) and surface plasmon resonance (BIAcore™) analysis, to identify one or more hybridomas

that produce an antibody that specifically binds with a specified antigen. Any form of the specified antigen may be used as the immunogen, *e.g.*, recombinant antigen, naturally occurring forms, any variants or fragments thereof, as well as antigenic peptide thereof.

[0074]One exemplary method of making antibodies includes screening protein expression libraries, *e.g.*, phage or ribosome display libraries. Phage display is described, for example, in Ladner *et al.*, U.S. Patent No. 5,223,409; Smith (1985) *Science* 228:1315-1317; Clackson *et al.* (1991) *Nature*, 352: 624-628; Marks *et al.* (1991) *J. Mol. Biol.*, 222: 581-597 WO 92/18619; WO 91/17271; WO 92/20791; WO 92/15679; WO 93/01288; WO 92/01047; WO 92/09690; and WO 90/02809.

[0075]In addition to the use of display libraries, the specified antigen can be used to immunize a non-human animal, *e.g.*, a rodent, *e.g.*, a mouse, hamster, or rat. In one embodiment, the non-human animal includes at least a part of a human immunoglobulin gene. For example, it is possible to engineer mouse strains deficient in mouse antibody production with large fragments of the human Ig loci. Using the hybridoma technology, antigen-specific monoclonal antibodies derived from the genes with the desired specificity may be produced and selected. *See, e.g.*, XENOMOUSE™, Green *et al.* (1994) *Nature Genetics* 7:13-21, US 2003-0070185, WO 96/34096, published Oct. 31, 1996, and PCT Application No. PCT/US96/05928, filed Apr. 29, 1996.

[0076]In another embodiment, a monoclonal antibody is obtained from the non-human animal, and then modified, *e.g.*, humanized, deimmunized, chimeric, may be produced using recombinant DNA techniques known in the art. A variety of approaches for making chimeric antibodies have been described. *See e.g.*, Morrison *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 81:6851, 1985; Takeda *et al.*, *Nature* 314:452, 1985, Cabilly *et al.*, U.S. Patent No. 4,816,567; Boss *et al.*, U.S. Patent No. 4,816,397; Tanaguchi *et al.*, European Patent Publication EP171496; European Patent Publication 0173494, United Kingdom Patent GB 2177096B. Humanized antibodies may also be produced, for example, using transgenic mice that express human heavy and light chain genes, but are incapable of expressing the endogenous mouse immunoglobulin heavy and light chain genes. Winter describes an exemplary CDR-grafting method that may be used to prepare the

humanized antibodies described herein (U.S. Patent No. 5,225,539). All of the CDRs of a particular human antibody may be replaced with at least a portion of a non-human CDR, or only some of the CDRs may be replaced with non-human CDRs. It is only necessary to replace the number of CDRs required for binding of the humanized antibody to a predetermined antigen.

[0077] Humanized antibodies or fragments thereof can be generated by replacing sequences of the Fv variable domain that are not directly involved in antigen binding with equivalent sequences from human Fv variable domains. Exemplary methods for generating humanized antibodies or fragments thereof are provided by Morrison (1985) *Science* 229:1202-1207; by Oi *et al.* (1986) *BioTechniques* 4:214; and by US 5,585,089; US 5,693,761; US 5,693,762; US 5,859,205; and US 6,407,213. Those methods include isolating, manipulating, and expressing the nucleic acid sequences that encode all or part of immunoglobulin Fv variable domains from at least one of a heavy or light chain. Such nucleic acids may be obtained from a hybridoma producing an antibody against a predetermined target, as described above, as well as from other sources. The recombinant DNA encoding the humanized antibody molecule can then be cloned into an appropriate expression vector.

[0078] In certain embodiments, a humanized antibody is optimized by the introduction of conservative substitutions, consensus sequence substitutions, germline substitutions and/or backmutations. Such altered immunoglobulin molecules can be made by any of several techniques known in the art, (e.g., Teng *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, 80: 7308-7312, 1983; Kozbor *et al.*, *Immunology Today*, 4: 7279, 1983; Olsson *et al.*, *Meth. Enzymol.*, 92: 3-16, 1982), and may be made according to the teachings of PCT Publication WO92/06193 or EP 0239400).

[0079] An antibody or fragment thereof may also be modified by specific deletion of human T cell epitopes or "deimmunization" by the methods disclosed in WO 98/52976 and WO 00/34317. Briefly, the heavy and light chain variable domains of an antibody can be analyzed for peptides that bind to MHC Class II; these peptides represent potential T-cell epitopes (as defined in WO 98/52976 and WO 00/34317). For detection of potential T-cell epitopes, a computer modeling approach termed "peptide threading" can be applied, and in addition a database of

human MHC class II binding peptides can be searched for motifs present in the V_H and V_L sequences, as described in WO 98/52976 and WO 00/34317. These motifs bind to any of the 18 major MHC class II DR allotypes, and thus constitute potential T cell epitopes. Potential T-cell epitopes detected can be eliminated by substituting small numbers of amino acid residues in the variable domains, or preferably, by single amino acid substitutions. Typically, conservative substitutions are made. Often, but not exclusively, an amino acid common to a position in human germline antibody sequences may be used. Human germline sequences, e.g., are disclosed in Tomlinson, *et al.* (1992) *J. Mol. Biol.* 227:776-798; Cook, G. P. *et al.* (1995) *Immunol. Today* Vol. 16 (5): 237-242; Chothia, D. *et al.* (1992) *J. Mol. Biol.* 227:799-817; and Tomlinson *et al.* (1995) *EMBO J.* 14:4628-4638. The V BASE directory provides a comprehensive directory of human immunoglobulin variable region sequences (compiled by Tomlinson, I.A. *et al.* MRC Centre for Protein Engineering, Cambridge, UK). These sequences can be used as a source of human sequence, e.g., for framework regions and CDRs. Consensus human framework regions can also be used, e.g., as described in U.S. Patent No. 6,300,064.

[0080]In certain embodiments, an antibody can contain an altered immunoglobulin constant or Fc region. For example, an antibody produced in accordance with the teachings herein may bind more strongly or with more specificity to effector molecules such as complement and/or Fc receptors, which can control several immune functions of the antibody such as effector cell activity, lysis, complement-mediated activity, antibody clearance, and antibody half-life. Typical Fc receptors that bind to an Fc region of an antibody (*e.g.*, an IgG antibody) include, but are not limited to, receptors of the FcγRI, FcγRII, and FcγRIII and FcRn subclasses, including allelic variants and alternatively spliced forms of these receptors. Fc receptors are reviewed in Ravetch and Kinet, *Annu. Rev. Immunol* 9:457-92, 1991; Capel *et al.*, *Immunomethods* 4:25-34, 1994; and de Haas *et al.*, *J. Lab. Clin. Med.* 126:330-41, 1995).

[0081]For additional antibody production techniques, see *Antibodies: A Laboratory Manual*, eds. Harlow *et al.*, Cold Spring Harbor Laboratory, 1988. The present invention is not necessarily limited to any particular source, method of production, or other special characteristics of an antibody.

[0082]Antibodies, also known as immunoglobulins, are typically tetrameric glycosylated proteins composed of two light (L) chains of approximately 25 kDa each and two heavy (H) chains of approximately 50 kDa each. Two types of light chain, termed lambda and kappa, may be found in antibodies. Depending on the amino acid sequence of the constant domain of heavy chains, immunoglobulins can be assigned to five major classes: A, D, E, G, and M, and several of these may be further divided into subclasses (isotypes), e.g., IgG₁, IgG₂, IgG₃, IgG₄, IgA₁, and IgA₂. Each light chain includes an N-terminal variable (V) domain (VL) and a constant (C) domain (CL). Each heavy chain includes an N-terminal V domain (VH), three or four C domains (CHs), and a hinge region. The CH domain most proximal to VH is designated as CH1. The VH and VL domains consist of four regions of relatively conserved sequences called framework regions (FR1, FR2, FR3, and FR4), which form a scaffold for three regions of hypervariable sequences (complementarity determining regions, CDRs). The CDRs contain most of the residues responsible for specific interactions of the antibody with the antigen. CDRs are referred to as CDR1, CDR2, and CDR3. Accordingly, CDR constituents on the heavy chain are referred to as H1, H2, and H3, while CDR constituents on the light chain are referred to as L1, L2, and L3.

[0083]CDR3 is typically the greatest source of molecular diversity within the antibody-binding site. H3, for example, can be as short as two amino acid residues or greater than 26 amino acids. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known in the art. For a review of the antibody structure, see *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, eds. Harlow et al., 1988. One of skill in the art will recognize that each subunit structure, e.g., a CH, VH, CL, VL, CDR, FR structure, comprises active fragments, e.g., the portion of the VH, VL, or CDR subunit that binds to the antigen, i.e., the antigen-binding fragment, or, e.g., the portion of the CH subunit that binds to and/or activates, e.g., an Fc receptor and/or complement. The CDRs typically refer to the Kabat CDRs, as described in *Sequences of Proteins of Immunological Interest*, US Department of Health and Human Services (1991), eds. Kabat et al. Another standard for characterizing the antigen binding site is to refer to the hypervariable loops as described by Chothia. See, e.g., Chothia, D. et al. (1992) *J. Mol. Biol.* 227:799-817; and Tomlinson et al. (1995)

EMBO J. 14:4628-4638. Still another standard is the AbM definition used by Oxford Molecular's AbM antibody modelling software. See, generally, e.g., *Protein Sequence and Structure Analysis of Antibody Variable Domains*. In: *Antibody Engineering Lab Manual* (Ed.: Duebel, S. and Kontermann, R., Springer-Verlag, Heidelberg). Embodiments described with respect to Kabat CDRs can alternatively be implemented using similar described relationships with respect to Chothia hypervariable loops or to the AbM-defined loops.

[0084] The Fab fragment (Fragment antigen-binding) consists of V_H-C_{H1} and V_L-C_L domains covalently linked by a disulfide bond between the constant regions. The F_v fragment is smaller and consists of V_H and V_L domains non-covalently linked. To overcome the tendency of non-covalently linked domains to dissociate, a single chain F_v fragment (scF_v) can be constructed. The scF_v contains a flexible polypeptide that links (1) the C-terminus of V_H to the N-terminus of V_L, or (2) the C-terminus of V_L to the N-terminus of V_H. A 15-mer (Gly₄Ser)₃ peptide may be used as a linker, but other linkers are known in the art.

[0085] The sequence of antibody genes after assembly and somatic mutation is highly varied, and these varied genes are estimated to encode 10¹⁰ different antibody molecules (Immunoglobulin Genes, 2nd ed., eds. Jonio et al., Academic Press, San Diego, CA, 1995).

[0086] A "bispecific" or "bifunctional antibody" is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. See, e.g., Songsivilai & Lachmann, *Clin. Exp. Immunol.* 79:315-321 (1990); Kostelny et al., *J. Immunol.* 148, 1547-1553 (1992). In one embodiment, the bispecific antibody comprises a first binding domain polypeptide, such as a Fab' fragment, linked via an immunoglobulin constant region to a second binding domain polypeptide.

[0087] Small Modular ImmunoPharmaceuticals (SMIP™) provide an example of a variant molecule comprising a binding domain polypeptide. SMIPs and their uses and applications are disclosed in, e.g., U.S. Published Patent Application. Nos. 2003/0118592, 2003/0133939, 2004/0058445, 2005/0136049, 2005/0175614, 2005/0180970, 2005/0186216, 2005/0202012, 2005/0202023, 2005/0202028, 2005/0202534, and 2005/0238646, and related patent family

members thereof.

[0088]A SMIPTM typically refers to a binding domain-immunoglobulin fusion protein that includes a binding domain polypeptide that is fused or otherwise connected to an immunoglobulin hinge or hinge-acting region polypeptide, which in turn is fused or otherwise connected to a region comprising one or more native or engineered constant regions from an immunoglobulin heavy chain, other than CH1, for example, the CH2 and CH3 regions of IgG and IgA, or the CH3 and CH4 regions of IgE (see e.g., U.S. 2005/0136049 by Ledbetter, J. *et al.*).

The binding domain-immunoglobulin fusion protein can further include a region that includes a native or engineered immunoglobulin heavy chain CH2 constant region polypeptide (or CH3 in the case of a construct derived in whole or in part from IgE) that is fused or otherwise connected to the hinge region polypeptide and a native or engineered immunoglobulin heavy chain CH3 constant region polypeptide (or CH4 in the case of a construct derived in whole or in part from IgE) that is fused or otherwise connected to the CH2 constant region polypeptide (or CH3 in the case of a construct derived in whole or in part from IgE). Typically, such binding domain-immunoglobulin fusion proteins are capable of at least one immunological activity selected from the group consisting of antibody dependent cell-mediated cytotoxicity, complement fixation, and/or binding to a target, for example, a target antigen, such as human IL-22.

[0089]Therapeutic proteins, i.e., a protein or peptide that has a biological effect on a region in the body on which it acts or on a region of the body on which it remotely acts via intermediates, are also useful for practicing the invention. A therapeutic protein can include peptide mimetics. Mimetics are peptide-containing molecules that mimic elements of protein secondary structure. See, for example, Johnson et al., "Peptide Turn Mimetics" in BIOTECHNOLOGY AND PHARMACY, Pezzuto et al., Eds., Chapman and Hall, New York (1993).

The underlying rationale behind the use of peptide mimetics is that the peptide backbone of proteins exists chiefly to orient amino acid side chains in such a way as to facilitate molecular interactions, such as those of antibody and antigen. A peptide mimetic is expected to permit molecular interactions similar to the natural

molecule. These principles may be used to engineer second generation molecules having many of the natural properties of the targeting peptides disclosed herein, but with altered and potentially improved characteristics.

[0090] Other embodiments of therapeutic proteins include fusion proteins. These molecules generally have all or a substantial portion of a targeting peptide, for example, IL-22 or an anti IL-22 antibody, linked at the N- or C-terminus, to all or a portion of a second polypeptide or protein. For example, fusions may employ leader sequences from other species to permit the recombinant expression of a protein in a heterologous host. Another useful fusion includes the addition of an immunologically active domain, such as an antibody epitope, to facilitate purification of the fusion protein. Inclusion of a cleavage site at or near the fusion junction will facilitate removal of the extraneous polypeptide after purification. Other useful fusions include linking of functional domains, such as active sites from enzymes, glycosylation domains, cellular targeting signals or transmembrane regions. Examples of proteins or peptides that may be incorporated into a fusion protein include cytostatic proteins, cytotoxic proteins, pro-apoptosis agents, anti-angiogenic agents, hormones, cytokines, growth factors, peptide drugs, antibodies, Fab fragments of antibodies, antigens, receptor proteins, enzymes, lectins, MHC proteins, cell adhesion proteins and binding proteins. Methods of generating fusion proteins are well known to those of skill in the art. Such proteins can be produced, for example, by chemical attachment using bifunctional cross-linking reagents, by de novo synthesis of the complete fusion protein, or by attachment of a DNA sequence encoding the targeting peptide to a DNA sequence encoding the second peptide or protein, followed by expression of the intact fusion protein.

[0091] In one embodiment, the targeting peptide, for example, IL-22 or an anti IL-22 antibody, is fused with an immunoglobulin heavy chain constant region, such as an Fc fragment, which contains two constant region domains and a hinge region but lacks the variable region (See, U.S. Pat. Nos. 6,018,026 and 5,750,375).

The Fc region may be a naturally occurring Fc region, or may be altered to improve certain qualities, such as therapeutic qualities, circulation time, reduced aggregation, etc. Peptides and proteins fused to an Fc region typically exhibit a greater half-life *in vivo* than the unfused counterpart. Also,

a fusion to an Fc region permits dimerization/multimerization of the fusion polypeptide.

[0092] VHH molecules (or nanobodies), as known to the skilled artisan, are heavy chain variable domains derived from immunoglobulins naturally devoid of light chains, such as those derived from Camelidae as described in WO9404678.

Such a VHH molecule can be derived from antibodies raised in Camelidae species, for example in camel, llama, dromedary, alpaca and guanaco and is sometimes called a camelid or camelized variable domain. See e.g., Muyldermans., *J. Biotechnology* (2001) 74(4):277-302.

Other species besides Camelidae may produce heavy chain antibodies naturally devoid of light chain. VHH molecules are about 10 times smaller than IgG molecules. They are single polypeptides and very stable, resisting extreme pH and temperature conditions. Moreover, they are resistant to the action of proteases which is not the case for conventional antibodies. Furthermore, *in vitro* expression of VHHs produces high yield, properly folded functional VHHs. In addition, antibodies generated in Camelids will recognize epitopes other than those recognized by antibodies generated *in vitro* through the use of antibody libraries or via immunization of mammals other than Camelids (see WO 9749805).

[0093] One aspect of the present invention comprises antibodies and antigen binding fragments that bind IL-22. The disclosure provides novel CDRs derived from human immunoglobulin gene libraries. The structure for carrying a CDR is generally an antibody heavy or light chain or portion thereof, where the CDR is located to a naturally occurring CDR region. The structures and locations of variable domains may be determined as described in Kabat et al., *Sequences of Proteins of Immunological Interest*, No. 91-3242, National Institutes of Health Publications, Bethesda, MD (1991).

[0094] DNA and amino acid (AA) sequences of illustrative embodiments of the anti-IL-22 antibodies of this invention, including their scFv fragments, V_H and V_L domains, and CDRs, are set forth in Figures 7-10 and enumerated in Tables 1 and 7. Twenty specific embodiments of the non-germlined antibodies are identified as GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 097D09, 062A09, 062G05, 087B03, 367D04, 368D04, 166B06, 166G05, 375G06, 376B10, 354A08, 355B06, 355E04,

and 356A11. The CDR positions in the V_H and V_L domains of the non-germlined antibodies are listed in Table 2. Fifteen specific embodiments of the germlined antibodies are identified as GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 062A09, 087B03, 166B06, 166G05, 354A08, 355B06, 355E04, 356A11, and 368D04.

Table 1A: Amino acid and Nucleotide Sequences of V_H and V_L Domains, F_V, and CDRs of Non-germlined

Antibodies

Region	Type	GIL01 SEQ ID	GIL16 SEQ ID	GIL45 SEQ ID	GIL60 SEQ ID	GIL68 SEQ ID	GIL92 SEQ ID	097D09 SEQ ID	062A09 SEQ ID	062G05 SEQ ID	087B03 SEQ ID
V _H	AA	NO:5	NO:23	NO:41	NO:59	NO:77	NO:95	NO:113	NO:131	NO:149	NO:167
V _L	AA	NO:6	NO:24	NO:42	NO:60	NO:78	NO:96	NO:114	NO:132	NO:150	NO:168
scFv	AA	NO:7	NO:25	NO:43	NO:61	NO:79	NO:97	NO:115	NO:133	NO:151	NO:169
H1	AA	NO:8	NO:26	NO:44	NO:62	NO:80	NO:98	NO:116	NO:134	NO:152	NO:170
H2	AA	NO:9	NO:27	NO:45	NO:63	NO:81	NO:99	NO:117	NO:135	NO:153	NO:171
H3	AA	NO:10	NO:28	NO:46	NO:64	NO:82	NO:100	NO:118	NO:136	NO:154	NO:172
L1	AA	NO:11	NO:29	NO:47	NO:65	NO:83	NO:101	NO:119	NO:137	NO:155	NO:173
L2	AA	NO:12	NO:30	NO:48	NO:66	NO:84	NO:102	NO:120	NO:138	NO:156	NO:174
L3	AA	NO:13	NO:31	NO:49	NO:67	NO:85	NO:103	NO:121	NO:139	NO:157	NO:175
V _H	DNA	NO:14	NO:32	NO:50	NO:68	NO:86	NO:104	NO:122	NO:140	NO:158	NO:176
V _L	DNA	NO:15	NO:33	NO:51	NO:69	NO:87	NO:105	NO:123	NO:141	NO:159	NO:177
scFv	DNA	NO:16	NO:34	NO:52	NO:70	NO:88	NO:106	NO:124	NO:142	NO:160	NO:178
H1	DNA	NO:17	NO:35	NO:53	NO:71	NO:89	NO:107	NO:125	NO:143	NO:161	NO:179
H2	DNA	NO:18	NO:36	NO:54	NO:72	NO:90	NO:108	NO:126	NO:144	NO:162	NO:180
H3	DNA	NO:19	NO:37	NO:55	NO:73	NO:91	NO:109	NO:127	NO:145	NO:163	NO:181
L1	DNA	NO:20	NO:38	NO:56	NO:74	NO:92	NO:110	NO:128	NO:146	NO:164	NO:182
L2	DNA	NO:21	NO:39	NO:57	NO:75	NO:93	NO:111	NO:129	NO:147	NO:165	NO:183
L3	DNA	NO:22	NO:40	NO:58	NO:76	NO:94	NO:112	NO:130	NO:148	NO:166	NO:184

Table 1B: Amino acid and Nucleotide Sequences of V_H and V_L Domains, F_V, and CDRs of Non-germlined Antibodies

Region	Type	367D04 SEQ ID	368D04 SEQ ID	166B06 SEQ ID	166G05 SEQ ID	375G06 SEQ ID	376B10 SEQ ID	354A08 SEQ ID	355B06 SEQ ID	355E04 SEQ ID	356A11 SEQ ID
V _H	AA	NO:185	NO:203	NO:221	NO:239	NO:257	NO:275	NO:293	NO:311	NO:329	NO:347
V _L	AA	NO:186	NO:204	NO:222	NO:240	NO:258	NO:276	NO:294	NO:312	NO:330	NO:348
scF _V	AA	NO:187	NO:205	NO:223	NO:241	NO:259	NO:277	NO:295	NO:313	NO:331	NO:349
H1	AA	NO:188	NO:206	NO:224	NO:242	NO:260	NO:278	NO:296	NO:314	NO:332	NO:350
H2	AA	NO:189	NO:207	NO:225	NO:243	NO:261	NO:279	NO:297	NO:315	NO:333	NO:351
H3	AA	NO:190	NO:208	NO:226	NO:244	NO:262	NO:280	NO:298	NO:316	NO:334	NO:352
L1	AA	NO:191	NO:209	NO:227	NO:245	NO:263	NO:281	NO:299	NO:317	NO:335	NO:353
L2	AA	NO:192	NO:210	NO:228	NO:246	NO:264	NO:282	NO:300	NO:318	NO:336	NO:354
L3	AA	NO:193	NO:211	NO:229	NO:247	NO:265	NO:283	NO:301	NO:319	NO:337	NO:355
V _H	DNA	NO:194	NO:212	NO:230	NO:248	NO:266	NO:284	NO:302	NO:320	NO:338	NO:356
V _L	DNA	NO:195	NO:213	NO:231	NO:249	NO:267	NO:285	NO:303	NO:321	NO:339	NO:357
scF _V	DNA	NO:196	NO:214	NO:232	NO:250	NO:268	NO:286	NO:304	NO:322	NO:340	NO:358
H1	DNA	NO:197	NO:215	NO:233	NO:251	NO:269	NO:287	NO:305	NO:323	NO:341	NO:359
H2	DNA	NO:198	NO:216	NO:234	NO:252	NO:270	NO:288	NO:306	NO:324	NO:342	NO:360
H3	DNA	NO:199	NO:217	NO:235	NO:253	NO:271	NO:289	NO:307	NO:325	NO:343	NO:361
L1	DNA	NO:200	NO:218	NO:236	NO:254	NO:272	NO:290	NO:308	NO:326	NO:344	NO:362
L2	DNA	NO:201	NO:219	NO:237	NO:255	NO:273	NO:291	NO:309	NO:327	NO:345	NO:363
L3	DNA	NO:202	NO:220	NO:238	NO:256	NO:274	NO:292	NO:310	NO:328	NO:346	NO:364

Table 2: Positions of CDRs within Non-germlined Antibody Amino Acid Sequences of V_H and V_L Domains

CDR	GIL01	GIL16	GIL45	GIL60	GIL68	GIL92	097D09	062A09	062G05	087B03
H1	31-35	31-35	31-35	31-35	31-35	31-35	31-35	31-35	31-35	31-35
H2	50-66	50-66	50-66	50-66	50-66	50-66	50-66	50-66	50-66	50-66
H3	99-108	99-108	99-108	99-110	99-108	99-110	99-108	99-108	99-108	99-110
L1	24-34	24-34	23-36	23-36	23-33	23-36	24-34	24-34	24-34	23-36
L2	50-56	50-56	52-58	52-58	49-55	52-58	50-56	50-56	50-56	52-58
L3	89-97	89-97	91-100	91-100	88-98	91-101	89-97	89-97	89-97	91-100

CDR	367D04	368D04	166B06	166G05	375G06	376B10	354A08	355B06	355E04	356A11
H1	31-35	31-35	31-35	31-35	31-35	31-35	30-34	31-35	31-35	31-35
H2	50-66	50-66	50-66	50-66	50-66	50-66	49-65	50-66	50-66	50-66
H3	99-110	99-110	99-108	99-108	99-108	99-108	98-109	99-110	99-110	99-110
L1	23-36	23-36	23-33	23-33	23-33	23-33	23-36	23-36	23-36	22-35
L2	52-58	52-58	49-55	49-55	49-55	49-55	52-58	52-58	52-58	51-58
L3	91-100	91-100	88-98	88-98	88-98	88-98	91-101	91-101	91-101	90-100

[0095] Anti-IL-22 antibodies of this invention may optionally comprise antibody constant regions or parts thereof. For example, a V_L domain may be attached at its C-terminal end to a light chain constant domain like C_k or C_λ . Similarly, a V_H domain or portion thereof may be attached to all or part of a heavy chain like IgA, IgD, IgE, IgG, and IgM, and any isotype subclass. Constant regions are known in the art (see, for example, Kabat et al., Sequences of Proteins of Immunological Interest, No. 91-3242, National Institutes of Health Publications, Bethesda, MD (1991)). Therefore, antibodies within the scope of this invention include V_H and V_L domains, or a portion thereof, combined with constant regions known in the art.

[0096] Certain embodiments comprise a V_H domain, a V_L domain, or a combination thereof, of the F_v fragment from GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 097D09, 062A09, 062G05, 087B03, 367D04, 368D04, 166B06, 166G05, 375G06, 376B10, 354A08, 355B06, 355E04, or 356A11. Another embodiment comprises a V_H domain, a V_L domain, or a combination thereof, of the F_v fragment from an antibody chosen from 356A11, 354A08, 087B03, and 368D04. Further embodiments comprise one, two, three, four, five or six complementarity determining regions (CDRs) from the V_H and V_L domains. Antibodies whose CDR sequences are included within SEQ ID NO:5-13, 23-31, 41-49, 59-67, 77-85, 95-103, 113-121, 131-139, 149-157, 167-175, 185-193, 203-211, 221-229, 239-247, 257-265, 275-283, 293-301, 311-319, 329-337, 347-355, 365-373, 383-391, 401-409, 419-427, 437-445, 455-463, 473-481, 491-499, 509-517, 527-535, 545-553, 563-571, 581-589, 599-607, or 617-625 are encompassed within the scope of this invention. For example, in one embodiment, an antibody comprises a H_3 fragment of the V_H domain of germlined or non-germlined GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 097D09, 062A09, 062G05, 087B03, 367D04, 368D04, 166B06, 166G05, 375G06, 376B10, 354A08, 355B06, 355E04, or 356A11 or from an antibody chosen from 356A11, 354A08, 087B03, and 368D04.

[0097] In certain embodiments, the V_H and/or V_L domains may be germlined, i.e., the framework regions (FR) of these domains are mutated using conventional molecular biology techniques to match those produced by the germline cells. In other embodiments, the FR sequences remain diverged from the consensus

germline sequences. In one embodiment of this invention, germlined antibodies are shown in Table 7.

[0098] In one embodiment, the invention provides amino acid and nucleic acid sequences for the germlined GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 097D09, 062A09, 062G05, 087B03, 367D04, 368D04, 166B06, 166G05, 375G06, 376B10, 354A08, 355B06, 355E04, or 356A11. Amino acid and nucleotide sequences for the V_H domain of the germlined GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 062A09, 087B03, 166B06, 166G05, 354A08, 355B06, 355E04, 356A11, and 368D04 are depicted in Table 7 and Figure 8. Amino acid and nucleotide sequences for the V_L domain of the germlined GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 062A09, 087B03, 166B06, 166G05, 354A08, 355B06, 355E04, 356A11, and 368D04 are also depicted in Table 7 and Figure 8.

[0099] In one embodiment, mutagenesis is used to make an antibody more similar to one or more germline sequences. This may be desirable when mutations are introduced into the framework region of an antibody through somatic mutagenesis or through error prone PCR. Germline sequences for the V_H and V_L domains can be identified by performing amino acid and nucleic acid sequence alignments against the VBASE database (MRC Center for Protein Engineering, UK). VBASE is a comprehensive directory of all human germline variable region sequences compiled from over a thousand published sequences, including those in the current releases of the Genbank and EMBL data libraries. In some embodiments, the FR regions of the scFvs are mutated in conformity with the closest matches in the VBASE database and the CDR portions are kept intact.

[00100] In certain embodiments, antibodies of this invention specifically react with an epitope that is the same as the epitope recognized by GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 097D09, 062A09, 062G05, 087B03, 367D04, 368D04, 166B06, 166G05, 375G06, 376B10, 354A08, 355B06, 355E04, or 356A11, such that they competitively inhibit the binding of GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 097D09, 062A09, 062G05, 087B03, 367D04, 368D04, 166B06, 166G05, 375G06, 376B10, 354A08, 355B06, 355E04, or 356A11 to human IL-22. Such antibodies can be determined in competitive binding assays. In one embodiment, the antibody, or antigen binding fragment thereof, binds to an IL-22 epitope that is recognized by 368D04, such that the antibody competitively

inhibits the binding of 368D04 to human IL-22. In another embodiment, the antibody, or antigen binding fragment thereof, binds to an IL-22 epitope that is recognized by 356A11, such that the antibody competitively inhibits the binding of 356A11 to human IL-22. In another embodiment, the antibody, or antigen binding fragment thereof, binds to an IL-22 epitope that is recognized by 354A08, such that the antibody competitively inhibits the binding of 354A08 to human IL-22. In another embodiment, the antibody, or antigen binding fragment thereof, binds to an IL-22 epitope that is recognized by 087B03, such that the antibody competitively inhibits the binding of 087B03 to human IL-22. In one embodiment, the association constant (K_A) of these antibodies for human IL-22 is at least 10^6 M^{-1} . In another embodiment, the association constant of these antibodies for human IL-22 is at least 10^9 M^{-1} . In other embodiments, the association constant of these antibodies for human IL-22 is at least 10^{10} M^{-1} , at least 10^{11} M^{-1} , or at least 10^{12} M^{-1} . The binding affinity may be determined using techniques known in the art, such as ELISA, biosensor technology, such as biospecific interaction analysis, or other techniques including those described in this application.

[00101] It is contemplated that antibodies of this invention may bind other proteins, such as, for example, recombinant proteins comprising all or a portion of IL-22.

[00102] One of ordinary skill in the art will recognize that the disclosed antibodies may be used to detect, measure, and/or inhibit proteins that differ somewhat from IL-22. For example, these proteins may be homologs of IL-22. Anti-IL-22 antibodies are expected to bind proteins that comprise a sequence which is at least about 60%, 70%, 80%, 90%, 95%, or more identical to any sequence of at least 100, 80, 60, 40, or 20 contiguous amino acids in the sequence set forth SEQ ID NO:1.

[00103] In addition to sequence homology analyses, epitope mapping (see, e.g., Epitope Mapping Protocols, ed. Morris, Humana Press, 1996), and secondary and tertiary structure analyses can be carried out to identify specific 3D structures assumed by the presently disclosed antibodies and their complexes with antigens. Such methods include, but are not limited to, X-ray crystallography (Engstrom (1974) Biochem. Exp. Biol., 11:7-13) and computer modeling of virtual representations of the present antibodies (Fletterick et al. (1986) Computer

Graphics and Molecular Modeling, in *Current Communications in Molecular Biology*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY).

[00104] The disclosure provides a method for obtaining anti-IL-22 antibodies that comprises creating antibodies with altered Table 1 V_H and/or V_L sequence(s). Such antibodies may be derived by a skilled artisan using techniques known in the art. For example, amino acid substitutions, deletions, or additions can be introduced in FR and/or CDR regions. FR changes are usually designed to improve the stability and immunogenicity of the antibody, while CDR changes are typically designed to increase antibody affinity for its antigen. The changes that increase affinity may be tested by altering CDR sequence and measuring antibody affinity for its target (see *Antibody Engineering*, 2nd ed., Oxford University Press, ed. Borrebaeck, 1995).

[00105] Antibodies whose CDR sequences differ insubstantially from those included in or included within the sequences in SEQ ID NO: 5-13, 23-31, 41-49, 59-67, 77-85, 95-103, 113-121, 131-139, 149-157, 167-175, 185-193, 203-211, 221-229, 239-247, 257-265, 275-283, 293-301, 311-319, 329-337, 347-355, 365-373, 383-391, 401-409, 419-427, 437-445, 455-463, 473-481, 491-499, 509-517, 527-535, 545-553, 563-571, 581-589, 599-607, or 617-625, are encompassed within the scope of this invention. Typically, this involves substitution of an amino acid with an amino acid having similar charge, hydrophobic, or stereochemical characteristics. More drastic substitutions in FR regions, in contrast to CDR regions, may also be made as long as they do not adversely affect (e.g., reduce affinity by more than 50% as compared to unsubstituted antibody) the binding properties of the antibody. Substitutions may also be made to germline the antibody or stabilize the antigen binding site.

[00106] Conservative modifications will produce molecules having functional and chemical characteristics similar to those of the molecule from which such modifications are made. In contrast, substantial modifications in the functional and/or chemical characteristics of the molecules may be accomplished by selecting substitutions in the amino acid sequence that differ significantly in their effect on maintaining (1) the structure of the molecular backbone in the area of the substitution, for example, as a sheet or helical conformation, (2) the charge or hydrophobicity of the molecule at the target site, or (3) the size of the molecule.

[00107] For example, a “conservative amino acid substitution” may involve a substitution of a native amino acid residue with a nonnative residue such that there is little or no effect on the polarity or charge of the amino acid residue at that position. (See, for example, MacLennan et al., 1998, *Acta Physiol. Scand. Suppl.* 643:55-67; Sasaki et al., 1998, *Adv. Biophys.* 35:1-24).

[00108] Desired amino acid substitutions (whether conservative or non-conservative) can be determined by those skilled in the art at the time such substitutions are desired. For example, amino acid substitutions can be used to identify important residues of the molecule sequence, or to increase or decrease the affinity of the molecules described herein. Exemplary amino acid substitutions include, but are not limited to, those set forth in Table 3.

Table 3: Amino Acid Substitutions

Original Residues	Exemplary Substitutions	More Conservative Substitutions
Ala (A)	Val, Leu, Ile	Val
Arg (R)	Lys, Gln, Asn	Lys
Asn (N)	Gln	Gln
Asp (D)	Glu	Glu
Cys (C)	Ser, Ala	Ser
Gln (Q)	Asn	Asn
Gly (G)	Pro, Ala	Ala
His (H)	Asn, Gln, Lys, Arg	Arg
Ile (I)	Leu, Val, Met, Ala, Phe, Norleucine	Leu
Leu (L)	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys (K)	Arg, 1, 4 Diamino-butyrlic Acid, Gln, Asn	Arg
Met (M)	Leu, Phe, Ile	Leu
Phe (F)	Leu, Val, Ile, Ala, Tyr	Leu
Pro (P)	Ala	Gly
Ser (S)	Thr, Ala, Cys	Thr
Thr (T)	Ser	Ser
Trp (W)	Tyr, Phe	Tyr
Tyr (Y)	Trp, Phe, Thr, Ser	Phe
Val (V)	Ile, Met, Leu, Phe, Ala, Norleucine	Leu

[00109] In certain embodiments, conservative amino acid substitutions also encompass non-naturally occurring amino acid residues which are typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems.

[00110] In one embodiment, the method for making a variant V_H domain comprises adding, deleting, or substituting at least one amino acid in the disclosed

V_H domains, or combining the disclosed V_H domains with at least one V_L domain, and testing the variant V_H domain for IL-22 binding or modulation of IL-22 activity.

[00111] An analogous method for making a variant V_L domain comprises adding, deleting, or substituting at least one amino acid in the disclosed V_L domains, or combining the disclosed V_L domains with at least one V_H domain, and testing the variant V_L domain for IL-22 binding or modulation of IL-22 activity.

[00112] A further aspect of the disclosure provides a method for preparing antibodies or antigen-binding fragments that specifically bind IL-22. The method comprises:

- (a) providing a starting repertoire of nucleic acids encoding a V_H domain which lacks at least one CDR or contains at least one CDR to be replaced;
- (b) inserting into or replacing the CDR region of the starting repertoire with at least one donor nucleic acid encoding an amino acid sequence as substantially set out herein for a V_H CDR, yielding a product repertoire;
- (c) expressing the nucleic acids of the product repertoire;
- (d) selecting a specific antigen-binding fragment that binds to IL-22; and
- (e) recovering the specific antigen-binding fragment or nucleic acid encoding it.

[00113] In an analogous method at least one V_L CDR of the invention is combined with a repertoire of nucleic acids encoding a V_L domain which lacks at least one CDR or contains at least one CDR to be replaced. The at least one V_H or V_L CDR may be a CDR1, a CDR2, a CDR3, or a combination thereof, including combinations of V_H and V_L CDRs, such as those set forth in Tables 1 or 7, including those set out in SEQ ID NO:8, 9, 10, 11, 12, 13, 26, 27, 28, 29, 30, 31, 44, 45, 46, 47, 48, 49, 62, 63, 64, 65, 66, 67, 80, 81, 82, 83, 84, 85, 98, 99, 100, 101, 102, 103, 116, 117, 118, 119, 120, 121, 134, 135, 136, 137, 138, 139, 152, 153, 154, 155, 156, 157, 170, 171, 172, 173, 174, 175, 188, 189, 190, 191, 192, 193, 206, 207, 208, 209, 210, 211, 224, 225, 226, 227, 228, 229, 242, 243, 244, 245, 246, 247, 260, 261, 262, 263, 264, 265, 278, 279, 280, 281, 282, 283, 296, 297, 298, 299, 300, 301, 314, 315, 316, 317, 318, 319, 332, 333, 334, 335, 336, 337, 350, 351, 352, 353, 354, 355, 368, 369, 370, 371, 372, 373, 386, 387, 388, 389, 390, 391, 404, 405, 406, 407, 408, 409, 422, 423, 424, 425, 426, 427, 440, 441, 442, 443, 444, 445, 458, 459, 460, 461, 462, 463, 476, 477, 478, 479, 480, 481, 494,

495, 496, 497, 498, 499, 512, 513, 514, 515, 516, 517, 530, 531, 532, 533, 534, 535, 548, 549, 550, 551, 552, 553, 566, 567, 568, 569, 570, 571, 584, 585, 586, 587, 588, 589, 602, 603, 604, 605, 606, 607, 620, 621, 622, 623, 624, or 625.

[00114] In one embodiment, the variable domain includes a CDR3 to be replaced or lacks a CDR3 encoding region and the at least one donor nucleic acid encodes an amino acid substantially as set out in SEQ ID NO:10, 13, 28, 31, 46, 49, 64, 67, 82, 85, 100, 103, 118, 121, 136, 139, 154, 157, 172, 175, 190, 193, 208, 211, 226, 229, 244, 247, 262, 265, 280, 283, 298, 301, 316, 319, 334, 337, 352, 355, 370, 373, 388, 391, 406, 409, 424, 427, 442, 445, 460, 463, 478, 481, 496, 499, 514, 517, 532, 535, 550, 553, 568, 571, 586, 589, 604, 607, 622, or 625.

[00115] In another embodiment, the variable domain includes a CDR1 to be replaced or lacks a CDR1 encoding region and the at least one donor nucleic acid encodes an amino acid sequence substantially as set out in SEQ ID NO:8, 11, 26, 29, 44, 47, 62, 65, 80, 83, 98, 101, 116, 119, 134, 137, 152, 155, 170, 173, 188, 191, 206, 209, 224, 227, 242, 245, 260, 263, 278, 281, 296, 299, 314, 317, 332, 335, 350, 353, 368, 371, 386, 389, 404, 407, 422, 425, 440, 443, 458, 461, 476, 479, 494, 497, 512, 515, 530, 533, 548, 551, 566, 569, 584, 587, 602, 605, 620, or 623.

[00116] In another embodiment, the variable domain includes a CDR2 to be replaced or lacks a CDR2 encoding region and the at least one donor nucleic acid encodes an amino acid sequence substantially as set out in SEQ ID NO:9, 12, 27, 30, 45, 48, 63, 66, 81, 84, 99, 102, 117, 120, 135, 138, 153, 156, 171, 174, 189, 192, 207, 210, 225, 228, 243, 246, 261, 264, 279, 282, 297, 300, 315, 318, 333, 336, 351, 354, 369, 372, 387, 390, 405, 408, 423, 426, 441, 444, 459, 462, 477, 480, 495, 498, 513, 516, 531, 534, 549, 552, 567, 570, 585, 588, 603, 606, 621, or 624.

[00117] In another embodiment, the variable domain includes a CDR3 to be replaced or lacks a CDR3 encoding region and further comprises a CDR1 to be replaced or lacks a CDR1 encoding region, where the at least one donor nucleic acid encodes an amino acid sequence substantially as set out in Tables 1 or 7.

[00118] In another embodiment, the variable domain includes a CDR3 to be replaced or lacks a CDR3 encoding region and further comprises a CDR2 to be

replaced or lacks a CDR2 encoding region, where the at least one donor nucleic acid encodes an amino acid sequence substantially as set out in Tables 1 or 7.

[00119] In another embodiment, the variable domain includes a CDR3 to be replaced or lacks a CDR3 encoding region and further comprises a CDR1 and a CDR2 to be replaced or lacks a CDR1 and a CDR2 encoding region, where the at least one donor nucleic acid encodes an amino acid sequence substantially as set out in Tables 1 or 7.

[00120] Using recombinant DNA methodology, a disclosed CDR sequence may be introduced into a repertoire of V_H or V_L domains lacking the respective CDR (Marks et al. (BioTechnology (1992) 10: 779-783). For example, a primer adjacent to the 5' end of the variable domain and a primer to the third FR can be used to generate a repertoire of variable domain sequences lacking CDR3. This repertoire can be combined with a CDR3 of a disclosed antibody. Using analogous techniques, portions of a disclosed CDR sequence may be shuffled with portions of CDR sequences from other antibodies to provide a repertoire of antigen-binding fragments that bind IL-22. Either repertoire can be expressed in a host system such as phage display (described in WO 92/01047 and its corresponding U.S. Patent No. 5,969,108) so suitable antigen-binding fragments that bind to IL-22 can be selected.

[00121] A further alternative uses random mutagenesis of the disclosed V_H or V_L sequences to generate variant V_H or V_L domains still capable of binding IL-22. A technique using error-prone PCR is described by Gram et al. (Proc. Nat. Acad. Sci. U.S.A. (1992) 89: 3576-3580).

[00122] Another method uses direct mutagenesis of the disclosed V_H or V_L sequences. Such techniques are disclosed by Barbas et al. (Proc. Nat. Acad. Sci. U.S.A. (1994) 91: 3809-3813) and Schier et al. (J. Mol. Biol. (1996) 263: 551-567).

[00123] A portion of a variable domain will comprise at least one CDR region substantially as set out herein and, optionally, intervening framework regions from the V_H or V_L domains as set out herein. The portion may include the C-terminal half of FR1 and/or the N-terminal half of FR4. Additional residues at the N-terminal or C-terminal end of the variable domain may not be the same residues found in naturally occurring antibodies. For example, construction of antibodies by

recombinant DNA techniques often introduces N- or C-terminal residues from its use of linkers. Some linkers may be used to join variable domains to other variable domains (e.g., diabodies), constant domains, or proteinaceous labels.

[00124] Although the embodiments illustrated in the Examples comprise a “matching” pair of V_H and V_L domains, a skilled artisan will recognize that alternative embodiments may comprise antigen-binding fragments containing only a single CDR from either V_L or V_H domain. Either one of the single chain specific antigen-binding domains can be used to screen for complementary domains capable of forming a two-domain specific antigen-binding fragment capable of, for example, binding to IL-22. The screening may be accomplished by phage display screening methods using the so-called hierarchical dual combinatorial approach disclosed in WO 92/01047. In this approach, an individual colony containing either a H or L chain clone is used to infect a complete library of clones encoding the other chain (L or H), and the resulting two-chain specific antigen-binding domain is selected in accordance with phage display techniques as described.

[00125] In some alternative embodiments, the anti-IL-22 antibodies can be linked to a protein (e.g., albumin) by chemical cross-linking or recombinant methods. The disclosed antibodies may also be linked to a variety of nonproteinaceous polymers (e.g., polyethylene glycol, polypropylene glycol, or polyoxyalkylenes) in manners set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192; or 4,179,337. The antibodies can be chemically modified by covalent conjugation to a polymer, for example, to increase their half-life in blood circulation. Exemplary polymers and attachment methods are shown in U.S. Pat. Nos. 4,766,106; 4,179,337; 4,495,285; and 4,609,546.

[00126] The disclosed antibodies can be modified to alter their glycosylation; that is, at least one carbohydrate moiety can be deleted or added to the antibody. Deletion or addition of glycosylation sites can be accomplished by changing amino acid sequence to delete or create glycosylation consensus sites, which are well known in the art. Another means of adding carbohydrate moieties is the chemical or enzymatic coupling of glycosides to amino acid residues of the antibody (see WO 87/05330 and Aplin et al. (1981) *CRC Crit. Rev. Biochem.*, 22: 259-306). Removal of carbohydrate moieties can also be accomplished chemically or enzymatically (see Hakimuddin et al. (1987) *Arch. Biochem. Biophys.*, 259: 52;

Edge et al. (1981) *Anal. Biochem.*, 118: 131; Thotakura et al. (1987) *Meth. Enzymol.*, 138: 350).

[00127] Methods for altering an antibody constant region are known in the art. Antibodies with altered function (e.g., altered affinity for an effector ligand such as FcR on a cell or the C1 component of complement) can be produced by replacing at least one amino acid residue in the constant portion of the antibody with a different residue (see e.g., EP 388,151 A1, US 5,624,821 and US 5,648,260). Similar types of alterations could be described which if applied to a murine or other species antibody would reduce or eliminate similar functions.

[00128] For example, it is possible to alter the affinity of an Fc region of an antibody (e.g., an IgG, such as a human IgG) for FcR (e.g., Fc gamma R1) or C1q. The affinity may be altered by replacing at least one specified residue with at least one residue having an appropriate functionality on its side chain, or by introducing a charged functional group, such as glutamate or aspartate, or perhaps an aromatic non-polar residue such as phenylalanine, tyrosine, tryptophan or alanine (see e.g., US 5,624,821).

[00129] For example, replacing residue 297 (asparagine) with alanine in the IgG constant region significantly inhibits recruitment of effector cells, while only slightly reducing (about three fold weaker) affinity for C1q (see e.g., US 5,624,821). The numbering of the residues in the heavy chain is that of the EU index (see Kabat et al., 1991 *supra*). This alteration destroys the glycosylation site and it is believed that the presence of carbohydrate is required for Fc receptor binding. Any other substitution at this site that destroys the glycosylation site is believed to cause a similar decrease in lytic activity. Other amino acid substitutions, e.g., changing any one of residues 318 (Glu), 320 (Lys) and 322 (Lys), to Ala, are also known to abolish C1q binding to the Fc region of IgG antibodies (see e.g., US 5,624,821).

[00130] Modified antibodies can be produced which have a reduced interaction with an Fc receptor. For example, it has been shown that in human IgG₃, which binds to the human Fc gamma R1 receptor, changing Leu 235 to Glu destroys its interaction with the receptor. Mutations on adjacent or close sites in the hinge link region of an antibody (e.g., replacing residues 234, 236 or 237 with Ala) can also be used to affect antibody affinity for the Fc gamma R1 receptor. The

numbering of the residues in the heavy chain is based in the EU index (see Kabat et al., 1991 *supra*).

[00131] Additional methods for altering the lytic activity of an antibody, for example, by altering at least one amino acid in the N-terminal region of the CH2 domain, are described in WO 94/29351 by Morgan et al. and US 5,624,821.

[00132] The antibodies of this invention may be tagged with a detectable or functional label. These labels include radiolabels (e.g., ^{131}I or ^{99}Tc), enzymatic labels (e.g., horseradish peroxidase or alkaline phosphatase), and other chemical moieties (e.g., biotin).

[00133] The invention may also feature an isolated antibody that binds to IL-22, in particular, human IL-22. In certain embodiments, the anti-IL-22 antibody may have at least one of the following characteristics: (1) it is a monoclonal or single specificity antibody; (2) it is a human antibody; (3) it is an *in vitro* generated antibody; (4) it is an *in vivo* generated antibody (e.g., transgenic mouse system); (5) it binds to IL-22 with an association constant of at least 10^{12} M^{-1} ; (6) it binds to IL-22 with an association constant of at least 10^{11} M^{-1} ; (7) it binds to IL-22 with an association constant of at least 10^{10} M^{-1} ; (8) it binds to IL-22 with an association constant of at least 10^9 M^{-1} ; (9) it binds to IL-22 with an association constant of at least 10^6 M^{-1} ; (10) it binds to IL-22 with a dissociation constant of 500 nM or less; (11) it binds to IL-22 with a dissociation constant of 10 nM or less; (12) it binds to IL-22 with a dissociation constant of 150 pM or less; (13) it binds to IL-22 with a dissociation constant of 60 pM or less; (14) it inhibits binding of IL-22 to IL-22R or a receptor complex of IL-22R and IL-10R2 with an IC_{50} of 10 nM or less; (15) it blocks IL-22 mediated proliferation of IL-22 receptor engineered BaF3 cells with an IC_{50} of 1 nM or less in one embodiment, with an IC_{50} of 150 pM or less in another embodiment, with an IC_{50} of 100 pM or less in another embodiment, and with an IC_{50} of 10 pM or less in another embodiment; and (16) it blocks IL-22 mediated GRO α secretion from HT29 with an IC_{50} of 1 nM or less in one embodiment, with an IC_{50} of 150 pM or less in another embodiment, and with an IC_{50} of 10 pM or less in another embodiment.

[00134] One of skill in the art will appreciate that the modifications described above are not all-exhaustive, and that many other modifications are obvious to a skilled artisan in light of the teachings of the present disclosure.

III. Nucleic Acids, Cloning and Expression Systems

[00135] The disclosure provides isolated nucleic acids encoding the disclosed antibodies. The nucleic acids may comprise DNA or RNA, and they may be synthetic (completely or partially) or recombinant (completely or partially). Reference to a nucleotide sequence as set out herein encompasses a DNA molecule with the specified sequence, and encompasses a RNA molecule with the specified sequence in which U is substituted for T.

[00136] Also provided are nucleic acids that comprise a coding sequence for one, two, or three CDR's, a V_H domain, a V_L domain, or combinations thereof, as disclosed herein, or a sequence substantially identical thereto (e.g., a sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99% or higher identical thereto, or which is capable of hybridizing under stringent conditions to the sequences disclosed).

[00137] In one embodiment, the isolated nucleic acids have nucleotide sequences encoding heavy chain and light chain variable regions of an anti-IL-22 antibody having at least one CDR chosen from the amino acid sequences of SEQ ID NO: 8-13, 26-31, 44-49, 62-67, 80-85, 98-103, 116-121, 134-139, 152-157, 170-175, 188-193, 206-211, 224-229, 242-247, 260-265, 278-283, 296-301, 314-319, 332-337, 350-355, 368-373, 386-391, 404-409, 422-427, 440-445, 458-463, 476-481, 494-499, 512-517, 530-535, 548-553, 566-571, 584-589, 602-607, or 620-625; or sequence encoding a CDR which differs by one or two amino acids from the sequences described herein.

[00138] The nucleic acid can encode only the light chain or the heavy chain variable region, or can also encode an antibody light or heavy chain constant region, operatively linked to the corresponding variable region. In one embodiment, the light chain variable region is linked to a constant region chosen from a kappa or a lambda constant region. The light chain constant region may also be a human kappa or lambda type. In another embodiment, the heavy chain variable region is linked to a heavy chain constant region of an antibody isotype chosen from IgG (e.g., IgG₁, IgG₂, IgG₃, IgG₄), IgM, IgA₁, IgA₂, IgD, and IgE. The heavy chain constant region may be an IgG (e.g., an IgG₁) isotype.

[00139] The nucleic acid compositions of the present invention, while often in the native sequence (of cDNA or genomic DNA or mixtures thereof) except

for modified restriction sites and the like, may be mutated in accordance with standard techniques to provide gene sequences. For coding sequences, these mutations, may affect amino acid sequence as desired. In particular, nucleotide sequences substantially identical to or derived from native V, D, J, constant, switches and other such sequences described herein are contemplated (where “derived” indicates that a sequence is identical or modified from another sequence).

[00140] In one embodiment, the nucleic acid differs (e.g., differs by substitution, insertion, or deletion) from that of the sequences provided (e.g., as follows: by at least one but less than 10, 20, 30, or 40 nucleotides; at least one but less than 1%, 5%, 10% or 20% of the nucleotides in the subject nucleic acid). If necessary for this analysis the sequences should be aligned for maximum homology. “Looped” out sequences from deletions or insertions, or mismatches, are considered differences. The difference may be at a nucleotide(s) encoding a non-essential residue(s), or the difference may be a conservative substitution(s).

[00141] The disclosure also provides nucleic acid constructs in the form of plasmids, vectors, transcription or expression cassettes, which comprise at least one nucleic acid as described herein.

[00142] The disclosure further provides a host cell that comprises at least one nucleic acid construct described herein.

[00143] Also provided are the methods of making the encoded protein(s) from the nucleic acid(s) comprising sequence described herein. The method comprises culturing host cells under appropriate conditions so they express the protein from the nucleic acid. Following expression and production, the V_H or V_L domain, or specific binding member may be isolated and/or purified using any suitable technique, then used as appropriate. The method can also include the steps of fusing a nucleic acid encoding a scFv with nucleic acids encoding a Fc portion of an antibody and expressing the fused nucleic acid in a cell. The method can also include a step of germlining.

[00144] Antigen-binding fragments, V_H and/or V_L domains, and encoding nucleic acid molecules and vectors may be isolated and/or purified from their natural environment, in substantially pure or homogenous form, or, in the case of

nucleic acid, free or substantially free of nucleic acid or genes of origin other than the sequence encoding a polypeptide with the require function.

[00145] Systems for cloning and expressing polypeptides in a variety of host cells are known in the art. Cells suitable for producing antibodies are described in, for example, Fernandez et al. (1999) *Gene Expression Systems*, Academic Press, eds. In brief, suitable host cells include mammalian cells, insect cells, plant cells, yeast cells, or prokaryotic cells, e.g., *E. coli*. Mammalian cells available in the art for heterologous polypeptide expression include lymphocytic cell lines (e.g., NSO), HEK293 cells, Chinese hamster ovary (CHO) cells, COS cells, HeLa cells, baby hamster kidney cells, oocyte cells, and cells from a transgenic animal, e.g., mammary epithelial cell. In one embodiment, the GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 097D09, 062A09, 062G05, 087B03, 367D04, 368D04, 166B06, 166G05, 375G06, 376B10, 354A08, 355B06, 355E04, and 356A11 antibodies are expressed in HEK293 or CHO cells. In another embodiment, a selection of antibodies chosen from 365A11, 354A08, 087B03, and 368D04 are expressed in HEK293 or CHO cells. In other embodiments, the nucleic acids encoding the antibodies of the invention are placed under the control of a tissue-specific promoter (e.g., a mammary specific promoter) and the antibodies are produced in transgenic animals. For example, the antibodies are secreted into the milk of the transgenic animal, such as a transgenic cow, pig, horse, sheep, goat or rodent.

[00146] Suitable vectors may be chosen or constructed to contain appropriate regulatory sequences, including promoter sequences, terminator sequences, polyadenylation sequences, enhancer sequences, marker genes, and other sequences. The vectors may also contain a plasmid or viral backbone. For details, see Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press (1989). Many established techniques used with vectors, including the manipulation, preparation, mutagenesis, sequencing, and transfection of DNA, are described in *Current Protocols in Molecular Biology*, Second Edition, Ausubel et al. eds., John Wiley & Sons (1992).

[00147] A further aspect of the disclosure provides a method of introducing the nucleic acid into a host cell. For eukaryotic cells, suitable transfection techniques may include calcium phosphate, DEAE-Dextran,

electroporation, liposome-mediated transfection, and transduction using retrovirus or other viruses, e.g., vaccinia or baculovirus. For bacterial cells, suitable techniques may include calcium chloride transformation, electroporation, and transfection using bacteriophage. DNA introduction may be followed by a selection method (e.g., drug resistance) to select cells that contain the nucleic acid.

IV. Uses of Anti-IL-22 Antibodies

[00148] Anti-IL-22 antibodies that act as antagonists to IL-22 can be used to regulate at least one IL-22-mediated immune response, such as acting on epithelial cells in solid tissue and indirectly modulating downstream immune responses, such as blocking expansion of T cell subsets, including, for example, T_H17 T cells.. In one embodiment, antibodies of the invention are used in a method for regulating an immune response, the method comprising contacting IL-22 with an antibody of the invention thereby regulating the immune response. In one embodiment, the immune response comprises cell proliferation, cytolytic activity, cytokine secretion, or chemokine secretion.

[00149] Accordingly, the antibodies of the invention can be used to directly or indirectly inhibit the activity (e.g., proliferation, differentiation, and/or survival) of an immune or hematopoietic cell (e.g., a cell of myeloid, lymphoid, or erythroid lineage, or precursor cells thereof), and, thus, can be used to treat a variety of immune disorders and hyperproliferative disorders. Non-limiting examples of immune disorders that can be treated include, but are not limited to, autoimmune disorders, e.g., arthritis (including rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, psoriatic arthritis, lupus-associated arthritis or ankylosing spondylitis), scleroderma, systemic lupus erythematosus, HIV, Sjogren's syndrome, vasculitis, multiple sclerosis, autoimmune thyroiditis, dermatitis (including atopic dermatitis and eczematous dermatitis), myasthenia gravis, inflammatory bowel disease (IBD), Crohn's disease, colitis, diabetes mellitus (type I); inflammatory conditions of, e.g., the skin (e.g., psoriasis), cardiovascular system (e.g., atherosclerosis), nervous system (e.g., Alzheimer's disease), liver (e.g., hepatitis), kidney (e.g., nephritis) and pancreas (e.g., pancreatitis); cardiovascular disorders, e.g., cholesterol metabolic disorders, oxygen free radical injury, ischemia; disorders associated with wound healing; respiratory disorders, e.g., asthma and COPD (e.g., cystic fibrosis); acute inflammatory conditions (e.g.,

endotoxemia, sepsis and septicaemia, toxic shock syndrome and infectious disease); transplant rejection and allergy. In one embodiment, the IL-22-associated disorder is, an arthritic disorder, e.g., a disorder chosen from one or more of rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, psoriatic arthritis, or ankylosing spondylitis; a respiratory disorder (e.g., asthma, chronic obstructive pulmonary disease (COPD)); or an inflammatory condition of, e.g., the skin (e.g., psoriasis), cardiovascular system (e.g., atherosclerosis), nervous system (e.g., Alzheimer's disease), liver (e.g., hepatitis), kidney (e.g., nephritis), pancreas (e.g., pancreatitis), and gastrointestinal organs, e.g., colitis, Crohn's disease and IBD; acute inflammatory conditions, e.g., endotoxemia, sepsis and septicaemia, toxic shock syndrome and infectious disease; multiple organ failure; respiratory disease (ARD); amyloidosis; nephropathies such as glomerulosclerosis, membranous neuropathy, renal arteriosclerosis, glomerulonephritis, fibroproliferative diseases of the kidney, as well as other kidney disfunctions and renal tumors. Because of IL-22's effects on epithelia, anti-IL-22 antibodies can be used to treat epithelial cancers, e.g., carcinoma, melanoma and others. For a description of a rationale for IL-22 inhibition in these and other disease states see WO 03/083062 (pages 58-75).

[00150] Multiple sclerosis is a central nervous system disease that is characterized by inflammation and loss of myelin sheaths—the fatty material that insulates nerves and is needed for proper nerve function. Inflammation that results from an immune response that is dependent on IL-22 can be treated with the antibodies and compositions of this invention. In the experimental autoimmune encephalitis (EAE) mouse model for multiple sclerosis (Tuohy et al. (J. Immunol. (1988) 141: 1126-1130), Sobel et al. (J. Immunol. (1984) 132: 2393-2401), and Traugott (Cell Immunol. (1989) 119: 114-129), treatment of mice with GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 097D09, 062A09, 062G05, 087B03, 367D04, 368D04, 166B06, 166G05, 375G06, 376B10, 354A08, 355B06, 355E04, or 356A11 injections prior (and continuously) to EAE induction may profoundly delay the onset of the disease. This can serve as a model for confirming use of the antibody of the invention. The antibodies of this invention may similarly be used to treat multiple sclerosis in humans.

[00151] Arthritis is a disease characterized by inflammation in the joints. Rheumatoid Arthritis (RA) is the most frequent form of arthritis, involving inflammation of connective tissue and the synovial membrane, a membrane that lines the joint. The inflamed synovial membrane often infiltrates the joint and damages joint cartilage and bone. IL-22 and IL-22R protein and/or transcript is associated with both human diseases. In RA synovial biopsies, IL-22 protein is detected in vimentin⁺ synovial fibroblasts and some CD68⁺ macrophages while IL-22R is detected in synovial fibroblasts. Treatment of synovial fibroblasts with IL-22 induces the production of monocyte chemoattractant protein-1, MCP-1, as well as general metabolic activity (Ikeuchi, H., et al. (2005) *Arthritis Rheum.* 52:1037-46). Inhibitors of IL-22 ameliorate symptoms of rheumatoid arthritis (WO 2005/000897 A2; U.S. Patent No. 6,939,545). Increased secretion of inflammatory cytokines and chemokines, and more importantly, increased disease resulting from immune responses that are dependent on IL-22 may be treated with the antibodies of this invention. Similarly, the antibodies and compositions of this invention may be used to treat RA or other arthritic diseases in humans.

[00152] Transplant rejection is the immunological phenomenon where tissues from a donor are specifically "attacked" by immune cells of the host. The principle "attacking" cells are T cells, whose T cell receptors recognize the donor's MHC molecules as "foreign." This recognition activates the T cells, which proliferate and secrete a variety of cytokines and cytolytic proteins that ultimately destroy the transplant. MLR and transplantation models have been described by *Current Protocols in Immunology*, Second Edition, Coligan et al. eds., John Wiley & Sons, 1994; Kasaian et al. (*Immunity* (2002) 16: 559-569); Fulmer et al. (*Am. J. Anat.* (1963) 113: 273-285), and Lenschow et al. (*Science* (1992) 257: 789-792). The antibodies and compositions of this invention may be used to reduce the MLR and treat transplant rejection and related diseases (e.g., graft versus host disease) in humans that are dependent on IL-22.

[00153] The antibodies of this invention can also be used to treat hyperproliferative disorders associated with aberrant activity of IL-22-responsive cells and IL-22R/IL-10R2-responsive cells by administering the antibodies in an amount sufficient to inhibit or reduce hyperproliferation of IL-22 and/or IL-22R and/or IL-10R2-responsive cells in a subject and allowing the antibodies to treat or

prevent the disorder. IL-22 and IL-22R expression is constitutive on epithelial cells in a number of tissues including, but not limited to, pancreas, lung, skin, gut, liver, kidney (Kotenko, S.V. et al. (2001) *J. Biol. Chem.* 276:2725-32; Xie, M.H. et al. (2000) *J. Biol. Chem.* 275:31335-9; Wolk, K. et al. (2004) *Immunity* 21:241-54). In addition, IL-22 receptor complex is also expressed on the surface of fibroblasts from the diseased joint and normal gut (Ikeuchi, H. et al. (2005) *Arthritis Rheum.* 52:1037-46; Andoh, A. et al. (2005) *Gastroenterology* 129:969-84). Neoplastic derivatives of these cell types may be hyper responsive to IL-22, modulating these cells ability to survive in the organism. Hence antibodies to IL-22 may be used to inhibit the progression of such neoplasms, e.g. squamous cell carcinomas, basal cell carcinomas, transitional cell papillomas and carcinomas, adenomas, adenocarcinoma, linitis plastica, insulinoma, glucagonoma, gastrinoma, vipoma, cholangiocarcinoma, hepatocellular carcinoma, adenoid cystic carcinoma, carcinoid tumor of appendix, prolactinoma, oncocytoma, hurthle cell adenoma, renal cell carcinoma, Grawitz tumor, multiple endocrine adenomas, endometroid adenoma, adnexal and skin appendage neoplasms, mucoepidermoid neoplasms, cystic, mucinous and serous neoplasms, cystadenoma, pseudomyxoma peritonei, ductal, lobular and medullary neoplasms, acinar cell neoplasms, complex epithelial neoplasms, Warthin's tumor, thymoma, specialized gonadal neoplasms, sex cord-stromal tumor, thecoma, granulosa cell tumor, arrhenoblastoma, sertoli-leydig cell tumor, paraganglioma, pheochromocytoma, glomus tumor, melanocytic nevus, malignant melanoma, melanoma, nodular melanoma, dysplastic nevus, lentigo maligna, superficial spreading melanoma, or acral lentiginous melanoma. While the IL-22 receptor is not detected on *ex vivo* naïve or activated immune cells, dysregulation of the receptor might make such derivative neoplastic cells responsive to IL-22 and thus inhibition by an antibody to IL-22.

[00154] In another aspect, the invention features a method of decreasing, inhibiting or reducing an acute phase response in a subject. The method includes administering to the subject an anti-IL-22 antibody or fragment thereof as described herein, in an amount sufficient to decrease, inhibit or reduce the acute phase response in the subject. In one embodiment, the subject is a mammal, e.g., a human suffering from an IL-22-associated disorder as described herein, including, e.g., respiratory disorders, inflammatory disorders and

autoimmune disorders. In one embodiment, the IL-22 binding agent is administered locally, e.g., topically, subcutaneously, or other administrations that are not in the general circulation.

[00155] IL-22 is believed to exert its inflammatory effects locally, e.g. by acting (e.g., directly acting) as a modular or a regulator of tissue inflammation as opposed to direct systemic effects. Accordingly, inhibition of IL-22 activity using, e.g. an anti-IL-22 antibody of the present invention may provide a more effective (e.g., less toxic) tissue-specific, anti-inflammatory agent than systemic anti-inflammatory modalities. Furthermore, inhibition of local IL-22 using, e.g., an anti-IL-22 antibody or fragment thereof described herein, may provide a useful candidate for combination with systemic anti-inflammatory modalities.

V. Combination Therapy

[00156] In one embodiment, a pharmaceutical composition comprising at least one anti-IL-22 antibody and at least one therapeutic agent is administered in combination therapy. The therapy is useful for treating pathological conditions or disorders, such as immune and inflammatory disorders. The term "in combination" in this context means that the antibody composition and the therapeutic agent are given substantially contemporaneously, either simultaneously or sequentially. In one embodiment, if given sequentially, at the onset of administration of the second compound, the first of the two compounds is still detectable at effective concentrations at the site of treatment. In another embodiment, if given sequentially, at the onset of administration of the second compound, the first of the two compounds is not detectable at effective concentrations at the site of treatment.

[00157] For example, the combination therapy can include at least one anti-IL-22 antibody co-formulated with, and/or co-administered with, at least one additional therapeutic agent. The additional agents may include at least one cytokine inhibitor, growth factor inhibitor, immunosuppressant, anti-inflammatory agent, metabolic inhibitor, enzyme inhibitor, cytotoxic agent, and cytostatic agent, as described in more detail below. In one embodiment, the additional agent is a standard treatment for arthritis, including, but not limited to, non-steroidal anti-inflammatory agents (NSAIDs); corticosteroids, including prednisolone, prednisone, cortisone, and triamcinolone; and disease modifying anti-rheumatic drugs

(DMARDs), such as methotrexate, hydroxychloroquine (Plaquenil™) and sulfasalazine, leflunomide (Arava™), tumor necrosis factor inhibitors, including etanercept (Enbrel™), infliximab (Remicade™) (with or without methotrexate), and adalimumab (Humira™), anti-CD20 antibody (e.g., Rituxan™), soluble interleukin-1 receptor, such as anakinra (Kineret™), gold, minocycline (Minocin™), penicillamine, and cytotoxic agents, including azathioprine, cyclophosphamide, and cyclosporine. Such combination therapies may advantageously utilize lower dosages of the administered therapeutic agents, thus avoiding possible toxicities or complications associated with the various monotherapies. Moreover, the additional therapeutic agents disclosed herein act on pathways in addition to or that differ from the IL-22/IL-22R/IL-10R2 pathway, and thus are expected to enhance and/or synergize with the effects of the anti-IL-22 antibodies.

[00158] Therapeutic agents used in combination with anti-IL-22 antibodies may be those agents that interfere at different stages in the autoimmune and subsequent inflammatory response. In one embodiment, at least one anti-IL-22 antibody described herein may be co-formulated with, and/or co-administered with, at least one cytokine and/or growth factor antagonist. The antagonists may include soluble receptors, peptide inhibitors, small molecules, ligand fusions, antibodies and binding fragments thereof (that bind cytokines or growth factors or their receptors or other cell surface molecules), and “anti-inflammatory cytokines” and agonists thereof.

[00159] Non-limiting examples of the agents that can be used in combination with the anti-IL-22 antibodies described herein, include, but are not limited to, antagonists of at least one interleukin (e.g., IL-1, IL-2, IL-6, IL-7, IL-8, IL-12 (or one of its subunits p35 or p40); IL-13, IL-15, IL-16, IL-17A-F (including heterodimers thereof, for example, IL-17A/IL-17F heterodimer), IL-18, IL-19, IL-20, IL-21, and IL-23 (or one of its subunits p19 or p40)); cytokine (e.g., TNF α , LT, EMAP-II, and GM-CSF); and growth factor (e.g., FGF and PDGF). The agents may also include, but not limited to, antagonists of at least one receptor for an interleukin, cytokine, and growth factor. Anti-IL-22 antibodies can also be combined with inhibitors (e.g., antibodies or binding fragments thereof) to cell surface molecules such as CD2, CD3, CD4, CD8, CD20 (e.g. Rituxan™), CD25, CD28, CD30, CD40, CD45, CD69, CD80 (B7.1), CD86 (B7.2), CD90, or their

ligands (e.g., CD154 (gp39, CD40L)), or LFA-1/ICAM-1 and VLA-4/VCAM-1 (Yusuf-Makagiansar et al. (2002) *Med Res Rev* 22(2):146-67)). In certain embodiments, antagonists that can be used in combination with anti-IL-22 antibodies described herein may include antagonists of IL-1, IL-12 (or one of its subunits p35 or p40), TNF α , IL-15, IL-17A-F (including heterodimers thereof, for example, IL-17A/IL-17F heterodimer), IL-18, IL-19, IL-20, IL-21, and IL-23 (or one of its subunits p19 or p40), and their receptors.

[00160] Examples of those agents include IL-12 antagonists (such as antibodies that bind IL-12 (see e.g., WO 00/56772) or one of its subunits p35 or p40); IL-12 receptor inhibitors (such as antibodies to the IL-12 receptor); and soluble IL-12 receptor and fragments thereof. Examples of IL-15 antagonists include antibodies against IL-15 or its receptor, soluble fragments of the IL-15 receptor, and IL-15-binding proteins. Examples of IL-18 antagonists include antibodies to IL-18, soluble fragments of the IL-18 receptor, and IL-18 binding proteins (IL-18BP, Mallet et al. (2001) *Circ. Res.* 28). Examples of IL-1 antagonists include Interleukin-1-Converting Enzyme (ICE) inhibitors (such as Vx740), IL-1 antagonists (e.g., IL-1RA (ANIKINRA, AMGEN)), sIL-1RII (Immunex), and anti-IL-1 receptor antibodies.

[00161] In one embodiment, the combination therapy includes at least one anti-IL-22 antibody co-formulated with, and/or co-administered with an antagonist, such as an antibody or antigen binding fragment thereof or a soluble receptor, of at least one of IL-17A, IL-17F, IL-17A/IL-17F heterodimer, or IL-23 (or one of its subunits p19 or p40).

[00162] Examples of TNF antagonists include antibodies to TNF (e.g., human TNF α), such as D2E7 (human anti-TNF α antibody, U.S. 6,258,562, HumiraTM, BASF); CDP-571/CDP-870/BAY-10-3356 (humanized anti-TNF α antibodies, Celltech/Pharmacia); cA2 (chimeric anti-TNF α antibody, RemicadeTM, Centocor); and anti-TNF antibody fragments (e.g., CPD870). Other examples include soluble TNF receptor (e.g., human p55 or p75) fragments and derivatives, such as p55 kdTNFR-IgG (55 kD TNF receptor-IgG fusion protein, LenerceptTM) and 75 kdTNFR-IgG (75 kD TNF receptor-IgG fusion protein, EnbrelTM, Immunex, see, e.g., *Arthritis & Rheumatism* (1994) Vol. 37, S295; *J. Invest. Med.* (1996) Vol. 44, 235A). Further examples include enzyme antagonists (e.g., TNF α converting

enzyme inhibitors (TACE) such as alpha-sulfonyl hydroxamic acid derivative (WO 01/55112) or N-hydroxyformamide inhibitor (GW 3333, -005, or -022)) and TNF-bp/s-TNFR (soluble TNF binding protein, see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S284; and *Am. J. Physiol. Heart Circ. Physiol.* (1995) Vol. 268, pp. 37-42). TNF antagonists may be soluble TNF receptor (e.g., human p55 or p75) fragments and derivatives, such as 75 kDTNFR-IgG; and TNF α converting enzyme (TACE) inhibitors.

[00163] In other embodiments, the anti-IL-22 antibodies described herein can be administered in combination with at least one of the following: IL-13 antagonists, such as soluble IL-13 receptors and/or anti-IL-13 antibodies; and IL-2 antagonists, such as IL-2 fusion proteins (e.g., DAB 486-IL-2 and/or DAB 389-IL-2, Seragen, see e.g., *Arthritis & Rheumatism* (1993) Vol. 36, 1223) and anti-IL-2R antibodies (e.g., anti-Tac (humanized antibody, Protein Design Labs, see *Cancer Res.* 1990 Mar 1;50(5):1495-502)). Another combination includes anti-IL-22 antibodies in combination with non-depleting anti-CD4 inhibitors such as IDEC-CE9.1/SB 210396 (anti-CD4 antibody, IDEC/SmithKline). Yet other combinations include anti-IL-22 antibodies with antagonists (such as antibodies, soluble receptors, or antagonistic ligands) of costimulatory molecules, such as CD80 (B7.1) and CD86 (B7.2); ICOSL, ICOS, CD28, and CTLA4 (e.g., CTLA4-Ig); P-selectin glycoprotein ligand (PSGL); and anti-inflammatory cytokines and agonists thereof (e.g., antibodies). The anti-inflammatory cytokines may include IL-4 (DNAX/Schering); IL-10 (SCH 52000, recombinant IL-10, DNAX/Schering); IL-13; and TGF.

[00164] In other embodiments, at least one anti-IL-22 antibody can be co-formulated with, and/or co-administered with, at least one anti-inflammatory drug, immunosuppressant, metabolic inhibitor, and enzymatic inhibitor. Non-limiting examples of the drugs or inhibitors that can be used in combination with the IL-22 antagonists described herein, include, but are not limited to, at least one of: non-steroidal anti-inflammatory drug (NSAID) (such as ibuprofen, Tenidap (see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S280)), Naproxen (see e.g., *Neuro Report* (1996) Vol. 7, pp. 1209-1213), Meloxicam, Piroxicam, Diclofenac, and Indomethacin); Sulfasalazine (see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S281); corticosteroid (such as prednisolone);

cytokine suppressive anti-inflammatory drug (CSAID); and an inhibitor of nucleotide biosynthesis (such as an inhibitor of purine biosynthesis (e.g., folate antagonist such as methotrexate) and an inhibitor of pyrimidine biosynthesis (e.g., a dihydroorotate dehydrogenase (DHODH) inhibitor such as leflunomide (see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S131; *Inflammation Research* (1996) Vol. 45, pp. 103-107)). Therapeutic agents for use in combination with IL-22/IL-22R or IL-22/IL-10R2 antagonists may include NSAIDs, CSAIDs, DHODH inhibitors (such as leflunomide), and folate antagonists (such as methotrexate).

[00165] Examples of additional inhibitors include at least one of: corticosteroid (oral, inhaled and local injection); immunosuppressant (such as cyclosporin and tacrolimus (FK-506)); a mTOR inhibitor (such as sirolimus (rapamycin) or a rapamycin derivative (e.g., ester rapamycin derivative such as CCI-779 (Elit. L. (2002) *Current Opinion Investig. Drugs* 3(8):1249-53; Huang, S. et al. (2002) *Current Opinion Investig. Drugs* 3(2):295-304)); an agent which interferes with the signaling of proinflammatory cytokines such as TNF α and IL-1 (e.g., IRAK, NIK, IKK, p38 or a MAP kinase inhibitor); a COX2 inhibitor (e.g., celecoxib and variants thereof (MK-966), see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S81); a phosphodiesterase inhibitor (such as R973401, see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S282)); a phospholipase inhibitor (e.g., an inhibitor of cytosolic phospholipase 2 (cPLA2) such as trifluoromethyl ketone analogs (U.S. 6,350,892)); an inhibitor of vascular endothelial cell growth factor (VEGF); an inhibitor of the VEGF receptor; and an inhibitor of angiogenesis. Therapeutic agents for use in combination with anti-IL-22 antibodies may include immunosuppressants (such as cyclosporine and tacrolimus (FK-506)); and mTOR inhibitors (such as sirolimus (rapamycin) or rapamycin derivatives (e.g., ester rapamycin derivatives such as CCI-779)); COX2 inhibitors (such as celecoxib and variants thereof); and phospholipase inhibitors (such as inhibitors of cytosolic phospholipase 2 (cPLA2) (e.g., trifluoromethyl ketone analogs)).

[00166] Examples of therapeutic agents that can be co-administered and/or co-formulated with at least one anti-IL-22 antibody, include, but are not limited to, at least one of: TNF antagonists (such as anti-TNF antibodies); soluble

fragments of TNF receptors (e.g., human p55 and p75) and derivatives thereof (such as p55 kdTNFR-IgG (55 kD TNF receptor-IgG fusion protein, Lenercept™) and 75 kdTNFR-IgG (75 kD TNF receptor-IgG fusion protein, Enbrel™)); TNF enzyme antagonists (such as TACE inhibitors); antagonists of IL-12 (or one of its subunits p35 or p40), IL-15, IL-17A-F (including heterodimers thereof, for example, IL-17A/IL-17F heterodimer), IL-18, IL-19, IL-20, IL-21, IL-22, and IL-23 (or one of its subunits p19 or p40); T cell and B cell depleting agents (such as anti-CD4 or anti-CD22 antibodies); small molecule inhibitors (such as methotrexate and leflunomide); sirolimus (rapamycin) and analogs thereof (such as CCI-779); Cox-2 and cPLA2 inhibitors; p38, TPL-2, Mk-2 and NFκB inhibitors; RAGE and soluble RAGE; P-selectin and PSGL-1 inhibitors (such as antibodies to and small molecule inhibitors); and estrogen receptor beta (ERB) agonists, and ERB-NFκB antagonists. Therapeutic agents that can be co-administered and/or co-formulated with at least one anti-IL-22 antibody may include at least one of: a soluble fragment of a TNF receptor (e.g., human p55 or p75) such as 75 kdTNFR-IgG (75 kD TNF receptor-IgG fusion protein, Enbrel™); methotrexate; leflunomide; and sirolimus (rapamycin) and analogs thereof (such as CCI-779).

[00167] The anti-IL-22 antibodies disclosed herein can be used in combination with other therapeutic agents to treat specific immune disorders as discussed in further detail below.

[00168] Non-limiting examples of agents for treating arthritic disorders (e.g., rheumatoid arthritis, inflammatory arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis and psoriatic arthritis), with which an anti-IL-22 antibody can be combined include at least one of the following: TNF antagonists (such as anti-TNF antibodies); soluble fragments of TNF receptors (e.g., human p55 and p75) and derivatives thereof (such as p55 kdTNFR-IgG (55 kD TNF receptor-IgG fusion protein, Lenercept™) and 75 kdTNFR-IgG (75 kD TNF receptor-IgG fusion protein, Enbrel™)); TNF enzyme antagonists (such as TACE inhibitors); antagonists of IL-12 (or one of its subunits p35 or p40), IL-15, IL-17A-F (including heterodimers thereof, for example, IL-17A/IL-17F heterodimer), IL-18, IL-19, IL-20, IL-21, IL-22, IL-23 (or one of its subunits p19 or p40), and IL-24; T cell and B cell depleting agents (such as anti-CD4, anti-CD20, or anti-CD22 antibodies); small molecule inhibitors (such as methotrexate and leflunomide);

sirolimus (rapamycin) and analogs thereof (e.g., CCI-779); Cox-2 and cPLA2 inhibitors; NSAIDs; p38, TPL-2, Mk-2, and NF κ B inhibitors; RAGE or soluble RAGE; P-selectin or PSGL-1 inhibitors (such as small molecule inhibitors and antibodies to); estrogen receptor beta (ERB) agonists, and ERB-NF κ B antagonists. Therapeutic agents that can be co-administered and/or co-formulated with at least one IL-22/IL-22R/IL-10R2 antagonist may include at least one of: a soluble fragment of a TNF receptor (e.g., human p55 or p75) such as 75 kD TNFR-IgG (75 kD TNF receptor-IgG fusion protein, EnbrelTM); methotrexate; leflunomide; and sirolimus (rapamycin) or an analog thereof (e.g., CCI-779).

[00169] Non-limiting examples of agents for treating multiple sclerosis with which anti-IL-22 antibody can be combined include interferon- β for example, IFN β -1a and IFN β -1b), copaxone, corticosteroids, IL-1 inhibitors, TNF inhibitors, antibodies to CD40 ligand, antibodies to CD80, and IL-12 antagonists, including antibodies that bind IL-12 (or one of its subunits p35 or p40).

[00170] Non-limiting examples of agents for treating inflammatory bowel disease or Crohn's disease with which an anti-IL-22 antibody can be combined include budenoside; epidermal growth factor; corticosteroids; cyclosporine; sulfasalazine; aminosalicylates; 6-mercaptopurine; azathioprine; metronidazole; lipoxigenase inhibitors; mesalamine; olsalazine; balsalazide; antioxidants; thromboxane inhibitors; IL-1 receptor antagonists; anti-IL-1 monoclonal antibodies; anti-IL-6 monoclonal antibodies; growth factors; elastase inhibitors; pyridinyl-imidazole compounds; TNF antagonists as described herein; IL-4, IL-10, IL-13, and/or TGF β or agonists thereof (e.g., agonist antibodies); IL-11; glucuronide- or dextran-conjugated prodrugs of prednisolone, dexamethasone or budesonide; ICAM-1 antisense phosphorothioate oligodeoxynucleotides (ISIS 2302; Isis Pharmaceuticals, Inc.); soluble complement receptor 1 (TP10; T Cell Sciences, Inc.); slow-release mesalazine; methotrexate; antagonists of Platelet Activating Factor (PAF); ciprofloxacin; and lignocaine.

[00171] In other embodiments, an anti-IL-22 antibody can be used in combination with at least one antibody directed at other targets involved in regulating immune responses, e.g., transplant rejection or graft versus host disease. Non-limiting examples of agents for treating immune responses with which an IL-22/IL-22R/IL10R2 antagonist of the invention can be combined include

the following: antibodies against cell surface molecules, including but not limited to CD25 (IL-2 receptor α), CD11a (LFA-1), CD54 (ICAM-1), CD4, CD45, CD28/CTLA4, CD80 (B7-1), CD86 (B7-2), or combinations thereof. In another embodiment, an anti-IL-22 antibody is used in combination with at least one general immunosuppressive agent, such as cyclosporin A or FK506.

[00172] Another aspect of the present invention accordingly relates to kits for carrying out the combined administration of the anti-IL-22 antibodies with other therapeutic agents. In one embodiment, the kit comprises at least one anti-IL-22 antibody formulated in a pharmaceutical carrier, and at least one therapeutic agent, formulated as appropriate in one or more separate pharmaceutical preparations.

VI. Diagnostic Uses

[00173] The antibodies may also be used to detect the presence of IL-22 in biological samples. By correlating the presence or level of these proteins with a medical condition, one of skill in the art can diagnose the associated medical condition. For example, IL-22 induces changes associated with those caused by inflammatory cytokines (such as IL-1 and TNF α), and inhibitors of IL-22 ameliorate symptoms of rheumatoid arthritis (WO 2005/000897 A2). Illustrative medical conditions that may be diagnosed by the antibodies of this invention include multiple sclerosis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, pancreatitis, and transplant rejection.

[00174] Antibody-based detection methods are well known in the art, and include ELISA, radioimmunoassays, immunoblots, Western blots, flow cytometry, immunofluorescence, immunoprecipitation, and other related techniques. The antibodies may be provided in a diagnostic kit that incorporates at least one of these procedures to detect IL-22. The kit may contain other components, packaging, instructions, or other material to aid the detection of the protein and use of the kit.

[00175] Antibodies may be modified with detectable markers, including ligand groups (e.g., biotin), fluorophores and chromophores, radioisotopes, electron-dense reagents, or enzymes. Enzymes are detected by their activity. For example, horseradish peroxidase is detected by its ability to convert tetramethylbenzidine (TMB) to a blue pigment, quantifiable with a

spectrophotometer. Other suitable binding partners include biotin and avidin, IgG and protein A, and other receptor-ligand pairs known in the art.

[00176] Antibodies can also be functionally linked (e.g., by chemical coupling, genetic fusion, non-covalent association or otherwise) to at least one other molecular entity, such as another antibody (e.g., a bispecific or a multispecific antibody), toxins, radioisotopes, cytotoxic or cytostatic agents, among others. Other permutations and possibilities are apparent to those of ordinary skill in the art, and they are considered equivalents within the scope of this invention.

VII. Pharmaceutical Compositions and Methods of Administration

[00177] Certain embodiments of the invention include compositions comprising the disclosed antibodies. The compositions may be suitable for pharmaceutical use and administration to patients. The compositions comprise an antibody of the present invention and a pharmaceutical excipient. As used herein, "pharmaceutical excipient" includes solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, etc., that are compatible with pharmaceutical administration. Use of these agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions. The pharmaceutical compositions may also be included in a container, pack, or dispenser together with instructions for administration.

[00178] A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Methods to accomplish the administration are known to those of ordinary skill in the art. Pharmaceutical compositions may be topically or orally administered, or capable of transmission across mucous membranes. Examples of administration of a pharmaceutical composition include oral ingestion or inhalation. Administration may also be intravenous, intraperitoneal, intramuscular, intracavity, subcutaneous, cutaneous, or transdermal.

[00179] Solutions or suspensions used for intradermal or subcutaneous application typically include at least one of the following components: a sterile diluent such as water, saline solution, fixed oils, polyethylene glycol, glycerine, propylene glycol, or other synthetic solvent; antibacterial agents such as benzyl

alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetate, citrate, or phosphate; and tonicity agents such as sodium chloride or dextrose. The pH can be adjusted with acids or bases. Such preparations may be enclosed in ampoules, disposable syringes, or multiple dose vials.

[00180] Solutions or suspensions used for intravenous administration include a carrier such as physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ), ethanol, or polyol. In all cases, the composition must be sterile and fluid for easy syringability. Proper fluidity can often be obtained using lecithin or surfactants. The composition must also be stable under the conditions of manufacture and storage. Prevention of microorganisms can be achieved with antibacterial and antifungal agents, e.g., parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, etc. In many cases, isotonic agents (sugar), polyalcohols (mannitol and sorbitol), or sodium chloride may be included in the composition. Prolonged absorption of the composition can be accomplished by adding an agent which delays absorption, e.g., aluminum monostearate and gelatin.

[00181] Oral compositions include an inert diluent or edible carrier. The composition can be enclosed in gelatin or compressed into tablets. For the purpose of oral administration, the antibodies can be incorporated with excipients and placed in tablets, troches, or capsules. Pharmaceutically compatible binding agents or adjuvant materials can be included in the composition. The tablets, troches, and capsules, may contain (1) a binder such as microcrystalline cellulose, gum tragacanth or gelatin; (2) an excipient such as starch or lactose, (3) a disintegrating agent such as alginic acid, Primogel, or corn starch; (4) a lubricant such as magnesium stearate; (5) a glidant such as colloidal silicon dioxide; or (6) a sweetening agent or a flavoring agent.

[00182] The composition may also be administered by a transmucosal or transdermal route. For example, antibodies that comprise a Fc portion may be capable of crossing mucous membranes in the intestine, mouth, or lungs (via Fc receptors). Transmucosal administration can be accomplished through the use of lozenges, nasal sprays, inhalers, or suppositories. Transdermal administration can also be accomplished through the use of a composition containing ointments,

salves, gels, or creams known in the art. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used. For administration by inhalation, the antibodies are delivered in an aerosol spray from a pressured container or dispenser, which contains a propellant (e.g., liquid or gas) or a nebulizer.

[00183] In certain embodiments, the antibodies of this invention are prepared with carriers to protect the antibodies against rapid elimination from the body. Biodegradable polymers (e.g., ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid) are often used. Methods for the preparation of such formulations are known by those skilled in the art. Liposomal suspensions can be used as pharmaceutically acceptable carriers too. The liposomes can be prepared according to established methods known in the art (U.S. Patent No. 4,522,811).

[00184] The antibodies or antibody compositions of the invention are administered in therapeutically effective amounts as described. Therapeutically effective amounts may vary with the subject's age, condition, sex, and severity of medical condition. Appropriate dosage may be determined by a physician based on clinical indications. The antibodies or compositions may be given as a bolus dose to maximize the circulating levels of antibodies for the greatest length of time. Continuous infusion may also be used after the bolus dose.

[00185] As used herein, the term "subject" is intended to include human and non-human animals. Subjects may include a human patient having a disorder characterized by cells that express IL-22, e.g., a cancer cell or an immune cell. The term "non-human animals" of the invention includes all vertebrates, such as non-human primates, sheep, dogs, cows, chickens, amphibians, reptiles, etc.

[00186] Examples of dosage ranges that can be administered to a subject can be chosen from: 1 μ g/kg to 20 mg/kg, 1 μ g/kg to 10 mg/kg, 1 μ g/kg to 1 mg/kg, 10 μ g/kg to 1 mg/kg, 10 μ g/kg to 100 μ g/kg, 100 μ g/kg to 1 mg/kg, 250 μ g/kg to 2 mg/kg, 250 μ g/kg to 1 mg/kg, 500 μ g/kg to 2 mg/kg, 500 μ g/kg to 1 mg/kg, 1 mg/kg to 2 mg/kg, 1 mg/kg to 5 mg/kg, 5 mg/kg to 10 mg/kg, 10 mg/kg to 20 mg/kg, 15 mg/kg to 20 mg/kg, 10 mg/kg to 25 mg/kg, 15 mg/kg to 25 mg/kg, 20 mg/kg to 25 mg/kg, and 20 mg/kg to 30 mg/kg (or higher). These dosages may be administered daily, weekly, biweekly, monthly, or less frequently, for example,

biannually, depending on dosage, method of administration, disorder or symptom(s) to be treated, and individual subject characteristics. Dosages can also be administered via continuous infusion (such as through a pump). The administered dose may also depend on the route of administration. For example, subcutaneous administration may require a higher dosage than intravenous administration.

[00187] In certain circumstances it may be advantageous to formulate 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 for the patient. Each dosage unit contains a predetermined quantity of antibody calculated to produce a therapeutic effect in association with the carrier. The dosage unit depends on the characteristics of the antibodies and the particular therapeutic effect to be achieved.

[00188] Toxicity and therapeutic efficacy of the composition can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD₅₀/ED₅₀. Antibodies that exhibit large therapeutic indices may be less toxic and/or more therapeutically effective.

[00189] The data obtained from the cell culture assays and animal studies can be used to formulate a dosage range in humans. The dosage of these compounds may lie within the range of circulating antibody concentrations in the blood, that includes an ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage composition form employed and the route of administration. For any antibody used in the present invention, the therapeutically effective dose can be estimated initially using cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC₅₀ (i.e., the concentration of antibody which achieves a half-maximal inhibition of symptoms). The effects of any particular dosage can be monitored by a suitable bioassay. Examples of suitable bioassays include DNA replication assays, transcription-based assays, IL-22/IL-22R binding assays, IL-

22/IL-10R2 binding assays, IL-22/IL-22R/IL-10R2, and other immunological assays.

EXAMPLES

Example 1: Selection of Anti-IL-22 scFv's

Selection of Parents GIL01 and GIL68

[00190] GIL01 and GIL68 were isolated from scFv libraries by soluble selection on IL-22. Soluble selections were carried out using biotinylated IL-22 with an N-terminal His/FLAG tagged protein (bio.IL-22 H/F). Bio.IL-22 H/F was initially used at a concentration of 100 nM. An scFv phagemid library, which is an expanded version of the 1.38×10^{10} library described (Vaughan et al., 1996), was used to select antibodies specific for IL-22. Purified scFv phage (10^{12} transducing units (tu)) were blocked for 30 minutes in 100 μ l 3% MPBS (3% milk powder in PBS), then bio.IL-22 H/F was added and incubated at room temperature for 1 hour. Phage/antigen was added to 50 μ l of Dynal M280 Streptavidin magnetic beads, which had been blocked for 1 hour at 37°C in 1 ml of 3% MPBS, then incubated for a further 15 minutes at room temperature. Beads were captured using a magnetic rack and washed 4x in 1 ml of 3% MPBS/ 0.1% (v/v) Tween 20 followed by three washes in PBS. After the last wash, beads were resuspended in 100 μ l PBS and used to infect 5 ml exponentially growing *E. coli* TG-1 cells. Cells and phage on beads were incubated for 1 hour at 37°C (30 minutes stationary, 30 minutes shaking at 250 rpm), then spread on 2TYAG plates. Plates were incubated at 30°C overnight and colonies visualized the next day. Colonies were scraped off the plates into 10 ml 2TY broth and 15% glycerol added for storage at -70°C.

[00191] Glycerol stock cultures from the first round panning selection were superinfected with helper phage and rescued to give scFv antibody-expressing phage particles for the second round of selection. A second and third round of soluble selection was carried out as described above, dropping the concentration of bio.IL-22 H/F to 50 nM.

Isolation of parents GIL16, GIL45, GIL60 and GIL92

[00192] GIL16, GIL45, GIL60 and GIL92 were isolated from scFv libraries by a combination of panning on an IL-22 fusion protein and soluble selection on bio.IL-22 H/F. Wells of a microtiter plate were coated with 10 μ g/ml (Dulbecco's PBS, pH 7.4) human IL-22 fusion protein and incubated overnight at

4°C. Wells were washed in PBS and blocked for 2 hours at 37°C in 3% MPBS. Purified phage (10^{12} tu) in 100 µl of 3% MPBS were added to blocked wells and incubated at room temperature for 1 hour. Wells were washed 10 times with PBST (PBS containing 0.1% v/v Tween™20), then 10 times with PBS. Bound phage particles were eluted with 100 µl trypsin solution (0.5 µg/ml trypsin in 50 mM Tris pH 8, 1 mM CaCl₂) for 30 minutes at 37°C. The eluted phage were used to infect 10 ml exponentially growing *E. coli* TG1. Infected cells were grown in 2TY broth for 1 hour at 37°C, as above, then streaked onto 2TYAG plates and incubated overnight at 30°C. Output colonies were scraped off the plates and phage rescued as described above. A second round of soluble selection was carried out as described above, using 100 nM bio.IL-22 H/F.

Example 2: ScFv Blocks Binding of IL-22 to IL-22R

[00193] Inhibition assays were performed on the parent antibodies GIL01, GIL16, GIL45, GIL60, GIL68, and GIL92 to identify antibodies that block or alter binding of IL-22 to IL-22R and/or IL-22 receptor complex. Crude scFv containing periplasmic extracts were screened for the ability to inhibit the binding of bio.IL-22 H/F to a human IL-22 receptor protein (hIL-22R). Output colonies from selections were picked into 96 well plates containing 100 µl 2TYAG. ScFv production was induced by addition of 1 mM IPTG to exponentially growing cultures and overnight incubation at 30°C. Periplasmic extracts were prepared (Griffiths et al., 1993) in 50 mM MOPS pH 7.4/ 0.5 mM EDTA / 0.5M Sorbitol.

[00194] Microtiter plates were coated with 1.25 µg/ml of an IL-22 receptor protein antibody (in PBS) for 1.5 hours at room temperature. Plates were then washed three times in PBS, and blocked for 1 hour at room temperature with PBS containing 2% milk powder (2% MPBS). After a further 3 washes, 50 µl of 25% cell conditioned medium containing an IL-22 receptor protein was added to each well, and incubated overnight at 4°C. The following day, 25 µl of sample and 25µl of bio.IL-22 H/F (54 ng/ml in PBS/0.05% BSA/0.05% Tween) were added to the washed plates, and incubated for 1.5 hours at room temperature. After 3 washes in PBST, binding of bio.IL-22 H/F was detected with Europium-Streptavidin and TRF detected with the DELFIA® reagent kit and Victor 2™ Plate Reader (Perkin Elmer).

[00195] Clones that showed inhibition of IL-22 binding were retested as purified scFv. Both the IL-22/IL-22R binding assay (described above) and the IL-22 / IL-22 receptor complex assay (described below) were used. ScFv concentrations were titrated in order to establish the clone potencies as measured by assay IC₅₀ values. These were determined using GraphPad Prism software and four-parameter logistic equation curve fitting. Sample results from the IL-22 receptor complex assay are shown in Figure 1.

Example 3: Verification of IL-22 binding by phage ELISA

[00196] To establish the specificity of the scFv's for IL-22, a phage ELISA was performed using IL-22 fusion protein, IL-22 H/F and an unrelated protein. Individual *E. coli* colonies containing phagemid were inoculated into 96 well plates containing 100 µl 2TYAG medium per well. M13K07 helper phage were added to a multiplicity of infection (moi) of 10 to the exponentially growing culture and the plates incubated an additional 1 hour at 37°C. Plates were centrifuged in a benchtop centrifuge at 2000 rpm for 10 minutes. The supernatant was removed and cell pellets were resuspended in 100 µl 2TYAK and incubated at 30°C overnight with shaking. The next day, plates were centrifuged at 2000 rpm for 10 minutes and 100 µl phage-containing supernatant from each well was transferred to a fresh 96 well plate. Phage samples were blocked in a final concentration of 3% MPBS for 1 hour at room temperature.

[00197] Microtiter plates were coated with 1 µg/ml IL-22 fusion protein, IL-22 H/F or an unrelated protein and incubated overnight at 4°C. After coating, the solutions were removed from the wells, and the plates blocked for 1 hour at room temperature in 3% MPBS. Plates were rinsed with PBS then 50 µl of pre-blocked phage was added to each well. The plates were incubated at room temperature for 1 hour, then washed with 3 changes of PBST followed by 3 changes of PBS. To each well, 50 µl of a 1:5000 dilution of anti-M13-HRP conjugate (Pharmacia) was added and the plates incubated at room temperature for 1 hour. Plates were washed 3 times with PBST then 3 times with PBS. Fifty µl of TMB substrate was added to each well and incubated until color development. The reaction was stopped by the addition of 25 µl of 0.5 M H₂SO₄, and the absorbance at 450 nm measured. These experiments confirmed the specific binding of scFv clones to IL-22.

Example 4: Conversion of scF_v to IgG

[00198] Heavy and light chain V regions from scFv clones were amplified with clone-specific primers. PCR products were digested with appropriate restriction enzymes and subcloned into vectors containing human IgG4 heavy chain constant domain (for V_H domains) or vectors containing human lambda or kappa light chain constant domains as appropriate (V_L domains). The closest human germlines of the V_H and V_L segments were determined and this information was used to indicate whether kappa or lambda light chain constant domains were used (Table 4). Correct insertion of V region domains into plasmids was verified by sequencing of plasmid DNA from individual *E. coli* colonies. Plasmids were prepared from *E. coli* cultures by standard techniques and heavy and light chain constructs co-transfected into HEK 293 EBNA cells using standard techniques. Secreted IgG was purified using protein A sepharose (Pharmacia) and buffer exchanged into PBS.

Table 4: V_H and V_L germlines of IL-22 neutralizing clones

Clone	V _H germline	V _L germline
GIL01	3-11 (DP35)	Vk1:L12
GIL16	1-18 (DP14)	Vk1:L12
GIL45	3-33 (DP50)	VL2:2a2 (DPL11)
GIL60	3-20 (DP32)	VL2:2a2 (DPL11)
GIL68	1-2 (DP8)	VL3:3h
GIL92	1-2 (DP8)	VL1:1e (DPL8)

[00199] Potency of purified IgG was verified in the biochemical IL-22 receptor complex inhibition assay as described below. IgG concentrations were

titrated in order to obtain potency values. Sample potency data is shown in Table 5.

Table 5: Potency of IL-22 scFv and IgG in the IL-22 receptor complex inhibition assay

Clone	ScFv potency (nM)	IgG potency (nM)
GIL01	104	13
GIL16	49	10
GIL60	43	15
GIL68	7	2
GIL92	16	unobtainable
GIL45	358	180

Example 5: IL-22 Antibody Optimization

[00200] Large ribosome display libraries were created and screened for scFv's that specifically recognized recombinant human IL-22, essentially as described in Hanes *et al.* (2000). Initially the five parent clones (GIL01, GIL16, GIL60, GIL68 and GIL92) were converted to ribosome display format, and this template was subsequently used for library creation. On the DNA level, a T7 promoter was added at the 5'-end for efficient transcription to mRNA. On the mRNA level, the construct contained a prokaryotic ribosome-binding site (Shine-Dalgarno sequence) and 5' & 3' stem loops for mRNA stability. At the 3' end of the single chain, the stop codon was removed and a portion of gIII was added to act as a spacer, allowing folding of the scFv away from the ribosomal tunnel (Hanes *et al.* 2000).

[00201] Ribosome display libraries derived from the lead clones were created by mutagenesis of the single chain complementarity determining regions (CDRs) using PCR with non-proofreading *Taq* DNA polymerase. Affinity based selections were performed where the library was incubated with bio.IL-22H/F, followed by streptavidin coated paramagnetic beads (Dynal M280). Tertiary complexes (mRNA-ribosome-scFv) were recovered by magnetic separation, while unbound complexes were washed away. The mRNAs encoding the bound scFvs

were then rescued by RT-PCR as described (Hanes *et al.*, 2000) and the selection process repeated with decreasing concentrations (100 nM - 10 pM over 5 rounds) of bio.IL-22H/F.

[00202] Error prone PCR was introduced to further increase library size. The error rate that was employed created, on average, 7.2 mutations per 1,000 bp after a standard PCR reaction based on the method of Cadwell and Joyce (1992). Initial error prone PCR reactions took place between the first and second rounds of selection.

[00203] V_H/V_L recombination libraries for each parent clone were prepared from the V_H and V_L CDR ribosome display outputs after either the second or fourth round of selections. The V_H portion of the V_H CDR selection output for a particular lineage was specifically PCR amplified, using clone specific primers. The V_L portion of the V_L CDR selection output for the same lineage was amplified separately. These two PCR products were recombined via an overlapping PCR reaction. This created a complete library of scFv products containing all components required for further rounds of ribosome display selection.

[00204] For some clones, phage display libraries were also utilized. Phage libraries were created by mutagenesis of single chain CDRs using PCR reactions with appropriate primers, and selected as described above. These outputs were also combined with ribosome display selection outputs to create V_H/V_L recombination libraries. The V_H selection outputs from the fourth round of ribosome display, together with the outputs from the third round of phage display, were recombined with the V_L outputs from the same lineage. This was achieved using clone specific primers and over-lapping PCR to produce V_H/V_L recombination libraries. Selections with soluble bio.IL-22 H/F continued in ribosome display format, as described above. The scFv regions of selection outputs were directionally cloned into pCANTAB6 for production of scFv for biochemical high throughput screening.

Example 6: Identification of optimized clones

[00205] Two assays were used for high throughput screening of selection outputs. Outputs derived from clones GIL01, GIL16 and GIL68 were screened in a homogeneous time resolved fluorescence assay (HTRF®, Cis

Biointernational), while GIL60 and GIL92 outputs were screened in a DELFIA® (Perkin Elmer) assay.

HTRF® epitope competition assay

[00206] Crude scFv containing culture supernatants from GIL01, GIL16 and GIL68 output clones were prepared as described above and screened for inhibition of bio.IL-22H/F binding GIL68 in an HTRF assay.

[00207] Cryptate labeled GIL68 IgG (labeling kit from Cis Biointernational) was diluted 400 fold in assay buffer (PBS/0.4M KF/ 0.05% BSA/0.05% Tween), followed by the addition of 7.5 nM Streptavidin XL665 (Xlent, Cis Biointernational). This solution was mixed with crude scFv sample (diluted 125x), and bio.IL-22H/F in a Packard black 384 well Optiplate (Perkin Elmer). Plates were incubated for 1 hour at room temperature then read using a Victor 2™ Plate Reader (Perkin Elmer). The 665 nM/620 nM emission ratio was used to calculate the percentage of specific binding in each well.

DELFIA® Time Resolved Fluorescence assay

[00208] GIL60 and GIL92 output clones were screened for inhibition of bio.IL-22H/F binding to an IL-22 receptor complex.

[00209] Microtiter plates were coated with an IL-22 receptor complex antibody (1 µg/ml in PBS), and incubated for 1.5 hours at room temperature. Plates were washed three times in PBST, and blocked for 1 hour at room temperature with 2% MPBS. After a further 3 washes, diluted cell conditioned medium containing an IL-22 receptor complex was added and incubated overnight at 4°C. Crude scFv supernatants were prepared as described above. The following day, 25 µl of diluted scFv sample and 25 µl of bio.IL-22 H/F (6 ng/ml) were added to the washed plates, and incubated for 1.5 hours at room temperature. Plates were washed 3 times in PBST, then binding of bio.IL-22H/F to the IL-22 receptor complex was detected with Europium-Streptavidin and the DELFIA® reagent kit (PerkinElmer). Time Resolved Fluorescence was measured using a Victor 2™ Plate Reader (Perkin Elmer).

[00210] Purified scFv from positive clones identified from the screening were tested in the DELFIA® IL-22 receptor complex competition assay as described above. A titration of scFv concentrations was used in order to establish the clone potency as measured by IC₅₀ values in the assay. Sample results are

shown in Figure 2. Fourteen optimized clones were designated 097D09, 062A09, 062G05, 087B03, 367D04, 368D04, 166B06, 166G05, 375G06, 376B10, 354A08, 355B06, 355E04, and 356A11.

Example 7: Ranking of Optimized Clones in the BAF3-IL-22 Proliferation

Assay

[00211] Proliferation assays were performed to assess the antibody's ability to block the IL-22 mediated BaF3 cell proliferation. BaF3 cells expressing hIL22R/hIL10R2 were generated by co-transfection of BaF3 cells with hIL22R-GFP and hIL10R2-YFP. BaF3 cells expressing both hIL22R and hIL10R2 (BaF3-IL-22 receptor cells) were sorted and collected by FACS.

[00212] BaF3-IL-22 receptor cells were routinely maintained in RPMI1640 with 10% FBS and 1 ng/mL murine IL-3. Immediately before assay setup, cells were washed 4 times in assay medium (RPMI1640 with 10% FBS, 100U/ml Penicillin and 100µg/ml Streptomycin), resuspended in assay medium and incubated at 37°C, 5% CO₂ for 6-8 hours. To prepare assay plates, 100 µl of cells (1x10⁵/ml in assay medium) were added to the central 60 wells of a 96 well flat-bottomed tissue culture plate (Costar). Test scFv or IgG samples were prepared by diluting the stock sample in assay medium followed by filtration through a 0.22 µm filter. Serial 5-fold dilutions of samples were prepared in a separate dilution plate. Cell containing wells were treated with 50 µl of sample followed by 50 µl of human IL-22, (40 ng/ml in assay medium), and were then incubated for 40 hours at 37°C in 5% CO₂. Control wells included media alone and cells either alone or in the presence of 10 ng/mL human IL-22.

[00213] Cell proliferation was detected by the addition of 20 µl of Alamar Blue (Serotec) to wells, followed by incubation for 5 hours ± 30 mins at 37°C in 5% CO₂. Plates were mixed by gentle tapping to ensure even signal throughout the wells before measurement of fluorescence (excitation=560 nM, emission=590 nM). EC₅₀ and IC₅₀ values were estimated using four-parameter logistic curve fitting (Graphpad Prism 2 Software) and were used to rank antibodies. Sample potency data for optimized scFvs and IgGs are shown in Table 6.

Table 6. IC₅₀ values of scFv and IgG clones in BaF3-IL-22 proliferation assay

Clone	Parent	IC ₅₀ of scFv (pM)	IC ₅₀ of IgG (pM)
097D09	GIL01	298±246	197±42
062A09	GIL16	267	83±37
062G05	GIL16	182	112±30
087B03	GIL60	212	105±17
367D04	GIL60	160±49	126±6
368D04	GIL60	186±66	127±10
166B06	GIL68	460	71±23
166G05	GIL68	204	97±23
375G06	GIL68	118±98	100±1
376B10	GIL68	104±47	119±6
354A08	GIL92	219±83	79±15*
355B06	GIL92	183±3	92±14*
355E04	GIL92	192±47	100±14*
356A11	GIL92	124±21	53±5*

*GIL92-derived clones were tested as germlined IgGs.

Example 8: Germlining

[00214] Sequence data for the six parent clones was used to identify the nearest germline sequence for the heavy and light chain of each clone. Appropriate mutations were made using standard site directed mutagenesis techniques with the appropriate mutagenic primers. Mutation of sequences was confirmed by sequence analysis. The sequences for the germlined clones and their scFv and V_H and V_L domains are shown in Table 7. Purified scFv from the germlined parent clones were tested in the biotinylated IL-22 binding IL-22 receptor complex competition assay as described earlier, in order to establish the clone potency as measured by IC₅₀ values in the assay. Results are summarized in Table 8.

Table 7A: Amino Acid and Nucleotide Sequences of V_H and V_L Domains, F_V, and CDRs of Germlined Antibodies (GIL01, GIL16, GIL45, GIL60, GIL68, GIL92, 062A09, and 087B03)

Region	Type	GIL01 SEQ ID	GIL16 SEQ ID	GIL45 SEQ ID	GIL60 SEQ ID	GIL68 SEQ ID	GIL92 SEQ ID	062A09 SEQ ID	087B03 SEQ ID
V _H	AA	NO:365	NO:383	NO:401	NO:419	NO:437	NO:455	NO:473	NO:491
V _L	AA	NO:366	NO:384	NO:402	NO:420	NO:438	NO:456	NO:474	NO:492
scF _v	AA	NO:367	NO:385	NO:403	NO:421	NO:439	NO:457	NO:475	NO:493
H1	AA	NO:368	NO:386	NO:404	NO:422	NO:440	NO:458	NO:476	NO:494
H2	AA	NO:369	NO:387	NO:405	NO:423	NO:441	NO:459	NO:477	NO:495
H3	AA	NO:370	NO:388	NO:406	NO:424	NO:442	NO:460	NO:478	NO:496
L1	AA	NO:371	NO:389	NO:407	NO:425	NO:443	NO:461	NO:479	NO:497
L2	AA	NO:372	NO:390	NO:408	NO:426	NO:444	NO:462	NO:480	NO:498
L3	AA	NO:373	NO:391	NO:409	NO:427	NO:445	NO:463	NO:481	NO:499
V _H	DNA	NO:374	NO:392	NO:410	NO:428	NO:446	NO:464	NO:482	NO:500
V _L	DNA	NO:375	NO:393	NO:411	NO:429	NO:447	NO:465	NO:483	NO:501
scF _v	DNA	NO:376	NO:394	NO:412	NO:430	NO:448	NO:466	NO:484	NO:502
H1	DNA	NO:377	NO:395	NO:413	NO:431	NO:449	NO:467	NO:485	NO:503
H2	DNA	NO:378	NO:396	NO:414	NO:432	NO:450	NO:468	NO:486	NO:504
H3	DNA	NO:379	NO:397	NO:415	NO:433	NO:451	NO:469	NO:487	NO:505
L1		NO:380	NO:398	NO:416	NO:434	NO:452	NO:470	NO:488	NO:506
L2	DNA	NO:381	NO:399	NO:417	NO:435	NO:453	NO:471	NO:489	NO:507
L3	DNA	NO:382	NO:400	NO:418	NO:436	NO:454	NO:472	NO:490	NO:508

Table 7B: Amino Acid and Nucleotide Sequences of V_H and V_L Domains, F_V, and CDRs of Germlined Antibodies (166B06, 166G05, 354A08, 355B06, 355E04, 356A11, and 368D04)

Region	Type	166B06 SEQ ID	166G05 SEQ ID	354A08	355B06 SEQ ID	355E04 SEQ ID	356A11 SEQ ID	368D04 SEQ ID
V _H	AA	NO:509	NO:527	NO:545	NO:563	NO:581	NO:599	NO:617
V _L	AA	NO:510	NO:528	NO:546	NO:564	NO:582	NO:600	NO:618
scF _V	AA	NO:511	NO:529	NO:547	NO:565	NO:583	NO:601	NO:619
H1	AA	NO:512	NO:530	NO:548	NO:566	NO:584	NO:602	NO:620
H2	AA	NO:513	NO:531	NO:549	NO:567	NO:585	NO:603	NO:621
H3	AA	NO:514	NO:532	NO:550	NO:568	NO:586	NO:604	NO:622
L1	AA	NO:515	NO:533	NO:551	NO:569	NO:587	NO:605	NO:623
L2	AA	NO:516	NO:534	NO:552	NO:570	NO:588	NO:606	NO:624
L3	AA	NO:517	NO:535	NO:553	NO:571	NO:589	NO:607	NO:625
V _H	DNA	NO:518	NO:536	NO:554	NO:572	NO:590	NO:608	NO:626
V _L	DNA	NO:519	NO:537	NO:555	NO:573	NO:591	NO:609	NO:627
scF _V	DNA	NO:520	NO:538	NO:556	NO:574	NO:592	NO:610	NO:628
H1	DNA	NO:521	NO:539	NO:557	NO:575	NO:593	NO:611	NO:629
H2	DNA	NO:522	NO:540	NO:558	NO:576	NO:594	NO:612	NO:630
H3	DNA	NO:523	NO:541	NO:559	NO:577	NO:595	NO:613	NO:631
L1	DNA	NO:524	NO:542	NO:560	NO:578	NO:596	NO:614	NO:632
L2	DNA	NO:525	NO:543	NO:561	NO:579	NO:597	NO:615	NO:633
L3	DNA	NO:526	NO:544	NO:562	NO:580	NO:598	NO:616	NO:634

Table 8: ScFv potencies of ungermlined and germlined parent clones in the IL-22 receptor competition assay

Parent clone scFv	Average IC ₅₀ nM in IL-22 competition assay	
	Parent	Fully germlined
GIL01	124±50	143±45
GIL16	44±1	38±1
GIL60	51±16	82±3
GIL68	9±1	14±1
GIL92	18±2	40±11

[00215] Nine of the optimized antibodies were germlined as described above. Eight germlined IgGs were tested in the BaF3-IL-22 proliferation assay as described above. Antibody IC₅₀ values from a representative experiment are shown in Table 9.

[00216] Antibody sequences were then sent to GENEART North America (28 Kirk Bradden Rd. East, Toronto, ON, Canada M8Y2E6), where they were synthesized for optimized expression in CHO cells using GENEART's proprietary optimization algorithm.

Table 9: IgG potencies of germlined optimized clones in the BaF3-IL-22R proliferation assay

Clone	Parent	IC ₅₀ (pM) of non-germlined IgG	IC ₅₀ (pM) of germlined IgG
087B03	GIL60	72±6	118±19
166B06	GIL68	109±16	169±32
166G05	GIL68	366±226*	109±31
356A11	GIL92	ND	53±5
355B06	GIL92	ND	92±14
355E04	GIL92	ND	100±14
354A08	GIL92	ND	79±15
062A09	GIL16	108±23	unobtainable

*sample contained precipitate ND= not determined

Example 9: Antibody inhibits IL-22 induced GROa secretion from HT29 cells

[00217] GROa assays were performed to assess the antibody's ability to block the IL-22 induced GROa secretion from HT29 cells. HT29 cells were seeded in 96 well flat bottom tissue culture plate (Corning Inc. Cat. #3595) in DMEM medium (DMEM + 10% FBS + 100 unit/ml penicillin and streptomycin + 2 mM Glutamine) at 5×10^4 /well. 10 ng/ml IL-22 was mixed with serially diluted antibody in DMEM medium and incubated for 30 min at 37°C. 24 hours after seeding, medium was removed from HT29 cells and pre-mixed IL-22 and antibody were added to the cells in 96 well plate.

[00218] After 48 hours of incubation at 37°C with 5% CO₂, medium was collected and secreted GROa was tested using Human GROa Immunoassay kit (R&D Systems, Cat. DGR00), according to the manufacturer's directions. Results are presented in Figure 3.

Example 10: Antibody binds to and inhibits different species IL-22

[00219] Cross species reactivity of germlined and non-germlined optimized antibodies were determined as follows: ELISA plates (Costar, Cat. #3590) were coated overnight with 1 µg/ml of rat, mouse, or human IL-22 or human IL-26 in PBS buffer. Plates were washed with PBST buffer (0.05% Tween20 in

PBS) 3 times, then blocked with 1% BSA (Sigma A8918) / PBST for 1 hr at RT. Antibodies were added at 1 µg/ml, incubated 1 hr at 25°C. The plates were washed, then HRP-conjugated goat anti-human IgG antibody (Southern Biotech Association, Cat. #2040-05) was added. The plates were incubated for 1 hour at 25°C, then washed with PBST, and developed with TMB (KPL, Cat. #50-76-04). Reaction was stopped with 0.18 M H₂SO₄. Plates were read at OD 450 nm. Results are presented in Figure 4.

[00220] These antibodies were also evaluated in both the GROa cell assay and BaF3-IL-22 proliferation assay. As shown in Tables 10(a) and 10(b), the antibodies blocked the activity of human, monkey, rat, and mouse IL-22 signalling via a human IL-22 receptor. 356A11 and 368D04 also demonstrated cross-species reactivity against murine, rat, and monkey IL-22 using real-time biospecific interaction analysis (BIA), as discussed further in Example 11.

[00221] **Table 10(a).** IL-22 antibodies are highly potent for blocking other species of IL-22 as shown in the GROa cell based assay system. Values shown represent IC₅₀ values in pM.

Protein ID	human IL-22	murine IL-22	rat IL-22	monkey IL-22
356A11	123.64	143.76	210.91	89.57
368D04	154.07	156.25	281.12	184.10
control 1	353.18	468.34	1161.57	343.19
control 2	1955.80	3399.79	10697.17	1459.27

[00222] **Table 10(b).** IL-22 antibodies are highly potent for blocking other species of IL-22 as shown in the BaF3 cell based assay system. Values shown represent IC₅₀ values in pM.

Protein ID	human IL-22	murine IL-22	rat IL-22	monkey IL-22
356A11	3.57	2.53	10.69	2.58
368D04	3.63	1.47	12.07	3.87
control 1	6.40	5~6	27.37	7.18
control 2	204.98	1033.26	2500.00	134.27

Example 11: Comparison of Binding Kinetics Between Rat Anti-IL-22 Monoclonal Antibodies and Human Anti-IL-22 Monoclonal Antibodies

[00223] The binding kinetics of human, monoclonal anti-IL-22 antibodies (356A11 and 368D04) and rat, monoclonal anti-IL-22 antibodies (P3/3 (Ab-02) and P3/2 (Ab-04) from WO 2005/000897 and WO 02/068476) to human IL-22 were evaluated by real-time biospecific interaction analysis (BIA) using surface plasmon resonance technology.

[00224] To prepare the biosensor surface for the rat monoclonal antibodies, Protein A/G (Pierce #21186, Rockford, IL) was immobilized onto a research-grade carboxymethyl dextran chip (CM5) using amine coupling. The surface was activated with EDC/NHS. The protein A/G was injected at a concentration of 50 µg/ml in sodium acetate buffer (pH 4.0). The immobilization was done using the wizard tools with aim of 3000 (RUs) for the protein A/G. Remaining activated groups were blocked with 1.0 M ethanolamine (pH 8.0). The first flow cell was used as a reference surface to correct for bulk refractive index, matrix effects, and non-specific binding. The second, third, and fourth flow cells were coated with the capturing molecule. The rat monoclonal antibodies Ab-02 and Ab-04, which bind to protein A/G, were captured onto the protein A/G surface by injecting 30 µl of a 1 µg/ml solution. The net difference between the baseline and the point approximately 90 seconds after completing Ab-02 or Ab-04 injection was used to represent the amount of ligand bound.

[00225] To prepare the biosensor surface for the human monoclonal antibodies, either human monoclonal antibody (356A11 or 368D04) or control antibody PD-1 (#17) were immobilized onto a research-grade carboxymethyl dextran chip (CM5) using standard amine coupling. The surface was activated with EDC/NHS. The capturing antibodies were injected at a concentration of 1 µg/ml in sodium acetate buffer (pH 5.5). Remaining activated groups were blocked with 1.0 M ethanolamine (pH 8.0). The first flow cell was used as a reference surface to correct for bulk refractive index, matrix effects, and non-specific binding. The second, third, and fourth flow cells were coated with the capturing molecule.

[00226] For Ab-02 and Ab-04, solutions of human IL-22 at 300, 100, 50, 25, 12.5, 6.4, 3.2, 1.6 and 0 nM concentrations were injected in triplicates at a flow rate of 30 µl per minute for 3 minutes and the amount of bound material as a function of time was recorded as sensorgrams. The dissociation phase was monitored in HBS/EP buffer for 10 minutes at the same flow rate followed by a 5 µl injection of 0.1% TFA and a 5 µl injection of glycine pH 1.5 to regenerate a fully active capturing surface.

[00227] For 356A11 and 368D04, solutions of human IL-22 at 400, 200, 100, 50, 25, 12.5, 6.25 and 0 nM were injected in triplicates at a flow rate of 100 µl per minute (high flow to avoid non specific binding) for 3 minutes, and the amount of bound material as a function of time was recorded as sensorgrams. The dissociation phase was monitored in HBS/EP buffer for 60 minutes at the same flow rate followed by two 5 µl injections of glycine pH 1.5 to regenerate a fully active capturing surface.

[00228] All kinetic experiments were done at 22.5°C in HBS/EP buffer. Blank and buffer effects were subtracted for each sensorgram using double referencing. In control experiments the first injection contained buffer.

[00229] The kinetic data were analyzed using BIAevaluation software 3.0.2 applied to a 1:1 model. The apparent dissociation (K_d) and association (K_a) rate constants were calculated from the appropriate regions of the sensorgrams using a global analysis. The affinity constants of the interaction between antibody and analyte were calculated from the kinetic rate constants by the following formulae: $K_D = K_d / K_a$, where K_D is the dissociation constant and $K_A = K_a / K_d$, where K_A is the association constant. The binding data for Ab-02 and AB-04 are

summarized in Tables 11A and 11B. The binding data for 356A11 and 368D04 are summarized in Table 12.

Table 11A. Kinetic parameters for the interaction between human IL-22 and anti-IL-22 antibodies Ab-02 and Ab-04

	Ab-02 k_a ($M^{-1}s^{-1}$)	Ab-02 k_d (s^{-1})	Ab-04 k_a ($M^{-1}s^{-1}$)	Ab-04 k_d (s^{-1})
Protein A/G	2.78 E+05	1.45 E- 03	5.15 E+05	1.23 E- 03

Table 11B. Kinetic data of rat monoclonal antibodies for human IL-22

Antibody	Ka (1/Ms)	Kd(1 /s)	KA (1/M)	KD (M)	Chi2
Ab-02	2.78 E+05	1.45 E-03	1.92 E+08	5.22 E-08	0.49
Ab-04	5.15 E+05	1.23 E-03	4.22 E+08	2.38 E-09	0.53

Table 12. Kinetic data of human monoclonal antibodies for human IL-22

Antibody	Ka (1/Ms)	Kd(1 /s)	KA (1/M)	KD (M)	Chi2
356A11	7.91 E+04	4.27 E-06	1.85 E+10	5.40 E-11	0.223
368D04	1.89 E+05	2.50 E-05	7.56 E+09	1.32 E-10	0.298

[00230] These results show that the human monoclonal anti-IL-22 antibodies of this invention have a significantly higher affinity for human IL-22 than the rat monoclonal anti-IL-22 antibodies Ab-02 and Ab-04, described in WO 2005/000897 and WO 02/068476 as having the ability to neutralize human IL-22. Specifically, the dissociation constant of 356A11 ($K_D = 5.40 \times 10^{-11}$ M or 0.054 nM) for human IL-22 is approximately 1000-fold and more than 40-fold greater than the

dissociation constants of Ab-02 ($K_D = 5.22 \times 10^{-8}$ M or 52 nM) and Ab-04 ($K_D = 2.38 \times 10^{-9}$ M or 2.38 nM), respectively. Similarly, 368D04 ($K_D = 1.32 \times 10^{-10}$ M or 0.132 nM) has an approximately 400-fold and 18-fold stronger affinity for human IL-22 than Ab-02 and Ab-04, respectively. The binding profiles of 356A11 and 36804 for monkey, murine, and rat IL-22 were similar to that of human IL-22 (data not shown).

[00231] The binding specificities of 356A11 and 368D04 were also evaluated using BIA. Neither antibody showed cross reactivity with human IL-10, human IL-19, human IL-20, human IL-24, human IL-28A, human IL-29, human IFN- α 2c, or human IFN- ω (data not shown).

Example 12: Model for Treatment of Arthritis

[00232] Arthritis is a disease characterized by inflammation in the joints. Rheumatoid Arthritis (RA) is the most frequent form of arthritis, involving inflammation of connective tissue and the synovial membrane, a membrane that lines the joint. The inflamed synovial membrane often infiltrates the joint and damages joint cartilage and bone. Both IL-22 and IL-22R protein and/or transcript are associated with human disease. In RA synovial biopsies, IL-22 protein is detected in vimentin⁺ synovial fibroblasts and some CD68⁺ macrophages while IL-22R is detected in synovial fibroblasts. Treatment of synovial fibroblasts with IL-22 induces the production of monocyte chemoattractant protein-1, MCP-1, as well as general metabolic activity (Ikeuchi, H. et al. (2005) *Arthritis Rheum.* 52:1037-46).

[00233] IL-22 is used to study its effect on cells from the synovial membrane, the membrane that lines the joints. Human fibroblast-like synoviocytes (HFLS) (Cell Applications (San Diego, CA)) are isolated from synovial tissues of rheumatoid arthritis patients undergoing joint surgery. HFLS are cultured with human IL-22 for 48 hours, and the supernatants are removed and tested for chemokines and cytokines by ELISA. IL-22 will increase HFLS secretion of chemokines MCP-1, Eotaxin, and IP-10, and cytokines TNF α , IL-6, and IL-8. These chemokines and cytokines are known in the art to promote inflammation through a number of activities, and increased concentrations in the joints caused by IL-22 exacerbates inflammation and RA.

[00234] IL-22 is used to regulate the clinical progression of CIA (Collagen Induced Arthritis). CIA is the standard mouse and rat model for studying

rheumatoid arthritis, see e.g., Holmdahl et al., (2002) Ageing Res. Rev., 1:135. On day 0, mice are injected with 100 μ g of Collagen Type II in complete Freund's adjuvant, and on day 21, the mice are boosted with 100 μ g of Collagen Type II in incomplete Freund's adjuvant. On day 21, the mice are also injected daily with 1 μ g of IL-22, and each day, the mice are examined for disease. The clinical signs are scored as follows: 0 = no swelling, 1 = 1 to 2 swollen digits or swollen ankle, 2 = more than 2 swollen digits or mild paw swelling, 3 = extensive paw swelling, and 4 = ankylosis of paw. Mice injected with PBS after the collagen injections progressively develop disease. Mice that are injected with IL-22 after the collagen injections progressively develop more severe disease. Because treatment with IL-22 specifically exacerbates CIA, treatment with anti-IL-22 antibodies, for example with germlined 087B03, 368D04, 354A08 or 356A11, is expected to suppress or delay CIA. Thus, since this model predicts treatment efficacy for RA, treatment with anti-IL-22 antibodies, including germlined or non-germlined 087B03, 368D04, 354A08 or 356A11, is expected to suppress or delay RA in humans.

Example 13: Treatment of Patients

[00235] Patients with an autoimmune disorder, respiratory disorder, inflammatory condition of the skin, cardiovascular system, nervous system, kidneys, liver and pancreas or transplant patients are among the types of patients that may be treated with the antibodies of the invention. Exemplary treatment regimens and expected outcomes of antibodies according to this invention, including 087B03, 368D04, 354A08, and 356A11, are provided below. Dosages and frequencies of administration other than those in Table 13 may also be used. The skilled artisan can adjust treatment regimens as necessary based on route of administration or other known variables, such as the age, weight, condition, sex, severity of medical condition, etc. of the patient to be treated.

Table 13: Treatment Regimens

Disorder	Treated with	Dosage Range	Frequency	Expected Outcome
Multiple Sclerosis	087B03, 368D04, 356A11, or 354A08	250 $\mu\text{g/kg}$ to 2 mg/kg	weekly, biweekly, or monthly	improvement or stabilization of condition
Rheumatoid Arthritis	087B03, 368D04, 356A11, or 354A08	250 $\mu\text{g/kg}$ to 2 mg/kg	weekly, biweekly, or monthly	improvement or stabilization of condition
Psoriasis	087B03, 368D04, 356A11, or 354A08	250 $\mu\text{g/kg}$ to 2 mg/kg	weekly, biweekly, or monthly	improvement or stabilization of condition
IBD	087B03, 368D04, 356A11, or 354A08	250 $\mu\text{g/kg}$ to 2 mg/kg	monthly, biweekly, or monthly	improvement or stabilization of condition
Alzheimer's Disease	087B03, 368D04, 356A11, or 354A08	250 $\mu\text{g/kg}$ to 2 mg/kg	monthly, biweekly, or monthly	improvement or stabilization of condition

[00236] The specification is most thoroughly understood in light of the teachings of the references cited within the specification. The embodiments within the specification provide an illustration of embodiments of the invention and should not be construed to limit the scope of the invention. The skilled artisan readily recognizes that many other embodiments are encompassed by the invention.

To the extent the material incorporated by reference contradicts or is inconsistent with this specification, the specification will supercede any such material. The citation of any references herein is not an admission that such references are prior art to the present invention.

[00237] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification, including claims, are to be understood as being modified in all instances by the term "about." Accordingly, unless otherwise indicated to the contrary, the numerical parameters are approximations and may vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding approaches.

[00238] Unless otherwise indicated, the term "at least" preceding a series of elements is to be understood to refer to every element in the series. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

CLAIMS

1. An antibody, or antigen-binding fragment thereof, that specifically binds to human IL-22, wherein the antibody, or antigen-binding fragment thereof, comprises:
 - (a) a V_H domain comprising an amino acid sequence which is at least 90% identical to the amino acid sequence set out in SEQ ID NO:23 and a V_L domain comprising an amino acid sequence which is at least 90% identical to the amino acid sequence set out in SEQ ID NO:24;
 - (b) a V_H domain comprising an amino acid sequence which is at least 90% identical to the amino acid sequence set out in SEQ ID NO:59 and a V_L domain comprising an amino acid sequence which is at least 90% identical to the amino acid sequence set out in SEQ ID NO:60;
 - (c) a V_H domain comprising an amino acid sequence which is at least 90% identical to the amino acid sequence set out in SEQ ID NO:77 and a V_L domain comprising an amino acid sequence which is at least 90% identical to the amino acid sequence set out in SEQ ID NO:78; or
 - (d) a V_H domain comprising an amino acid sequence which is at least 90% identical to the amino acid sequence set out in SEQ ID NO:95 and a V_L domain comprising an amino acid sequence which is at least 90% identical to the amino acid sequence set out in SEQ ID NO:96;

and wherein (i) the association constant of the antibody for human IL-22 is at least 10^{10} M^{-1} as measured by real-time biospecific interaction analysis using surface plasmon resonance technology, (ii) the antibody blocks IL-22 mediated proliferation of BaF3 cells with an IC_{50} of 150 pM or less and wherein the BaF3 cells comprise a human IL-22 receptor; or (iii) the antibody blocks IL-22 mediated GRO α secretion from HT29 cells with an IC_{50} of 150 pM or less.

2. The antibody of claim 1, wherein in part (a):
 - a) the V_H domain comprises the amino acid sequence set out in SEQ ID NO:131 and the V_L domain comprises the amino acid sequence set out in SEQ ID NO:132; or
 - b) the V_H domain comprises the amino acid sequence set out in SEQ ID NO:149 and the V_L domain comprises the amino acid sequence set out in SEQ ID NO:150.
3. The antibody of claim 1, wherein in part (b):

- a) the V_H domain comprises the amino acid sequence set out in SEQ ID NO:617 and the V_L domain comprises the amino acid sequence set out in SEQ ID NO:618;
 - b) the V_H domain comprises the amino acid sequence set out in SEQ ID NO:491 and the V_L domain comprises the amino acid sequence set out in SEQ ID NO:492;
 - c) the V_H domain comprises the amino acid sequence set out in SEQ ID NO:167 and the V_L domain comprises the amino acid sequence set out in SEQ ID NO:168;
 - d) the V_H domain comprises the amino acid sequence set out in SEQ ID NO:185 and the V_L domain comprises the amino acid sequence set out in SEQ ID NO:186; or
 - e) the V_H domain comprises the amino acid sequence set out in SEQ ID NO:203 and the V_L domain comprises the amino acid sequence set out in SEQ ID NO:204.
4. The antibody of claim 1, wherein in part (c):
- a) the V_H domain comprises the amino acid sequence set out in SEQ ID NO:527 and the V_L domain comprises the amino acid sequence set out in SEQ ID NO:528;
 - b) the V_H domain comprises the amino acid sequence set out in SEQ ID NO:221 and the V_L domain comprises the amino acid sequence set out in SEQ ID NO:222;
 - c) the V_H domain comprises the amino acid sequence set out in SEQ ID NO:239 and the V_L domain comprises the amino acid sequence set out in SEQ ID NO:240;
 - d) the V_H domain comprises the amino acid sequence set out in SEQ ID NO:257 and the V_L domain comprises the amino acid sequence set out in SEQ ID NO:258; or
 - e) the V_H domain comprises the amino acid sequence set out in SEQ ID NO:275 and the V_L domain comprises the amino acid sequence set out in SEQ ID NO:276.
5. The antibody of claim 1, wherein in part (d):
- a) the V_H domain comprises the amino acid sequence set out in SEQ ID NO:599 and the V_L domain comprises the amino acid sequence set out in SEQ ID NO:600;
 - b) the V_H domain comprises the amino acid sequence set out in SEQ ID NO:581 and the V_L domain comprises the amino acid sequence set out in SEQ ID NO:582;
 - c) the V_H domain comprises the amino acid sequence set out in SEQ ID NO:563 and the V_L domain comprises the amino acid sequence set out in SEQ ID NO:564; or

- d) the V_H domain comprises the amino acid sequence set out in SEQ ID NO:545 and the V_L domain comprises the amino acid sequence set out in SEQ ID NO:546.
6. The antibody of claim 3, wherein the V_H domain comprises the amino acid sequence set out in SEQ ID NO:617 and the V_L domain comprises the amino acid sequence set out in SEQ ID NO:618.
7. The antibody of claim 5, wherein the V_H domain comprises the amino acid sequence set out in SEQ ID NO:599 and the V_L domain comprises the amino acid sequence set out in SEQ ID NO:600.
8. The antibody of claim 1, wherein:
- (a) the V_H domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:134, SEQ ID NO:135, and SEQ ID NO:136 and the V_L domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:137, SEQ ID NO:138, and SEQ ID NO:139;
- (b) the V_H domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:152, SEQ ID NO:153, and SEQ ID NO:154 and the V_L domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:155, SEQ ID NO:156, and SEQ ID NO:157;
- (c) the V_H domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:170, SEQ ID NO:171, and SEQ ID NO:172 and the V_L domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:173, SEQ ID NO:174, and SEQ ID NO:175;
- (d) the V_H domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:188, SEQ ID NO:189, and SEQ ID NO:190 and the V_L domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:191, SEQ ID NO:192, and SEQ ID NO:193;
- (e) the V_H domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:206, SEQ ID NO:207, and SEQ ID NO:208 and the V_L domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:209, SEQ ID NO:210, and SEQ ID NO:211;

(f) the V_H domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:224, SEQ ID NO:225, and SEQ ID NO:226 and the V_L domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:227, SEQ ID NO:228, and SEQ ID NO:229;

(g) the V_H domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:242, SEQ ID NO:243, and SEQ ID NO:244 and the V_L domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:245, SEQ ID NO:246, and SEQ ID NO:247;

(h) the V_H domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:260, SEQ ID NO:261, and SEQ ID NO:262 and the V_L domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:263, SEQ ID NO:264, and SEQ ID NO:265;

(i) the V_H domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:278, SEQ ID NO:279, and SEQ ID NO:280 and the V_L domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:281, SEQ ID NO:282, and SEQ ID NO:283;

(j) the V_H domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:494, SEQ ID NO:495, and SEQ ID NO:496 and the V_L domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:497, SEQ ID NO:498, and SEQ ID NO:499;

(k) the V_H domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:530, SEQ ID NO:531, and SEQ ID NO:532 and the V_L domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:533, SEQ ID NO:534, and SEQ ID NO:535;

(l) the V_H domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:548, SEQ ID NO:549, and SEQ ID NO:550 and the V_L domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:551, SEQ ID NO:552, and SEQ ID NO:553;

(m) the V_H domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:566, SEQ ID NO:567, and SEQ ID NO:568 and the V_L domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:569, SEQ ID NO:570, and SEQ ID NO:571;

(n) the V_H domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:584, SEQ ID NO:585, and SEQ ID NO:586 and the V_L domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:587, SEQ ID NO:588, and SEQ ID NO:589;

(o) the V_H domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:602, SEQ ID NO:603, and SEQ ID NO:604 and the V_L domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:605, SEQ ID NO:606, and SEQ ID NO:607; or

(p) the V_H domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:620, SEQ ID NO:621, and SEQ ID NO:622 and the V_L domain comprises three CDRs comprising amino acid sequences that differ by one or two amino acids from at least one of the amino acid sequences of SEQ ID NO:623, SEQ ID NO:624, and SEQ ID NO:625.

9. An antibody, or antigen-binding fragment thereof, that specifically binds to IL-22, wherein the antibody, or antigen-binding fragment thereof, comprises:

(a) a V_H domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:134, SEQ ID NO:135, and SEQ ID NO:136 and a V_L domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:137, SEQ ID NO:138, and SEQ ID NO:139;

(b) a V_H domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:152, SEQ ID NO:153, and SEQ ID NO:154 and a V_L domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:155, SEQ ID NO:156, and SEQ ID NO:157;

(c) a V_H domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:170, SEQ ID NO:171, and SEQ ID NO:172 and a V_L domain comprising three CDRs

comprising the amino acid sequences of SEQ ID NO:173, SEQ ID NO:174, and SEQ ID NO:175;

(d) a V_H domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:188, SEQ ID NO:189, and SEQ ID NO:190 and a V_L domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:191, SEQ ID NO:192, and SEQ ID NO:193;

(e) a V_H domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:206, SEQ ID NO:207, and SEQ ID NO:208 and a V_L domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:209, SEQ ID NO:210, and SEQ ID NO:211;

(f) a V_H domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:224, SEQ ID NO:225, and SEQ ID NO:226 and a V_L domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:227, SEQ ID NO:228, and SEQ ID NO:229;

(g) a V_H domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:242, SEQ ID NO:243, and SEQ ID NO:244 and a V_L domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:245, SEQ ID NO:246, and SEQ ID NO:247;

(h) a V_H domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:260, SEQ ID NO:261, and SEQ ID NO:262 and a V_L domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:263, SEQ ID NO:264, and SEQ ID NO:265;

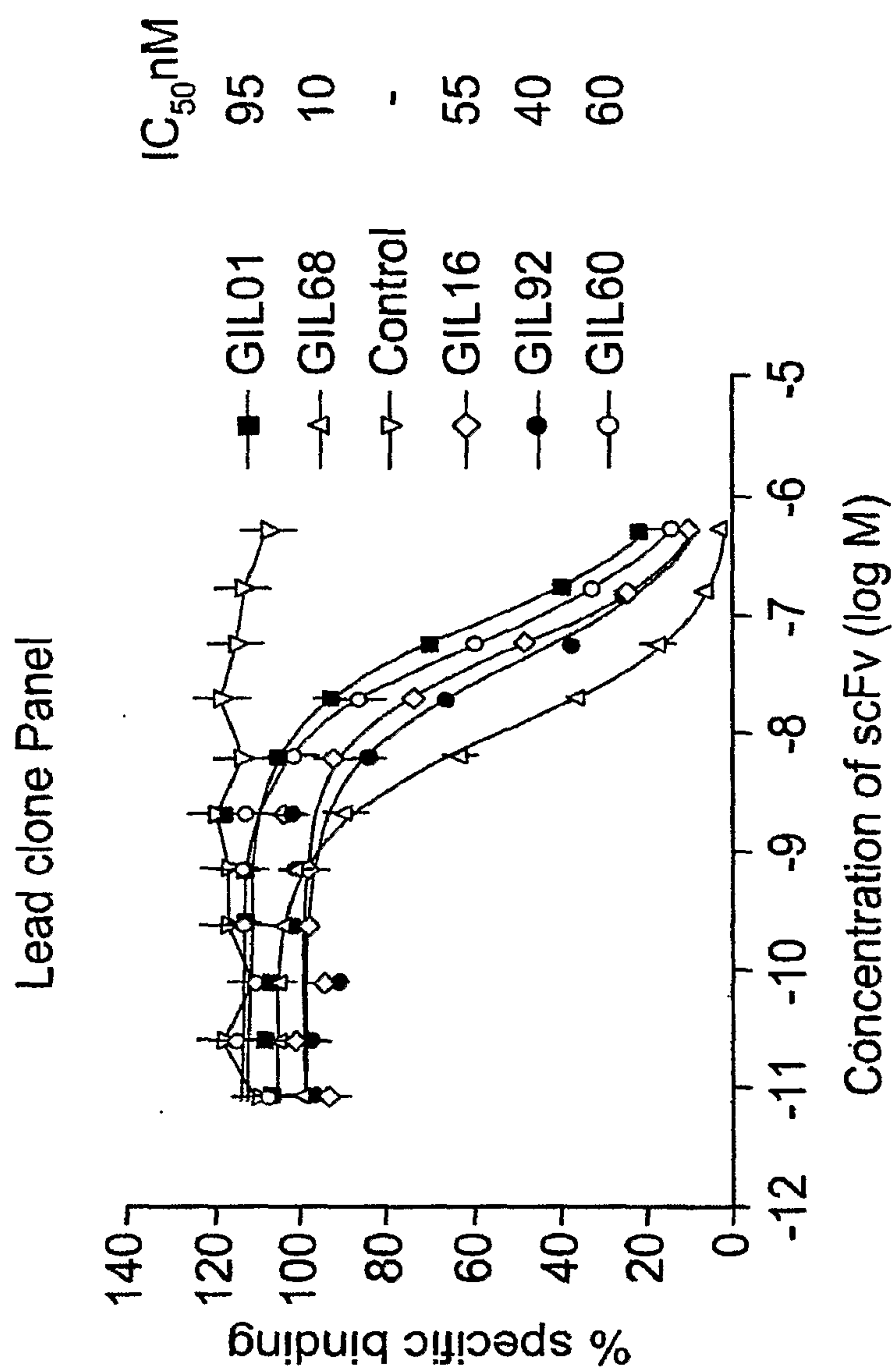
(i) a V_H domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:278, SEQ ID NO:279, and SEQ ID NO:280 and a V_L domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:281, SEQ ID NO:282, and SEQ ID NO:283;

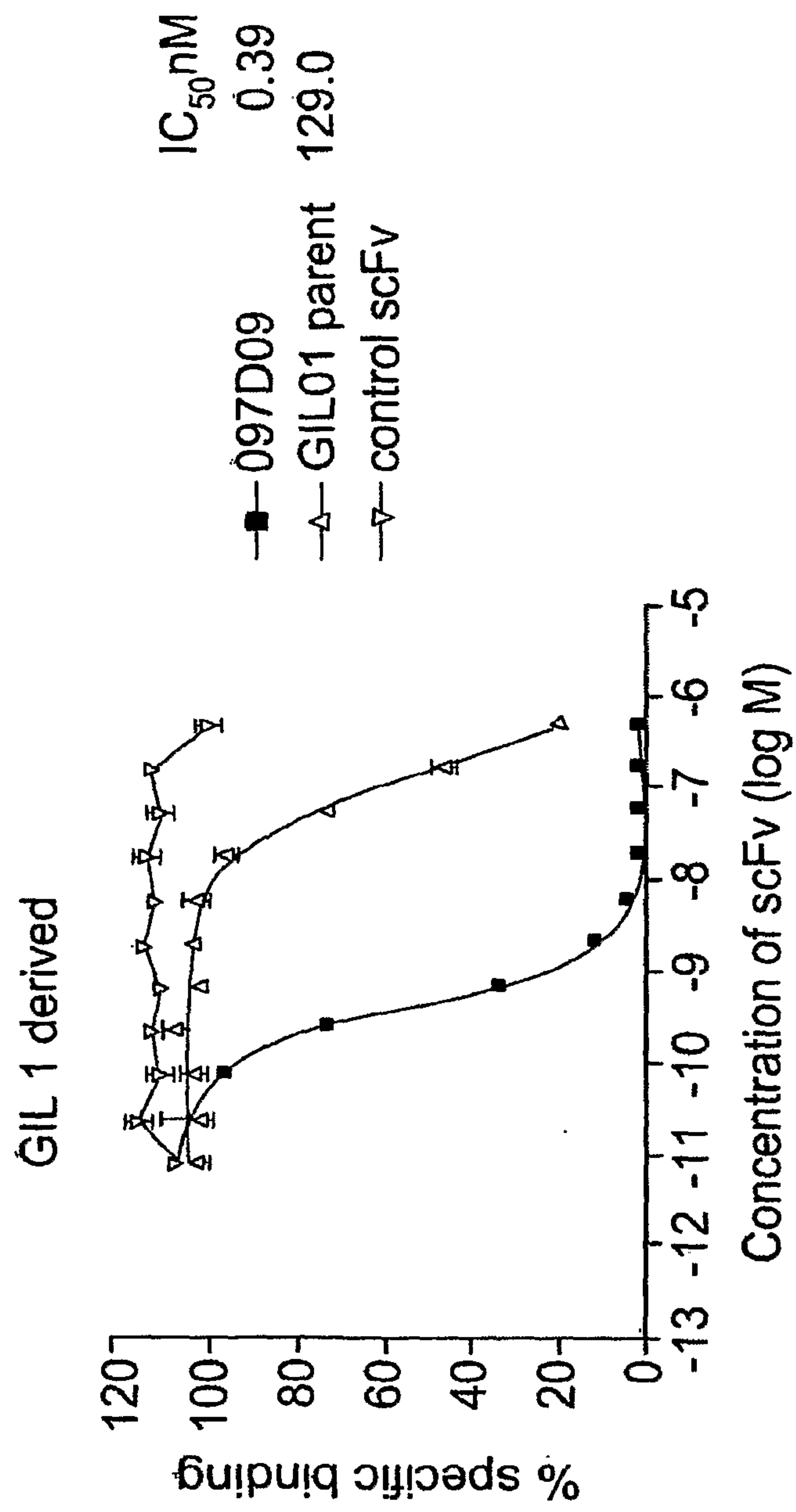
(j) a V_H domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:494, SEQ ID NO:495, and SEQ ID NO:496 and a V_L domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:497, SEQ ID NO:498, and SEQ ID NO:499;

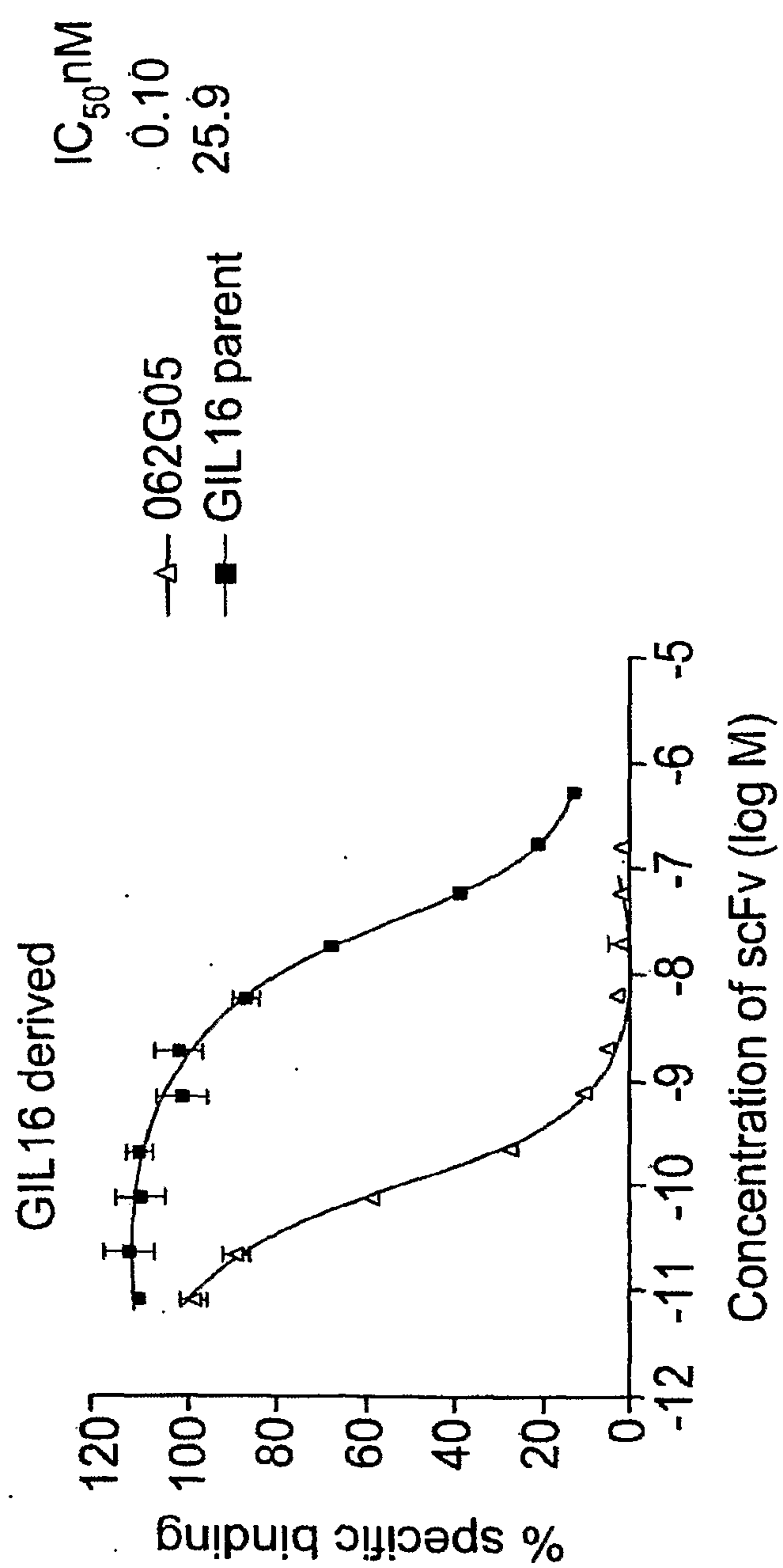
(k) a V_H domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:530, SEQ ID NO:531, and SEQ ID NO:532 and a V_L domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:533, SEQ ID NO:534, and SEQ ID NO:535;

- (l) a V_H domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:548, SEQ ID NO:549, and SEQ ID NO:550 and a V_L domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:551, SEQ ID NO:552, and SEQ ID NO:553;
- (m) a V_H domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:566, SEQ ID NO:567, and SEQ ID NO:568 and a V_L domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:569, SEQ ID NO:570, and SEQ ID NO:571;
- (n) a V_H domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:584, SEQ ID NO:585, and SEQ ID NO:586 and a V_L domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:587, SEQ ID NO:588, and SEQ ID NO:589;
- (o) a V_H domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:602, SEQ ID NO:603, and SEQ ID NO:604 and a V_L domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:605, SEQ ID NO:606, and SEQ ID NO:607; or
- (p) a V_H domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:620, SEQ ID NO:621, and SEQ ID NO:622 and a V_L domain comprising three CDRs comprising the amino acid sequences of SEQ ID NO:623, SEQ ID NO:624, and SEQ ID NO:625.
10. The antibody of claim 9, wherein the V_H domain comprises three CDRs comprising the amino acid sequences of SEQ ID NO:602, SEQ ID NO:603, and SEQ ID NO:604 and the V_L domain comprises three CDRs comprising the amino acid sequences of SEQ ID NO:605, SEQ ID NO:606, and SEQ ID NO:607.
 11. The antibody of claim 9, wherein the V_H domain comprises three CDRs comprising the amino acid sequences of SEQ ID NO:620, SEQ ID NO:621, and SEQ ID NO:622 and the V_L domain comprises three CDRs comprising the amino acid sequences of SEQ ID NO:623, SEQ ID NO:624, and SEQ ID NO:625.
 12. The antibody of any one of claims 1-11, wherein:
 - (a) the antibody inhibits the binding of IL-22 to IL-22R or a receptor complex comprising IL-22R and IL-10R2;
 - (b) the antibody is human; or

- (c) the antibody is IgG1 or IgG4.
13. A pharmaceutical composition comprising the antibody of any one of claims 1-12.
 14. An isolated nucleic acid encoding the antibody of any one of claims 1-11.
 15. An expression vector comprising the nucleic acid of claim 14.
 16. A host cell transformed with the vector of claim 15.
 17. The host cell of claim 16, wherein the host cell is a bacterium, mammalian cell, yeast cell, plant cell, or an insect cell.
 18. A method of producing an antibody that binds to IL-22, comprising culturing the host cell of claim 17 under conditions that allow expression of the antibody, and isolating the antibody from the cell culture.
 19. A diagnostic kit comprising the antibody of any one of claims 1-11 and an additional component, packaging, instructions, or other material to help detect the IL-22 protein and use the kit.

**FIG. 1**

**FIG. 2A**

**FIG. 2B**

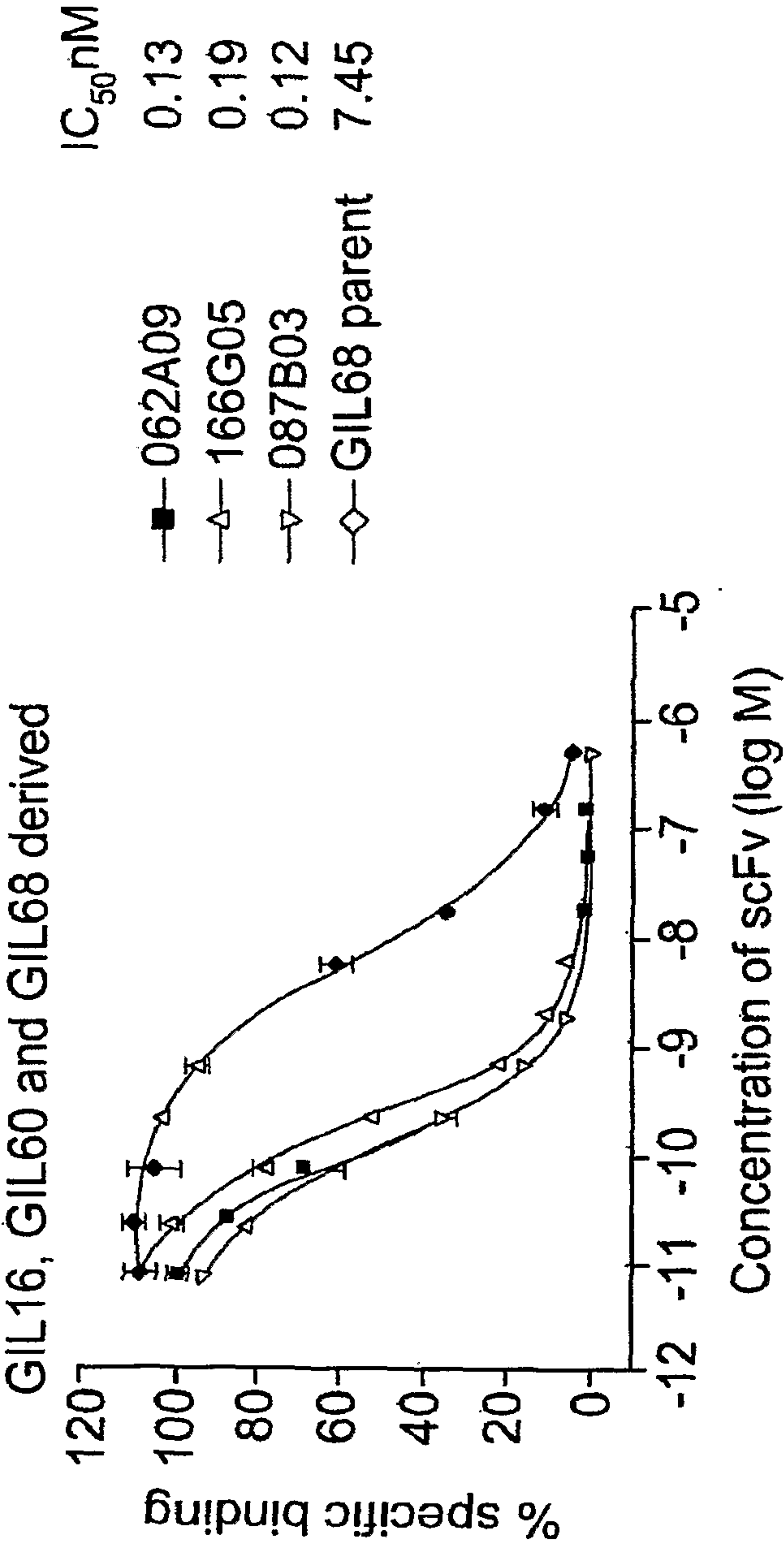
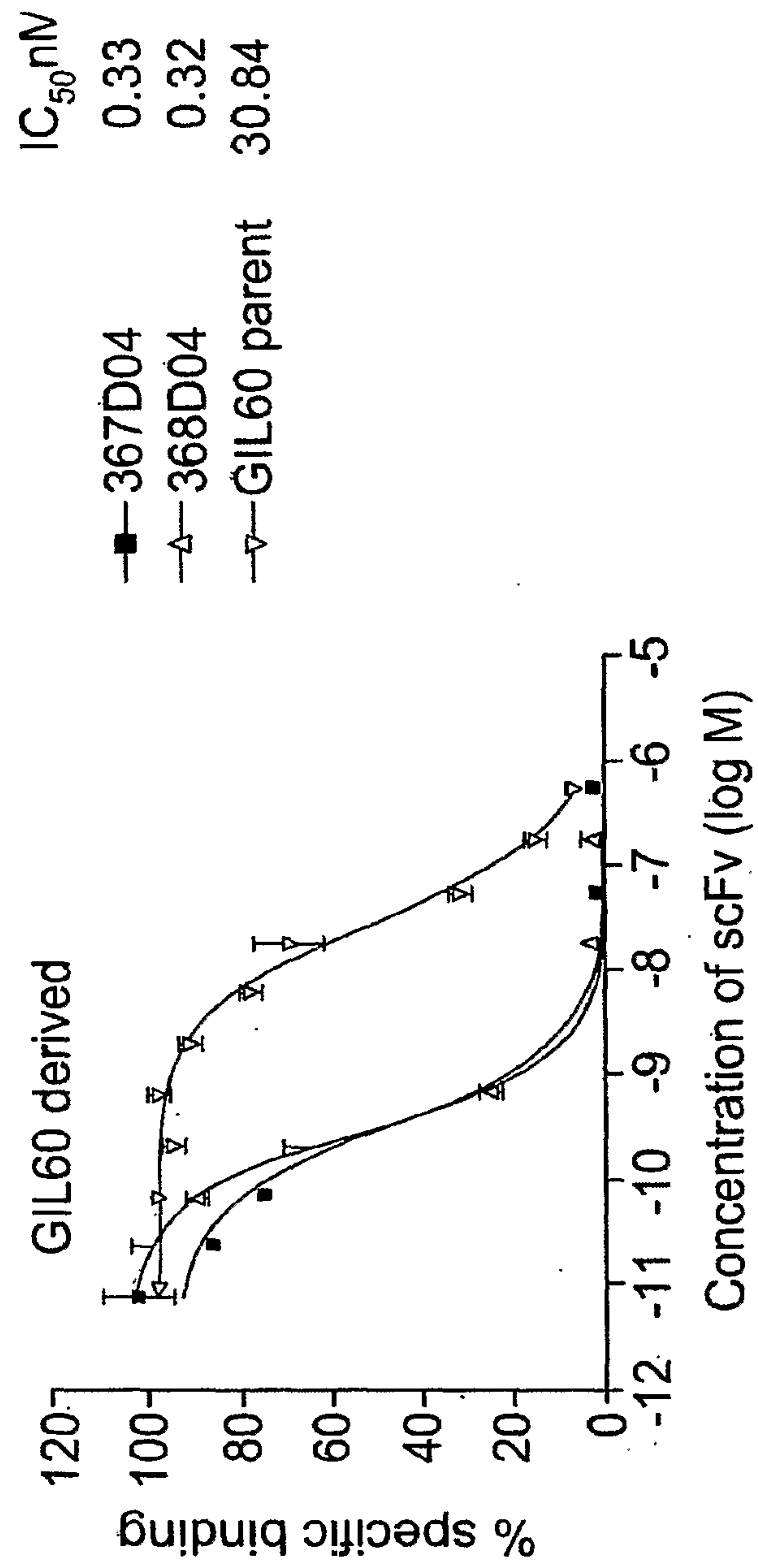


FIG. 2C

**FIG. 2D**

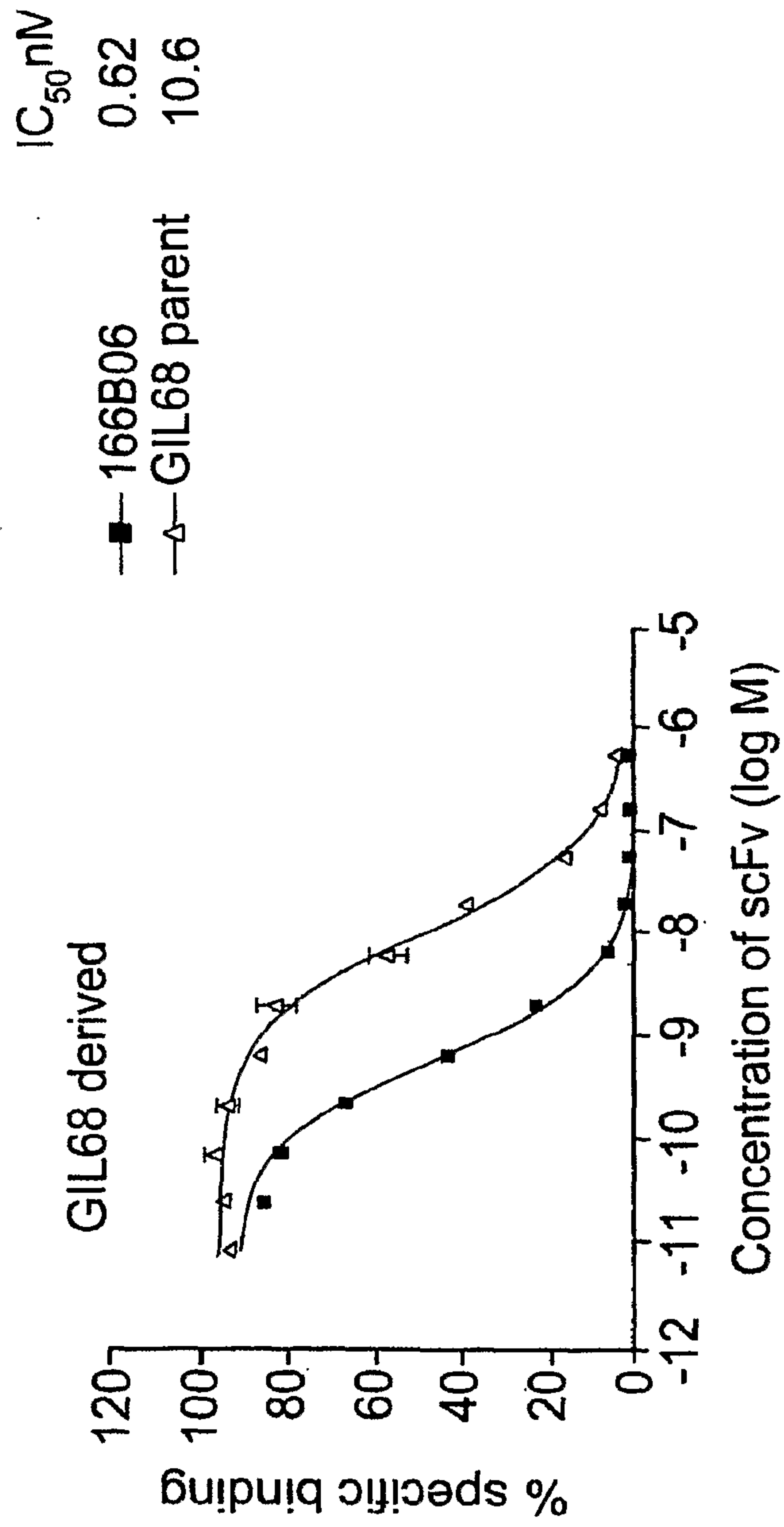
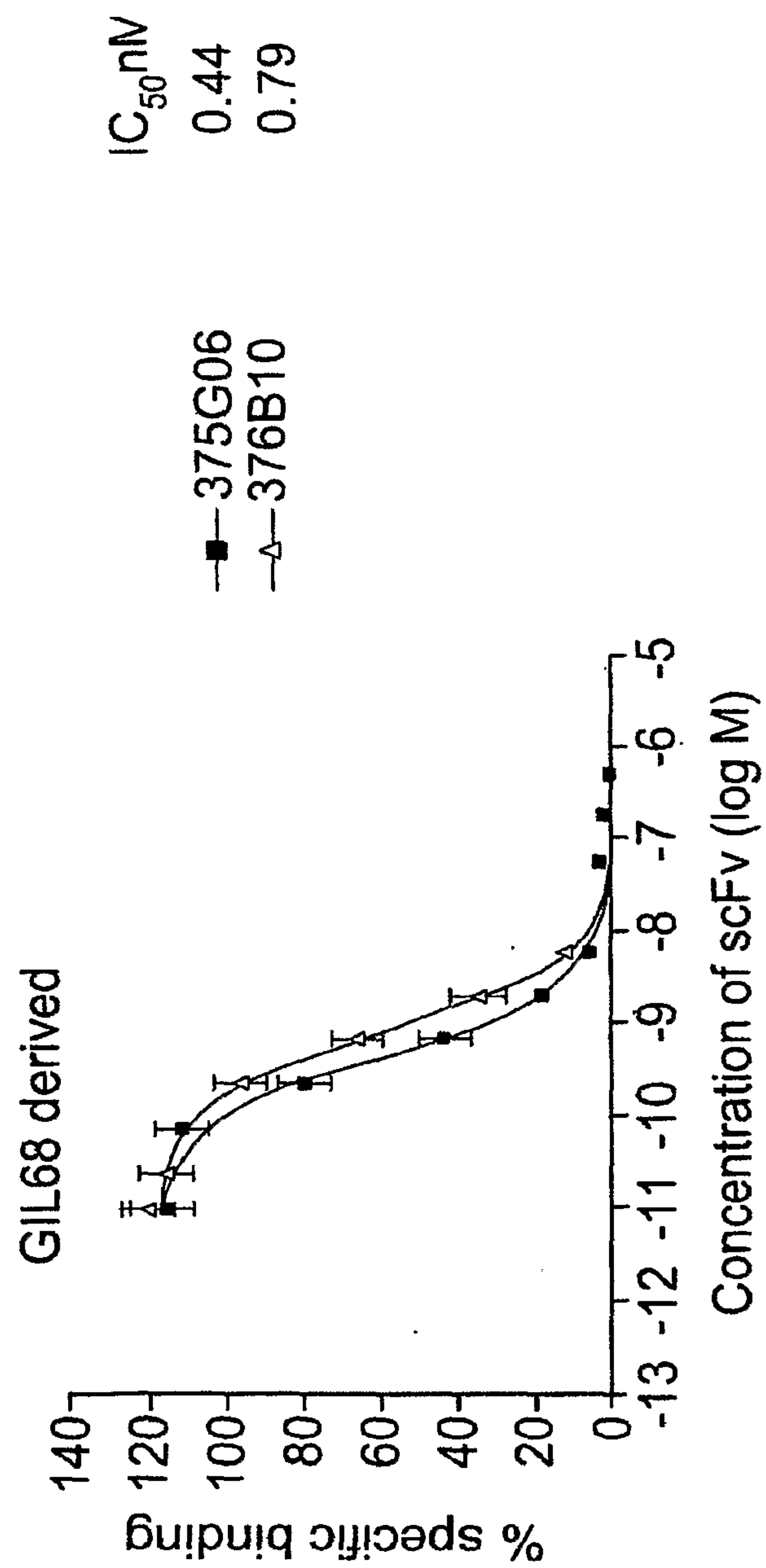
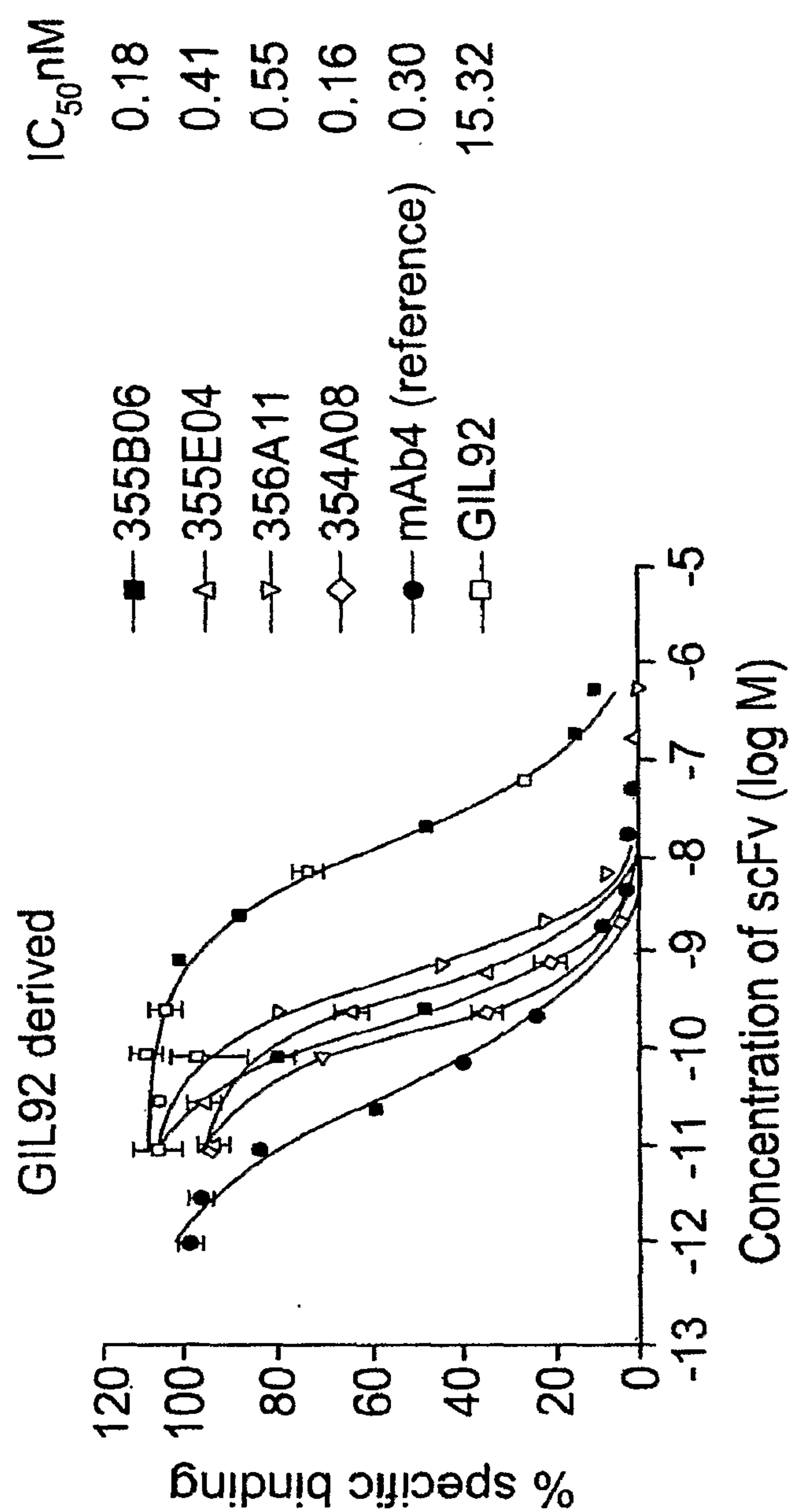


FIG. 2E

**FIG. 2F**

**FIG. 2G**

Germlined IgG

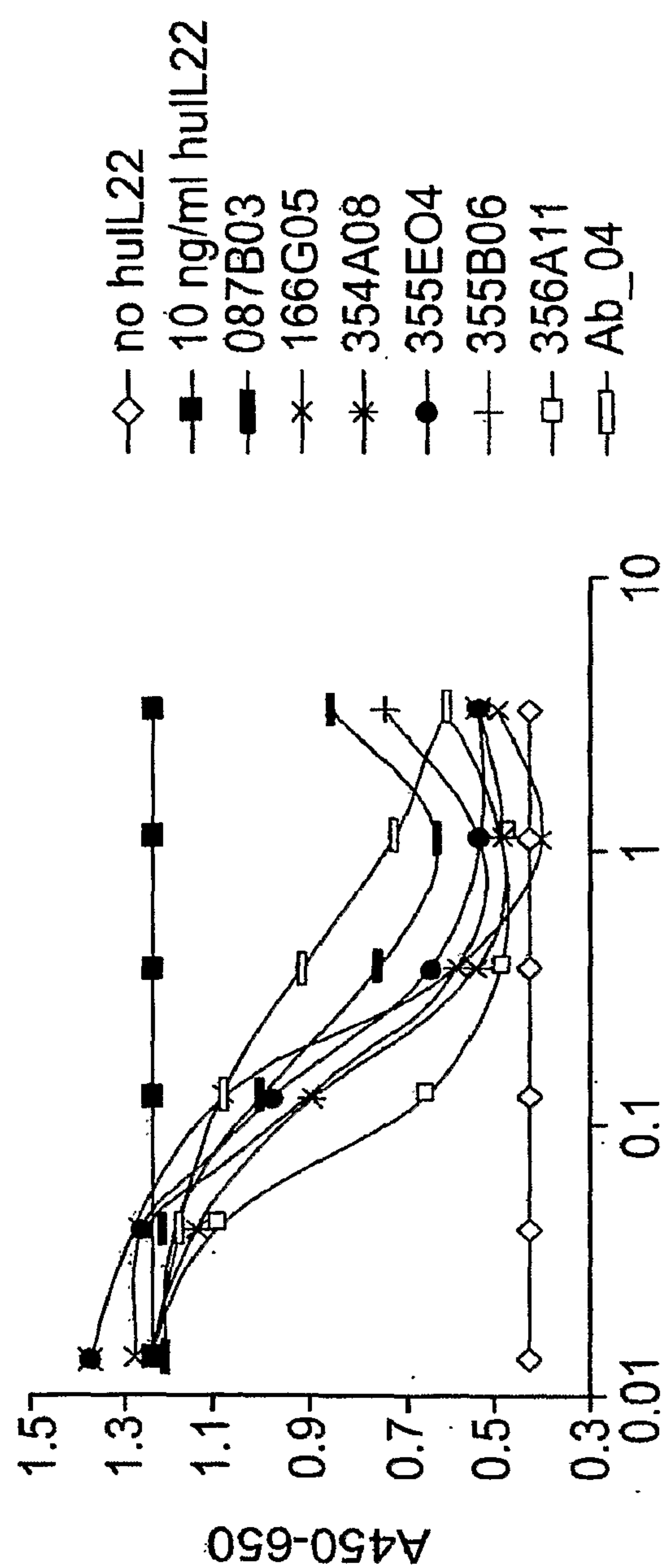
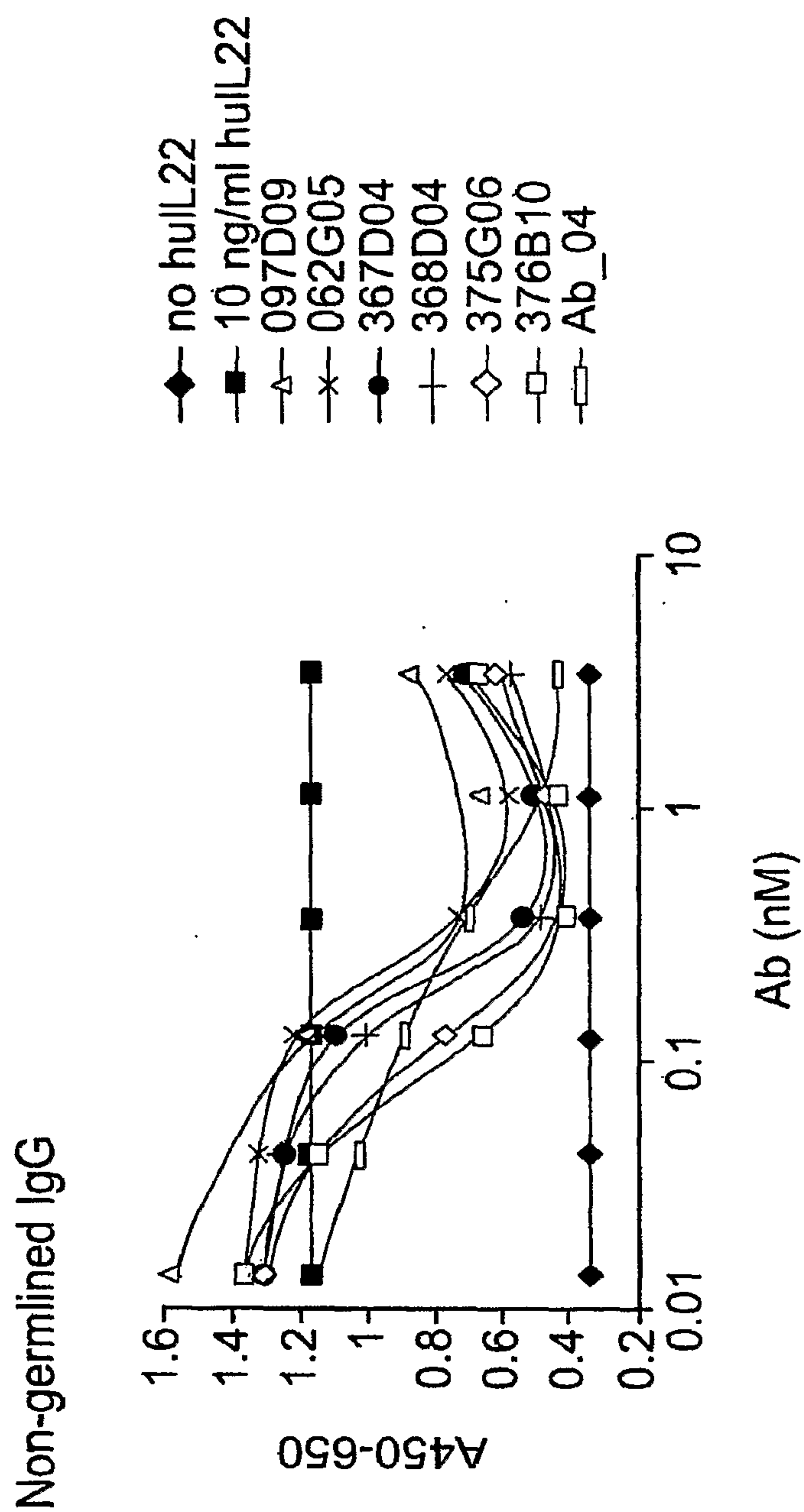


FIG. 3A

**FIG. 3B**

Germlined IgG

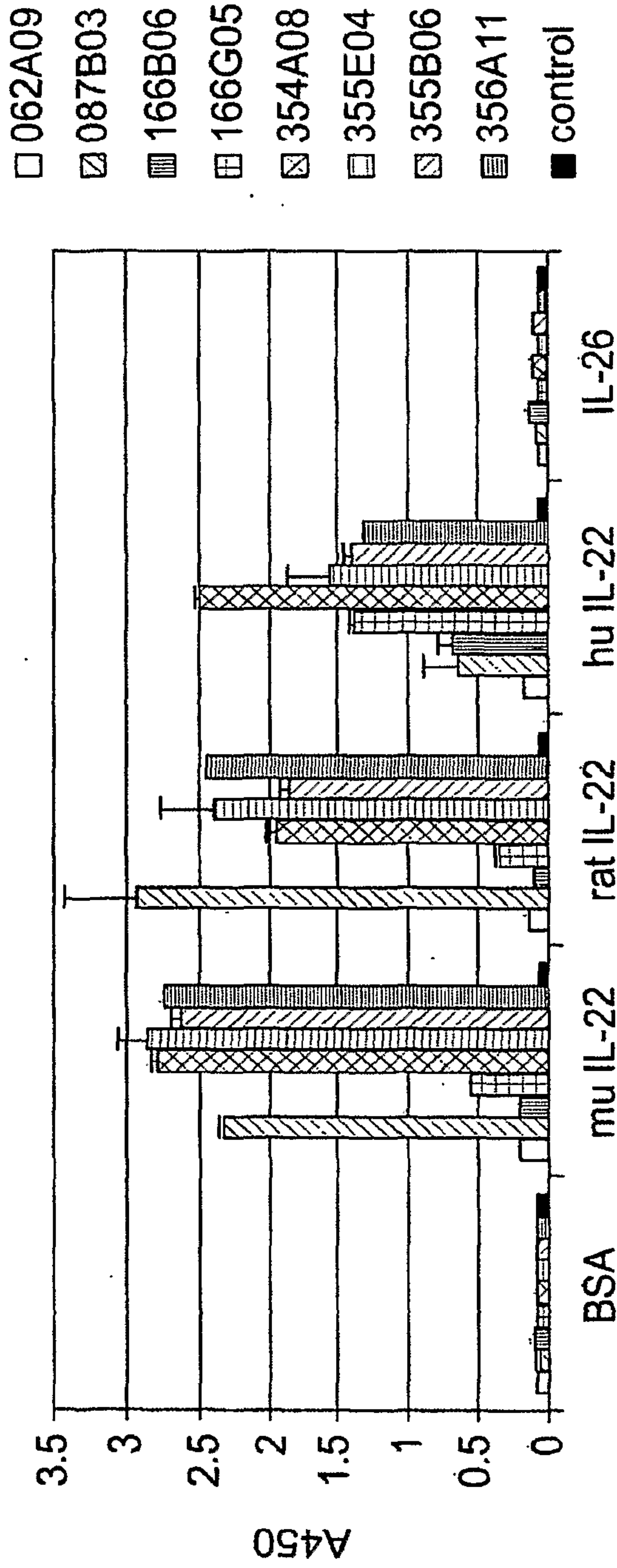


FIG. 4A

Non-Germlined IgG

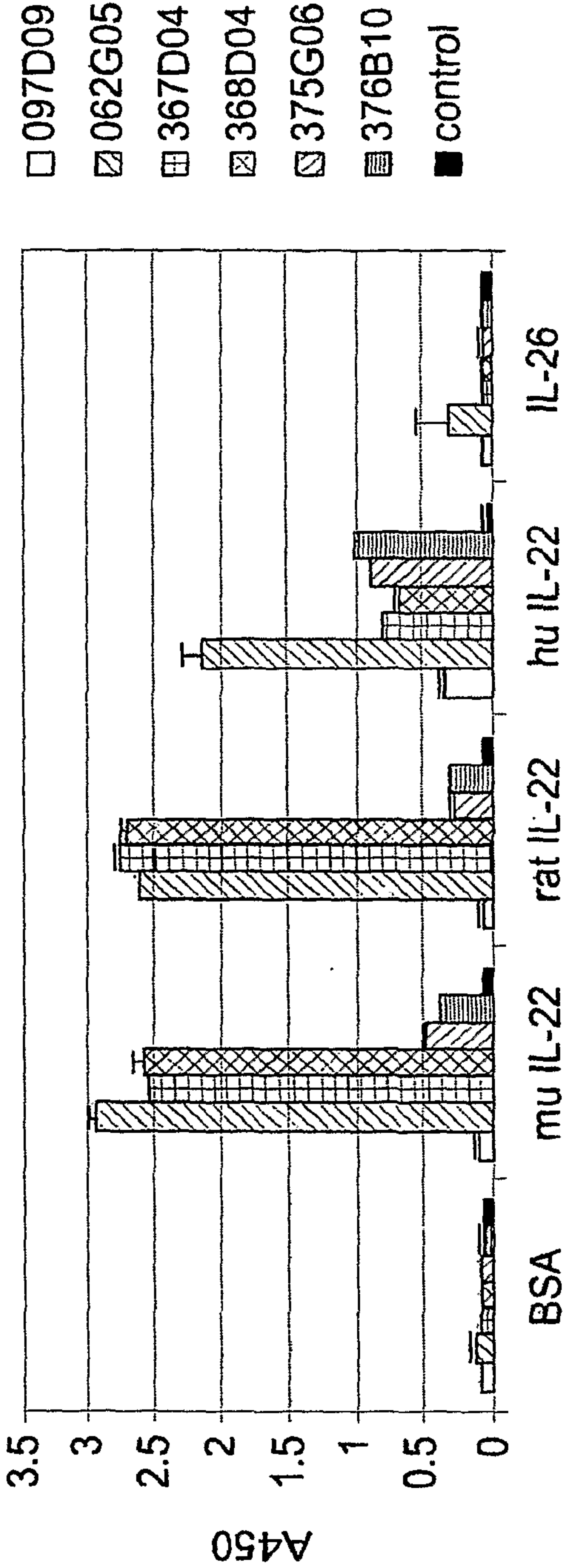


FIG. 4B

SEQ ID NO:1

1 MAALQKSVSS FLMGTLATSC LLLLALLVQG GAAAPISSHC RLDKSNFQQP
51 YITNRTFMLA KEASLADNNT DVRLIGEKLF HGVSMSERCY LMKQVLNFTL
101 EEVLFPQSDR FQPYMQEWPFLARLSNRLST CHIEGDDLHI QARNVQKLKD
151 TVKKLGESGE IKAIGELDLL FMSLRNACI

SEQ ID NO:2

1 GAATTCGGCC AAAGAGGCCT ACAGGTTCTC CTTCCCCAGT CACCAGTTGC
51 TCGAGTTAGA ATTGTCTGCA ATGGCCGCCC TGCAGAAATC TGTGAGCTCT
101 TTCCTTATGG GGACCCTGGC CACCAGCTGC CTCCTTCTCT TGGCCCTCTT
151 GGTACAGGGA GGAGCAGCTG CGCCCATCAG CTCCCAGTGC AGGCTTGACA
201 AGTCCAACCTT CCAGCAGCCC TATATCACCA ACCGCACCTT CATGCTGGCT
251 AAGGAGGCTA GCTTGGCTGA TAACAACACA GACGTTTCGTC TCATTGGGGA
301 GAAACTGTTC CACGGAGTCA GTATGAGTGA GCGCTGCTAT CTGATGAAGC
351 AGGTGCTGAA CTTCAACCCTT GAAGAAGTGC TGTTCCTCA ATCTGATAGG
401 TTCCAGCCTT ATATGCAGGA GGTGGTGCCC TTCCTGGCCA GGCTCAGCAA
451 CAGGCTAAGC ACATGTCATA TTGAAGGTGA TGACCTGCAT ATCCAGAGGA
501 ATGTGCAAAA GCTGAAGGAC ACAGTGAAAA AGCTTGGAGA GAGTGGAGAG
551 ATCAAAGCAA TTGGAGAACT GGATTGCTG TTTATGTCTC TGAGAAATGC
601 CTGCATTTGA CCAGAGCAAA GCTGAAAAAT GAATAACTAA CCCCTTTCC
651 CTGCTAGAAA TAACAATTAG ATGCCCAAAA GCGATTTTTT TTAACCAAAA
701 GGAAGATGGG AAGCCAACT CCATCATGAT GGGTGGATTC CAAATGAACC
751 CCTGCGTTAG TTACAAAGGA AACCAATGCC ACTTTTGTTT ATAAGACCAG
801 AAGGTAGACT TTCTAAGCAT AGATATTTAT TGATAACATT TCATTGTAAC
851 TGGTGTTCTA TACACAGAAA ACAATTTATT TTTTAAATAA TTGTCTTTTT
901 CCATAAAAAA GATTACTTTC CATTCCTTTA GGGGAAAAAA CCCCTAAATA
951 GCTTCATGTT TCCATAATCA GTACTTTATA TTTATAAATG TATTTATTAT
1001 TATTATAAGA CTGCATTTTA TTTATATCAT TTTATTAATA TGGATTTATT
1051 TATAGAAACA TCATTCGATA TTGCTACTTG AGTGTAAGGC TAATATTGAT
1101 ATTTATGACA ATAATTATAG AGCTATAACA TGTTTATTTG ACCTCAATAA
1151 AACTTGGAT ATCCTAAAAA AAAAAAAAAA AAAGCGGCCG C

FIG. 5

SEQ ID NO:3

MAVLQKSMSFSLMGTLAASCLLLIALWAQEANALPVNTRCKLEVS NFQOPYI
VNRTFMLAKEASLADNNTDVRLIGEKLF RGVSAKDQCYLMKQVLNFTLEDVL
LPQSDRFQPYMQEVVPFLTKLSNQLSSCHISGDDQNIQKNVRRLKETVKKLG
ESGEIKAIGELDLLFMSLRNACV

SEQ ID NO:4

ATGGCTGTCCTGCAGAAATCTATGAGTTTTTCCCTTATGGGGACTTTGGC
CGCCAGCTGCCTGCTTCTCATTGCCCTGTGGGCCCAGGAGGCAAATGCGC
TGCCCGTCAACACCCGGTGCAAGCTTGAGGTGTCCAACCTCCAGCAGCCG
TACATCGTCAACCGCACCTTTATGCTGGCCAAGGAGGCCAGCCTTGCAGA
TAACAACACAGACGTCCGGCTCATCGGGGAGAACTGTTCCGAGGAGTCA
GTGCTAAAGATCAGTGCTACCTGATGAAGCAGGTGCTCAACTTCACCCTG
GAAGACGTTCTGCTCCCCCAGTCAGACAGGTTCCAGCCCTACATGCAGGA
GGTGGTACCTTTCCTGACCAAACCTCAGCAATCAGCTCAGCTCCTGTCACA
TCAGCGGTGACGACCAGAACATCCAGAAGAATGTCAGAAGGCTGAAGGAG
ACAGTGAAAAAGCTTGGAGAGAGTGGAGAGATCAAGGCGATTGGGGAACT
GGACCTGCTGTTTATGTCTCTGAGAAATGCTTGCGTCTGA

FIG. 6

GIL01

V_H (SEQ ID NO:5) with H1, H2, and H3 underlined (SEQ ID NO:8-10, respectively)

E V Q L V E S G G L V T P G G S L R L S C A A S G F T F S
D Y Y M S W I R Q A P G R G L E W V S A I S G S G S T Y Y
A D S V K G R I T I S R D N A K N S L Y L Q M S S L R S E D
T A V Y Y C A R G L W V W D P L D Y W G R G T L V T V S S

V_H (SEQ ID NO:14) with H1, H2, and H3 underlined (SEQ ID NO:17-19, respectively)

GAGGTGAGTTGGTGGAGTCTGGGGGAGGCTTGGTCACGCCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCAACCTTCAGTGACTACTACATGAGCTGGATCCGCCAGGCTCCAGG
GAGGGGCTGGAGTGGTCTCAGCTATTAGTGGTAGTGGTAGCACATACTACGAGACTCCGTGAAGGGCGGATCACCATCTCCAGAGACAAACGCCAAGAACTCACTGTATCTGCAAAATGA
GCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGGCTTTGGGTTTGGGATCCTCTTGACTACTGGGCGAGAGGAACCTGGTCAACCGTCTCCTCA

V_L (SEQ ID NO:6) with L1, L2, and L3 underlined (SEQ ID NO:11-13, respectively)

D I Q M T Q S P S T L S A S I G D R V T I T C R A S E G I Y H
W L A W Y Q Q K P G K A P K L I Y K A S S L A S G A P S R F
S G S G S G T D F T L T I S S L Q P D D F A T Y Y C Q Q Y S N
Y P L T F G G G T K L E I K R

V_L (SEQ ID NO:15) with L1, L2, and L3 underlined (SEQ ID NO:20-22, respectively)

GACATCCAGATGACCCAGTCTCCTTCCACCCCTGTCTGCATCTATTGGAGACAGAGTCACCATCACCTGCCGGGCCAGTGAGGGTATTATCACTGGCTGGTATCAGCAGAAGCCAGG
GAAAGCCCTAAACTCCTGATCTATAAGGCCTCTAGTTAGCCAGTGGGGCCCCCATCAAGGTTCAAGGTCAGCGGCAGTGGATCTGGGACAGATTTCACCTCTCACCATCAGCAGCCTGCAGCCTGATG
ATTTTGCAACTTATTACTGCCAACAAATATAGTAATTATCCGCTCACTTTCGGCGGAGGACCAAGCTGGAGATCAAACGT

FIG. 7

GIL16

V_H (SEQ ID NO:23) with H1, H2, and H3 underlined (SEQ ID NO:26-28, respectively)

Q V Q L V E S G A E V K K P G A S V K V S C K A S G Y T F T S Y G I
S W V R Q A P G Q G L E W M G W I S A Y T G N T N Y A Q K F Q G R V
T M T D T S T S T A Y M E L R S L R S D D T A V Y Y C A R D R G Y
Y D A F D I W G Q G T L V T V S S

V_H (SEQ ID NO:32) with H1, H2, and H3 underlined (SEQ ID NO:35-37, respectively)

CAGGTGCAGCTGGTGGAGTCTGGAGCTGAGGTGAAGAAGCCCTGGGGCCTCAGTGAAGGCTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAGTTATGGIATC
AGCTGGGTGGACAGGCCCTGGACAAAGGCTTGAGTGGATGGATGCGCTTACACTGGTAACACAAACTATGCACAGAAAGTTCCAGGGCAGAGTC
ACCATGACCACAGACACATCCACGAGCACAGCCTACATGGAAGTGAAGGAGCCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGAGATCGTGGATAC
TATGATGCTTTTGATATCTGGGGCCAAAGGCACCCCTGGTCACCGTCTCCTCA

V_L (SEQ ID NO:24) with L1, L2, and L3 underlined (SEQ ID NO:29-31, respectively)

D I Q M T Q S P S T L S A S I G D R V T I T C R A S E G I Y H W L A
W Y Q Q K P G K A P K L L I Y K A S S L A S G A P S R F S G S G S G
T D F T L T I S S L Q P D D F A T Y Y C Q Q Y S N Y P L T F G G G T
K L E I K R

V_L (SEQ ID NO:33) with L1, L2, and L3 underlined (SEQ ID NO:38-40, respectively)

GACATCCAGATGACCCAGTCTCCTTCCACCCCTGTCTGCATCTATTGGAGACAGAGTCACCATCACCTGCCGGGCCAGTGAGGGTATTATCACCTGGTTGGCC
TGGTATCAGCAGAAGCCAGGAAAGCCCTAAACTCCTGATCTATAGGCCCTCTAGTTAGCCAGTGGGGCCCCCATCAAGGTTACCGGCAGTGGATCTGGG
ACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAACAATATAGTAATTATCCGCTCACTTTCGGCGGAGGACC
AAGCTGGAGATCAACGT

FIG. 7(cont.)

GIL45

V_H (SEQ ID NO:41) with H1, H2, and H3 underlined (SEQ ID NO:44-46, respectively)

Q M Q L V Q S G G G V V Q P G R S L R L S C A A S G F T F S N Y G M Y W V R Q
A P G K G L E W V A H I W Y D G S N E K Y A D S V K G R M T V S R D N S R N T
L Y L Q M N S L R A E D T A V Y Y C A T E Q H W I T A F D I W G K G T L V T V
S S

V_H (SEQ ID NO:50) with H1, H2, and H3 underlined (SEQ ID NO:53-55, respectively)

CAGATGCAGCTGGTGGGAGGCGTGGTCCAGCCTGGAGGTCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTAACATGGCATGTACTGGTCCGCCA
GGCTCCAGGCAAGGGCTGGAGTGGTGGCACATATTGGTATGATGGAAGTAATGAAAGTATGCAGACTCCGTGAAGGCCGAATGACCGTCTCCAGAGACAATTCAGGAACA
CGTTGTATTGCAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGGCAGAGACAACACTGGATTACTGCTTTTGATATCTGGGGCAAGCACCCCTGGTCACCGTCTCCTCA

V_L (SEQ ID NO:42) with L1, L2, and L3 underlined (SEQ ID NO:47-49, respectively)

Q S V L T Q P A S V S G S P G Q S I T I S C T G T S S D V G G Y N Y V S W Y Q
Q H P G K A P K L M I Y E G S K R P S G V S N R F S G S K S G N T A S L T I S
G L Q A E D E A D Y Y C S S Y T T R S T R V F G G G T K L T V L G

V_L (SEQ ID NO:51) with L1, L2, and L3 underlined (SEQ ID NO:56-58, respectively)

CAGTCTGTGCTAGCTCAGCCTGCCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCACCTGGAACACAGCAGTGACGTTGGTGGTTATAACTATGTCTCCTGGTACCA
ACAACACCCAGGCAAGCCCCCAACTCATGATTATGAGGGCAGTAAGCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACAAATCT
CTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACTGCAGCTCATATACAACCCAGGACACTCGAGTTTTCGGCGGAGGACCAAGCTGACCGTCCCTAGGT

FIG. 7(cont.)

GIL60

V_H (SEQ ID NO:59) with H1, H2, and H3 underlined (SEQ ID NO:62-64, respectively)

E V Q L V E S G G G V R P G G S L R L S C A A S G F T F D D Y G M N
W V R Q A P G K G L E W V S G V N W N G G T R D Y A A S V K G R F T I
S R D N A K N S L Y L Q M N S L R A E D T A L Y Y C A R G W Y S G S F
Y Y F G Y W G R G T L V T V S S

V_H (SEQ ID NO:68) with H1, H2, and H3 underlined (SEQ ID NO:71-73, respectively)

GAGGTGCAGCTGGTGGAGTCCGGGGAGGTGGTACGGCTGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTGACGATTATGGCATGAA
CTGGTCCGCAAGCTCCAGGGAAGGGTGGAGTGGTCTCTGGTGTAAATTGGAATGGTGACAGAGATTATGACGCTCCGTGAAGGCCGATTACACCA
TCTCCAGAGACAAAGCAAGAACTCCCTGTATCTGCAATGAACAGTCTGAGAGCCGAGACACGGCCTTGTTACTGTGCGAGAGGATGGTATAGTGGGAGC
TTCTACTACTTTGGCTACTGGGGCCGAGGAACCCCTGGTCACCGTCTCCTCA

V_L (SEQ ID NO:60) with L1, L2, and L3 underlined (SEQ ID NO:65-67, respectively)

Q A V L T Q P S S V S G S P G Q S I T I S C T G A S G D V G A Y N F V
S W Y Q Q H P P G K T P K L I I Y D V N K R P S G V S N R F S G S K S G
N T A S L T I S G L Q A E D E S D Y Y C S S Y T S T F S V V F G G G T
K V T V L G

V_L (SEQ ID NO:69) with L1, L2, and L3 underlined (SEQ ID NO:74-76, respectively)

CAGGCTGTGCTGACTCAGCCGTCCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCAGCTGGAGCCAGGGTGACGTTGGTGCTTATAACTTTGT
CTCCTGGTACCACAACACCCAGGCAAAACCCCAACTCATATTATGATGTCAATAAGCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTG
GCAACACGGCCTCCCTGACCATCTCTGGGTCCAGGCCGAGGACGAGTCTGATTATTACTGCAGCTCATATACAAGCACCTTCTCTGTGGTATTGGCGGAGGG
ACCAAGGTCACCGTCCCTAGGT

FIG. 7(cont.)

GIL68

V_H (SEQ ID NO:77) with H1, H2, and H3 underlined (SEQ ID NO:80-82, respectively)

E V Q L V Q S G A E V K K P G A S V K V S C Q A S G Y T F S D Y Y I H W V R Q T P G
Q G F E W M G W V N P D T G G T R Y A Q K F O G W V T M T R D M S N T T A Y M E L P
R L R D D T A V Y Y C A R D L T G F D P F D I W G Q G T L V T V S S

V_H (SEQ ID NO:86) with H1, H2, and H3 underlined (SEQ ID NO:89-91, respectively)

GAGGTGCAGCTGGTGCAGTCTGGGGCTGAGTGAAGAAGCCTGGGGCTCAGTGAAGTCTCCTGTTCAGGCTTCTGGATACACCTTCAGCGATTACTATATTCACITGGTGCGACAGACCCCTGGA
CAAGGGTTGAGTGGATGGATGGGTCAACCTGACACTGGTGGCACAAGATACGGCAGAGTTTCAGGGCTGGGTCAATGACACAGGACATGTCCAACACACAGCCTACATGGAGCTGCCCC
AGGCTGAGAGACGACGACGCGCGTATATTACTGTGCGAGAGATCTAACTGGATTGTGATCCTTTTGATATCTGGGGCCAGGGAACCCCTGGTCACCGTCTCCTCA

V_L (SEQ ID NO:78) with L1, L2, and L3 underlined (SEQ ID NO:83-85, respectively)

Q S V L T Q P P S V S V A P G K T A T I T C G G N N F R N K R V H W Y Q Q R P G Q A
P V L V I Y Y D S D R P S G I P E R F S G S R S G N T A T L T I S R V E A G D E A D
F Y C Q V W D S S T D R P L F G G G T K L T V L G

V_L (SEQ ID NO:87) with L1, L2, and L3 underlined (SEQ ID NO:92-94, respectively)

CAGTCIGTGTGACTCAGCCACCCCTCAGTGTGAGTGGCCCCAGGAAGACGGCCACGATTACCTGTGGGGAAACAACACTTCGAAATAAAGAGTACACTGGTATCAGCAGAGGCCAGGCCAGG
CCCCTGCTCTGATCTATTATGATTGATTCAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCCGTCTGTGGGAACACGGCCACCCCTGACCATCAGCAGGGTCCGAGGCCGGGATGAGGC
CGACTTTTACTGTCAGGTGTGGGATAGTAGTACTGATCGTCCGCTGTTCGGCGGAGGACCAAGCTGACCCGTCCTAGGT

FIG. 7(cont.)

GIL92

V_H (SEQ ID NO:95) with H1, H2, and H3 underlined (SEQ ID NO:98-100, respectively)

Q V Q L V Q S G A E V K K P G A S V K V S C K A S G Y T F T D Y Y
M H W V R Q Q A P G Q G L E W V G W I N P Y T G G A F Y A O K F R G
R V T M T R D T S I N T A Y M E L S R L G S D D T A V Y Y C A R E
P E K F D F W G G D N W G R G T M V T V S S

V_H (SEQ ID NO:104) with H1, H2, and H3 underlined (SEQ ID NO:107-109, respectively)

CAGGTCAGCTGCTGAGTCTGGGCTGAGGTGAAGAAGCCTGGGCCCTCAGTGAAGTCTCCTGCAAGGCTTCTGGATACACCTTCACCGACTACTA
TATGCACTGGTGGACAGGCCCTGGACAAGGCTTGAGTGGTGATCAACCTTATCTGCTGGCGCATCTATGCACAGAAAGTTTCGGG
GCAGGTCACAAATGACAGGACACGTCCATCAACACAGCCTACATGAGCTGAGCAGACTGGGATCTGACGACACGGCCGTGTATTATTGTGCGGAGA
GAACCTGAAAAATTCGATTTTGGGGGGTGACAACTGGGGCGGGGACAATGGTCACCGTCTCTCTCA

V_L (SEQ ID NO:96) with L1, L2, and L3 underlined (SEQ ID NO:101-103, respectively)

Q A V L T Q P S S V S G A P G Q R V T I S C T G S S S N I G A G Y
G V H W Y Q Q L P G T A P K L L I Y G N S N R P S G V P D R F S G
S K S G T S A S L A I T G L Q A E D E A D Y Y C Q S Y D S S L S G
Y V F G T G T Q L L T V L G

V_L (SEQ ID NO:105) with L1, L2, and L3 underlined (SEQ ID NO:110-112, respectively)

CAGGCTGTGCTGACTCAGCCGTCCTCAGTGTCTGGGGCCCCAGGCAGAGGTCACCATCTCCTGCACTGGGAGCAGCTCCAACATCGGGGCAGGTTA
TGGGTACACTGGTACCACAGCTTCCAGGAACAGCCCCCAAACCTCATCTATGGTACAGCAATCGGCCCTCAGGGGTCCCTGACCGATTCTCTG
GCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCAGTGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCCAGTCTCTATGACAGCAGCCTGAGT
GGTTATGCTTCGGAACCTGGGACCCAGCTCACCGTCTCTAGGT

FIG. 7 (cont.)

097D09

V_H (SEQ ID NO:113) with H1, H2, and H3 underlined (SEQ ID NO:116-118, respectively)

E V Q L V E S G G G L V T P G G S L R L S C A A S G F T F S D Y Y M
S W V R Q A P G R G L E W V S A I S G S G S T Y Y A D S V K G R I
T I S R D N A K N S L Y L Q M S S L R S E D T A V Y Y C A R G L W V
W D P L D Y W G R G T L V T V S S

V_H (SEQ ID NO:122) with H1, H2, and H3 underlined (SEQ ID NO:125-127, respectively)

GAGGTGCAGCTGGTGGAGCTGGGGAGGCTTGGTCACGCCCTGGAGGTCCTCTGAGACTCTCCTGTGCAGCCTCTGGATTACACCTTCAGTGACTACTACATG
AGCTGGTCCGCCAGGCTCCAGGGAGGGGCTGGAGTGGTCTCAGCTATTAGTGGTAGTGGTAGCACATATACTACGAGACTCCGTGAAGGCCGGATC
ACCATCTCCAGAGACACGCCAAGAACTCACTGTATCTGCAATGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGGCTTTGSGTT
TGGGATCCTCTTGACTACTGGGCAGAGAACCTGTGTCACCGTCTCCTCA

V_L (SEQ ID NO:114) with L1, L2, and L3 underlined (SEQ ID NO:119-121, respectively)

D I Q M T Q S P S T L S A S I G D R V T I T C R A S E G I Y H W L A
W Y Q Q K P G K A P K L L I Y K A S S L A S G A P S R F S G S G F G
T D F T L T I S S L Q P D D F A T Y Y C Q O Y S E F A W T F G G G T
K L E I K R

V_L (SEQ ID NO:123) with L1, L2, and L3 underlined (SEQ ID NO:128-130, respectively)

GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTATTGGAGACAGAGTCACCATCACCTGCCGGGCCAGTGAGGGTATTATCAGTGGTTGGCC
TGGTATCAGCAGAGCCAGGAAAGCCCCTAACTCCTGATCTATAAGGCCCTCTAGTTAGCCAGTGGGGCCCCCATCAAGTTTCAGCGGCAGTGGATTGGG
ACCGATTTCACCTCACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAACAAATACAGCGAGTTCGCCCTGGACCTTCGGCGGAGGACC
AAGCTGGAGATCAACGTF

FIG. 7(cont.)

062A09

V_H (SEQ ID NO:131) with H1, H2, and H3 underlined (SEQ ID NO:134-136, respectively)

Q V Q L V E S G A E V K K P G A S V K V S C K A S G Y T F T S Y G I
S W V R Q A P G Q G L E W M G W V S A Y T G N T N Y A O K F O G R V
 T M T T D T S T S T A Y M E L R G L R S D D T A V Y Y C A R D R G Y
Y D A F D I W G Q G T L V T V S S

V_H (SEQ ID NO:84) with H1, H2, and H3 underlined (SEQ ID NO:143-145, respectively)

AGGTGCAGCTGGTGGAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCTCAGTGAAGGCTTCTGGTTACACCTTTACCAGTTATGGTATCA
GCTGGTGGACAGGCCCTGGACAGGGCTTGAGTGGATGGGATGGGCTTACACTGGTAACACAACTATGCACAGAAGTCCAGGGCAGAGTCA
 CCATGACCACAGACATCCACGACAGCCTACATGAAGTGAAGGCTGAGATCTGACGACACGGCGTGATTTACTGTGCGAGAGATCGTGGATACT
ATGATGCTTTTGATATCTGGGGCCAGGCACCCCTGGTCACCGTCTCTCA

L (SEQ ID NO:132) with L1, L2, and L3 underlined (SEQ ID NO:137-139, respectively)

I Q M T Q S P S T L S A S I G D R V T I T C R A S E G I Y H W L A W
 Y Q Q K P G K A P K L L I Y K A S S L A S G A P S R F S G S G F G T
 D F T L T I S S L Q P D D F A T Y Y C Q Q M G E Y N A T I G G G T K
 L E I K R

L (SEQ ID NO:141) with L1, L2, and L3 underlined (SEQ ID NO:146-148, respectively)

ACATCCAGATGACCCAGTCTCCTTCCACCCCTGCTGCATCTATTGGAGACAGATCACCATCCTGCCGGGCCAGTGAGGGTATTATCACTGGTTGGCCT
 GGATCAGCAGAAGCCAGGGAAGCCCTAAACTCCTGATCTATAAGGCCCTCTAGTTTAGCCAGTGGGGCCCCCATCAAGGTTCAAGCGCAGTGGATTGGGA
 CAGATTTCACCTCACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAACAAATGGGGCGAGTACAACGCCCATCGGGCGAGGGACCA
 AGCTGGAGATCAACCGT

FIG. 7(cont.)

062G05

V_H (SEQ ID NO:149) with H1, H2, and H3 underlined (SEQ ID NO:152-154, respectively)

Q V Q L V E S G A E V K K P G A S V K V S C K A S G Y T F T S Y G I S
W V R Q A P G Q G L E W M G W I S A Y T G N T N Y A O K F O G R V T M
T T D T S T S T A Y M E L R S L R S D D T A V Y Y C A R D R G Y Y D A
F D I W G Q G T L V T V S S

V_H (SEQ ID NO:158) with H1, H2, and H3 underlined (SEQ ID NO:161-163, respectively)

CAGGTGCAGCTGGTGGAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAAGTTATGGTATCAGC
TGGGTCCGACAGGCCCTGGACAAGGCTTGAGTGGATGGGATGGATCAGCGCTTACACTGGTAACACA AACTATGCACAGAAGTTCACAGGGCAGAGTCACCATG
ACCACAGACACATCCACGAGCACAGCCCTACATGGAACTGAGGAGCCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGAGATCGTGGATACTATGATGCT
TTCGATATCTGGGGCCAGGCACCCCTGGTCACCGTCTCTCA

V_L (SEQ ID NO:150) with L1, L2, and L3 underlined (SEQ ID NO:155-157, respectively)

D I Q M T Q S P S T L S A S I G D R V T I T C R A S E G I Y H W L A W
Y Q Q K P G K A P K L L I Y K A S S L A S G A P S R F S G S G F G T D
F T L T I S S L Q P D D F A T Y Y C O O M G E W K A A F G G G T K L E
I K R

V_L (SEQ ID NO:159) with L1, L2, and L3 underlined (SEQ ID NO:164-166, respectively)

GACATCCAGATGACCCAGTCTCCTCCACCCTGTCTGCACTATTGGAGACAGAGTCACCATCACCTGCCGGCCAGTGAGGGTATTATCACTGGTTGGCCTGG
TATCAGCAGAGCCAGGGAAAGCCCTAACTCCTGATCTATAAGGCCTCTAGTTAGCCAGTGGGCCCCCATCAAGTTACGCGGCAGTGGATTTCGGGACAGAT
TTCACCTCTCACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTCTCCCAACAATGGGGAGTGGAGGGCCCTTCGGCGGAGGGACCAAGCTGGAGATCAACCGT

FIG. 7(cont.)

087B03

V_H (SEQ ID NO:167) with H1, H2, and H3 underlined (SEQ ID NO:170-172, respectively)

E V Q L V E S G G G V R P G G S L R L S C A A S G F T F D D Y G M N
W V R Q A P G K G L E W V S G V N W N G G T R D Y A A S V K G R F T I
S R D N A K N S L Y L Q M N S L R A E D T A L Y Y C A R G W Y S G A A
W N M G Y W G R G T L V T V S S

V_H (SEQ ID NO:176) with H1, H2, and H3 underlined (SEQ ID NO:179-181, respectively)

GAGTGCAGCTGGTGGAGTCCGGGGAGGTGTGGTACGGCCCTGGGGGTCCCTGAGACCTCTCTGTCAGCCTCTGGATTACACCTTTGACGATTATGGCATGAAC
TGGTCCGCCAAGCTCCAGGAAGGGCTGGAGTGGTCTCTGGTGTAAATTGGAATGTTGTACAGAGATTATGCAGCCTCCGTGAAGGCCGATTACCATC
TCCAGAGACAACGCCAAGAACTCCCTGTATCTGCAATGAACAGTCTGAGAGCCGAGACACGGCCTTGTTACTGTGCGAGAGGATGGTATAGTGGGGCCGCG
TGGAACATGGGCTACTGGGGCCGAGGAACCCCTGGTCACCGTCTCTCA

V_L (SEQ ID NO:168) with L1, L2, and L3 underlined (SEQ ID NO:173-175, respectively)

Q A V L T Q P S S V S G S P G Q S I T I S C T G A S G D V G A Y N F V
S W Y Q Q H P G K T P K L I I Y D V N K R P S G V S N R F S G S K S S
N T A S L T I S G L Q A E D E S D Y Y C S S Y T S T F S V V F G G G T
K V T V L G

V_L (SEQ ID NO:177) with L1, L2, and L3 underlined (SEQ ID NO:182-184, respectively)

CAGGCTGTGCTGACTCAGCCGTCCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCACTGGAGCCAGCGGTGACGTGGTGGCTTATAACTTTGTC
TCCTGGTACCAACAACAGCCAGGCAAAACCCCAACTCATAATTATGATGTCAATAAGCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTAGC
AACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCCGAGGAGTCTGATTATTACTGCAGCTCATATACAAGCACCTTCTCTGTGGTATTTGGCGGAGGGACC
AAGTCACCGTCCCTAGGT

FIG. 7(cont.)

367D04

V_H (SEQ ID NO:185) with H1, H2, and H3 underlined (SEQ ID NO:188-190, respectively)

E V Q L V E S G G V R P G G S L R L S C A A S G F T F D D Y G M N W V
R Q A P G K G L E W V S G V N W N G G T R D Y A A S V K G R F T I S R D N
A K N S L Y L Q M N S L R A E D T A L Y Y C A R G W Y S G S P W S L G H W
G R G T L V T V S S

V_H (SEQ ID NO:194) with H1, H2, and H3 underlined (SEQ ID NO:197-199, respectively)

GAGGTGAGCTGGTGGAGTCCGGGGGAGGTGTGGTACGGCTGGGGGTCCCTGAGACTCTCCTGTGCAGCCCTCTGGATTACCTTTGACGATTATGGCATGAAGTGGGT
CCGCCAAGCTCCAGGAAGGGCTGGAGTGGTCTCTGGTGTAAATTGGAATGGTGATACAGAGATTATGCAGCTCCGTGAAGGGCCGATTACCATCTCCAGAGACA
ACGCCAAGAACTCCCTGTATCTGCAATGAACAGTCTGAGAGCCGAGGACACGGCTTGTATTACTGTGCGAGAGGATGGTATAGTGGAGCCCGTGGTGGTGGCCAC
TGGGGCCGAGGAACCTGGTCAACCTCTCTCA

V_L (SEQ ID NO:186) with L1, L2, and L3 underlined (SEQ ID NO:191-193, respectively)

Q A V L T Q P S S V S G S P G Q S V T I S C T G A S G D V G A Y N F V S W
Y Q Q H P G K T P K L I I Y D V N K R P S G V S N R F S G S K S G N T A S
L T I S R L Q A E D E S D Y Y C S S Y T S R Y T E F G G G T K V T V L G

V_L (SEQ ID NO:195) with L1, L2, and L3 underlined (SEQ ID NO:200-202, respectively)

CAGGTGTGCTGACTCAGCCGTCTCCGTGTCTGGTCTCCTGGACAGTCCGTCAACCATCTCCTGCACCTGGAGCCAGCGGTGACGTTGGTGGTCTTATAACTTTGTCTCTCTG
GTACCAACAACACCCAGGCAAAACCCCAACTCATAATTTATGATGTCAATAAGCGGCCCTCAGGGGTTCTAATCGCTTCTCTGGCTCCCAAGTCTGGCAACACGGCCT
CCCTGACCATCTCTAGGCTCCAGGCCGAGGACGAGTCTGATTATTACTGCAGCTCATATACATCGAGGTACACGACCGAGTTGGCGGAGGACCAAGGTCACCGTCTCTAGGT

FIG. 7(cont.)

368D04

V_H (SEQ ID NO:203) with H1, H2, and H3 underlined (SEQ ID NO:206-208, respectively)

E V Q L V E S G G G V P G G S L R L S C A A S G F T F D D Y G M N W
V R Q A P G K G L E W V S G V N W N G G T R D Y A A S V K G R F T I S R
D N A K N S L Y L Q M N S L R A E D T A L Y Y C A R G W Y S G A A W N M
G Y W G R G T L V T V S S

V_H (SEQ ID NO:212) with H1, H2, and H3 underlined (SEQ ID NO:215-217, respectively)

GAGGTGCAGCTGGTGGAGTCCGGGGGAGGTGTGGTACGGCCTGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACACCTTTGACGATTATGGCATGAAC TG
GGTCCGCCAAGCTCCAGGAAGGGCTGGAGTGGGTCTCTGGTGTAAATTGGAATGGTGTACCCAGAGATTATGCAGCCTCCGTGAAGGCCGATTACACCATCTCCA
GAGACAAGCCCAAGAACTCCCTGTATCTGCAAAATGAACAGTCTGAGAGCCGAGGACACGGCCTTGTTACTGTGCGAGAGGATGGTATAGTGGGCCCGGTGGAAC
ATGGGCTACTGGGGCCGAGGAACCTGGTCACCGTCTCCTCA

V_L (SEQ ID NO:204) with L1, L2, and L3 underlined (SEQ ID NO:209-211, respectively)

Q A V L T Q P S S V S G S P G Q S I T I S C T G A S G D V G A Y N F V S
W Y Q Q H P G K T P K L I I Y D V N K R P S G V S N R F S G S K S G N T
A S L T I S G L Q A E D E S D Y Y C A S L V S D F S V V F G G G T K V T
V L G

V_L (SEQ ID NO:213) with L1, L2, and L3 underlined (SEQ ID NO:218-220, respectively)

CAGGCTGTGCTGACTCAGCCGTCCTCGTGTCTGGTCCCTGGACAGTCGATCACCATCTCCTGCACCTGGAGCCAGCGGTGACGTTGGTCTTATAACTTTGTCTC
CTGGTACCAACAACCCAGGCAAAACCCCAACTCATATTATGATGTCATAAAGCGGCCCTCAGGGGTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACA
CGGCCTCCCTGACCAATCTCTGGCTCCAGGCGGAGGACGAGTCTGATTATTACTGCGCCTCCCTGCTCCGACTTCTCTGTGGTATTGGCGGAGGACCAAGTCAACCGTCTTAGGT

FIG. 7(cont.)

166B06

V_H (SEQ ID NO:221) with H1, H2, and H3 underlined (SEQ ID NO:224-226, respectively)

E V Q L V Q S G A E V K K P G A S V K V S C Q A S G Y T F S D Y Y I H W
V R Q T P G Q G F E W M G W V N P D T G G T R Y A Q K F O G W V T M T R
D M S N T T A Y M E L P R L R D D T A V Y Y C A R D L T G F D P F D I
W G Q G T L V T V S S

V_H (SEQ ID NO:230) with H1, H2, and H3 underlined (SEQ ID NO:233-235, respectively)

GAGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCTCAGTGAAGGTCTCCTGTCAAGCTTCTGGATACACCTTCAGCGATTACTATATTCACTG
GGTGGACACAGCCCTGGACAGGGTTTGAGTGGATGGGTCAAGCTGACACTGGTGGCACAGATACGGCAGAGTTTCAGGGCTGGGTACAAATGACCA
GGGACATGTCCAACACACAGCTACATGGAGCTGCCAGGCTGAGAGACGACACGGCGTATATTACTGTGCGAGAGATCTAACTGGATTGATCCTTTTGAT
ATCTGGGGCCAGGGAACCCCTGGTCACCGTCTCCTCA

V_L (SEQ ID NO:222) with L1, L2, and L3 underlined (SEQ ID NO:227-229, respectively)

Q S V L T Q P P S V S V A P G K T A T I T C G G N N F R N K R V H W Y Q
Q R P G Q A P V L V I Y Y D S D R P S G I P E R F S G S R S G N T A T L
T I S R V E A G D E A D F Y C Q V W D L F N D N G V F G G T K L T V L
G

V_L (SEQ ID NO:231) with L1, L2, and L3 underlined (SEQ ID NO:236-238, respectively)

CAGTCTGTGCTGACTCAGCCACCCCTCAGTGTGAGTGGCCAGGAAGACGGCCACGATTACCTGTGGGGAAACAACCTTCGAAATAAAGAGTACACTGGTATCA
GCAGAGGCCAGGCCCCCTGTCTGTGTATATGACTCAGACCGGCCCTCAGGATCCCTGAGCGATTCTCTGGCTCCCGCTCTGGGAACACGGCCACCC
TGACCATCAGCGGTGAGCGCGGGATGAGCCGACTTTTACTGTCAAGGTGTGGGATCTCTTCAACGACAAACGGCGGTTCGGCGGAGGGACCAAGCTGACCGTCTCTAGGT

FIG. 7(cont.)

166G05

V_H (SEQ ID NO:239) with H1, H2, and H3 underlined (SEQ ID NO:242-244, respectively)

E V Q L V Q S G A E V K K P G A S V K V S C Q A S G Y T F S D Y Y I H W V
R Q T P G Q G F E W M G W V N P D T G G T R Y A Q K F Q G W V T M T R D M
S N T T A Y M E L P R L R D D D T A V Y Y C A R D L T G F D P F D I W G Q
G T L V T V S S

V_H (SEQ ID NO:248) with H1, H2, and H3 underlined (SEQ ID NO:251-253, respectively)

GAGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGCTCAGTGAAGTCTCCTGTCTCAGGCTTCTGGATACACCTTCAGCGATTACTATCTACTGGGT
GGACAGACCCCTGGACAAGGTTTGAGTGGATGGGATGGTCAACCTGACACTGGTGGCACAAGATACGGCGCAGAAGTTTCAGGGCTGGGTCAACAATGACCAAGGACA
TGTCACAACACACAGCCTACATGGAGCTGCCAGGCTGAGAGACGACACGCGGTATATTACTGTGCGAGAGATCTAACTGGATTGATCCTTTTGATATCTGGGGC
CAGGAACCTGGTCACCGTCTCTCA

V_L (SEQ ID NO:240) with L1, L2, and L3 underlined (SEQ ID NO:245-247, respectively)

Q S V L T Q P P S V S V A P G K T A T I T C G G N N F R N K R V H W Y Q Q
R P G Q A P V L V I Y Y D S D R P S G I P E R F S G S R S G N T A T L T I
S R V E A G D E A D F Y C Q V W D F L T D S G S F G G G T K L T V L G

V_L (SEQ ID NO:249) with L1, L2, and L3 underlined (SEQ ID NO:254-256, respectively)

CAGTCTGTGCTGACTCAGCCACCCCTCAGTGTCTCAGTGGCCCCAGGAAGACGGCCACAATTACCTGTGGGGGAACAACCTTCGAAATAAAGAGTACACTGGTATCAGCA
GAGCCAGGCCAGGCCCTGTCTGTGTCATCTATATGATTCAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCCGCTCTGGGAACACGGCCACCCCTGACCA
TCAGCAGGTCTGAGCCGGGATGAGCCGACTTTTACTGTCTCAGGTGTGGGATTTCTTCAACCGACTCGGGGTCTTCGGCGGAGGACCAAGCTGACCGTCTTAGGT

FIG. 7(cont.)

375G06

V_H (SEQ ID NO:257) with H1, H2, and H3 underlined (SEQ ID NO:260-262, respectively)

E V Q L V Q S G A E V K K P G A S V K V S C Q A S G Y T F S D Y Y I H W
V R Q T P G Q G F E W M G W V N P D T G G T R Y A Q K F O G W V T M T R
D M S N T T A Y M E L P R L R D D D T A V Y Y C A R D L T G Y D Y Y D R
W G Q G T L V T V S S

V_H (SEQ ID NO:266) with H1, H2, and H3 underlined (SEQ ID NO:269-271, respectively)

GAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCTCAGTGAAGGTCTCCTGTGAGGCTTCTGGATACACCTTCAGCGATTACTATATTCACTG
GGTGGACAGACCCCTGGACAAAGGTTTGAGTGGATGGGTCAACCTGACACTGGTGGCACAAGATACGGCCAGAAAGTTTCAGGGCTGGTGCACAATGACCA
GGGACATGTCCAACACACAGCCTACATGGAGTGGCAGGCTGAGAGACGACACGGCCGTATATTACTGTGCGAGAGATCTTAACCTGGATACGACTACTACGAC
CGGTGGGGCCAGGAACCTGGTCAACCGTCTCCTCA

V_L (SEQ ID NO:258) with L1, L2, and L3 underlined (SEQ ID NO:263-265, respectively)

Q S V L T Q P P S M S V A P G K T A T I T C G G N N F R N K R V H W Y Q
Q R P G Q A P V L V I Y Y D S D R P S G I P E R F S G S R S G N T A T L
T I S R V E A G D E A D F Y C Q V W D F L A D E A M F G G C T K L T V L

V_L (SEQ ID NO:267) with L1, L2, and L3 underlined (SEQ ID NO:272-274, respectively)

CAGTCTGTGCTGACTCAGCCGCCCTCAATGTCAAGTGGCCCGCAGGAAGACGGCCACGATTACCTGTGGGGAAACAACACTTTCGAAATAAAGAGTACACTGGTATCA
GCAGAGGCCAGGCCAGCCCTGTCTCTGGTCACTATTAATGATTACAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCCGCTCTGGGAACACGGCCACCC
TGACCATCAGAGGTGCGAGGCCGGGATGAGGCCGACTTTTACTGTCAAGTGTGGATTTCCTCGCCGACGAGCGGATGTTCGGCGGAGGACCAAGCTGACCGTCTCTAGGT

FIG. 7(cont.)

376B10

V_H (SEQ ID NO:275) with H1, H2, and H3 underlined (SEQ ID NO:278-280, respectively)

E V Q L V Q S G A E V K K P G A S V K V S C Q A S G Y T F S D Y Y I H
W V R Q T P G Q G F E W M G W V N P D T G G T R Y A Q K F O G W V T M
T R D M S N T T A Y M E L P G L R D D D T A V Y Y C A R D L T G Y D Q
Y T A W G Q G T L V T V S S

V_H (SEQ ID NO:284) with H1, H2, and H3 underlined (SEQ ID NO:287-289, respectively)

GAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCCTGGGGCTCAGTGAAGTCTCCTGTGAGGCTTCTGGATACACCTTCAGCGATTACTATATTCA
CTGGGTCCGACAGACCCAGGACAAGGTTTGAGTGGATGGGTCAACCTGACACTGGTGGCACGAGATACGGCGAGAAGTTTCAGGGCTGGGTCACAA
TGACCAGGGACATGTCCAAACACCACAGCCTACATGGAGCTGCCCGGCTGAGAGACGACACGGCCGTATATTACTGTCCGAGAGATCTAACTGGGTACGAC
CAGTACACGGCTGGGGCCAGGAACCTGTGTCACCGTCTCCTCA

V_L (SEQ ID NO:276) with L1, L2, and L3 underlined (SEQ ID NO:281-283, respectively)

Q S V L T Q P P S V S V A P G K T A T I T C G G N N F R N K R V H W Y
Q Q R P G Q A P V L V I Y Y D S D R P S G I P E R F S G S R S G N T A
T L T I S R V E A G D E A D F Y C S T F D P F T D R P L F G G G T K L
T V L G

V_L (SEQ ID NO:285) with L1, L2, and L3 underlined (SEQ ID NO:290-292, respectively)

CAGTCTGTGCTGACTCAGCCACCCCTCAGTGTGAGTGGCCAGGAAGACGGCCACGATTACCTGTGGGGAAACAACCTTCGAAATAAAGAGTACACTGGTA
TCAGCAGAGGGCCAGGCCCTGTCTGTCATCTATTATGATTACAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCCGCTCTGGGAACACGG
CCACCTGACCATCAGAGGTGAGGCCGGGATGAGGCCGACTTTTACTGTAGCACCTTCGACCCCTTCACCTGATCGTCCGCTGTTCGGCGGAGGACCAAG
CTGACCGTCTTAGGT

FIG. 7(cont.)

354A08

V_H (SEQ ID NO:293) with H1, H2, and H3 underlined (SEQ ID NO:296-298, respectively)

QVQLVQSGAEKKPGASVKVSKASGYTFTDY²⁹⁶YMHNVROAPGQGLEWVGNINPYTGGAFYAOKERGRVTMT²⁹⁷RDTSINTAYMELSR²⁹⁸LGSDDTAVYYCAREPEREGGSTG
QVWGRGTMVTVSS

V_H (SEQ ID NO:302) with H1, H2, and H3 underlined (SEQ ID NO:305-307, respectively)

CAGGTCCAGTTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCC³⁰⁵TGGGGCTCAGTGAAGGTCTC³⁰⁶CTGCAAGGCTTCTGGATACACCTTCAC³⁰⁷CGACTACTATATGCACTG
GGTGGACAGGCCCTGGACAAGGCTTGAGTGGGTGGGATGGA³⁰⁸TCAACCTTATACCTGG³⁰⁹TGGCGCATTCTATGCACAGAAGT³¹⁰TCGGGGCAGGTCACAATGACCA
GGGACACGTCCATCAACACAGCCTACATGGAGCTAAGCAGACTGGGATCTGACGACACGGCCGTGTA³¹¹TATTGTGCGAGAGAACC³¹²TGAAAGATTCGGG³¹³CGACTCCACG
GGCAGGTCTGGGGCGGGGACAATGGTCACCGTCTCGAGT

V_L (SEQ ID NO:294) with L1, L2, and L3 underlined (SEQ ID NO:299-301, respectively)

QAVLTQPSVSGAPRQRTISCTGSSSNIGAGYGVH²⁹⁹VQQLPGTAPKLLIYGNSNRPSGV³⁰⁰PDREFSGSKGTSASLAITGLQAEDEAD³⁰¹YYCYHWDKEOSGYVFGTGTQLTVLSA

V_L (SEQ ID NO:303) with L1, L2, and L3 underlined (SEQ ID NO:308-310, respectively)

CAGGCTGTGCTGACTCAGCCGTCCCTCAGTGTCTFGGGCCCCAAGGCAGAGGTCACCATCTCCTGCAC³⁰⁸TGGGAGCAGCTCCAACATCGGGCAGGTTATGGGTACA
CTGGTACCAACAGCTTCCAGGAACAGCCCCCAACTCCTCATCTATGGTAACAGCAATCGGCCCTCAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCT
CAGCCTCCCTGGCCATCACTGGGCTCCAGGCTGAGGATGAGGCTGATTACTGCTACCACTGGGACAAGGAGCAGAGTGGTTATGTCTTCGGAAC³⁰⁹ACTGGGACCCAG
CTCACCGTTTAAAGTGGC

FIG. 7(cont.)

355B06

V_H (SEQ ID NO:311) with H1, H2, and H3 underlined (SEQ ID NO:314-316, respectively)

EVQLVQSGAEVKKPGASVKVSCOASGYTFTDYYMHVVRQAPGQGLEWVINPYTGSAFYAOKFRGRATMTRNTSINTAYMELSRLGSDDDTAVYYCAREPEKEFGES
SGQLWGRGTMVTISS

V_H (SEQ ID NO:320) with H1, H2, and H3 underlined (SEQ ID NO:323-325, respectively)

GAAGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGTCTCCTGTCAGGCTTCTGGATACACCTTCACCGACTACTATATGCACT
GGGTGCGACAGGCCCTTGACACAGGCTTGAGTGGGTGGGTGGATCAACCTTATACTGGTAGCGCATTCTATGCACAGAAAGTTTCGGGGCCAGGGCCACAATGAC
CAGGAACACGTCCATCAACACAGCCTACATGGAGCTGAGCAGACTGGGATCTGACGACACGGCCGTGTATTATTGTGCGAGAGAACCTGAAAAAATTCGGGGAGTCC
AGCGGCCAGTTGTGGGCGGGGGACAATGGTCACCATCTCGAGT

V_L (SEQ ID NO:312) with L1, L2, and L3 underlined (SEQ ID NO:317-319, respectively)

QAVLTQPSSVSGAPGQRVTISCTGSSSNIGPGYGVHWYQQLPGTAPKLLIYGDSNRPSGVPDREFSGSKSGTSASLAITGLQAEDEADYYCOSYDSGLSGYVFGTGTQLTVLSA

V_L (SEQ ID NO:321) with L1, L2, and L3 underlined (SEQ ID NO:326-328, respectively)

CAGGCTGTGCTGACTCAGCCGTCCTCAGTGTCTGGGGCCCCAGGGCAGAGGGTCACCATCTCCTGCACTGGGAGCAGCTCCCAACATCGGGGCCAGGTTATGGTGTAC
ACTGGTACCAACAGCTTCCAGGAACAGCCCCCAAACTCCTCATCTATGGTGACAGCAATCGGCCCTCAGGGGTCCCTGACCGATTCTCTGGCTCCAAAGTCTGGCAC
CTCAGCCTCCCTGGCCATCACTGGGCTCCAGGCCGAGGATGAGGCTGATTATTACTGCCAGTCCTATGACACGGCCCTGAGTGGTTATGTCTTCGGAACTGGGACC
CAGCTCACCGTTTTAAGTGG

FIG. 7(cont.)

355E04

V_H (SEQ ID NO:329) with H1, H2, and H3 underlined (SEQ ID NO:332-334, respectively)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTHYYMHVVRQAPGQGLEWVGNINPYTGGAFAOKFOGRVTMTRDTSINTAYMELSRLGSDDDTAVYYCAREPEKEDSPN
AEIWGRGTMVTISS

V_H (SEQ ID NO:338) with H1, H2, and H3 underlined (SEQ ID NO:341-343, respectively)

CAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAAAGCCCTGGGGCCTCAGTGAAGTCTCCTGCAAGGCTTCTGGATACACCTTCACCCACTACTATATGCACTG
GGTCCGACAGGCCCCCTGGACAAGGCTTGAGTGGGTGGATCAACCCTTATACTGTGGCGCATTCATGCACAGAAGTTTCAGGGCAGGGTCACAATGACCA
GGGACACGTCCATCAACACAGCCFACATGGAGCTGAGCAGACTGGGATCTGACGACACGGCCGTGTATTATTGTGCGGAGAGAACCTGAAAAATTCGACTCGGCCGAAC
GCCGAGATCTGGGGCCGGGACAAATGGTCACCATCTCGAGT

V_L (SEQ ID NO:330) with L1, L2, and L3 underlined (SEQ ID NO:335-337, respectively)

QAVLTQPSSVSGAPGQRVTISCTGSSSNIGAGYGVHWYQQLPGTAPKLLIYGNSNRPSGVDPDRFSGSKGTSASLAITGLQAEDEADYYCOSYDSSLSGYVFGTGTQLTVLSA

V_L (SEQ ID NO:339) with L1, L2, and L3 underlined (SEQ ID NO:344-346, respectively)

CAGGCTGTGCTGACTCAGCCGTCCTCAGTGTCTGGGGCCCCAGGGCAGAGGGTCACCATCTCCTGCACTGGGAGCAGCTCCACACATCGGGGCAGGTTATGGGTGTACA
CTGGTACCAACAGCTTCCAGGAACAGCCCCCAACTCCTCATCTATGGTAAACAGCAATCGGCCCTCAGGGGTCCCTGACCGATTCTCTGGCTCCAAAGTCTGGCACCT
CAGCCTCCCTGGCCATCACTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCCAGTCCTATGACAGCAGCCTGAGTGGTTATGTCTTCCGGAACCGGGACCCCAG
CTCACCGTTTAAAGTGGC

FIG. 7(cont.)

356A11

V_H (SEQ ID NO:347) with H1, H2, and H3 underlined (SEQ ID NO:350-352, respectively)

QVQLVQSGAEVKKPGASVKVSKASGYTFTNYYMHVVRQAPGQGLEWVGVINPYTGSAFYAOKERGRVTMTTRDTSINTAYMELSRLGSDDTAVYYCAREPE
KFDSDDSDVWGRGTMVTVSG

V_H (SEQ ID NO:356) with H1, H2, and H3 underlined (SEQ ID NO:359-361, respectively)

CAGGTTCAGCTGGTGCAGTCTGGGGCTGAGTGAAGAAGCCTGGGGCCCTCAGTGAAGGCTCCTCGCAAGGCTTCTGGATACACCTTCACCAACTACTATAT
GCACTGGTCGGACAGGCCCTGGACAGGGCTTGAGTGGTGGGATGGATCAACCCCTTATATACTGGTAGCGCATTCTATGCACAGAGTTTCGGGGCAGGG
TTACAATGACCAGGGACACGTCCATCAACACAGCCTACATGGAGCTGAGCAGACTGGGATCTGACGACACGGCCGTGTATTATTGTGCGAGAGAACCTGAA
AAATTCGACTCCGACGACTCCGACGCTCGGGCCGCGGACAAATGGTCACCGTCTCGGGT

V_L (SEQ ID NO:348) with L1, L2, and L3 underlined (SEQ ID NO:353-355, respectively)

QAVLTPPSVGAPGQRVITSGSSNIGAGYGVHWYQQLPGTAPKLILYGDSRRSGVPDRFSGSKGTSASLAITGLQAEDEADYYCOSYDNSLSGVYFGTGTQLTVLSA

V_L (SEQ ID NO:357) with L1, L2, and L3 underlined (SEQ ID NO:362-364, respectively)

CAGGCTGTGCTGACTCAGCCGCCCTCAGTGTCTGGGGCCCCAGGGCAGAGGTCACCATCTCCTGCACTGGGAGCAGCTCCAAACATCGGGGCAGGTTATGG
TGTACACTGGTACCAACAGCTTCCAGGAACAGCCCCCAACTCATCTATGGTGACAGCAGTCGGCCCTCAGGGGTCCTGACCGATTCTCTGGCTCCA
AGTCTGGCACCTCAGCCTCCCTGGCCATCACTGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCCAGTCCCTATGACACACAGCCTGAGCGGTTATGTC
TTCGGAACTGGGACCCAGCTCACCGTTTAAGTGCG

FIG. 7(cont.)

GIL01

V_H (SEQ ID NO:365) with H1, H2, and H3 underlined (SEQ ID NO:368-370, respectively)

Q V Q L V E S G G G L V K P G G S L R L S C A A S G F T F S D Y Y M S W I R Q
A P G K G L E W V S A I S G S G S T Y Y A D S V K G R I T I S R D N A K N S
L Y L Q M N S L R A E D T A V Y Y C A R G L W V W D P L D Y W G R G T L V T V
S S

V_H (SEQ ID NO:374) with H1, H2, and H3 underlined (SEQ ID NO:377-379, respectively)

CAAGTCAGCTGGTGGAGTCTGGGGAGGCTTGGTCAAGCCTGGAGGTCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTGACTACTACATGAGCTGGATCCGCCA
GGCTCCAGGAAGGGCTGGAGTGGGTCTCAGCTATTAGTGGTAGGACATACCTAGCAGACTCCGTGAAGGGCCGGATCACCATCTCCAGAGACAAACGCCAAGAACT
CACTGTATCTGCAATGAACAGCCTGAGAGCTGAGGACACGGCCGTGTATTACTGTGGAGAGGGCTTTGGGTTTGGGATCCTCTTACTACTGGGGCAGAGAAACCTGGTCACCGTCTCTTCA

V_L (SEQ ID NO:366) with L1, L2, and L3 underlined (SEQ ID NO:371-373, respectively)

D I Q M T Q S P S T L S A S V G D R V T I T C R A S E G I Y H W L A W Y Q Q K
P G K A P K L I Y K A S S L A S G V P S R F S G S G S G T E F T L T I S S L
Q P D D F A T Y Y C O Q Y S N Y P L T F G G G T K V E I K R

V_L (SEQ ID NO:375) with L1, L2, and L3 underlined (SEQ ID NO:380-382, respectively)

GACATCCAGATGACCCAGTCTCCTTCCACCCCTGTCTGCATCTGTGGAGACAGAGTCACCATCACCCTGCCGGGCCAGTGAGGGTATTATCACTGGTTGGCTGGTATCAGCAGAA
GCCAGGAAAGCCCCTAACCTCCTGATCTATAAGCCCTCTAGTTAGCCAGTGGGTCCCATCAAGTTCAAGGTTCAAGGTCAGCGGCAGTGGATCTGGGACAGAGTTCACTCTCACCATCAGCAGCC
TGCAGCCTGATGATTTTGCAACTTATTACTGCCAACAATATAGTAATTATCCGCTCACTTTCGGGGAGGGACCAAGGTGGAGATCAAAACGT

FIG. 8

GIL16

V_H (SEQ ID NO:383) with H1, H2, and H3 underlined (SEQ ID NO:386-388, respectively)

Q V Q L V Q S G A E V K K P G A S V K V S C K A S G Y T F T S Y G I S W V
R Q A P G Q G L E W M G W I S A Y T G N T N Y A Q K F Q G R V T M T T D T
S T S T A Y M E L R S L R S D D T A V Y Y C A R D R G Y Y D A F D I W G Q
G T L V T V S S

V_H (SEQ ID NO:392) with H1, H2, and H3 underlined (SEQ ID NO:395-397, respectively)

CAGGTGCAGCTGGTGCAGCTGAGGTGAAGAAGCCTGGGGCTCAGTGAAGGTCCTCTGCAAGGCTTCTGTTACACCTTTACCAAGTTAAGTATCAGCTGGGT
GCGACAGGCCCTGGACAAGGCTTGAGTGGATGGATCAGCGCTTACACTGGTAACACAACTATGCACAGAAGTCCAGGGCAGAGTCACCATGACACAGACA
CATCCAGGACACAGCCTACATGGAACCTGAGATCTGACGACACGGCCGTGTTACTGTGCGAGAGATCGTGGGATCTATGATGCTTTTGATATCTGGGGC
CAAGGCACCCCTGGTCACCGTCTCCTCA

V_L (SEQ ID NO:384) with L1, L2, and L3 underlined (SEQ ID NO:389-391, respectively)

D I Q M T Q S P S T L S A S V G D R V T I T C R A S E G I Y H W L A W Y Q
Q K P G K A P K L L I Y K A S S L A S G V P S R F S G S G S G T E F T L T
I S S L Q P D D F A T Y Y C Q Q Y S N Y P L T F G G G T K V E I K R

V_L (SEQ ID NO:393) with L1, L2, and L3 underlined (SEQ ID NO:398-400, respectively)

GACATCCAGATGACCCAGTCTCCTCCACCCCTGTCTGCATCTGTTGGAGACAGATCACCATCACCCTGCCGGCCAGTGAGGTATTATCACTGGTGGCCTGGTATCA
GCAGAAGCCAGGAAAGCCCTAAACTCCTGATCTATAAGGCTCTAGTTAGCCAGTGGGTCCCATCAAGTTCAAGGTTCAAGGTTGATCTGGACAGAGTTCACTCTCA
CCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAACAATATAGTAATTATCCGCTCACTTCGGCGGAGGACCAAGTGGAGATCAAAACGT

FIG. 8(cont.)

GIL45

V_H (SEQ ID NO:401) with H1, H2, and H3 underlined (SEQ ID NO:404-406, respectively)

Q M Q L V E S G G G V V Q P G R S L R L S C A A S G F T F S N Y G M
Y W V R Q A P G K G L E W V A H I W Y D G S N E K Y A D S V K G R M
T V S R D N S K N T L Y L Q M N S L R A E D T A V Y Y C A T E O H W
I T A F D I W G K G T L V T V S S

V_H (SEQ ID NO:410) with H1, H2, and H3 underlined (SEQ ID NO:413-415, respectively)

CAGATGCAGCTGGTGAGTCTGGGGAGGCGTGGTCCAGCCTGGAGGTCCTGAGACTCTCTGTGCAGCCTCTGGATTCACCTTCAGTAACATATGGCAT
GTACTGGGTCCGCCAGGCTCCAGGCAAGGGCTGGAGTGGTGACATATTTGGTATGATGGAAGTAATGAAAGATATGCAGACTCCGTGAAGGCCGAA
TGACCGTCTCCAGAGACAATTCCAAGAACACGTTGTATTTGCAATATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGGCAGAGCAACAC
TGGATTACTGCTTTTGATATCTGGGGCAAGGAACCTGGTCACCGTCTCTCA

V_L (SEQ ID NO:402) with L1, L2, and L3 underlined (SEQ ID NO:407-409, respectively)

Q S A L T Q P A S V S G S P G Q S I T I S C T G T S S D V G G Y N Y
V S W Y Q Q H P G K A P K L M I Y E G S K R P S G V S N R F S G S K
S G N T A S L T I S G L Q A E D E A D Y Y C S S Y T T R S T R V F G
G G T K L T V L G

V_L (SEQ ID NO:411) with L1, L2, and L3 underlined (SEQ ID NO:416-418, respectively)

CAGTCTGCCCTGACTCAGCCTGCCCTCCGTGTCTGGTCTCCTGGACAGTCGATCACCATCTCTGCCTGGAACCCAGCAGTGACGTTGGTGGTTATACTA
TGCTCTCCTGGTACCAACAACACCCAGGCAAGCCCCAACTCATGATTATGAGGCAGTAAGCGGCCCTCAGGGGTTCTTAATCGCTTCTCTGGCTCCA
AGTCTGGCAACACGGCCTCCCTGACAATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTACTGAGCTCATATACAACCCAGGACCTCGAGTTTTC
GGCGGAGGACCAAGCTGACCGTCTTAGGT

FIG. 8(cont.)

GIL60

V_H (SEQ ID NO:419) with H1, H2, and H3 underlined (SEQ ID NO:422-424, respectively)

E V Q L V E S G G G V R P G G S L R L S C A A S G F T F D D Y G M N W V
R Q A P G K G L E W V S G V N W N G G T R D Y A A S V K G R F T I S R D N
A K N S L Y L Q M N S L R A E D T A L Y H C A R G W Y S G S F Y Y F G Y W
G R G T L V T V S S

V_H (SEQ ID NO:428) with H1, H2, and H3 underlined (SEQ ID NO:431-433, respectively)

GAGGTGACGTGTTGGAGAGCGGGGAGGTGTGGTACGGCTGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACACCTTTGACGATTATGGCATGAACCTGGGTC
CGCCAAAGCTCCAGGAAGGGCTGGAGTGGTCTCTGGTGTAAATTGGAATGGTGTACCAAGATTATGCAGCCTCCGTGAAGGCCGATTCACCATCTCCAGAGACAAC
GCCAAGAACTCCCTGTATCTGCAATGAACAGTCTGAGAGCCGAGCACGGCCCTTGTATCACTGTGCGAGAGGATGGTATAGTGGAGCTTCTACTACTTTGGCTACTGG
GGCCGAGGAACCTGGTCACCGTCTCTCA

V_L (SEQ ID NO:420) with L1, L2, and L3 underlined (SEQ ID NO:425-427, respectively)

Q A A L T Q P A S V S G S P G Q S I T I S C T G A S G D V G A Y N F V S W
Y Q Q H P G K A P K L I I Y D V N K R P S G V S N R F S G S K S G N T A S
L T I S G L Q A E D E A D Y Y C S S Y T S T F S V V F G G G T K L T V L G

V_L (SEQ ID NO:429) with L1, L2, and L3 underlined (SEQ ID NO:434-436, respectively)

CAGGCTGGCTGACTCAGCCGGCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCACGTGGAGCCAGCGGTGACGTTGGTGGCTTATAACTTTGTCTCTGG
TACCAACAACACCCAGGCAAGCCCCAACTCATAATTATGATGTCAATAAGCGGCCCTCAGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCCTCC
CTGACCACTCTCTGGGCTCCAGGCCGAGGACGAGGCTGATTATTACTGCAGCTCATATACAGCACCTTCTCTGTGGTATTGGCGGAGGACCAAGCTGACCGTCTCTAGGT

FIG. 8(cont.)

GIL68

V_H (SEQ ID NO:437) with H1, H2, and H3 underlined (SEQ ID NO:440-442, respectively)

Q V Q L V Q S G A E V K K P G A S V K V S C K A S G Y T F S D Y Y I H W V R Q
A P G Q G L E W M G W V N P D T G G T R Y A Q K F O G R V T M T R D M S I S T
A Y M E L S R L R S D D T A V Y Y C A R D L T G F D P F D I W G Q Q G T L V T V
S S

V_H (SEQ ID NO:446) with H1, H2, and H3 underlined (SEQ ID NO:449-451, respectively)

CAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCCTGGGGCTCAGTGAAGTCTCCTGTAAGGCTTCTGGATACACCTTCAGCGATTACTATATCAGTGGTGGACA
GGCCCTGGACAAGGTTGGAGTGGATGGGTCAACCTGACACTGGTGGCACAAGATAGCGCAGAAGTTTCAGGGCCGGTCAATGACCAGGACATGTCCATCTCCA
CAGCCTACATGGAGCTGTCCAGGCTGAGAAGCGACACAGGCCGTATATTACTGTGCGAGAGATCTAAGTTCCTTTTGATATCTGGGGCCAGGAACCTGGTCACCGTCTCCTCA

V_L (SEQ ID NO:438) with L1, L2, and L3 underlined (SEQ ID NO:443-445, respectively)

S S V L T Q P P S V S V A P G K T A R I T C G G N N F R N K R V H W Y Q Q K P
G Q A P V L V I Y Y D S D R P S G I P E R F S G S R S G N T A T L T I S R V E
A G D E A D Y Y C O V W D S S T D R P L F G G G T K L T V L G

V_L (SEQ ID NO:447) with L1, L2, and L3 underlined (SEQ ID NO:452-454, respectively)

TCGTCTGTGCTGACTCAGCCACCCTCAGTGTCTCAGTGGCCCCCAGGAAGACGGCCCGCATTAACCTGTGGGGAAACAACCTTCGAAATAAAGAGTACACTGGTATCAGCAGAAGCC
AGCCAGGCCCCCTGTCTGTGTCATCTATTATGATTCAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCCGCTCTGGGAACACGGCCACCCCTGACCATCAGCAGGTCG
AGCCGGGGATGAGCCGACTATTACTGTACGGTGTGGGATAGTAGTATCGTCCGCTGTCGGGGAGGACCAAGCTGACCGTCTTAGGT

FIG. 8(cont.)

GIL92

V_H (SEQ ID NO:455) with H1, H2, and H3 underlined (SEQ ID NO:458-460, respectively)

Q V Q L V Q S G A E V K K P G A S V K V S C K A S G Y T F T D Y Y M H W V R
Q A P G Q G L E W V G W I N P Y T G G A F Y A O K F R G R V T M T R D T S I
S T A Y M E L S R L R S D D T A V Y Y C A R E P E K F D F W G G D N W G R G
T L V T V S S

V_H (SEQ ID NO:464) with H1, H2, and H3 underlined (SEQ ID NO:467-469, respectively)

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGTCTCCTGCAAGGCTTCTGGATACACCTTCCCGACTACTATATGCACTGGGTGG
ACAGCCCCCTGGACAAGGCTTGAGTGGGTGGGATGATCAACCTTATCTATGCTGGCGCATTCATGACACAGAGTTTCGGGGCAGGTTCACAATGACCCAGGACACGTCCA
TCAGCACAGCCTACATGGAGCTGACGAGCTGAGATCTGACGACACGGCCGTGTATTATTGTGCGAGAGACCTGAAATAATTGATTTTGGGGGGGTGACAACTGGGGCCGG
GGGACATTGGTCACCGTCTCCTCA

V_L (SEQ ID NO:456) with L1, L2, and L3 underlined (SEQ ID NO:461-463, respectively)

Q A V L T Q P P S V S G A P G Q R V T I S C T G S S S N I G A G Y G V H W Y
Q Q L P G T A P K L L I Y G N S N R P S G V P D R F S G S K S G T S A S L A
I T G L Q A E D E A D Y Y C O S Y D S S L S G Y V F G G G T Q L T V L G

V_L (SEQ ID NO:465) with L1, L2, and L3 underlined (SEQ ID NO:470-472, respectively)

CAGGCTGTGCTCAGCCGCCGTGAGTGTCTGGGGCCAGGGCAGAGGTCACCATCTCCTGCACCTGGGAGCAGCTCCACATCGGGGCAGGTTATGGTGTACACTGGTA
CCAACAGCTTCCAGGAACAGCCCCCAACTCCTCATCTATGGTAACAGCAATCGGCCCTCAGGGGTCCCTGACCCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGG
CCATCACTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCCAGTCCCTATGACAGCAGCCTGAGTGGTTATGCTCTCGGAGGTGGGACCCAGCTCACCCTCCTAGGT

FIG. 8(cont.)

062A09

V_H (SEQ ID NO:473) with H1, H2, and H3 underlined (SEQ ID NO:476-478, respectively)

Q V Q L V Q S G A E V K K P G A S V K V S C K A S G Y T F T S Y G I S W
V R Q A P G Q G L E W M G W V S A Y T G N T N Y A O K F O G R V T M T T
D T S T S T A Y M E L R S L R S D D T A V Y Y C A R D R G Y Y D A F D I
W G Q G T L V T V S S

V_H (SEQ ID NO:482) with H1, H2, and H3 underlined (SEQ ID NO:485-487, respectively)

CAGGTGCAGCTGGTGAGCTGAGGTGAAGAGCCTGGGGCCTCAGTGAAGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAAGTTATGGTATCAGCTG
GGTCCGACAGGCCCTGGACAAGGCTTGAGTGGATGGGTGAGCTGCTTACACTGGTAACACAACTATGCACAGAAGTCCAGGGCAGAGTCACCATGACCA
CAGACACATCCACGAGCACAGCCTACATGGAAGCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGAGATCGTGGATACTATGATGCTTTTGAT
ATCTGGGGCCAAGCACCCCTGGTCACCGTCTCCTCA

V_L (SEQ ID NO:474) with L1, L2, and L3 underlined (SEQ ID NO:479-481, respectively)

D I Q M T Q S P S T L S A S V G D R V T I T C R A S E G I Y H W L A W Y
Q Q K P G K A P K L L I Y K A S S L A S G V P S R F S G S G T E F T
L T I S S L Q P P D D F A T Y Y C Q O M G E Y N A T F G G G T K V E I K R

V_L (SEQ ID NO:483) with L1, L2, and L3 underlined (SEQ ID NO:488-490, respectively)

GACATCCAGATGACCCAGTCTCCTCCACCCCTGTCTGCATCTGTTGGAGACAGAGTCACCATCACCTGCCGGCCAGTGAGGGTATTATCACTGGTGGCCTGGTA
TCAGCAGAAGCCAGGGAAGCCCTAAACTCCTGATCTATAAGGCTCTAGTTTAGCCAGTGGGTCCCATCAAGGTTACGGCAGTGGATCTGGGACAGAGTTCA
CTCTCACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAACAAATGGGCGGAGTACAAGCCACCTTCGGCGGAGGCCAACAGGTGGAGATCAACGCT

FIG. 8(cont.)

087B03

V_H (SEQ ID NO:491) with H1, H2, and H3 underlined (SEQ ID NO:494-496, respectively)

E V Q L V E S G G G V R P G G S L R L S C A A S G F T F D D Y G M N W V
R Q A P G K G L E W V S G V N G G T R D Y A A S V K G R F T I S R D N
A K N S L Y L Q M N S L R A E D T A L Y H C A R G W Y S G A A W N M G Y W
G R G T L V T V S S

V_H (SEQ ID NO:500) with H1, H2, and H3 underlined (SEQ ID NO:503-505, respectively)

GAGGTGAGCTGGTGGAGAGCGGGGAGGTGTGGTACGGCCTGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGACGATTATGGCATGAAGTGGTC
CGCCAAGCTCCAGGAAGGGCTGGAGTGGTCTCTGGTGAATGGTGTACAGAGATTATGCAGCCTCCGTGAAGGGCCGATTACCATCTCCAGAGACAAC
GCCAAGAACTCCCTGTATCTGCAATGAACAGTCTGAGAGCCGAGGACACGGCCTTGTATCACTGTGCGAGAGATGGTATAGTGGGCGCGGTGGAACATGGGCTACTGG
GGCCGAGGAACCTGGTCACCGTCTCCTCA

V_L (SEQ ID NO:492) with L1, L2, and L3 underlined (SEQ ID NO:497-499, respectively)

Q A A L T Q P A S V S G S P G Q S I T I S C T G A S G D V G A Y N F V S W
Y Q Q H P G K A P K L I I Y D V N K R P S G V S N R F S G S K S G N T A S
L T I S G L Q A E D E A D Y Y C S S Y T S T F S V V F G G G T K L T V L G

V_L (SEQ ID NO:501) with L1, L2, and L3 underlined (SEQ ID NO:506-508, respectively)

CAGGCTGGCTGACTCAGCCGGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCACITGGAGCCAGCGGTGACGTTGGTGCTTATAACTTTGTCTCCTGG
TACCAACAACACCCAGGCAAGCCCCCAACTCATATTATGATGTCAATAAGCGGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCC
CTGACCATCTCTGGGCTCCAGGCCGAGGACGAGGCTGATTATTACTGCAGCTCATATACAGCACCTTCTCTGTGGTATTGGCGGAGGACCAAGCTGACCGTCCTAGGT

FIG. 8(cont.)

166B06

V_H (SEQ ID NO:509) with H1, H2, and H3 underlined (SEQ ID NO:512-514, respectively)

Q V Q L V Q S G A E V K K P G A S V K V S C K A S G Y T F S D Y Y I H W V
R Q A P G Q G L E W M G W V N P D T G G T R Y A O K F O G R V T M T R D M
S I S T A Y M E L S R L R S D D T A V Y Y C A R D L T G F D P F D I W G Q
G T L V T V S S

V_H (SEQ ID NO:518) with H1, H2, and H3 underlined (SEQ ID NO:521-523, respectively)

CAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGCCCTCAGTGAAGGTCTCTGTAGGCTTCTGGATACACCTTCAGCGATTACTATATTCACCTGGGT
GCGACAGGCCCTGGACAAAGGTTGGAGTGGATGGGTCAACCTGACACTGGTGGCACAAGATACGCCGAGAAGTTTCAGGGCCGGGTCAATGACCCAGGGACA
TGTCATCTCCACAGCCTACATGAGCTGTCCAGGCTGAGAAGCGACGACGCGCGTATATTACTGTCCGAGAGATCTAACTGGATTTCATCCTTTTGATATCTGCGGC
CAGGGAACCTGGTCACCGTCTCCTCA

V_L (SEQ ID NO:510) with L1, L2, and L3 underlined (SEQ ID NO:515-517, respectively)

S S V L T Q P P S V S V A P G K T A R I T C G G N N F R N K V H W Y Q Q K
P G Q A P V L V I Y Y D S D R P S G I P E R F S G S R S G N T A T L T I S
R V E A G D E A D Y Y C O V W D L F N D N G V F G G G T K L T V L G

V_L (SEQ ID NO:519) with L1, L2, and L3 underlined (SEQ ID NO:524-526, respectively)

TCGTCTGTGCTGACTCAGCCACCCTCAGTGTCTAGTGGCCCCAGGAAAGACGGCCCCGCAATTACCTGTGGGGGAACAACATTTCGAAATAAAGAGTACACTGGTATCAGCA
GAAGCCAGGCCCTGTCTGTGTCATCTATTATGATTTCAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCCGCTCTGGGAACACGGCCACCTGACCA
TCAGCAGGGTCGAGGCCGGGATGAGGCCGACTATTACTGTCTCAGGTGTGGGATCTCTCAACGACAACGGCGTGTTCGGGGAGGGACCAAGCTGACCGTCCCTAGGT

FIG. 8(cont.)

166G05

V_H (SEQ ID NO:527) with H1, H2, and H3 underlined (SEQ ID NO:530-532, respectively)

Q V Q L V Q S G A E V K K P G A S V K V S C K A S G Y T F S D Y Y I H W V R
Q A P G Q G L E W M G W V N P D T G G T R Y A Q K F Q G R V T M T R D M S I
S T A Y M E L S R L R S D D T A V Y Y C A R D L T G F D P F D I W G Q G T L
V T V S S

V_H (SEQ ID NO:536) with H1, H2, and H3 underlined (SEQ ID NO:539-541, respectively)

CAGGTCACGCTGCTGGGCTGAGGTGAAGAAGCCTGGGCTCAGTGAAGCTCTCTGTAAGGCTCTGGATACACCTTCAGCGATTAATACTGCTGGTGGC
ACAGGCCCTGGACAAGGTTGGAGTGGATGGATGGTCAACCTGACACTGGTGCCACAAGATACCGCGAGAAGTTTCAGGGCCGGGTCAACAATGACCAGGACATGTCCA
TCTCCACAGCCTACATGGAGCTGTCCAGGCTGAGAAGCGGACACACGGCCGTATATTACTGTGCGAGAGATCTAACTGGATTGATCCTTTTGATATCTGGGGCCAGGGAACC
CTGGTCACCGTCTCCTCA

V_L (SEQ ID NO:528) with L1, L2, and L3 underlined (SEQ ID NO:533-535, respectively)

S S V L T Q P P S V S V A P G K T A R I T C G G N N F R N K R V H W Y Q Q K
P G Q A P V L V I Y Y C O V W D F L T D S G S F G G G T K L T V L G
V E A G D E A D Y Y C O V W D F L T D S G S F G G G T K L T V L G

V_L (SEQ ID NO:537) with L1, L2, and L3 underlined (SEQ ID NO:542-544, respectively)

TCGTCTGTGCTGACTCAGCCACCCCTCAGTGTGAGTGGGCCCCAGGAAAGACGGCCCCGATTACCTGTGGGGGAAACAACACTTTCGAAATAAAGAGTACACTGGTATCAGCAGAA
GCCAGGCCAGGCCCTGTCTCTGGTCACTCTATTATGATTCAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCGCTCTGGGACACACGGCCACCTGACCATCAGCA
GGTCCAGGCCGGGATGAGGCCGACTATTACTGTCTAGGTGTGGGATTTCCTCACCAGTCTGGGTCGTTCCGGGAGGACCAAGCTGACCGTCCCTAGGT

FIG. 8(cont.)

354A08

V_H (SEQ ID NO:545) with H1, H2, and H3 underlined (SEQ ID NO:548-550, respectively)

Q V Q L V Q S G A E V K K P G A S V K V S C K A S G Y T F T D Y Y M H W V R
Q A P G Q G L E W V G W I N P Y T G G A F Y A O K F R G R V T M T R D T S I
S T A Y M E L S R L R S D D T A V Y Y C A R E P E R F G D S T G O V W G R G
T L V T V S S

V_H (SEQ ID NO:554) with H1, H2, and H3 underlined (SEQ ID NO:557-559, respectively)

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGTCTCCTGCAAGGCTTCTGGATACACCTTCACCGACTACTATATGCACTGGGTGCG
ACAGCCCCCTGGACAAGGCTTGAGTGGGTGGATGGATCAACCTTATCTGCTGGGCGCATCTATGACACAGAAGTTTCGGGGCAGGGTCACAATGACCAAGGACACGTCCA
TCAGCACAGCCTACATGGAGCTGACGAGACTGAGATCTGACGACACGGCCGTGTATTGTGCGAGAGAACCTGAAAGATTCTGGCGACTCCACGGGCAGGTCCTGGGGCCCGG
GGGACATTGGTCACCGTCTCTCTCA

V_L (SEQ ID NO:546) with L1, L2, and L3 underlined (SEQ ID NO:551-553, respectively)

Q A V L T Q P P S V S G A P G Q R V T I S C T G S S S N I G A G Y G V H W Y
Q Q L P G T A P K L L I Y G N S N R P S G V P D R F S G S K S G T S A S L A
I T G L Q A E D E A D Y Y C Y H W D K E Q S G Y V F G G G T Q L T V L G

V_L (SEQ ID NO:555) with L1, L2, and L3 underlined (SEQ ID NO:560-562, respectively)

CAGGTGTGCTGACTCAGCCGCGTCAAGTGTCTGGGGCCCGAGGAGAGGTCACCAATCTCTGCACTGGGAGCAGCTCCAAACATCGGGGCAGGTTATGGTGACACTGGTA
CCAACAGCTTCCAGGAACAGCCCCCAACTCTCATCTATGGTAACAGCAATCGGCCCTCAGGGTCCCTGACCGATTCTCTGGCTCCAAAGTCTGGCACCTCAGCCTCCCTGG
CCATCACTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGTACCACTGGGACAAGGAGCAGAGTGGTTATGTCTTCGGAGGTGGGACCCAGCTCACCGTCCCTAGGT

FIG. 8(cont.)

355B06

V_H (SEQ ID NO:563) with H1, H2, and H3 underlined (SEQ ID NO:566-568, respectively)

Q V Q L V Q S G A E V K K P G A S V K V S C K A S G Y T F T D Y Y M H W V
R Q A P G Q G L E W V G W I N P Y T G S A F Y A O K F R G R V T M T R D T
S I S T A Y M E L S R L R S D D T A V Y Y C A R E P E K F G E S S G O L W
G R G T L V T V S S

V_H (SEQ ID NO:572) with H1, H2, and H3 underlined (SEQ ID NO:575-577, respectively)

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCTCAGTGAAGGCTCTCTGATACACCTTCACCGACTACTATATGCACTGGGTG
CGACAGGCCCTGGACAAGGCTTGAGTGGGTGGATGATCAACCTTATCTAGTGGCTTCTATGACACAGAACTTCGGGGCAGGGTCACAATGACCCAGGACACG
TCCATCAGCACAGCCTACATGGAGCTGAGCAGACTGAGATCTGACGACACGGCCGTGTATTATTGTGGCAGAGAACCTGAAATTCGGCCGAGTCCAGCGCCAGTTGTGG
GGCCGGGGACATTGGTCACCGTCTCTCTCA

V_L (SEQ ID NO:564) with L1, L2, and L3 underlined (SEQ ID NO:569-571, respectively)

Q A V L T Q P P S V S G A P G Q R V T I S C T G S S S N I G A G Y G V H W
Y Q Q L P G T A P K L L I Y G D S N R P S G V P D R F S G S K S G T S A S
L A I T G L Q A E D E A D Y Y C Q S Y D S G L S G Y V F G G G T Q L T V L
G

V_L (SEQ ID NO:573) with L1, L2, and L3 underlined (SEQ ID NO:578-580, respectively)

CAGGCTGTGCTGACTCAGCCCGCTCAGTGTCTGGGGCCCCAGGGCAGAGGTCACCATCTCTGACTGGGAGCAGCTCCAACATCGGGCAGGTTATGGTGTACTGG
TACCAACAGCTTCCAGGAACAGCCCCCAACTCCTCATCTATGGTGACAGCAATCGGCCCTCAGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCC
CTGGCCATCACTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCCAGTCTCTATGACAGCGGCTGAGTGGTTATGTCTTCGGAGGTGGGACCCAGCTCACCGTCTCTAGGT

FIG. 8(cont.)

355E04

V_H (SEQ ID NO:581) with H1, H2, and H3 underlined (SEQ ID NO:584-586, respectively)

Q V Q L V Q S G A E V K K P G A S V K V S C K A S G Y T F T H Y Y
M H W V R Q A P G Q G L E W V G W I N P Y T G G A F Y A O K F O G
R V T M T R D T S I S T A Y M E L S R L R S D D T A V Y Y C A R E
P E K F D S P N A E I W G R G T L V T V S S

V_H (SEQ ID NO:590) with H1, H2, and H3 underlined (SEQ ID NO:593-595, respectively)

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCCTGGGCTCAGTGAAGTCTCCTGCAAGGCTTCTGGATACACCTTCACCCACTACTAT
ATGCACCTGGTGGACAGGCCCTGGACAAAGGCTTGAGTGGGTGGATGATCAACCCCTTATCTGTTGGCGCATCTATGACAGAAAGTTTCAGGGC
AGGGTCACAATGACCAGGACACGTCCATCAGACAGCCTACATGGAGCTGAGCAGACTGAGATCTGACGACAGGCGGTGTTATTGTCGAGAGAGAA
CCTGAAAATTTCGACTCGCCGAACGCCGAGATCTGGGGCCGGGACATTGGTCAACCGTCTCTCTCA

V_L (SEQ ID NO:582) with L1, L2, and L3 underlined (SEQ ID NO:587-589, respectively)

Q A V L T Q P P S V S G A P G Q R V T I S C T G S S S N I G A G Y
G V H W Y Q Q L P G T A P K L L I Y G N S N R P S G V P D R F S G
S K S G T S A S L A I T G L Q A E D E A D Y Y C Q S Y D S S L S G
Y V F G G G T Q L T V L G

V_L (SEQ ID NO:591) with L1, L2, and L3 underlined (SEQ ID NO:596-598, respectively)

CAGGCTGTGCTGACTCAGCCGCCGTGAGTGTCTGGGGCCCCAGGGCAGAGGGTCACCATCTCCTGCACCTGGGAGCAGCTCCCAACATCGGGGCAGGTTAT
GGTGTAACACTGGTACCAACAGCTTCCAGGAACAGCCCCCAACTCCTCATCTATGGTAACAGCAATCGGCCCTCAGGGGTCCCTGACCGATTCTCTGGC
TCCAAAGTCTGGCACCTCAGCCTCCCTGGCCATCACTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCCAGTCCCTATGACAGCAGCCTGAGTGGT
TATGTCTTCGGAGGTGGGACCCAGCTCACCGTCTCTAGGT

FIG. 8(cont.)

356A11

V_H (SEQ ID NO:599) with H1, H2, and H3 underlined (SEQ ID NO:602-604, respectively)

Q V Q L V Q S G A E V K K P G A S V K V S C K A S G Y T F T N Y Y M H W
V R Q A P G Q G L E W V G W I N P Y T G S A F Y A Q K F R G R V T M T R
D T S I S T A Y M E L S R L R S D D T A V Y Y C A R E P E K F D S D D S
D V W G R G T L V T V S S

V_H (SEQ ID NO:608) with H1, H2, and H3 underlined (SEQ ID NO:611-613, respectively)

CAGGTGAGCTGTCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATACACCTTCACCACTACTATATGCACTGG
GTGCGACAGGCCCTGGACAAGGCTTGAGTGGGTGGATGCAACCCCTTATCTGCTAGCGCATCTATGCACAGAAAGTTTCGGGGCAGGGTCACAATGACCCAGG
GACACGTCCATCAGCACAGCCTACATGGAGCTGAGACTGAGATCTGACGACACGGCCGTGTATTATTGTCGGAGAGAACCTGAAAAATTCGACTCCGACGACTCC
GACGCTGGGGCCGGGACATTTGGTCACCGTCTCTCA

V_L (SEQ ID NO:600) with L1, L2, and L3 underlined (SEQ ID NO:605-607, respectively)

Q A V L T Q P P S V S G A P G Q R V T I S C T G S S S N I G A G Y G V H
W Y Q Q L P G T A P K L L I Y G D S N R P S G V P D R F S G S K S G T S
A S L A I T G L Q A E D E A D Y Y C Q S Y D N S L S G Y V F G G T Q L
T V L G

V_L (SEQ ID NO:609) with L1, L2, and L3 underlined (SEQ ID NO:614-616, respectively)

CAGGCTGTGCTGACTAGCCGCGTCAGTCTCTGGGGCCCGAGGGCAGAGGGTCACCATCTCCTGCACCTGGGAGCAGCTCCAACATCGGGCAGGTTATGGTGACAC
TGGTACCAACAGCTTCCAGGAACAGCCCCCAACTCCTCATCTATGGTGACAGCAATCGGCCCTCAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCA
GCCTCCCTGGCCATCACTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCCAGTCTTATGCAACAGCCCTGACGGTTATGCTTCGGAGGTGGGACCCAGCTCACCGTCCCTAGGT

FIG. 8(cont.)

368D04

V_H (SEQ ID NO:617) with H1, H2, and H3 underlined (SEQ ID NO:620-622, respectively)

EVQLVESGGG VVRPGGSLRL SCAASGFTFD DYGMNWVRQA PGKGLEWVSG

VNWNNGGTRDY AASVKGRFTI SRDNAKNSLY LQMNSLRAED TALYHCARGW

YSGAAWNMGY WGRGTLVTVS S

V_H (SEQ ID NO:626) with H1, H2, and H3 underlined (SEQ ID NO:629-631, respectively)

GAGGTGCAGCTGGTGGAGAGCGCGGAGGCGGTGGTGAGACCAAGCGGCGAGCTGAGCTGCCCGCCAGGGCTTCACTTCGACGACTACGGCATGAA
CTGGGTGAGGCAGGCCCCAGGCAAGGCGCTGGAGTGGTGTCCGGCGTGAACGGCGGACCAAGAGACTACGGCGCTCTGTGAAGGCAGATTACCCA
TCAGCCGGGACAAACGCCAAGAACAGCCTGTACTGTCAGATGAACAGCCTGAGAGCCGAGGACACCGCCCTGTACCACTGGCGCCAGAGGCTGGTACAGCGGAGGCC
GCCTGGAACATGGGCTACTGGGGCAGAGGACCCCTGGTGACCGTGTCCAGC

V_L (SEQ ID NO:618) with L1, L2, and L3 underlined (SEQ ID NO:623-625, respectively)

QAALTQPASV SGSPGOSITI SCTGASGDVG AYNEVSWYQQ HPGKAPKLII

YDVNKRRESGV SNRESGSKSG NTASLTISGL QAEDEADYYC ASIVSDESIV

FGGGTKLTVL

V_L (SEQ ID NO:627) with L1, L2, and L3 underlined (SEQ ID NO:632-634, respectively)

CAGGCGCCCTGACCCAGCCCGCAGCGTGTCTGGCAGCCCGCAGGCATCACCATCAGCTGCCCGCGGCGGCGGATGTGGCGGCTACAACTTCGT
GTCCCTGTATCAGCAGCACCCCGCAAGGCCCAAGCTGATCATCTACGACGTGAACAAGAGACCCAGCGCGGTGTCCAACAGATTACGGCGCAGCAAGAGCG
GCAACACCGCGCCTGACCATCAGCGGACTGCAGGCCGAGGCGGACTACTGCGCCAGCGCTGGTGTCCGACTTCAGCGTGTGTTCGGCGGAGGC
ACCAAGCTGACCGTGCTG

FIG. 8(cont.)

GAAGTCAGCTGGTGGAGTCTGGGGAGGCTTGGTCACGCCCTGGAGGGT
CCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTGACTACTA
CATGAGCTGGATCCGCCAGGCTCAGGAGGGGCTGGAGTGGTCTCA
GGCTATTAGTGGTAGTGGTAGCACATACTACGCAGACTCCGTGAAGG
GCCGGATCACCATCTCCAGAGACAACGCCAAGAACTCACTGTATCTGCA
AATGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTCCGAGA
GGGCTTTGGGTTTGGGATCCTCTTGACTACTGGGGCAGAGGAACCCCTGG
TCAACCGTCTCTTCAGGTGGAGCGGGTTCAGGCGGAGGTGGCAGCGGCGG
TTGGCGGATCGGACATCCAGATGACCCAGTCTCCTTCCACCCCTGTCTGCA
TCTATTGGAGACAGATCACCATCACCTGCCGGGCCAGTGAGGGTATTT
ATCACTGGTTGGCCTGGTATCAGCAGAACCCAGGAAAGCCCCCTAAACT
CCTGATCTATAAGGCCCTCTAGTTTAGCCAGTGGGGCCCCCATCAAGGTTT
AGCGGCAGTGGATCTGGGACAGATTTCACCTCTCACCATCAGCAGCCTGC
AGCCTGATGATTTTGCAACTTATTACTGCCAACAATATAGTAATTATCC
GCTCACTTTCGGCGGAGGACCAGCTGGAGATCAAAACGTGCGGCCGCA

GIL16

SEQ ID NO:25

Q	V	Q	L	V	E	S	G	A	E	V	K	K	P	G	A	S	V	K	V	S	C	K	A	S	G	Y	T	F
T	S	Y	G	I	S	W	V	R	Q	A	P	G	Q	G	L	E	W	W	M	G	I	S	A	Y	T	G	N	T
N	Y	A	Q	K	F	Q	G	R	V	T	M	T	R	G	Y	D	S	T	S	A	Y	M	E	L	R	S	L	R
S	D	D	T	A	V	Y	Y	C	A	R	D	R	G	Y	Y	D	A	D	F	I	W	G	Q	G	T	L	V	T
V	S	S	G	G	G	G	S	G	G	G	G	S	G	Y	G	G	S	D	I	M	Q	S	P	S	Q	S	T	L
S	A	S	I	G	D	R	V	T	I	T	C	R	A	S	E	G	I	Y	H	L	A	W	Y	Q	Q	K	P	T
G	K	A	P	K	L	L	I	Y	K	A	S	S	L	A	S	G	A	P	S	R	F	S	G	S	G	T	F	F
D	F	T	L	T	I	S	S	L	Q	P	D	D	F	A	T	Y	Y	C	Q	Q	Y	N	Y	P	L	T	F	F
G	G	G	T	K	L	E	I	K	R	A	A	A	A	A	A	A	A	A	Q	Q	Y	S	Y	P	L	T	F	F

SEQ ID NO:34

CAGGTGCAGCTGGTGGAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGTCTCTGCAAGGCTTCTGGTTACACCTTTACCAGTTATGGTA
TCAGCTGGGTGCGACAGGCCCTGGACAAGGCTTGAGTGGATGGATGG
ATCAGCGCTTACACTGGTAACACAACATATGCACAGAAGTTCCAGGGCAG
AGTACCATGACCACAGACACATCCACGACACAGCCTACATGGAACTGA
GGAGCCTGAGATCTGACGACACGCGGTGTATACTGTCCGAGAGATCGT
GGATACTATGATGCTTTTGATATCTGGGCCAAGCACCCCTGTCACCGT
CTCCTCAGGTGAGGCGGTTCAGGCGGAGGTGGCAGCGCGGTGGCGGAT
CGGACATCCAGATGACCCAGTCTCCTCCACCCGTGCTGCATCTATTGGA
GACAGAGTACCATCACCTGCGGCCAGTGAGGGTATTTATCACTGGTT
GGCCTGGTATCAGCAGAAGCCAGGAAAGCCCTAAACTCCTGATCTATA
AGGCCCTCTAGTTTAGCCAGTGGGGCCCATCAAGTTCAGCGCAGTGGA
TCTGGGACAGATTCTCACTCTCACCATCAGCAGCCTGCAGCCTGATGATTT
TGCAACTTATTACTGCCAACAATATAGTAATTATCCGCTCACTTTCGGCG
GAGGGACCAAGCTGGAGATCAAACGTGCGGCGCA

FIG. 9(cont.)

GIL45

SEQ ID NO:43

Q M Q L V Q S G G G V V Q P G R S L R L S C A A S G T F S
N Y G M Y W V R Q A P G K D N S R N T V A H Y L I W Q M N S L R A E K Y
A D S V K G C A T E Q H W I T A F D I W G K G T L V S G S L R A E D
T A V Y Y C A G G S G G G S Q S V L T Q S A S S G Q
G G S G A G G S G G G S Q S V L T Q S A S S G Q
S I T I S C T G T S S D V G Y N Y V S G S K P A S P G A P
K L M I Y E G S K R P S G V S N R F S G S K S T R S G G T K
I S G L Q A E D E A D Y Y C S S Y T T R S G G T K
L T V L G A A H

SEQ ID NO:52

CAGATGCAGCTGGTGCAGTCTGGGGAGCGGTGGTCCAGCCTGGAGGT
CCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTAACATATGG
CATGTACTGGTCCGCCAGGCTCCAGGCAAGGGCTGGAGTGGTGCA
CATATTTGGTATGATGGAAGTAATGAAAGTATGCAGACTCCGTGAAGG
GCCGAATGACCGTCTCCAGAGACAATTCAGGAACACGTTGTATTGCA
AATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGACA
GAGCAACACTGGATTACTGCTTTTGATATCTGGGGCAAGCACCCCTGG
TCACCGTCTCCTCAGGTGGAGCGGTTACGGCGCAGGTGGCAGCGCGG
TGGCGGATCGCAGTCTGTGCTGACTCAGCCTGCCCTCCGTGTCTGGGTCT
CCTGGACAGTCGATCACCATCTCCTGCACCTGGAACCCAGCAGTGACGTG
GTGGTTATAACTAATGTCCTCCTGGTACCAACAACACCCAGGCAAGCCCC
CAAACTCATGATTATGAGGCGAGTAAGCGGCCCTCAGGGTTTCTAAT
CGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACAATCTCTG
GGCTCCAGGCTGAGGACGAGGCTGATTATTACTGCAGCTCATATACAAC
CAGGAGCACTCGAGTTTTCGGCGGAGGACCAAGCTGACCGTCCCTAGGT
GCGGCCGCA

FIG. 9(cont.)

GIL60

SEQ ID NO:61.

E V Q L V E S G G V V R P G G G S L R L S C A A S G F T F D
D Y G M N W V R Q A P G K G L E W V S L V S L G Y L Q M N S L L R A E D
A A S V K G R F T I S Y W G S G S A Q A Y N F W G T R V T V S
T A L Y Y C A R G G S G S G S A Q A Y N F W G T R V T V S
S G G G S I T I I Y D V N K R P S G V C S S T S Y Q S V F G S
P G Q S I T I I Y D V N K R P S G V C S S T S Y Q S V F G S
K T P K L I I Y D V N K R P S G V C S S T S Y Q S V F G S
S L T I S G L Q A E D E S D Y Y C S S T S Y Q S V F G S
G T K V T V L G A A

SEQ ID NO:70

GAGGTGCAGCTGGTGGAGTCCGGGGGAGGTGTGGTACGGCCTGGGGGT
CCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTGACGATTATGG
CATGAAGTGGTCCGCCAAGCTCCAGGGAAGGGCTGGAGTGGTCTCT
GGTGTAAATGGGAATGGTGGTACCAGAGATTATGCAGCCTCCGTGAAGG
GCCGATTACCATCTCCAGAGACAACGCCAAGAACTCCCTGTATCTGCA
AATGAACAGCTGAGAGCCGAGGACACGGCCTTGTATTACTGTGCGAGA
GGATGGTATAGTGGGAGCTTCTACTACTTGGCTACTGGGCGCGAGGAA
CCCTGGTCACCGTCTCGAGTGGAGGCGGCTTCAGGCGGAGGTGGCTC
TGGCGGTGGCGGAAGTGCACAGGCTGTGCTGACTCAGCCGCTCCGTG
TCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCACTGGAGCCAGCG
GTGACGTTGGTGTATATACTTTGTCTCCTGGTACCAACAACACCCAGG
CAAAACCCCAACTCATATAATTATGATGTCAATAAGCGCCCTCAGGG
GTTTCTAATCGCTTCTGTGGCTCCAAGTCTGGCAACACGGCCTCCCTGA
CCATCTCTGGGCTCCAGGCCGAGGACGAGTCTGATTATTACTGCAGCTC
ATATACAAGCACCTTCTCTGTGGTATTGGCGGAGGGACCAAGTCAACC
GTCCTAGGTGGGCC

FIG. 9(cont.)

GIL68

SEQ ID NO:79

E V Q L V Q S G A E V K K P G A S V G Y K W M E L P Q D A S G G T F Y T S D
Y Y I H W V R Q T P G Q G F E W M A Y Q P P G G T R Y T A Q
K F Q G W V T M T R D M S N T I W G Q R L V A T R L R S G A V
Y Y C A R D L T G F D P F D I W G Q P R T A V V A P I S R V L G A
G G G S G G S A Q S V L T Q Q Q N F L
T C G G N F R N K R V H W Y Q Q N F L
D R P S G I P E R F S G S R S G N F L
A D F Y C Q V W D S S T D R P L

SEQ ID NO:88

GAAGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTCTCCTGTCAAGCTTCTGGATACACCTTCAGCGATTACTATA
TTCACCTGGTGGACAGACCCCTGGACAAGGTTTGAAGTGGATGGATGG
GTCAACCCCTGACACTGGTGGCACAAAGATACGCCGAGAAGTTTCAGGGCTG
GGTCACCATGACCAGGGACATGTCCAACACACAGCCTACATGGAGCTGC
CCAGGCTGAGAGACGACACAGCGCCGTATATTACTGTGCGAGAGATCTA
ACTGGATTGTGATCCCTTTGATATCTGGGCCAGGAAACCCTGGTCACCGT
CTCGAGTGGAGGCGGGTTCAAGCGGAGGTGGCTCTGGCGGTGGCGGAA
GTGCACAGTCTGTGCTGACTCAGCCACCCTCAGTGTCAAGTGGCCCAAGGA
AAGACGGCCACGATTACCTGTGGGGGAAACAACCTTCGAAATAAAGAGT
ACACTGGTATCAGCAGAGGCCAGGCCAGGCCCTGTCTGTCATCTATT
ATGATTCAGACCGGCCCTCAGGATCCCTGAGCGATTCTCTGGCTCCCGC
TCTGGGAACACGGCCACCCTGACCATCAGCAGGTCGAGGCCGGGATGA
GGCCGACTTTTACTGTCAAGTGTGGATAGTAGTACTGATCGTCCGCTGT
TCGGCGGAGGACCAAGCTGACCGTCCTAGGTGCGGCGCA

FIG. 9(cont.)

GIL92

SEQ ID NO:97

Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S	V	K	V	S	C	K	A	S	G	Y	T	F	T	D	Y	Y	
M	H	W	V	R	Q	A	P	G	Q	G	L	E	W	V	G	A	W	I	N	P	Y	T	G	G	A	F	Y	A	Q	K	F	R	G
R	V	T	M	T	R	D	T	S	I	N	T	A	Y	M	E	L	S	S	R	L	G	S	D	D	T	A	V	Y	Y	C	A	R	E
P	E	K	F	D	F	W	G	G	D	N	W	G	R	G	T	M	V	V	T	V	S	S	G	G	G	G	S	G	T	G	S	S	N
G	G	S	A	Q	A	V	L	T	Q	P	S	S	S	V	S	G	A	A	P	G	Q	R	V	T	I	S	C	T	G	S	S	N	
I	G	A	G	Y	G	V	H	W	Y	Q	Q	L	P	G	T	A	P	K	L	L	I	Y	G	N	S	N	R	P	S	G	V	P	
D	R	F	S	G	S	K	S	G	T	S	A	S	L	A	I	T	G	L	Q	A	E	D	E	A	D	Y	Y	C	Q	S	Y	D	
S	S	L	S	G	Y	V	F	G	T	G	T	Q	L	T	V	L	S	A	A	A													

SEQ ID NO:106

CAGGTCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTCCTGCAAGGCTTCGGATACACCTTCACCGACTACTATA
TGCACCTGGGTGCGACAGGCCCTGGACAAGGCTTGAGTGGTGGATGG
ATCAACCCTTATACTGGTGGCGCATTCCTATGCACAGAAGTTTCGGGGCAG
GGTCACCATGACCAGGACACGTCCTCATCAACACAGCCTACATGGAGCTGA
GCAGACTGGGATCTGACGACACAGCCCGTGTTATTTGTGCGAGAGAACCT
GAAAAATTCGATTTTGGGGGGGTGACAACTGGGGCCGGGGACAAATGGT
CACCGTCTCGAGTGGAGCGCGGTTTCAGCGGAGGTGGCTCTGGCGGTG
GCGGAAGTGCACAGGCTGTGCTGACTCAGCCGTCCTCAGTGTCTGGGGCC
CCAGGGCAGAGGTCACCATCTCCTGCCACTGGGAGCAGCTCCAACATCGG
GGCAGGTTATGGTGTAACACTGGTACCAACACAGCTTCCAGGAACAGCCCCCA
AACTCCTCATCTATGGTAACAGCAATCGGCCCTCAGGGTCCCTGACCGA
TTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCAGTGGCT
CCAGGCTGAGGATGAGGCTGATTATCTGCTCCAGTCCCTATGACAGCAGCC
TGAGTGGTTATGCTCTCGGAAGTGGGACCCAGCTCACCGTTTAAAGTGGC
GCCGCA

FIG. 9(cont.)

097D09

SEQ ID NO:115

EVQLVESGGGLVTPGGSRLRLSCAASGFTESDYMSWVRQAPGRGLEWVSAIS
GSGGSTYYADSVKGRITISRDNAKNSLYLQMSLRSEDTAVYYCARGLWVWD
PLDYWGRGTLVTVSSGGSGGGGGGGSDIQMTQSPSTLSASIGDRVITIT
CRASEGIYHHLAWYQQKPKAPKLLIYKASSLASGAPSRFSGSGFGTDFTLT
ISSLPQDDFATYYCQOYSEFAWTFGGGTKLEIKRAAAH

SEQ ID NO:124

GAGGTGCAGCTGGTGGAGTCTGGGGAGGCTTGGTACGCCCTGGAGGGT
CCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTGACTACTA
CATGAGCTGGTCCGCCAGGCTCCAGGAGGGGCTGGAGTGGTCTCA
GCTATTAGTGGTAGTGGTAGCACATACGACAGACTCCGTGAAGG
GCCGGATCACCATCTCCAGAGACAACGCCAAGAACTCACTGTATCTGCA
AATGAGCAGCCTGAGATCTGAGGACACGCCCGTGTTACTGTGCGAGA
GGGCTTTGGGTTTGGGATCCTCTTGACTACTGGGCAGAGGAACCCCTGG
TCACCGTCTCTTCAGGTGGGGCGGTTTCAGGCGGAGGTGGCAGCGGCGG
TGGCGGATCGGACATCCAGATGACCCAGTCCCCTTCCACCCGTCTGCA
TCTATTGGAGACAGAGTCACCATCACCTGCCGGCCAGTGAGGGTATTT
ATCACTGGTTGGCCTGGTATCAGCAGAAGCCAGGAAAGCCCTAAACT
CCTGATCTATAAGGCCTCTAGTTTAGCCAGTGGGGCCCCCATCAAGTTC
AGCGGCAGTGGATTTGGGACAGATTTCACCTCTCACCATCAGCAGCCTGC
AGCCTGATGATTTTGCAACTTATTACTGCCAACAAATACAGCGAGTTCGC
CTGGACCTTCGGCGGAGGGACCAAGCTGGAGATCAAAACGTGCGGCCGCA
CAT

FIG. 9(cont.)

062A09

SEQ ID NO:133

QVQLVESGAEVKKPGASVKVSCKASGYTFTSYGIGSWVRQAPGQGLEWMGWV
SAYTGNTNYAOKFOGRVTMTTDTSTSTAYMELRLRSDDDTAVYYCARDRGY
YDAYDIWGQGLTVTVSSGGGGGGGGSDIQMTQSPSTLSASIGDRV
TITCRASEGIYHWLAWYQQKPGKAPKLLIYKASSLASGAPSRFSGSGFGTD
FTLTISSLQPDDFATYYCOOMGEYNATIGGGTKLEIKRAAAH

SEQ ID NO:142

CAGGTGCAGCTGGTGGAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAGTTATGGTA
TCAGCTGGGTGCGACAGGCCCTGGACAAGGCTTGAGTGGATGGGATGG
GTCAGCGCTTACACTGGTAACACAACTATGCACAGAAGTTCCAGGGCAG
AGTCACCATGACCACAGACACATCCACGAGCACAGCCTACATGGAACCTGA
GGGGCCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGAGATCGT
GGATACTATGATGCTTATGATACTGGGGCCAAGCACCCCTGGTCACCGT
CTCCTCAGGTGGAGCGGTTTCAGCGGAGGTGGCAGCGCGGTGGCGGAT
CGGACATCCAGATGACCCAGTCTCCTTCCACCTGTCTGCATCTATTGGA
GACAGAGTCACCATCACCTGCCGGCCAGTGAGGGTATTATCACTGGTT
GGCCTGGTATCAGCAGAAGCCAGGAAAGCCCCCTAAACTCCTGATCTATA
AGGCCTCTAGTTTAGCCAGTGGGGCCCCCATCAAGGTTACGGGCAGTGGA
TTTGGGACAGATTTCACCTCTCACCATCAGCAGCCTGCAGCCTGATGATTT
TGCAACTTATTACTGCCAACAAATGGGCGAGTACAACGCCACCATCGGCG
GAGGACCAAGCTGGAGATCAAACTGCGGCGCCGACAT

FIG. 9(cont.)

062G05

SEQ ID NO:151

QVQLVESGAEVKKPGASVKVSKASGYTFTSYGISWVRQAPGQGLEWMGWI
SAYTGNTNYAOKFOGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDRGY
YDAFDIWGQGTLVTVSSGGGGSGGGGGSDIQMTQSPSTLSASIGDRV
TITCRASEGIYHWLAWYQQKPKAPKLLIYKASSLASGAPSRFSGSGFGTD
FTLTISSLQPDDEFATYYCQOMGEWKAAFGGGTKLEIKRAAAH

SEQ ID NO:160

CAGGTGCAGCTGGTGGAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTCTCCTGCAAGCTTCTGGTTACACCTTTACCAGTTATGGTA
TCAGCTGGGTCCGACAGGCCCTCGACAAGGCTTGAGTGGATGGGATGG
ATCAGCGCTTACACTGGTAACACAAACTATGCACAGAAAGTTCCAGGGCAG
AGTCACCATGACCAAGACACATCCACGACACAGCCTACATGGAACTGA
GGAGCCTGAGATCTGACGACACGCCCGTGTA~~TACTGTCCGAGAGATCGT~~
GGATACTATGATGCTTTCGATATCTGGGGCCAAGCACCCCTGGTCACCGT
CTCCTCAGGTGGGGCGGTTCAGCGGAGGTGGCAGCGCGGTGGCGGAT
CGGACATCCAGATGACCCAGTCTCCTCCACCCCTGTCTGCATCTATTGGA
GACAGAGTCACCATCACCTGCCGGCCAGTGAGGGTATTATCACCTGGTT
GGCCTGGTATCAGCAGAAGCCAGGGAAGCCCTAACTCCTGATCTATA
AGGCCCTCTAGTTTAGCCAGTGGGGCCCCCATCAAGTTCAGCGGCAGTGGA
TTTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGATGATTT
TGCAACTTATTACTGCCAACAATGGGGAGTGGAGCGCGCCTTCGGCG
GAGGGACCAAGCTGGAGATCAAAACGTGGCGCGGCACAT

FIG. 9(cont.)

087B03

SEQ ID NO:169

EVQLVESGGGVVRPGGSLRLSCAASGFTFDDYGMNWRQAPGKGLEWVSGV
NWNGGTRDYAASVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARGWYS
GAAWNMGYWGRGTLVTVSSGGGGGGGSAQAVLTQPSVSGSPGQ
SITISCTGASGDVGAYNFVSWYQHPGKTPKLIIYDVNKRPSGVSNRFSGS
KSSNTASLTISGLQAEDESSYTSFSVVFGGTKVTVLGAAAH

SEQ ID NO:178

CGAGGTGCAGCTGGTGAGTCCGGGGGAGGTGTGGTACGGCCTGGGGGTCCCTG
AGACTCTCCTGTGCAGCCTCTGGATTACACCTTTGACGATTATGGCATGAAC TG
TCCGCCAAGCTCCAGGAAGGGCTGGAGTGGTCTCTGGTGTAA TTGGAATGG
TGGTACCAGAGATTATGCAGCCTCCGTGAAGGCCGATTACCATCTCCAGAGAC
AACGCCAAGAACTCCCTGTATCTGCAAAATGAACAGTCTGAGAGCCGAGACACGG
CCTTGATTACTGTGCCGAGAGGATGGTATAGTGGGCCCGTGGAACATGGGCTA
CTGGGCCGAGGAACCTGGTCACCGTCTCGAGTGAGGCGCGGTTTCAGGCGGA
GGTGGCTCTGGCGGTGGCGGAAGTGCACAGGCTGTGCTGACTCAGCCGTCCTCCG
TGCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCACTGGAGCCAGCGGTGA
CGTTGGTGCTTATAACTTTGTCTCCTGGTACCAACAACCAGCAAAACCCCC
AAACTCATAATTTATGATGTCAATAAGCGGCCCTCAGGGTTTCTAATCGCTTCT
CTGGCTCCAAGTCTAGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCCGA
GGACGAGTCTGATTATTACTGCAGCTCATATACAGCACCTTCTCTGTGGTATT
GGCGGAGGACCAAGGTCACCGTCCCTAGGTGCGGCGGCACAT

FIG. 9(cont.)

367D04

SEQ ID NO:187

EVQLVESGGGVRRPGGSLRLSCAASGFTFDDYGMNWVRQAPKGLEWVSG
VNWNGGTRDYAASVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARGW
YSGSPWSLGHWGRGTLVTVSSGGGGGGGGGGGGGGGGGGGGGGGGGGGGG
GGGSAQAVLTQPSVSGSPGQSVTISCTGASGDVGAYNEVSWYQQHPGK
TPKLIIDVNRKPSGVSNRFSGSKSGNTASLTISRQLQAEDESYYCSSYT
SRYTTEFGGGTKVTVLGAAAH

SEQ ID NO:196

GAGGTGCAGCTGGTGGAGTCCGGGGGAGGTGTGTTACGGCCTGGGGGGT
CCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTGACGATTATGG
CATGAACCTGGTCCGCCAAGCTCCAGGAAGGGCTGGAGTGGTCTCT
GGTGTTAATTGGAATGGTGTTACCAGAGATTATGCAGCCTCCGTGAAGG
GCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTATCTGCA
AATGAACAGCTGTAGAGCCGAGGACACGGCCTTGTTACTGTCCGAGA
GGATGGTATAGTGGAGCCCGTGTCGCTGGGCCACTGGGCCGAGGAA
CCCTGGTCACCGTCTCGAGTGGAGGGCGGGTTCAGGCGGAGGTGGCTC
TGCGGTTAGCGAGGTGGCTCTGGCGGTAGCGGAGGTGGCTCTAGCGGA
GGTGGCTCTGGCGGTGGCGGAAGTGCACAGGCTGTGCTGACTCAGCCGT
CCTCCGTGTCTGGGTCTCCTGACAGTCGGTCACCATCTCCTGCACTGG
AGCCAGCGGTGACGTTGGTGCTTATAACTTTGTCTCCTGGTACCAACAA
CACCCAGGCAAAACCCCAAACTCATATTTATGATGTCAATAAGCGGC
CCTCAGGGGTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGC
CTCCCTGACCATCTCTAGGCTCCAGGCCGAGGACGAGTCTGATTATTAC
TGCAGCTCATATACATCGAGGTACACGACCGAGTTTGGCGGAGGGACCA
AGGTCACCGTCTCTAGGTGCGGCCGCACAT

FIG. 9(cont.)

368D04

SEQ ID NO:205

EVQLVESGGGVVRPGSLRLSCAASGFTFDDYGMNWVRQAPKGLEWVSG
VNWNGGTRDYAASVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARGW
YSGAAWNMGYWGRGTLVTVSSGGSGGGSGGGSGGGSGGGSGGGGS
AQAVLTQPSVSGSPGQSIITISCTGASGDVGAYNEFSWYQQHPGKTPKLI
IYDVNKRPSGVSNRFSGSKSGNTASLTISGLQAEDESDYYCASLVSDFSV
VFGGCTKVTVLGAAAH

SEQ ID NO:214

GAGGTGCAGCTGGTGGAGTCCGGGGGAGGTGTGGTACGGCCTGGGGGGT
CCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTGACGATTATGG
CATGAACTGGTCCGCCAAGCTCCAGGGAAGGGCTGGAGTGGTCTCT
GGTGTTAATTGGAATGGTGGTACCAGAGATTATGCAGCCTCCGTGAAGG
GCCGATTCAACCATCTCCAGAGACAACGCCAAGAACTCCCTGTATCTGCA
AATGAACAGTCTGAGAGCCGAGGACACGGCCTTGTAATTACTGTGCGAGA
GGATGGTATAGTGGGCCCGCTGGAAACATGGGCTACTGGGCCCGAGGAA
CCCTGGTCACCGTCTCGAGTGGAGCGCGGTTTCAGCGGAGGTGGCTC
TGGTGGTAGCGGAGGTGGCTCTGGCGGTGGCGGAGGTGGCTCTGGCGGT
GGCGGAAGTGCACAGGCTGTGCTGACTCAGCCGTCCTCCGTGTCTGGGT
CCCCTGGACAGTCGATCACCATCTCCTGCACTGGAGCCAGCGGTGACGT
TGGTGCTTATAACTTTGTCTCCTGGTACCACACACCCAGCCAAAACC
CCCAAACTCATATAATTATGATGTCATAAGCGGCCCTCAGGGTTTCTA
ATCGCTTCTCTGGCTCCAAAGTCTGGCAACACGGCCTCCCTGACCATCTC
TGGGCTCCAGGCCGAGGACGAGTCTGATTATTACTGCCCTCCCTCGTC
TCCGACTTCTGTGGTATTGGCGGAGGACCAAGGTCACCGTCCCTAG
GTGCGGCCGCACAT

FIG. 9(cont.)

166B06

SEQ ID NO:223

EVQLVQSGAEVKKPGASVKVSQASGYTFSDYYIHWVRQTPGQGF^{EW}MGWV
NPDTGGTRYAOKFQGWVTMTDRDMSNTTAYMELPRLRDDDTAVYYCARDLTG
FD^{PE}FDIWGQGLTVTVSSGGSSGGSGGSAQSVLTQPPSVSVAPGKTA
TITCGGNFRNKR^{VHWYQQRPQAPVLVIYYDS}DRPSGIPERFSGSRSGNT
ATLTISRVEAGDEADFYCQVWDLFNDNGVFGGGTKLTVLGAAAH

SEQ ID NO:232

GAAGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTCTCCTGTCAAGGCTCTGGATACACCTTCAGCGATTACTATA
TTCACTGGGTGCGACAGACCCCTGGACAAGGTTTGAGTGGATGGGATGG
GTCAACCCCTGACACTGGTGGCACAAGATACCGCGAGAAGTTTCAGGGCTG
GGTCACAATGACCAGGGACATGTCCAACACACAGCCTACATGGAGCTGC
CCAGGCTGAGAGACGACACAGGCCGTATATTACTGTGCGAGAGATCTA
ACTGGATTTGATCCCTTTTGATATCTGGGCCAGGAAACCCTGGTCACCGT
CTCGAGTGGAGCGGCAGTTCAGGTGGAGTGCTCTGGCGGTGGCGGAA
GTGCACAGTCTGTGCTGACTCAGCCACCCTCAGTGTCAGTGGCCCCAGGA
AAGACGGCCACGATTACCTGTGGGGAAACAAC^{TTTCGAAATAAA}AAGAGT
ACACTGGTATCAGCAGAGGCCAGGCCAGCCCCCTGTCCTGGTCATCTATT
ATGATT^{CAGACCGGCCCTCAGG}GATCCCTGAGCGATTCTCTGGCTCCCGC
TCTGGGAACACGGCCACCCTGACCATCAGCAGGTCGAGGCCGGGATGA
GGCCGACTTTTACTGT^{CAGGTGTGGATCTCTTCA}ACGACAACGGCGTGT
T^{CGGCGGAGGACCAAGCTGACCGT}CCTAGGTGCGGCCGCACAT

FIG. 9(cont.)

166G05

SEQ ID NO:241

EVQLVQSGAEVKKPGASVKVSCQASGYTFSDYIHWVRQTPGQGFWMGVV
NPDTGGTRYAOKFOGWVTMRDMSNTTAYMELPRLRDDDTAVYYCARDLTG
FDPFDIWGQGLVTVSSGGSGGGGSAQSVLTQPPSVSVAPGKTA
TITCGGNFRNKRHVHWYQQRPGQAPVLVIYDSDRPSGIPERFSGSRSGNT
ATLTISRVEAGDEADFYCQVWDFLTDSGSFGGGTKLTVLGAAAH

SEQ ID NO:250

GAAGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTCTCCTGTCAGGCTTCTGGATACACCTTCAGCGATTACTATA
TTCAC TGGGTGCGACAGACCCCTGGACAAGGTTTGAGTGGATGGGATGG
GTCAACCCGTGACACTGGTGGCACAAGATACGGCAGAAAGTTTCAGGGCTG
GGTCACAAATGACCAGGGACATGTCCAACACACAGCCTACATGGAGCTGC
CCAGGCTGAGAGACGACGACACGCCGTATATTACTGTCCGAGAGATCTA
ACTGGATTTGATCCTTTTGATATCTGGGCCAGGAAACCCTGGTCACCGT
CTCGAGTGGAGGGCGGTTTCAGCGGAGGTGGCTCTGGCGGTGGCGGAA
GTGCACAGTCTGTGCTGACTCAGCCACCCTCAGTGTCA GTGGCCCCAGGA
AAGACGGCCACAATTACCTGTGGGGAAACAAC TTCGAAATAAAAGAGT
ACACTGGTATCAGCAGAGGCCAGGCCAGGCCCTGTCTGGTCATCTATT
ATGATTCAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCCCC
TCTGGGAACACGGCCACCCTGACCATCAGCAGGTCGAGGCCGGGATGA
GGCCGACTTTTACTGT CAGGTGTGGGATTTCCCTCACCGACTCGGGTCTGT
TCGGCGGAGGACCAAGCTGACCGTCTAGGTGCGGCCGCACAT

FIG. 9(cont.)

375G06

SEQ ID NO:259

EVQLVQSGAEVKKPGASVKVSCQASGYTFSDY¹YIHWVRQTPGQGF²EW³MGW⁴
VNPDTGGTRYAOKFQGW⁵VTMT⁶RDMSNTTAYMELPRLRDDDTAVYYCARDL⁷
TG⁸YDY⁹DRWGQGLVTVSSGGGGGGGGGGGGGGGGGGGGGGGGGGGSAQ¹⁰
SVLTQPPSMSVAPGKTATITCGGNFRNKR¹¹VHWYQORPGQAPVLVIYYDS¹²
DRPSGIPERFSGSRSGNTATLTISRVEAGDEADFYCQVWDFLADEAMFEGG¹³
GTKLTVLGAAAH¹⁴

SEQ ID NO:268

GAAGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGCCTC¹
AGTGAAGGTCTCCTGTCTCAGGCTTCTGGATACACCTTCAGCGATTACTATA²
TTCAC³TGGTGCACAGACCCCTGGACAAGGTTTGAGTGGATGGGATGG⁴
GTCAACCCCTGACACTGGTGGCACAAAGATACGGCAGAAAGTTTCAGGGCTG⁵
GGTCACAATGACCAGGGACATGTCCAACACACAGCCTACATGGAGCTGC⁶
CCAGGCTGAGAGACGACGACACGCGCCGTATATTACTGTGCGAGAGATCTA⁷
ACTGGATACGACTACTACGACCGGTGGGGCCAGGGAACCCCTGGTCACCGT⁸
CTCGAGTGGAGCGCGGTTTCAGCGGAGGTGGCTCTGGCGGTGGTGGAG⁹
GTGGCTCTGGCGGTGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGCACAG¹⁰
TCTGTGCTGACTCAGCCGCCCTCAATGTCAGTGGCCCCAGGAAGACGGC¹¹
CACGATTACCTGTGGGGAAACAAC¹²TTTCGAAATAAAAGAGTACACTGGT¹³
ATCAGCAGAGGCCAGGCCAGCCCCCTGTCTCTGGTCATCTATTATGATTCA¹⁴
GACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCCGCTCTGGGAA¹⁵
CACGGCCACCCCTGACCATCAGCAGGTCGAGGCCGGGATGAGGCCGACT¹⁶
TTTACTGTCAGGTGTGGGATTTCCTCGCCGACGAGGCGGATGTTCCGGCGGA¹⁷
GGGACCAAGCTGACCGTCTCTAGGTGCGGGCCGCACAT¹⁸

FIG. 9(cont.)

376B10

SEQ ID NO:277

EVQLVQSGAEVKKPGASVKVSCQASGYTFSDYIHWVRQTPGQGFEWMGW
VNPDTGGTRYAOKFOGWVTMRDMSNTTAYMELPGLRDDDTAVYYCARDL
TGYDQYTAWGQGTLVTVSSGGSGGGGSAQSVLTQPPSVSVAPG
KTATITCGGNFRNKRHVHWYQORPGQAPVLVIYDSDRPSGIPERFSGSR
SGNTATLTISRVEAGDEADFYCSTFDPFTDRPLFGGGTKLTVLGAAAH

SEQ ID NO:286

GAAGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTCTCCTGTCAGGCTTCTGGATACACCTTCAGCGATTACTATA
TTCACCTGGTGCACAGACCCACGACAAGGTTTGAGTGGATGGGATGG
GTCAACCTGACACTGGTGGCACGAGATACGGCAGAAAGTTTCAGGGCTG
GGTCACAAATGACCAGGGACATGTCCAACACACAGCCTACATGGAGCTGC
CCGGCTGAGAGACGACGACACGCCGTATATTACTGTCCGAGAGATCTA
ACTGGGTACGACCAGTACACGGCCTGGGGCCAGGGAACCTGGTCACCGT
CTCGAGTGGAGCGCGGTTTCAGCGGAGGTGGCTCTGGCGGTGGCGGAA
GTGCACAGTCTGTGCTGACTCAGCCACCCTCAGTGTCAGTGGCCCCAGGA
AAGACGGCCACGATTACCTGTGGGGGAACAACACTTCGAAATAAAAGAGT
ACACTGGTATCAGCAGAGGCCAGGCCAGCCCCCTGTCTGTCTATCTATT
ATGATTTCAGACCGCCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCCCG
TCTGGGAACACGGCCACCCTGACCATCAGCAGGTCGAGGCCGGGATGA
GGCCGACTTTTACTGTAGCACCTTCGACCCCTTCACTGATCGTCCGCTGT
TCGGCGAGGACCAAGCTGACCGTCTCTAGTGGCGCCGCACAT

FIG. 9(cont.)

354A08

SEQ ID NO:295

QVQLVQSGAEKKPGASVKVSKASGYTFTDYMHVVRQAPGQGLEWVGWIN
PYTGAFYAOKFRGRVTMTRDTSINTAYMELSRLGSDDTAVYYCAREPERF
GDSTGVWGRGTMVTVSSGGGGGGGSGGSRSAQAVLTQPSVSGAPRQR
VTISCTGSSSNIGAGYGVHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSK
SGTSASLAITGLQAEDEADYYCYHWDKEQSGYVFGTGTQLTVLSA

SEQ ID NO:304

CAGGTCCAGTTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTCCTGCAAGCTTCTGGATACACCTTCACCGACTACTATA
TGCACTGGGTCCGACAGGCCCTGGACAAGGCTTGAGTGGTGGGATGG
ATCAACCCTTATACTGGTGGCGCATTTCTATGCACAGAAGTTTCGGGGCAG
GGTCACAATGACCAGGACACGTCCTCATCAACACAGCCTACATGGAGCTAA
GCAGACTGGGATCTGACGACACGGCCGTGTATTATTGTGCGAGAGAACCT
GAAAGATTCCGGGACTCCACGGGGCAGGCTCTGGGGCCGGGGACAAATGGT
CACCGTCTCGAGTGGGGCGGGGTTTCAGGGGAGGTGGCTCTGGCGGTA
GCAGAAGTGCACAGGCTGTGCTGACTCAGCCGTCCTCAGTGTCTGGGGCC
CCAAGGCAGAGGTCACCATCTCCTGCACCTGGGAGCAGCTCCAACATCGG
GGCAGGTTATGGGTACACTGGTACCAACAGCTTCCAGGAACAGCCCCCA
AACTCCTCATCTATGGTAACAGCAATCGGCCCTCAGGGTCCCTGACCGA
TTCCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCACTGGGCT
CCAGGCTGAGGATGAGGCTGATTATTACTGCTACCACCTGGGACAAAGGAGC
AGAGTGGTTATGTCTTCGGAACTGGGACCCAGCTCACCGTTTTAAGTGCG

FIG. 9(cont.)

355B06

SEQ ID NO:313

EVQLVQSGAEVKKPGASVKVSCQASGYTFTDY¹YMHWVRQAPGQGLEWVGWI
NPYTGS²AFYAOKFRGRATMTRNTSINTAYMEL³SR⁴LGSD⁵DDTAVYYCAREPEK
FGESSGOLWGRGTMVTISSGGGSGGGSGGSAQA⁶VL⁷TQ⁸PSSVSGAPGQ
RVTISCTGSSSNIGPGYGVHWYQQ⁹LP¹⁰GTAPKLLIYGDSNRPSGVPDRFSGS
KSGTSASLAITGLQAEDEADY¹¹YCQSYDSGLSGYVFGTGTQ¹²LT¹³VL¹⁴SA

SEQ ID NO:322

GAAGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTCTCCTGTCAGGCTTCTGGATACACCTTCACCGACTACTATA
TGCACTGGGTGCGACAGGCCCTGGACAAGGCTTGAGTGGGTGGGTGG
ATCAACCCTTATAC¹TGGTAGCGCATTC²ATGCACAGAAGTTTCGGGGCAG
GGCCACAATGACCAGGAACACGTCCATCAACACAGCCTACATGGAGCTGA
GCAGACTGGGATCTGACGACACGCCCGTGTA³TATTGTGCGAGAGAACCT
GAAAAATTTCGGCGAGTCCAGCGGCCAGTTGTGGGCCGGGGACAATGGT
CACCATCTCGAGTGGAGCGCGGTTCA⁴GCGGAGGTGGCTCTGGCGGTA
GCGGAAGTGCACAGGCTGTGCTGACTCAGCCGTCC⁵TCAGTGTCTGGGGCC
CCAGGGCAGAGGTCACCATCTCCTGCACTGGGAGCAGCTCCAACATCGG
GGCAGGTTATGGTGTACACTGGTACCAACAGCTTCCAGGAACAGCCCCCA
AACTCCCTCATCTATGGTGACAGCAATCGGCCCTCAGGGGTCCCTGACCGA
TTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCACTGGGCT
CCAGGCCGAGGATGAGGCTGATTACTGCCAGTCC⁶TATGACAGCGGCC
TGAGTGGTTATGTCTTCGGAAC⁷TGGGACCCAGCTCACCGTTTAAAGTGGC

FIG. 9(cont.)

355E04

SEQ ID NO:331

QVQLVQSGAEVKKPGASVKVCKASGYTFTHYYMHWVRQAPGQGLEWVGWI
NPYTGGAFYAOKFOGRVTMTTRDTSINTAYMELSRIGSDDTAVYYCAREPEK
FDSPNAEIIWGRGTMVTISSEGGSGGGSGSAQAVLTQPSVSGAPGQ
RVTISCTGSSSNIGAGYGVHWYQQLPGTAPKLLIYGNRNRPSPGVPDRFSGS
KSGTSASLAITGLQAEDEADYYCQSYDSSLSGYVFGTGTQLTVLSA

SEQ ID NO:340

CAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAAAGCCTGGGGCCTC
AGTGAAGGTCTCCTGCAAGCTTCTGGATACACCTTCACCCACTACTATA
TGCACTGGGTCCGACAGGCCCTGGACAAGGCTTGAGTGGTGGGATGG
ATCAACCCTTATACTGGTGGCGCATTCTATGCACAGAAAGTTTCAGGGCAG
GGTCACAATGACCAGGGACACGTCCATCAACACAGCCTACATGGAGCTGA
GCAGACTGGGATCTGACGACACGCCGTGTATTATTGTCGAGAGAACCT
GAAAAATTTCGACTCGCCGAACGCCGAGATCTGGGCCGGGACAAATGGT
CACCATCTCGAGTGAAGCGCGGTTTCAGCGGAGGTGGCTCTGGCGGTA
GCGGAAGTGCACAGGCTGTGCTGACTCAGCCGTCCTCAGTGTCTGGGGCC
CCAGGGCAGAGGTCACCATCTCCTGCACTGGGAGCAGCTCCAACATCGG
GGCAGGTTATGGTGTACACTGGTACCAACAGCTTCCAGGAACAGCCCCCA
AACTCCTCATCTATGGTAACAGCAATCGGCCCTCAGGGTCCCTGACCGA
TTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCACTGGGCT
CCAGGCTGAGGATGAGGCTGATTATTACTGCCAGTCCCTATGACAGCAGCC
TGAGTGGTTATGTCTTCCGGAACCGGACCCAGCTCACCGTTTAAAGTGG

FIG. 9(cont.)

356A11

SEQ ID NO:349

QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYMHVVRQAPGQGLEWVGWI
NPYTGSAFYAQKFRGRVTMTRDTSINTAYMELSRLGSDDTAVYYCAREPEK
FDSDSDVWGRGTMVTVSGGGSSGGSGGSAQAVLTPPSVSGAPGQR
VTISCTGSSSNIGAGYGVHWYQQLPGTAPKLIIYGDSSRPSGVPDRFSGSK
SGTSASLAITGLQAEDEADYYCQSYDNSLSGYVFGTGTQLTVLSA

SEQ ID NO:358

CAGGTTCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAACCTGGGGCTC
AGTGAAGGTCCTCGAAGGCTTCTGGATACACCTTACCAACTACTATA
TGCACTGGTCCGACAGGCCCTGGACAGGGCTTGAGTGGGTGGATGG
ATCAACCCTTATACTGGTAGCGCATCTATATGCACAGAACTTCGGGGCAG
GGTTACAATGACCAGGACACGTCCATCAACACAGCCTACATGGAGCTGA
GCAGACTGGGATCTGACGACACGGCCGTGTATTATGTGCGAGAGAACCT
GAAAAATTCGACTCCGACGACTCCGACGCTCTGGGCCCGCGGACAAATGGT
CACCGTCTCGGTGGAGCGGCAGTTCAGCGGAGGTGCTCTGGCGGTA
GCGGAAGTGACAGGCTGTGCTGACTCAGCCGCCCTCAGTGTCTGGGGCC
CCAGGCAGAGGTCACCATCTCCTGCACTGGGAGCAGCTCCAACATCGG
GGCAGGTTATGGTGTACACCTGTACCAACAGCTTCCAGGAACAGCCCCCA
AACTCATCATCTATGGTGACAGCAGTCGGCCCTCAGGGTCCCTGACCGA
TTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCACTGGGCT
CCAGGCTGAGGATGAGGCTGATTACTGCCAGTCCTATGACAAACAGCC
TGAGCGGTTATGCTTCGGAACTGGGACCCAGCTCACCGTTTAAAGTCCG

FIG. 9(cont.)

GIL01

SEQ ID NO:367

QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSAIS
GSGSTYYADSVKGRITISRDNAKNSLYLQMNSLRAEDTAVYYCARGLWVWD
PLDYWGRGTLVTVSSGGGGGGGGGGSDIQMTQSPSTLSASVGDRVTTIT
CRASEGIYHWLAWYQQKPGKAPKLLIYKASSLASGVPSRFSSGSGTDF~~TT~~LT
 ISSLPDDFATYYCQQYSNYPLTFGGGTKVEIKRA

SEQ ID NO:376

CAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTC
 CCTGAGACTCTCCTGTGCAGCCTCTGGATTACACCTTCAGTGACTACTACA
TGAGCTGATCCGCCAGGCTCCAGGAAGGGCTGGAGTGGTCTCAGCT
ATTAGTGTAGTGGTGTAGCACATACTACGCAGACTCCGTGAAGGCCG
GATCACCATCTCCAGAGACAACGCCAAGAACTCACTGTATCTGCAAAATGA
ACAGCCTGAGAGCTGAGGACACGCCCGTGTTATTACTGTGCGAGAGGGCTT
TGGGTTTGGGATCCTCTTGACTACTGGGCCAGAGGAACCCCTGGTCACCGT
CTCTTCAGGTGGAGCGGTTCAGCGGAGGTGGCAGCGCGGTGGCGGAT
 CGGACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTTGGA
 GACAGAGTCACCATCACCTGCCGGCCAGTGAGGGTATTATCACTGGTT
GGCCTGGTATCAGCAGAAGCCAGGAAAGCCCTAAACTCCTGATCTATA
AGGCCCTCTAGTTTAGCCAGTGGGTCCCATCAAGGTTCAGCGGCAGTGGA
TCTGGGACAGATTTCACCTCTCACCATCAGCAGCCTGCAGCCTGATGATTT
TGCAACTTATTACTGCCAACAAATATAGTAATTATCCGCTCACTTTCGGCG
 GAGGGACCAAGGTGGAGATCAAACGTGCG

FIG. 10

GIL16

SEQ ID NO:385

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMGWI
SAYTGNNTNYAQKFQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDRGY
YDAFDIWGQGTLLVTVSSGGSGGGGGGSDIQMTQSPSTLSASVGD
RV
TITCRASEGIYHWLAWYQQKPGKAPKLLIYKASSLASGVPSRFSGSGSGTE
FTLTISSLQPDDFATYYCQQYSNYPLTFGGGTKVEIKRA

SEQ ID NO:394

CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTCTCCTGCAAGGCTTCTGTTACACCTTTACCAGTTATGGTA
TCAGCTGGGTGGACAGGCCCTGGACAAGGCTTGAGTGGATGGGATGG
ATCAGCGCTTACACTGGTAACACAAACTATGCACAGAAGTTCAGGGCAG
AGTCACCATGACACAGACACATCCACGACACAGCCTACATGGAACCTGA
GGAGCCTGAGATCTGACGACACGGCCGTGATTACTGTGCGAGAGATCGT
GGATACTATGATGCTTTTGATAATCTGGGGCCAAAGCACCCCTGGTCACCGT
CTCCTCAGGTGGAGCGGTTACGGCGGAGGTGGCAGCGCGGTGGCGGAT
CGGACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTGGA
GACAGAGTCACCATCACCTGCCGGCCAGTGAGGGTATTATCAGTGGTT
GGCCTGGTATCAGCAGAAGCCAGGGAAGCCCCCTAAACTCCTGATCTATA
AGGCCCTCTAGTTTAGCCAGTGGGTCCCATCAAGGTTACGGCAGTGGA
TCTGGGACAGAGTTCACTCTCACCATCAGCAGCCTGCAGCCTGATGATTT
TGCAACTTATTACTGCCCAACAATAAGTAATTATCCGCTCACITTCGGCG
GAGGGACCAAGGTGGAGATCAAAACGTGCG

FIG. 10(cont.)

GIL45

SEQ ID NO:403

QMQLVESGGVVQPGRSLRLSCAASGFTFSNYGMYWVRQAPKGLEWVAHI
WYDGSNEKYADSVKGRMTVSRDNSKNTLYLQMNLSLRAEDTAVYYCATEQHW
 ITAFDIWGKGTLTVSSGGGSGAGSGGGGSQSALTQPASVSGSPGQSIT
ISCTGTSSDVGGNYVSWYQQHPGKAPKLMIEGSKRPSGVSNRFSGSKSG
NTASLTISGLQAEDEADYYCSSYTRSTRVFGGGTKLTVLGA

SEQ ID NO:412

CAGATGCAGCTGGTGGAGTCTGGGGAGCGGTGGTCCAGCCTGGGAGGT
 CCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTA^{ACT}ATATGG
CATGTACTGGTCCGCCAGGCTCCAGGCAAGGGCTGGAGTGGGTGGCA
CATATTGGTATGATGGAAGTAATGAAAAGTATGCAGACTCCGTGAAGG
GCCGAATGACCGTCTCCAGAGACAAATCCAAAGAACACGTTGTATTGCA
 AATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGACA
GAGCAACACTGGATTACTGCTTTTGATACTGGGCAAGCACCCCTGG
 TCACCGTCTCCTCAGGTGGAGCGGTTCAGGCGCAGGTGGCAGCGGCGG
 TGGCGGATCACAGTCTGCGCTGACTCAGCCTGCCCTCCGTGTCTGGGTCT
 CCTGGACAGTCGATCACCATCTCCTGCACTGGAAACCAGCAGTGACGTTG
GTGGTTATAACTATGTCTCCTGGTACCAACAACACCCAGGCAAGCCCC
CAAACTCATGATTATGAGGGCAGTAAGCGGCCCTCAGGGGTTTCTAAT
 CGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACAATCTCTG
 GGCTCCAGGCTGAGGACGAGGCTGATTATTACTGCAGCTCATATACAAC
CAGGAGCACTCGAGTTTTCGGCGGAGGACCAAGCTGACCGTCCTAGGT
 GCG

FIG. 10(cont.)

GIL60

SEQ ID NO:421

EVQLVESGGGVVRPGGSLRLSCAASGFTFDDYGMNWVRQAPKGLEWVSG
VNWNGGTRDYAASVKGRFTISRDNAKNSLYLQMNSLRAEDTALYHCARGW
YSGSFYFEGYWGRGTLVTVSSGGSGGGGSAQAALTQPASVSGS
PGQSITISCTGASGDVGAYNEFSWYQQHPGKAPKLIIYDVNKRPSGVSNR
FSGSKSGNTASLTISGLQAEDEADYYCSSYTSTFSVVFGGGTKLTVLGA

SEQ ID NO:430

GAGGTGCAGCTGGTGGAGTCCGGGGGAGGTGTGGTACGGCCTGGGGGGTC
CCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTGACGATTATGGCA
TGAACTGGGTCGCCCAAGCTCCAGGGAAGGGCTGGAGTGGTCTCTTGGT
GTTAATTGGAATGGTGGTACCAAGATTATGCAGCCTCCGTGAAGGCCCG
ATTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTATCTGCAAATGA
ACAGTCTGAGAGCCGAGGACACGGCCTTGATCACTGTGCGAGAGGATGG
TATAGTGGAGCTTCTACTACTTTGGCTACTGGGCCGAGGAACCCCTGGT
CACCGTCTCGAGTGGAGCGCGGTTCAGCGGAGGTGGCTCTGGCGGTG
GCGGAAGTGCACAGGCTGCGCTGACTCAGCCGGCCTCCGTGTCTGGGTCT
CCTGGACAGTCGATCACCATCTCCTGCACTGGAGCCAGCGGTGACGTTGG
TGCTTATAACTTTGTCTCCTGGTACCAACAACACCCAGGCAAGCCCCCA
AACTCATAATTATGATGTCAATAAGCGGCCCTCAGGGTTTCTAATCGC
TTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCT
CCAGGCCGAGGACGAGGCTGATTATTACTGCAGCTCATATACAAGCACCT
TCCTCTGGTATTTGGCGGAGGACCAAGCTCACCGTCTCTAGGTGCG

FIG. 10(cont.)

GIL68

SEQ ID NO: 439

QVQLVQSGAEVKKPGASVKVCKASGYTFSDYIYIHWVRQAPGQGLEWMGWV
 NPDTGGTRYAOKFOGRVTMTRDMSISTAYMELSRLSDDTAVYYCARDLTIG
 FDPFDIWGQGLVTVSSGGGGGGGGSSVLTQPPSVSVAPGKTA
 RITCGGNFRNKRHVHWYQKPGAPVLVIYDSDRPSGIPERFSGSRSGNT
 ATLTISRVEAGDEADYYCQVWDSSTDRPLFGGGTKLTVLGA

SEQ ID NO: 448

CAAGTCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAACCCTGGGGCCTC
 AGTGAAGTCTCCTGTAAAGCTTCTGGATACACCTTCAGCGATTACTATA
 TTCACTGGGTCCGACAGGCCCTGGACAAGGTTGGAGTGGATGGATGG
 GTCAACCCTGACACTGGTGGCACAAGATACGCCAGAAAGTTTCAGGGCCG
 GGTCACAATGACCAGGACATGTCCATCTCCACAGCCTACATGGAGCTGT
 CCAGGCTGAGAAGCGACGACACGGCCGTATATTACTGTGCGAGAGATCTA
 ACTGGATTTGATCCTTTTGATATCTGGGGCCAGGAAACCCTGGTCACCGT
 CTCGAGTGGAGCGCGGTTTCAGCGGAGGTGGCTCTGGCGGTGGCGGAA
 GTGCATCGTCTGTGCTGACTCAGCCACCCTCAGTGTCAGTGGCCCCAGGA
 AAGACGGCCCGCATTACCTGTGGGGAAACAACCTTCGAAATAAAAGAGT
 ACACTGGTATCAGCAGAAGCCAGGCCCGCCCTGTCTGGTCATCTATT
 ATGATTCAGACCGCCCTCAGGATCCCTGAGCGATTCTCTGGCTCCCGC
 TCTGGGAACACGGCCACCCTGACCATCAGCAGGTCGAGGCCGGGATGA
 GGCCGACTATTACTGTCAGGTGTGGGATAGTAGTACTGATCGTCCGCTGT
 TCGGGGAGGGACCAAGCTGACCGTCTCTAGGTGCG

FIG. 10(cont.)

GIL92

SEQ ID NO:457

QVQLVQSGAEVKKPGASVKVSCKASGYTFTDYYMHWVRQAPGQGLEWVGWI
NPYTGGAIFYAOKFRGRVTMRDTSISTAYMELSRLRSDDTAVYYCAREPEK
FDFWGGDNWGRGTLVTVSSGGGGSGGGGSAQAVLTPPSVSGAPGQ
RVTISCTGSSSNIGAGYGVHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGS
KSGTSASLAITGLQAEDEADYYCQSYDSSLSGYVFGGGTQLTVLSA

SEQ ID NO:466

CAGGTCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTCTCCTGCAAGCTTCTGGATACACCTTCACCGACTACTATA
TGCACTGGTGCACAGGCCCTGGACAAGGCTTCAGTGGGTGGGATGG
ATCAACCCCTTATACTGGTGGCGCATTCTATGCACAGAAGTTTCGGGGCAG
GGTCACAATGACCAGGGACACGTCCATACACACAGCCTACATGGAGCTGA
GCAGACTGAGATCTGACGACACGCCCGTGTATTATGTGCGAGAGAACCT
GAAAAATTCGATTTTGGGGGGTGACAACTGGGCCCGGGGACATTGGT
CACCGTCTCGAGTGAGGCGCGGTTCAGGCGGAGGTGGCTCTGGCGGTG
GCGGAAGTGACAGGCTGTGCTGACTCAGCCCGCTCAGTGTCTGGGGCC
CCAGGCAGAGGTCACCATCTCCTGCACTGGGAGCAGCTCCAACATCGG
GGCAGGTTATGGTGTACACTGGTACCAACAGCTTCCAGGAACAGCCCCCA
AACTCCTCATCTATGGTAACAGCAATCGGCCCTCAGGGGTCCCTGACCGA
TTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCACTGGGCT
CCAGGCTGAGGATGAGGCTGATTATTACTGCCAGTCCCTATGACAGCAGCC
TGAGTGGTTATGTCTTCGGAGGTGGGACCCAGCTCACCGTTTAAAGTGCG

FIG. 10(cont.)

062A09

SEQ ID NO:475

Q V Q L V Q S S G A E V K K P G A S V K V K V S C K A S G Y T
F T S Y G I S S W V R Q R V C A P G Q T D R G Y G S G W T A S A Y T G
N T N Y A Q K F Q Y V Y G G S G D R Y C A R D R G Y D A F D I Y M E L R
S L R S D D T A V Y G G S G D R Y C A R D R G Y D A F D I Y M E L R G
T L V T V S S G G V G D R V T I Y K A S L A S F S E G I Y Q M T Q
S P S T L S A S V G D R V T I Y K A S L A S F S E G I Y Q M T Q A
W Y Q Q K P G K A P K L T I S S L Q P D D F A T Y P S R F
S G S G S G T F F T L T I S S L Q P D D F A T Y P S R F Q
M G E Y N A T F G G T K V E I K R

SEQ ID NO:484

CAGGTGCAGTGGTGAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGTCTCCTGCAAGGCTTCTGGTTACACCTTTACCAGTTATGGTA
TCAGCTGGGTGCGACAGGCCCCCTGGACAAGGCTTGAGTGGATGGATGG
GTCAGCGCTTACACTGGTAACACAACTATGCACAGAAGTTCCAGGGCAG
AGTCACCATGACACAGACACATCCACGAGCACAGCCTACATGGAACTGA
GGAGCCTGAGATCTGACGACACGCGGTGTATTACTGTGCGAGAGATCGT
GGATACTATGATGCTTTTGATATCTGGGGCCAAAGCACCCCTGGTCACCGT
CTCCTCAGGTGGAGCGGTTTCAGCGGAGGTGGCAGCGCGGTGGCGGAT
CGGACATCCAGATGACCCAGTCTCCTTCCACCCCTGTCTGCATCTGTTGGA
GACAGAGTCACCATCACCTGCCGGCCAGTGAGGGTATTATCACTGGTT
GGCCTGGTATCAGCAGAAGCCAGGGAAGCCCCCTAAACTCCTGATCTATA
AGGCCTCTAGTTTAGCCAGTGGGTCCCATCAAGGTTACGCGGCAGTGA
TCTGGGACAGAGTTCACTCTCACCATCAGCAGCCTGCAGCCTGATGATTT
TGCAACTTATTACTGCCAACAAATGGGCGAGTACAACGCCACCTTCGGCG
GAGGACCAAGGTGGAGATCAACCGT

FIG. 10(cont.)

087B03

SEQ ID NO:493

E	V	Q	L	V	E	S	G	G	G	G	G	G	G	G	G	G	G	L	S	L	R	L	S	C	A	A	S	G	G	F	T	R	D	Y
D	Y	G	M	N	W	V	R	F	Q	A	I	S	R	D	N	A	K	N	S	V	S	L	G	V	N	Q	M	N	S	L	R	A	E	D
A	A	S	V	K	G	A	R	G	W	Y	S	G	A	A	W	N	M	G	Y	Y	L	W	G	R	G	P	G	T	A	V	S	S	G	A
T	A	L	Y	H	C	S	G	G	G	S	G	G	G	S	A	Q	A	A	A	N	F	V	S	G	T	Q	P	A	S	V	S	G	S	A
S	G	G	S	I	T	I	S	C	T	G	A	S	G	D	V	G	A	Y	N	F	S	G	S	G	W	S	Y	Q	S	H	P	G	A	
P	G	Q	S	I	T	I	S	D	V	N	K	R	P	S	G	V	S	S	R	F	S	S	G	S	G	S	F	S	V	F	G	G	A	
K	A	P	K	L	I	I	Y	A	E	D	E	A	D	Y	Y	C	S	S	Y	T	S	S	T	S	T	S	F	S	V	F	G	G	A	
S	L	T	I	S	G	L	Q	A	E	D	E	A	D	Y	Y	C	S	S	Y	T	S	S	T	S	T	S	F	S	V	F	G	G	A	
G	T	K	L	T	V	L	G																											

SEQ ID NO:502

GAGGTGCAGCTGGTGGAGAGCGGGGAGGTGTGGTACGGCCTGGGGGGTC
CCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTTGACGATTATGGCA
TGAAC TGGTCCGCCAAGCTCCAGGAAGGGCTGGAGTGGTCTCTGGT
GTTAATTGGAATGGTGTACCAAGAGATTATGCAGCCTCCGTGAAGGCCG
ATTACCATCTCCAGAGACACGCCAAGAACTCCCTGTATCTGCAAAATGA
ACAGCTGAGAGCCGAGGACACGGCCTTGTATCACTGTGCGAGAGGATGG
TATAGTGGGCGCGGTGGAAACATGGGCTACTGGGCGCGAGGAACCTGGT
CACCGTCTCCTCAGGAGCGCGGTTCAGGCGGAGGTGGCTCTGGCGGTG
GCGGAAGTGCACAGGCTGCGCTGACTCAGCCGCGCTCCGTGTCTGGGTCT
CCTGGACAGTCGATCACCATCTCCTGCACTGGAGCCAGCGGTGACGTTGG
TGCTTATAACTTTGTCTCCTGGTACCAACAACACCCAGGCAAGCCCCCA
AACTCATAAATTTATGATGTCAATAAGCGGCCCTCAGGGGTTTCTAATCGC
TTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCT
CCAGGCCGAGGACGAGGCTGATTATTACTGCAGCTCATATACAAGCACCT
TCTCTGTGGTATTTGGCGGAGGACCAAGCTGACCGTCCCTAGGT

FIG. 10(cont.)

166B06

SEQ ID NO:511

Q V Q L V Q S G A E V K K P G Q G A S V K V S C K A S G Y T
F S D Y Y I H W V R Q A P G Q G L E M S I S T A Y M E L S
G T R Y A Q K F Q G R Y C A R D L T G G S G S T F D I W G Q G
R L R S D D T A V Y S S G G T A R G G S G G G N F R N K R V H
T L V T V S S G G P A P G K V L T I S R V E R F
Q P P S V S V A P G Q A P T A T F G G
W Y Q Q K P G Q A P T A T F G G
S G S R S G N T A T F G G
W D L F N D N G V

SEQ ID NO:520

CAGGTCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGCCCTC
AGTGAAGGTCTCCTGTAGGCTTCTGGATACACCTTCAGCGATTACTATA
TTCACCTGGTGGACAGGCCCTGGACAAGGTTGGAGTGGATGGGATGG
GTCAACCTGACACTGGTGGCACAAGATACGCCGAGAAGTTTCAGGGCCG
GGTCACAATGACCAGGACATGTCCATCTCCACAGCCTACATGGAGCTGT
CCAGGCTGAGAAGCGACGACACGGCCGTATATTACTGTGCGAGAGATCTA
ACTGGATTGGATCCTTTTGATATCTGGGCCAGGAAACCCTGTACCCGT
CTCCTCAGGAGGGCGAGTTCAGGTGGAGGTGGCTCTGGCGGTGGCGAA
GTGCATCGTCTGTGCTGACTCAGCCACCTCAGTGTGAGTGGCCCCAGGA
AAGACGGCCCCGATTACCTGTGGGGAAACAACCTTCGAAATAAAGAGT
ACACTGGTATCAGCAGAAGCCAGGCCCTGTCTCTGTCATCTATT
ATGATTTCAGACCGGCCCTCAGGATCCCTGAGCGATTCTCTGGCTCCCGC
TCTGGGAACACGGCCACCTGACCATCAGCAGGTCGAGCCGGGATGA
GGCCGACTATTACTGTCAAGGTGTGGATCTCTTCAACGACAACGGCGTGT
TCGGCGGAGGACCAAGCTGACCGTCCCTAGGT

FIG. 10(cont.)

166G05

SEQ ID NO:529

Q V Q L V Q S G A E V K K P G Q A S V K V S V T G
F S D Y Y I H W V Q A P G Q G L E M S I S G W C K A S G Y T G
G T R Y A Q K F Q A V Y C A R D L T S T A Y M E L S G
R L R S D D T A V Y C A R D L T S T A Y M E L S G
T L V T V S S G G V G G S G G G S A S S V L T
Q P P S V S V A P G K T A R I Y D S G N F R N K R V H
W Y Q Q K P G Q A P T A T V I S R G I P E R F
S G S R S G N T A T V I S R G I P E R F
W D F L T D S G S F G G T K L T V L G

SEQ ID NO:538

CAGGTCAGCTGGTGAGTCTGGGGCTGAGGTGAAGAAGCCTGGGCCCTC
AGTGAAGGTCTCCTGTAGGCTTCTGGATACACCTTCAGCGATTACTATA
TTCACCTGGTGCACAGGCCCTGGACAAGGTTGAGTGGATGGATGG
GTCAACCTGACACTGGTGGCACAGAATACGGCGAGAAGTTTCAGGGCCG
GGTCACAAATGACCAGGACATGTCCATCTCCACAGCCTACATGGAGCTGT
CCAGGCTGAGAAGCGACGACACGGCCGTATATTACTGTGCGAGAGATCTA
ACTGGATTGATCCTTTTGATATCTGGGGCCAGGGAACCTGTCACCGT
CTCCTCAGGAGCGCGGTTACGGCGAGGTGGCTCTGGCGGTGGCGGAA
GTGCATCGTCTGTGCTGACTCAGCCACCCCTCAGTGTGAGTGGCCCGAGGA
AAGACGGCCCGCATTACCTGTGGGGGAACAACACTTCGAAATAAAGAGT
ACACTGGTATCAGCAGAAGCCAGGCCAGGCCCTGTCTGTCATCTATT
ATGATTTCAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCTCCCGC
TCTGGGAACACGGCCACCCCTGACCATCAGCAGGTGCGAGCCGGGATGA
GGCCGACTATTACTGTGAGGTGTGGGATTTCCTCACCGACTCGGGTCTGT
TCGGCGGAGGACCAAGCTGACCGTCCCTAGGT

FIG. 10(cont.)

354A08

SEQ ID NO:547

Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	A	S	V	K	V	S	C	K	A	S	G	Y	T	F	T
D	Y	Y	M	H	W	V	R	Q	A	P	G	Q	G	L	E	W	S	V	G	W	I	N	P	Y	T	G	A	F	Y
A	Q	K	F	R	G	A	R	V	T	E	P	R	F	G	D	S	T	A	Y	M	E	L	S	R	L	R	S	D	D
T	A	V	Y	Y	C	A	R	G	G	S	G	G	S	R	S	A	Q	A	V	W	G	R	T	P	S	V	T	V	S
S	G	G	G	G	S	G	G	G	G	T	G	S	S	N	I	G	A	V	L	T	Q	P	P	S	V	S	G	A	G
P	G	Q	R	V	T	I	S	C	T	G	S	S	S	N	I	G	A	G	Y	G	V	H	W	Y	Q	Q	L	P	G
T	A	P	K	L	L	I	Y	G	N	S	N	R	P	S	G	V	P	D	R	F	S	G	S	K	S	G	T	S	A
S	L	A	I	T	G	L	Q	A	E	D	E	A	D	Y	Y	C	Y	H	W	D	K	E	Q	S	G	Y	V	F	G
G	G	T	Q	L	T	V	L	G																					

SEQ ID NO:556

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTCTCCTGCAAGGCTTCTGGATACACCTTCACCCGACTACTATA
TGCACTGGGTGCGACAGGCCCTGGACAAGGCTTGAGTGGTGGATGG
ATCAACCCCTTATACTGGTGGCCGATTCATGCACAGAAGTTTCGGGGCAG
GGTCACAATGACCAGGGACACGTCATCAGCACAGCCTACATGGAGCTGA
GCAGACTGAGATCTGACGACACAGCCGCTGTATTATTGTCCGAGAGAACCT
GAAAGATTCCGGCGACTCCACGGGCAGGTCTGGGCCGGGGACATTGGT
CACCGTCTCCTCAGGGGGCGGGTTCAGGCCGAGGTGGCTCTGGCGGTA
GCAGAAGTGCACAGGCTGTGCTGACTCAGCCGCCGTCAGTGTCTGGGGCC
CCAGGCAGAGGTCACCATCTCCTGCACTGGGAGCAGCTCCAACATCGG
GGCAGGTTATGGTGTACACTGTGTACCAACAGCTTCAGGAACAGCCCCCA
AACTCCTCATCTATGGTAAACAGCAATCGGCCCTCAGGGTCCCTGACCGA
TTCTCTGGCTCCAAGTCTGGCACCTCAGCCCTCCCTGGCCATCAGTGGCT
CCAGGCTGAGGATGAGGCTGATTATTACTGTACCACTGGGACAAGGAGC
AGAGTGGTTATGCTCTCGGAGGTGGGACCCAGCTCACCGTCCCTAGGT

FIG. 10(cont.)

355B06

SEQ ID NO:565

Q V Q L V Q S G A E V K K P G A S V K V S G Y T
F T D Y Y M H W V R Q A P G Q G L E T W S I S G Y T G
S A F Y A Q K F R Y C A R E P D T A Y M E L S
R L R S D D T A V S S G A P G G S G E S S G S A Q L W G
R G T L V T V S S G A P G G Q R V T I S C T G S S A Q A V
L T Q P P S V S S G A P G G Q R V T I S C T G S S S N I G A
G Y G V H W Y Q Q L P G G T A P K L L I T G L Q A E D E A D
V P D R F S G S K S G L S G Y V F G G T Q L T V L G
Y Y C Q S Y D S G L S G Y V F G G T Q L T V L G

SEQ ID NO:574

CAGGTGCAGCTGGTGAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTCTCCTGCAAGGCTTCTGGATACACCTTCACCGACTACTATA
TGCACTGGGTGCGACAGGCCCTGGACAAGGCTTGAGTGGGTGGATGG
ATCAACCCCTTACTGGTAGCGCTTCTATGCACAGAAGTTTCGGGGCAG
GGTCACAAATGACCAGGACACGTCCATCAGCACAGCCTACATGGAGCTGA
GCAGACTGAGATCTGACGACACGCGCGTGATTAATTGTCGAGAGAACCT
GAAAAATTTCGGGAGTCCAGCGGCCAGTTGTGGGGCCGGGACATTGGT
CACCGTCTCCTCAGGAGCGCGGTTTCAGGCGGAGGTGGCTCTGGCGGTA
GCGGAAGTGCACAGGCTGTGCTGACTCAGCCGCCGTCAGTGTCTGGGGCC
CCAGGGCAGAGGTCACCATCTCTGCACTGGGAGCAGCTCCAACATCGG
GGCAGGTTATGGTGTA CACTGGTACCAACAGCTTCCAGGAACAGCCCCA
AACTCCTCATCTATGGTGACAGCAATCGGCCCTCAGGGGTCCCTGACCGA
TTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCAGTGGGT
CCAGGCTGAGGATGAGGCTGATTATTACTGCCAGTCCCTATGACAGCGGC
TGAGTGGTTATGCTTCGGAGGTGGGACCCAGCTCACCCTCCTAGGT

FIG. 10(cont.)

355E04

SEQ ID NO:583

Q V Q L V Q S G A E V K K P K A S V K V S C K A S G Y T
F T H Y Y M H W V R Q A P P A L E W V V G W I N P Y T G
G A F Y A Q K T A V Y C A R E P D S P N A E I W G S
R L R S D D T V S S E G G Y C A R E P D S P N A E I W G S
R G T L V T V S S E G G Y C A R E P D S P N A E I W G S
L T Q P P S V Y Q Q L P G T S A S L A I T G L Q L T V L G
G Y G V H W Y Q Q L P G T S A S L A I T G L Q L T V L G
V P D R F S G S K S L S L S G Y V F G G G A D
Y Y C Q S Y D S S L S L S G Y V F G G G A D

SEQ ID NO:592

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTCTCCTGCAAGGCTTCTGGATACACCTTCACCCACTACTATA
TGCACTGGGTGGACAGGCCCTGGACAAGGCTTGAGTGGTGGGATGG
ATCAACCCCTTATACTGGTGGCGATTCTATGCACAGAAGTTTCAGGGCAG
GGTCACAATGACCAGGACACGTCCATCAGCACAGCCTACATGGAGCTGA
GCAGACTGAGATCTGACGACACGGCCGTGTTATTGTCGAGAGAACCT
GAAAATTTCGACTCGCCGAACGCCGAGATCTGGGCCGGGGACATTGGT
CACCGTCTCCTCAGAAAGCGCGGTTACGGCGAGGTGGCTCTGGCGGTA
GCGGAAGTGCACAGGCTGTGTACTCAGCCGCCGTGAGTGTCTGGGGCC
CCAGGCGAGAGGTCACCATCTCCTGCACCTGGGAGCAGCTCCAACATCGG
GGCAGGTTATGGTGTACACTGGTACCAACAGCTTCCAGGAACAGCCCCCA
AACCTCCTCATCTATGGTAACAGCAATCGGCCCTCAGGGTCCCTGACCGA
TTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGCCATCACTGGGCT
CCAGGCTGAGGATGAGGCTGATTATTACTGCCAGTCCCTATGACAGCAGCC
TGAGTGGTTATGCTTCCGAGGTGGGACCCAGCTCACCGTCTCTAGGT

FIG. 10(cont.)

356A11

SEQ ID NO:601

Q V Q L V Q S G A E V K K P G A S V K V S C K A S G Y T
F T N Y Y M H V R Q A P G Q G L E W V K V S G W I N P Y T G
S A F Y A Q K F R G Y C A R E P G G T R D T S I S T A Y M E L S
R L R S D D T A V Y G G S S G G G S G S D S D V W G
R G T L V T V S S G A P G Q S R V T I S C T G S S A Q A V
L T Q P P S V S G A P G Q R V T I S C T G S S S N I G A
G Y G V H W Y Q Q L P G T A P K L I Y G D S N R P S G
V P D R F S S G S K S G T S A S L A I T G L Q A E D E A D
Y Y C Q S Y D N S L S G Y V F G G T Q L L T V L G

SEQ ID NO:610

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTCTCCTGCAAGGCTTCTGGATACACCTTCACCAACTACTATA
TGCACTGGTGCACAGGCCCTGGACAAGGCTTGAGTGGTGGATGG
ATCAACCCCTTACTGGTAGCGCATCTATGCACAGAAGTTTCGGGGCAG
GGTCACAAATGACCAGGGACACGTCCTCATCAGCACAGCCTACATGGAGCTGA
GCAGACTGAGATCTGACGACACAGGCCGTGTTATTGTGCGAGAGAACCT
GAAAATTCGACTCCGACGACTCCGACGTCTGGGCCCGGGACATTTGGT
CACCGTCTCCTCAGGAGCGGCAGTTCAGCGGAGGTGGCTCTGGCGGTA
GCGGAAGTGCACAGGCTGTGCTGACTCAGCCCGCTCAGTGTCTGGGGCC
CCAGGGCAGAGGTCAACCATCTCCTGCACTGGGAGCAGCTCCAACATCGG
GGCAGGTTATGGTGTAACACTGGTACCAACAGCTTCCAGGAACAGCCCCCA
AACTCCTCATCTATGGTGACAGCAATCGGCCCTCAGGGGTCCCTGACCGA
TTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCAGTGGGCT
CCAGGCTGAGGATGAGGCTGATTACTGCCAGTCCCTATGACAACAGCC
TGAGCGGTTATGCTTCCGAGGTGGGACCCAGCTCACCGTCCCTAGGT

FIG. 10(cont.)

368D04

SEQ ID NO:619

EVQLVESGGGVVRPGGSLRLSCAASGFTFDDYGMNWNVRQAPKGLEWVSGV
NWNGGTRDYAASVKGRFTISRDNAKNSLYLQMNSLRAEDTALYHCARGWYS
GAWNMGYWGRGTLVTVSSGGGGGGGGGGGGGGGGGGGGGGGGGSAQA
ALTQPASVSGSPGQSIITISCTGASGDVGAYNFVSWYQQHPGKAPKLIIDV
NKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCASLVDSFVVFEGG
TKLTVL

SEQ ID NO:628

GAGGTGCAGCTGGTGAGAGCGGGGAGGCGTGGTGAGACCAGCGGCA
GCCTGAGACTGAGCTGCGCCGCCAGCGGCTTCACTTCGACGACTACGG
CATGAACTGGTGAGGACGCCCCCAGGCAAGGCCCTGGAGTGGGTGCC
GGCGTGAACTGGAACGGCGCACCCAGAGACTACGCCCTCTGTGAAGG
GCAGATTACCATCAGCCGGGACACGCCAAGAACAGCCTGTACCTGCA
GATGAACAGCCTGAGAGCCGAGACACCGCCCTGTACCACTGCCCCAGA
GGCTGGTACAGCGGAGCCGCTGGAAACATGGGCTACTGGGCGAGAGCA
CCCTGGTGACCGTGTCACGCGAGCGCGGTTTCAGCGGAGGTGGCTC
TGGTGGTAGCGAGGTGGCTCTGGCGGTGGCGGAGGTGGCTCTGGCGGT
GGCGAAGTGACAGCGCCGCCCTGACCCAGCCCGCCAGCGTGTCTGGCA
GCCCAGGCCAGACATCACCATCAGCTGCACCGGCGCCAGCGCGATGT
GGGCGCCTACAACTTCGTGTCCTGGTATCAGCAGCACCCCGCAAGGCC
CCCAAGCTGATCATCTACGACGTGAACAAGAGACCCAGCGGCGTGTCCA
ACAGATTACGGCGCAGCAAGAGCGGCAACACCGCCAGCCTGACCATCAG
CGGACTGCAGGCCGAGGACGAGGCCGACTACTGCGCCAGCCTGGTG
TCCGACTTCAGCGTGGTGTCTCGCGGAGGCACCAAGCTGACCGTGCTG

FIG. 10(cont.)

Lead clone Panel

