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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 form these organs are responsive

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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 IFNα/β, IFNγ, 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-λR1/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., IFNγR1) based on its high affinity for the cytokine. The other chain (e.g., IFNγR2) 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 erythematosis, 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 GROa 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 GROa 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: IgG_1, IgG_2, IgG_3, IgG_4, IgM, IgA_1, IgA_2, 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 $IgG_{1\kappa}$ or $IgG_{1\gamma}$.

[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 erythematosis, 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 respone 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 GROa 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 Altshul 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: 581-597WO 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., IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2. 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 the 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 $(Gly_4Ser)_3$ 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 10^{10} 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, all of which are hereby incorporated by reference herein in their entireties.

[0088]A SMIP™ 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.*, which is incorporated by reference, for a more complete description). 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), incorporated herein by reference. 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, cytocidal 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, incorporated herein by reference). 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, incorporated herein by reference. Such a VHH molecule can be derived from antibodies raised in Camelidae species, for example in camel, llama, dromedary, alpaca and guanaco and is sometomes called a camelid or camelized variable domain. *See e.g.*, Muyldermans., *J. Biotechnology* (2001) 74(4):277-302, incorporated herein by reference. 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, which is incorporated herein by reference).

[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 scF_v 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, Fv, 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
scF_v	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, Fv, and CDRs of Non-germlined Antibodies

Region	Type	367D04 SEQ ID	368D04 SEQ ID	166B06 SEQ ID	166G05 SEQ ID	375G05 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 Cκ or Cλ. 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 H3 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 (Engstom (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-butyric 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 Clq (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 Clq 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 IgG_3, 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 GROa 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., IgG_1, IgG_2, IgG_3, IgG_4), IgM, IgA_1, IgA_2, IgD, and IgE. The heavy chain constant region may be an IgG (e.g., an IgG_1) 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 erythematosis, 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 adminstering 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 cyctic 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 neoplams, cystic, mucinous and serous neoplasms, cystadenoma, pseudomyxoma peritonei, ductal, lobular and medullary neoplasms, acinar cell neoplasns, 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, malanocytic 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., TNFα, 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), TNFα, 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 TNFα), such as D2E7 (human anti-TNFα antibody, U.S. 6,258,562, Humira™, BASF); CDP-571/CDP-870/BAY-10-3356 (humanized anti-TNFα antibodies, Celltech/Pharmacia); cA2 (chimeric anti-TNFα antibody, Remicade™, 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, Lenercept™) and 75 kdTNFR-IgG (75 kD TNF receptor-IgG fusion protein, Enbrel™, Immunex, see, e.g., Arthritis & Rheumatism (1994) Vol. 37, S295; J. Invest. Med. (1996) Vol. 44, 235A). Further examples include enzyme antagonists (e.g., TNFα 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 TNFα 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 TNFα 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 immunosuppresants (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-NFkb 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 NFκB 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-NFκB 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 kdTNFR-IgG (75 kD TNF receptor-IgG fusion protein, Enbrel™); 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, IFNβ-1a and IFNβ-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; lipoxygenase 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 TGFβ 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 TNFα), 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 μg/kg to 20 mg/kg, 1 μg/kg to 10 mg/kg, 1 μg/kg to 1 mg/kg, 10 μg/kg to 1 mg/kg, 10 μg/kg to 100 μg/kg, 100 μg/kg to 1 mg/kg, 250 μg/kg to 2 mg/kg, 250 μg/kg to 1 mg/kg, 500 μg/kg to 2 mg/kg, 500 μg/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 LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (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 LD_{50}/ED_{50}. 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 ED_{50} 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 IC_{50} (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 $1.38x10^{10}$ 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 µl 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 µl of Dynal M280 Streptavidin magnetic beads, which had been blocked for 1 hour at 37ºC 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 µl 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 37ºC (30 minutes stationary, 30 minutes shaking at 250 rpm), then spread on 2TYAG plates. Plates were incubated at 30ºC 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 –70ºC.

[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 µg/ml (Dulbecco's PBS, pH 7.4) human IL-22 fusion protein and incubated overnight at

4ºC. Wells were washed in PBS and blocked for 2 hours at 37ºC 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 Tween20), 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 $CaCl_2$) for 30 minutes at 37ºC. 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 37ºC, as above, then streaked onto 2TYAG plates and incubated overnight at 30ºC. 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 IC_{50} 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 37ºC. 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 30ºC 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 4ºC. 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 H_2SO_4, 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 IC_{50} 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% CO_2 for 6-8 hours. To prepare assay plates, 100 µl of cells ($1x10^5$/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% CO_2. 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% CO_2. Plates were mixed by gentle tapping to ensure even signal throughout the wells before measurement of fluorescence (excitation=560 nM, emission=590 nM). EC_{50} and IC_{50} 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. IC_{50} 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 IC_{50} 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 clone s 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 IC_{50} 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 x 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% CO_2, 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 25ºC. 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 25ºC, then washed with PBST, and developed with TMB (KPL, Cat. #50-76-04). Reaction was stopped with 0.18 M H_2S0_4. 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 IC_{50} 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 IC_{50} 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 1µg/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 22.5ºC 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 x 10^{-8} M or 52 nM) and Ab-04 (K_D = 2.38 x 10^{-9} M or 2.38 nM), respectively. Similarly, 368D04 (K_D = 1.32 x 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-α2c, 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 TNFα, 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 μg of Collagen Type II in complete Freund's adjuvant, and on day 21, the mice are boosted with 100 μg of Collagen Type II in incomplete Freund's adjuvant. On day 21, the mice are also injected daily with 1 μg 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 µg/kg to 2 mg/kg	weekly, biweekly, or monthly	improvement or stabilization of condition
Rheumatoid Arthritis	087B03, 368D04, 356A11, or 354A08	250 µg/kg to 2 mg/kg	weekly, biweekly, or monthly	improvement or stabilization of condition
Psoriasis	087B03, 368D04, 356A11, or 354A08	250 µg/kg to 2 mg/kg	weekly, biweekly, or monthly	improvement or stabilization of condition
IBD	087B03, 368D04, 356A11, or 354A08	250 µg/kg to 2 mg/kg	monthly, biweekly, or monthly	improvement or stabilization of condition
Alzheimer's Disease	087B03, 368D04, 356A11, or 354A08	250 µg/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. All publications and patents cited in this disclosure are incorporated by reference in

their entirety. 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.

CLAIMS

We claim:

1. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to IL-22, wherein the antibody, or antigen-binding fragment thereof, comprises an amino acid sequence which is at least 95% identical to the amino acid sequence shown in SEQ ID NO:5, 6, 7, 23, 24, 25, 41, 42, 43, 59, 60, 61, 77, 78, 79, 95, 96, 97, 113, 114, 115, 131, 132, 133, 149, 150, 151, 167, 168, 169, 185, 186, 187, 203, 204, 205, 221, 222, 223, 239, 240, 241, 257, 258, 259, 275, 276, 277, 293, 294, 295, 311, 312, 313, 329, 330, 331, 347, 348, 349, 365, 366, 367, 383, 384, 385, 401, 402, 403, 419, 420, 421, 437, 438, 439, 455, 456, 457, 473, 474, 475, 491, 492, 493, 509, 510, 511, 527, 528, 529, 545, 546, 547, 563, 564, 565, 581, 582, 583, 599, 600, 601, 617, 618, or 619.

2. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to IL-22, wherein the antibody, or antigen-binding fragment thereof, comprises an amino acid sequence encoded by a nucleotide sequence which is at least 95% identical to the nucleotide sequence shown in SEQ ID NO:14, 15, 16, 32, 33, 34, 50, 51, 52, 68, 69, 70, 86, 87, 88, 104, 105, 106, 122, 123, 124, 140, 141, 142, 158, 159, 160, 176, 177, 178, 194, 195, 196, 212, 213, 214, 230, 231, 232, 248, 249, 250, 266, 267, 268, 284, 285, 286, 302, 303, 304, 320, 321, 322, 338, 339, 340, 356, 357, 358, 374, 375, 376, 392, 393, 394, 410, 411, 412, 428, 429, 430, 446, 447, 448, 464, 465, 466, 482, 483, 484, 500, 501, 502, 518, 519, 520, 536, 537, 538, 554, 555, 556, 572, 573, 574, 590, 591, 592, 608, 609, 610, 626, 627, or 628.

3. The antibody of claim 1, comprising the amino acid sequence as set out in SEQ ID NO:5, 6, 7, 23, 24, 25, 41, 42, 43, 59, 60, 61, 77, 78, 79, 95, 96, 97, 113, 114, 115, 131, 132, 133, 149, 150, 151, 167, 168, 169, 185, 186, 187, 203, 204, 205, 221, 222, 223, 239, 240, 241, 257, 258, 259, 275, 276, 277, 293, 294, 295, 311, 312, 313, 329, 330, 331, 347, 348, 349, 365, 366, 367, 383, 384, 385, 401, 402, 403, 419, 420, 421, 437, 438, 439, 455, 456, 457, 473, 474, 475, 491, 492, 493, 509, 510, 511, 527, 528, 529, 545, 546, 547, 563, 564, 565, 581, 582, 583, 599, 600, 601, 617, 618, or 619.

4. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to IL-22, wherein the antibody, or antigen-binding fragment thereof, comprises a V_L domain having a light chain variable region and a V_H domain having a heavy chain variable region, wherein the heavy chain variable region comprises one or more of SEQ ID NO:8, 9, 10, 26, 27, 28, 44, 45, 46, 62, 63, 64, 80, 81, 82, 98, 99, 100, 116, 117, 118, 134, 135, 136, 152, 153, 154, 170, 171, 172, 188, 189, 190, 206, 207, 208, 224, 225, 226, 242, 243, 244, 260, 261, 262, 278, 279, 280, 296, 297, 298, 314, 315, 316, 332, 333, 334, 350, 351, 352, 368, 369, 370, 386, 387, 388, 404, 405, 406, 422, 423, 424, 440, 441, 442, 458, 459, 460, 476, 477, 478, 494, 495, 496, 512, 513, 514, 530, 531, 532, 548, 549, 550, 566, 567, 568, 584, 585, 586, 602, 603, 604, 620, 621, or 622.

5. The antibody of claim 4, wherein the light chain variable region comprises one or more of SEQ ID NO:11, 12, 13, 29, 30, 31, 47, 48, 49, 65, 66, 67, 83, 84, 85, 101, 102, 103, 119, 120, 121, 137, 138, 139, 155, 156, 157, 173, 174, 175, 191, 192, 193, 209, 210, 211, 227, 228, 229, 245, 246, 247, 263, 264, 265, 281, 282, 283, 299, 300, 301, 317, 318, 319, 335, 336, 337, 353, 354, 355, 371, 372, 373, 389, 390, 391, 407, 408, 409, 425, 426, 427, 443, 444, 445, 461, 462, 463, 479, 480, 481, 497, 498, 499, 515, 516, 517, 533, 534, 535, 551, 552, 553, 569, 570, 571, 587, 588, 589, 605, 606, 607, 623, 624, and 625.

6. The antibody of claim 5, wherein the V_H domain comprises the amino acid sequence of any one of 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 and the V_L domain comprises the amino acid sequence of any one of 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.

7. The antibody of claim 6, wherein:

a) the V_H domain comprises the amino acid sequence set out in SEQ ID NO:167 or 491; and

b) the V_L domain comprises the amino acid sequence set out in SEQ ID NO:168 or 492.

8. The antibody of claim 6, wherein:

a) the V_H domain comprises the amino acid sequence set out in SEQ ID NO:293 or 545; and

b) the V_L domain comprises the amino acid sequence set out in SEQ ID NO:294 or 546.

9. The antibody of claim 6, wherein:

a) the V_H domain comprises the amino acid sequence set out in SEQ ID NO:203 or 617; and

b) the V_L domain comprises the amino acid sequence set out in SEQ ID NO:204 or 618.

10. The antibody of claim 6, wherein:

a) the V_H domain comprises the amino acid sequence set out in SEQ ID NO:347 or 599; and

b) the V_L domain comprises the amino acid sequence set out in SEQ ID NO:348 or 600.

11. The antibody of claim 4, wherein the heavy chain variable region comprises:

a) SEQ ID NO:170 or 494,

b) SEQ ID NO:171 or 495; and

c) SEQ ID NO:172 or 496.

12. The antibody of claim 4, wherein the heavy chain variable region comprises:

a) SEQ ID NO:296 or 548,

b) SEQ ID NO:297 or 549; and

c) SEQ ID NO:298 or 550.

13. The antibody of claim 4, wherein the heavy chain variable region comprises:

a) SEQ ID NO:206 or 620,

b) SEQ ID NO:207 or 621; and

c) SEQ ID NO:208 or 622.

14. The antibody of claim 4, wherein the heavy chain variable region comprises:

a) SEQ ID NO:350 or 602,

b) SEQ ID NO:351 or 603; and

c) SEQ ID NO:352 or 604.

15. The antibody of claim 11, wherein the light chain variable region comprises:

a) SEQ ID NO:173 or 497,

b) SEQ ID NO:174 or 498; and

c) SEQ ID NO:175 or 499.

16. The antibody of claim 12, wherein the light chain variable region comprises:

a) SEQ ID NO:299 or 551,

b) SEQ ID NO:300 or 552; and

c) SEQ ID NO:301 or 553.

17. The antibody of claim 13, wherein the light chain variable region comprises:

a) SEQ ID NO:209 or 623,

b) SEQ ID NO:210 or 624; and

c) SEQ ID NO:211 or 625.

18. The antibody of claim 14, wherein the light chain variable region comprises:

a) SEQ ID NO:353 or 605,
b) SEQ ID NO:354 or 606; and
c) SEQ ID NO:355 or 607.

19. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to an IL-22 epitope that is 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 the antibody competitively inhibits 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.

20. The antibody of claim 19, comprising a V_H domain, a V_L domain, or a F_v fragment as set out in SEQ ID NO:5, 6, 7, 23, 24, 25, 41, 42, 43, 59, 60, 61, 77, 78, 79, 95, 96, 97, 113, 114, 115, 131, 132, 133, 149, 150, 151, 167, 168, 169, 185, 186, 187, 203, 204, 205, 221, 222, 223, 239, 240, 241, 257, 258, 259, 275, 276, 277, 293, 294, 295, 311, 312, 313, 329, 330, 331, 347, 348, 349, 365, 366, 367, 383, 384, 385, 401, 402, 403, 419, 420, 421, 437, 438, 439, 455, 456, 457, 473, 474, 475, 491, 492, 493, 509, 510, 511, 527, 528, 529, 545, 546, 547, 563, 564, 565, 581, 582, 583, 599, 600, 601, 617, 618, or 619.

21. The antibody of claim 20, wherein the V_H domain comprises SEQ ID NO:167 or 491.

22. The antibody of claim 21, wherein the V_L domain comprises SEQ ID NO:168 or 492.

23. The antibody of claim 20, wherein the V_H domain comprises SEQ ID NO:293 or 545.

24. The antibody of claim 23, wherein the V_L domain comprises SEQ ID NO:294 or 546.

25. The antibody of claim 20, wherein the V_H domain comprises SEQ ID NO:203 or 617.

26. The antibody of claim 25, wherein the V_L domain comprises SEQ ID NO:204 or 618.

27. The antibody of claim 20, wherein the V_H domain comprises SEQ ID NO:347 or 599.

28. The antibody of claim 27, wherein the V_L domain comprises SEQ ID NO:348 or 600.

29. The antibody of claim 19 that specifically 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.

30. The antibody of claim 19 that specifically 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.

31. The antibody of claim 19 that specifically 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.

32. The antibody of claim 19 that specifically 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.

33. The antibody of claim 22, wherein the antibody is 087B03.

34. The antibody of claim 24, wherein the antibody is 354A08.

35. The antibody of claim 26, wherein the antibody is 368D04.

36. The antibody of claim 28, wherein the antibody is 356A11.

37. The antibody of claim 1or 2, wherein the association constant of the antibody for human IL-22 is at least 10^{10} M^{-1}.

38. The antibody of claim 1 or 2, wherein 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.

39. The antibody of claim 1 or 2, wherein the antibody blocks IL-22 mediated GROa secretion from HT29 cells with an IC_{50} of 150 pM or less.

40. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to IL-22, wherein the association constant of the antibody for human IL-22 is at least 10^{10} M^{-1}.

41. An isolated antibody, or antigen-binding fragment thereof, wherein 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.

42. The antibody of claim 1 or 2, wherein the antibody specifically binds to an amino acid sequence that is at least 95% identical to any sequence of at least 100 contiguous amino acids in the sequence set forth SEQ ID NO:1.

43. The antibody of claim 1 or 2, wherein the antibody inhibits the binding of IL-22 to IL-22R or a receptor complex comprising IL-22R and IL-10R2.

44. The antibody of claim 1 or 2, wherein the antibody is human.

45. The antibody of claim 1 or 2, wherein the antibody is IgG1 or IgG4.

46. A pharmaceutical composition comprising the antibody of claim 1 or 2.

47. An isolated nucleic acid encoding the antibody of claim 1 or 2.

48. An expression vector comprising the nucleic acid of claim 47.

49. A host cell transformed with the vector of claim 48.

50. The host cell of claim 49, wherein the host cell is a bacteria, mammalian cell, yeast cell, plant cell, or an insect cell.

51. A method of producing an antibody that binds to IL-22, comprising culturing the host cell of claim 50 under conditions that allow expression of the antibody, and isolating the antibody from the cell culture.

52. The nucleic acid of claim 47, wherein the nucleic acid encodes a protein comprising an amino acid sequence set out in one of 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.

53. The nucleic acid of claim 52, wherein the nucleic acid comprises a nucleotide sequence of one of SEQ ID NO:14-22, 32-40, 50-58, 68-76, 86-94, 104-112, 122-130, 140-148, 158-166, 176-184, 194-202, 212-220, 230-238, 248-256, 266-274, 284-292, 302-310, 320-328, 338-346, 356-364, 374-382, 392-400, 410-418, 428-436, 446-454, 464-472, 482-490, 500-508, 518-526, 536-544, 554-562, 572-580, 590-598, 608-616, or 626-634.

54. The nucleic acid of claim 52, wherein the nucleic acid encodes a protein comprising an amino acid sequence set out in SEQ ID NO:167, 168, 169, 170, 171, 172, 173, 174, 175, 491, 492, 493, 494, 495, 496, 497, 498, or 499.

55. The nucleic acid of claim 52, wherein the nucleic acid encodes a protein comprising an amino acid sequence set out in SEQ ID NO:293, 294, 295, 296, 297, 298, 299, 300, 301, 545, 546, 547, 548, 549, 550, 551, 552, or 553.

56. The nucleic acid of claim 52, wherein the nucleic acid encodes a protein comprising an amino acid sequence set out in SEQ ID NO:203, 204, 205, 206, 207, 208, 209, 210, 211, 617, 618, 619, 620, 621, 622, 623, 624, or 625.

57. The nucleic acid of claim 52, wherein the nucleic acid encodes a protein comprising an amino acid sequence set out in SEQ ID NO:347, 348, 349, 350, 351, 352, 353, 354, 355, 599, 600, 601, 602, 603, 604, 605, 606, or 607.

58. The nucleic acid of claim 53, wherein the the nucleic acid comprises a nucleotide sequence of SEQ ID NO:176, 177, 178, 179, 180, 181, 182, 183, 184, 500, 501, 502, 503, 504, 505, 506, 507, or 508.

59. The nucleic acid of claim 53, wherein the the nucleic acid comprises a nucleotide sequence of SEQ ID NO:302, 303, 304, 305, 306, 307, 308, 309, 310, 554, 555, 556, 557, 558, 559, 560, 561, or 562.

60. The nucleic acid of claim 53, wherein the the nucleic acid comprises a nucleotide sequence of SEQ ID NO:212, 213, 214, 215, 216, 217, 218, 219, 220, 626, 627, 628, 629, 630, 631, 632, 633, or 634.

61. The nucleic acid of claim 53, wherein the the nucleic acid comprises a nucleotide sequence of SEQ ID NO:356, 357, 358, 359, 360, 361, 362, 363, 364, 608, 609, 610, 611, 612, 613, 614, 615, or 616.

62. A diagnostic kit comprising the antibody of claim 1 or 2.

SEQUENCE LISTING

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CAMBRIDGE ANTIBODY TECHNOLOGY LIMITED

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<150> 60/774,596
<151> 2006-02-21

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<170> PatentIn version 3.3

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Ala His Ile Trp Tyr Asp Gly Ser Asn Glu Lys Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Met Thr Val Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Glu Gln His Trp Ile Thr Ala Phe Asp Ile Trp Gly Lys Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 42
<211> 111
<212> PRT
<213> Homo sapiens

<400> 42
Gln Ser Val Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Glu Gly Ser Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

```
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Thr Arg
                85                  90                  95

Ser Thr Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110
```

<210> 43
<211> 249
<212> PRT
<213> Homo sapiens

<400> 43

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Gln Met Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
            20                  25                  30

Gly Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala His Ile Trp Tyr Asp Gly Ser Asn Glu Lys Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Met Thr Val Ser Arg Asp Asn Ser Arg Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Thr Glu Gln His Trp Ile Thr Ala Phe Asp Ile Trp Gly Lys Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Ala Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gln Ser Val Leu Thr Gln Pro Ala Ser Val
    130                 135                 140

Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser
145                 150                 155                 160

Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro
                165                 170                 175
```

```
Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg Pro Ser
            180                 185                 190

Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser
        195                 200                 205

Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys
    210                 215                 220

Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly Thr Lys
225                 230                 235                 240

Leu Thr Val Leu Gly Ala Ala Ala His
                245
```

<210> 44
<211> 5
<212> PRT
<213> Homo sapiens

<400> 44
Asn Tyr Gly Met Tyr
1   5

<210> 45
<211> 17
<212> PRT
<213> Homo sapiens

<400> 45
His Ile Trp Tyr Asp Gly Ser Asn Glu Lys Tyr Ala Asp Ser Val Lys
1   5   10   15

Gly

<210> 46
<211> 10
<212> PRT
<213> Homo sapiens

<400> 46
Glu Gln His Trp Ile Thr Ala Phe Asp Ile
1   5   10

<210> 47
<211> 14
<212> PRT
<213> Homo sapiens

<400> 47
Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> 48
<211> 7
<212> PRT
<213> Homo sapiens

<400> 48
Glu Gly Ser Lys Arg Pro Ser
1 5

<210> 49
<211> 10
<212> PRT
<213> Homo sapiens

<400> 49
Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val
1 5 10

<210> 50
<211> 357
<212> DNA
<213> Homo sapiens

<400> 50
cagatgcagc tggtgcagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt aactatggca tgtactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcacat atttggtatg atggaagtaa tgaaaagtat 180

gcagactccg tgaagggccg aatgaccgtc tccagagaca attccaggaa cacgttgtat 240

ttgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gacagagcaa 300

cactggatta ctgcttttga tatctggggc aaaggcaccc tggtcaccgt ctcctca 357

<210> 51
<211> 333
<212> DNA
<213> Homo sapiens

<400> 51
cagtctgtgc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc 60

tcctgcactg gaaccagcag tgacgttggt ggttataact atgtctcctg gtaccaacaa 120

cacccaggca aagcccccaa actcatgatt tatgagggca gtaagcggcc ctcaggggtt 180

tctaatcgct tctctggctc caagtctggc aacacggcct ccctgacaat ctctgggctc 240

caggctgagg acgaggctga ttattactgc agctcatata caaccaggag cactcgagtt 300

ttcggcggag ggaccaagct gaccgtccta ggt 333

<210> 52
<211> 744
<212> DNA
<213> Homo sapiens

<400> 52
cagatgcagc tggtgcagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt aactatggca tgtactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcacat atttggtatg atggaagtaa tgaaaagtat 180

gcagactccg tgaagggccg aatgaccgtc tccagagaca attccaggaa cacgttgtat 240

ttgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gacagagcaa 300

cactggatta ctgcttttga tatctggggc aaaggcaccc tggtcaccgt ctcctcaggt 360

ggaggcggtt caggcgcagg tggcagcggc ggtggcggat cgcagtctgt gctgactcag 420

cctgcctccg tgtctgggtc tcctggacag tcgatcacca tctcctgcac tggaaccagc 480

agtgacgttg gtggttataa ctatgtctcc tggtaccaac aacacccagg caaagccccc 540

aaactcatga tttatgaggg cagtaagcgg ccctcagggg tttctaatcg cttctctggc 600

tccaagtctg gcaacacggc ctccctgaca atctctgggc tccaggctga ggacgaggct 660

gattattact gcagctcata tacaaccagg agcactcgag ttttcggcgg agggaccaag 720

ctgaccgtcc taggtgcggc cgca 744

<210> 53
<211> 15
<212> DNA
<213> Homo sapiens

<400> 53
aactatggca tgtac 15

<210> 54
<211> 51
<212> DNA
<213> Homo sapiens

<400> 54
catatttggt atgatggaag taatgaaaag tatgcagact ccgtgaaggg c 51

<210> 55
<211> 30
<212> DNA
<213> Homo sapiens

<400> 55
gagcaacact ggattactgc ttttgatatc 30

<210> 56
<211> 42
<212> DNA
<213> Homo sapiens

<400> 56
actggaacca gcagtgacgt tggtggttat aactatgtct cc 42

<210> 57
<211> 21
<212> DNA
<213> Homo sapiens

<400> 57
gagggcagta agcggccctc a 21

<210> 58
<211> 30
<212> DNA
<213> Homo sapiens

<400> 58
agctcatata caaccaggag cactcgagtt 30

<210> 59
<211> 121
<212> PRT
<213> Homo sapiens

<400> 59
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

```
Ser Gly Val Asn Trp Asn Gly Gly Thr Arg Asp Tyr Ala Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Trp Tyr Ser Gly Ser Phe Tyr Tyr Phe Gly Tyr Trp Gly
            100                 105                 110

Arg Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 60
<211> 111
<212> PRT
<213> Homo sapiens

<400> 60

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Gln Ala Val Leu Thr Gln Pro Ser Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15

Ser Ile Thr Ile Ser Cys Thr Gly Ala Ser Gly Asp Val Gly Ala Tyr
            20                  25                  30

Asn Phe Val Ser Trp Tyr Gln Gln His Pro Gly Lys Thr Pro Lys Leu
        35                  40                  45

Ile Ile Tyr Asp Val Asn Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Glu Ser Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Thr
                85                  90                  95

Phe Ser Val Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly
            100                 105                 110
```

<210> 61
<211> 250
<212> PRT
<213> Homo sapiens

<400> 61

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Arg Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Val Asn Gly Asn Gly Gly Thr Arg Asp Tyr Ala Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Trp Tyr Ser Gly Ser Phe Tyr Tyr Phe Gly Tyr Trp Gly
            100                 105                 110

Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ala Val Leu Thr Gln Pro
    130                 135                 140

Ser Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr
145                 150                 155                 160

Gly Ala Ser Gly Asp Val Gly Ala Tyr Asn Phe Val Ser Trp Tyr Gln
                165                 170                 175

Gln His Pro Gly Lys Thr Pro Lys Leu Ile Ile Tyr Asp Val Asn Lys
            180                 185                 190

Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn
        195                 200                 205

Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ser Asp
    210                 215                 220
```

Tyr Tyr Cys Ser Ser Tyr Thr Ser Thr Phe Ser Val Val Phe Gly Gly
225 230 235 240

Gly Thr Lys Val Thr Val Leu Gly Ala Ala
245 250

<210> 62
<211> 5
<212> PRT
<213> Homo sapiens

<400> 62
Asp Tyr Gly Met Asn
1 5

<210> 63
<211> 17
<212> PRT
<213> Homo sapiens

<400> 63
Gly Val Asn Trp Asn Gly Gly Thr Arg Asp Tyr Ala Ala Ser Val Lys
1 5 10 15

Gly

<210> 64
<211> 12
<212> PRT
<213> Homo sapiens

<400> 64
Gly Trp Tyr Ser Gly Ser Phe Tyr Tyr Phe Gly Tyr
1 5 10

<210> 65
<211> 14
<212> PRT
<213> Homo sapiens

<400> 65
Thr Gly Ala Ser Gly Asp Val Gly Ala Tyr Asn Phe Val Ser
1 5 10

<210> 66
<211> 7
<212> PRT
<213> Homo sapiens

<400> 66
Asp Val Asn Lys Arg Pro Ser
1 5

<210> 67
<211> 10
<212> PRT
<213> Homo sapiens

<400> 67
Ser Ser Tyr Thr Ser Thr Phe Ser Val Val
1 5 10

<210> 68
<211> 363
<212> DNA
<213> Homo sapiens

<400> 68
gaggtgcagc tggtggagtc cgggggaggt gtggtacggc ctgggggGTC cctgagactc 60

tcctgtgcag cctctggatt cacctttgac gattatggca tgaactgggt ccgccaagct 120

ccagggaagg ggctggagtg ggtctctggt gttaattgga atggtggtac cagagattat 180

gcagcctccg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240

ctgcaaatga acagtctgag agccgaggac acggccttgt attactgtgc gagaggatgg 300

tatagtggga gcttctacta ctttggctac tggggccgag gaaccctggt caccgtctcc 360

tca 363

<210> 69
<211> 333
<212> DNA
<213> Homo sapiens

<400> 69
caggctgtgc tgactcagcc gtcctccgtg tctgggtctc ctggacagtc gatcaccatc 60

tcctgcactg gagccagcgg tgacgttggt gcttataact ttgtctcctg gtaccaacaa 120

cacccaggca aaacccccaa actcataatt tatgatgtca ataagcggcc ctcaggggtt 180

tctaatcgct tctctggctc caagtctggc aacacggcct ccctgaccat ctctgggctc 240

caggccgagg acgagtctga ttattactgc agctcatata caagcacctt ctctgtggta 300

tttggcggag ggaccaaggt caccgtccta ggt 333

<210> 70
<211> 750
<212> DNA
<213> Homo sapiens

<400> 70
gaggtgcagc tggtggagtc cgggggaggt gtggtacggc ctgggggGTC cctgagactc 60

tcctgtgcag cctctggatt cacctttgac gattatggca tgaactgggt ccgccaagct 120

ccagggaagg ggctggagtg ggtctctggt gttaatggga atggtggtac cagagattat 180

gcagcctccg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240

ctgcaaatga acagtctgag agccgaggac acggccttgt attactgtgc gagaggatgg 300

tatagtggga gcttctacta ctttggctac tggggccgag gaaccctggt caccgtctcg 360

agtggaggcg gcggttcagg cggaggtggc tctggcggtg gcggaagtgc acaggctgtg 420

ctgactcagc cgtcctccgt gtctgggtct cctggacagt cgatcaccat ctcctgcact 480

ggagccagcg gtgacgttgg tgcttataac tttgtctcct ggtaccaaca acacccaggc 540

aaaaccccca aactcataat ttatgatgtc aataagcggc cctcaggggt ttctaatcgc 600

ttctctggct ccaagtctgg caacacggcc tccctgacca tctctgggct ccaggccgag 660

gacgagtctg attattactg cagctcatat acaagcacct tctctgtggt atttggcgga 720

gggaccaagg tcaccgtcct aggtgcggcc 750

<210> 71
<211> 15
<212> DNA
<213> Homo sapiens

<400> 71
gattatggca tgaac 15

<210> 72
<211> 51
<212> DNA
<213> Homo sapiens

<400> 72
ggtgttaatt ggaatggtgg taccagagat tatgcagcct ccgtgaaggg c 51

<210> 73
<211> 36
<212> DNA
<213> Homo sapiens

<400> 73
ggatggtata gtgggagctt ctactacttt ggctac 36

<210> 74
<211> 42
<212> DNA
<213> Homo sapiens

<400> 74
actggagcca gcggtgacgt tggtgcttat aactttgtct cc 42

<210> 75
<211> 21
<212> DNA
<213> Homo sapiens

<400> 75
gatgtcaata agcggccctc a 21

<210> 76
<211> 30
<212> DNA
<213> Homo sapiens

<400> 76
agctcatata caagcacctt ctctgtggta 30

<210> 77
<211> 119
<212> PRT
<213> Homo sapiens

<400> 77
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Gln Ala Ser Gly Tyr Thr Phe Ser Asp Tyr
20 25 30

Tyr Ile His Trp Val Arg Gln Thr Pro Gly Gln Gly Phe Glu Trp Met
35 40 45

Gly Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Trp Val Thr Met Thr Arg Asp Met Ser Asn Thr Thr Ala Tyr
65 70 75 80

Met Glu Leu Pro Arg Leu Arg Asp Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

```
Ala Arg Asp Leu Thr Gly Phe Asp Pro Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115
```

<210> 78
<211> 109
<212> PRT
<213> Homo sapiens

<400> 78

```
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys
1               5                   10                  15

Thr Ala Thr Ile Thr Cys Gly Gly Asn Asn Phe Arg Asn Lys Arg Val
            20                  25                  30

His Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60

Arg Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65                  70                  75                  80

Asp Glu Ala Asp Phe Tyr Cys Gln Val Trp Asp Ser Ser Thr Asp Arg
                85                  90                  95

Pro Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105
```

<210> 79
<211> 247
<212> PRT
<213> Homo sapiens

<400> 79

```
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Gln Ala Ser Gly Tyr Thr Phe Ser Asp Tyr
            20                  25                  30
```

```
Tyr Ile His Trp Val Arg Gln Thr Pro Gly Gln Gly Phe Glu Trp Met
        35                  40                  45

Gly Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Trp Val Thr Met Thr Arg Asp Met Ser Asn Thr Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Pro Arg Leu Arg Asp Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Leu Thr Gly Phe Asp Pro Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Ala Gln Ser Val Leu Thr Gln Pro Pro Ser
    130                 135                 140

Val Ser Val Ala Pro Gly Lys Thr Ala Thr Ile Thr Cys Gly Gly Asn
145                 150                 155                 160

Asn Phe Arg Asn Lys Arg Val His Trp Tyr Gln Gln Arg Pro Gly Gln
                165                 170                 175

Ala Pro Val Leu Val Ile Tyr Tyr Asp Ser Asp Arg Pro Ser Gly Ile
            180                 185                 190

Pro Glu Arg Phe Ser Gly Ser Arg Ser Gly Asn Thr Ala Thr Leu Thr
        195                 200                 205

Ile Ser Arg Val Glu Ala Gly Asp Glu Ala Asp Phe Tyr Cys Gln Val
    210                 215                 220

Trp Asp Ser Ser Thr Asp Arg Pro Leu Phe Gly Gly Gly Thr Lys Leu
225                 230                 235                 240

Thr Val Leu Gly Ala Ala Ala
                245
```

<210> 80
<211> 5
<212> PRT
<213> Homo sapiens

<400> 80
Asp Tyr Tyr Ile His
1 5

<210> 81
<211> 17
<212> PRT
<213> Homo sapiens

<400> 81
Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 82
<211> 10
<212> PRT
<213> Homo sapiens

<400> 82
Asp Leu Thr Gly Phe Asp Pro Phe Asp Ile
1 5 10

<210> 83
<211> 11
<212> PRT
<213> Homo sapiens

<400> 83
Gly Gly Asn Asn Phe Arg Asn Lys Arg Val His
1 5 10

<210> 84
<211> 7
<212> PRT
<213> Homo sapiens

<400> 84
Tyr Asp Ser Asp Arg Pro Ser
1 5

<210> 85
<211> 11
<212> PRT
<213> Homo sapiens

<400> 85
Gln Val Trp Asp Ser Ser Thr Asp Arg Pro Leu
1 5 10

<210> 86
<211> 357
<212> DNA
<213> Homo sapiens

<400> 86
gaggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgtcagg cttctggata caccttcagc gattactata ttcactgggt gcgacagacc 120

cctggacaag ggtttgagtg gatgggatgg gtcaaccctg acactggtgg cacaagatac 180

gcgcagaagt ttcagggctg ggtcacaatg accagggaca tgtccaacac cacagcctac 240

atggagctgc ccaggctgag agacgacgac acggccgtat attactgtgc gagagatcta 300

actggatttg atccttttga tatctggggc cagggaaccc tggtcaccgt ctcctca 357

<210> 87
<211> 327
<212> DNA
<213> Homo sapiens

<400> 87
cagtctgtgc tgactcagcc accctcagtg tcagtggccc caggaaagac ggccacgatt 60

acctgtgggg gaaacaactt tcgaaataaa agagtacact ggtatcagca gaggccaggc 120

caggcccctg tcctggtcat ctattatgat tcagaccggc cctcagggat ccctgagcga 180

ttctctggct cccgctctgg gaacacggcc accctgacca tcagcagggt cgaggccggg 240

gatgaggccg acttttactg tcaggtgtgg gatagtagta ctgatcgtcc gctgttcggc 300

ggagggacca agctgaccgt cctaggt 327

<210> 88
<211> 741
<212> DNA
<213> Homo sapiens

<400> 88
gaagtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgtcagg cttctggata caccttcagc gattactata ttcactgggt gcgacagacc 120

cctggacaag ggtttgagtg gatgggatgg gtcaaccctg acactggtgg cacaagatac 180

gcgcagaagt ttcagggctg ggtcaccatg accagggaca tgtccaacac cacagcctac 240

atggagctgc ccaggctgag agacgacgac acggccgtat attactgtgc gagagatcta 300

actggatttg atccttttga tatctggggc cagggaaccc tggtcaccgt ctcgagtgga 360

ggcggcggtt caggcggagg tggctctggc ggtggcggaa gtgcacagtc tgtgctgact 420

cagccaccct cagtgtcagt ggccccagga aagacggcca cgattacctg tgggggaaac 480

aactttcgaa ataaaagagt acactggtat cagcagaggc caggccaggc ccctgtcctg 540

gtcatctatt atgattcaga ccggccctca gggatccctg agcgattctc tggctcccgc 600

tctgggaaca cggccaccct gaccatcagc agggtcgagg ccggggatga ggccgacttt 660

tactgtcagg tgtgggatag tagtactgat cgtccgctgt tcggcggagg gaccaagctg 720

accgtcctag gtgcggccgc a 741

<210> 89
<211> 15
<212> DNA
<213> Homo sapiens

<400> 89
gattactata ttcac 15

<210> 90
<211> 51
<212> DNA
<213> Homo sapiens

<400> 90
tgggtcaacc ctgacactgg tggcacaaga tacgcgcaga agtttcaggg c 51

<210> 91
<211> 30
<212> DNA
<213> Homo sapiens

<400> 91
gatctaactg gatttgatcc ttttgatatc 30

<210> 92
<211> 33
<212> DNA
<213> Homo sapiens

<400> 92
gggggaaaca actttcgaaa taaaagagta cac 33

<210> 93
<211> 21
<212> DNA
<213> Homo sapiens

<400> 93
tatgattcag accggccctc a 21

<210> 94
<211> 33
<212> DNA
<213> Homo sapiens

<400> 94
caggtgtggg atagtagtac tgatcgtccg ctg 33

<210> 95
<211> 121
<212> PRT
<213> Homo sapiens

<400> 95
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45

Gly Trp Ile Asn Pro Tyr Thr Gly Gly Ala Phe Tyr Ala Gln Lys Phe
50 55 60

Arg Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Asn Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Gly Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Pro Glu Lys Phe Asp Phe Trp Gly Gly Asp Asn Trp Gly
100 105 110

Arg Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 96
<211> 112
<212> PRT
<213> Homo sapiens

<400> 96
Gln Ala Val Leu Thr Gln Pro Ser Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Gly Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
85 90 95

Leu Ser Gly Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr Val Leu Gly
100 105 110

<210> 97
<211> 252
<212> PRT
<213> Homo sapiens

<400> 97
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45

Gly Trp Ile Asn Pro Tyr Thr Gly Gly Ala Phe Tyr Ala Gln Lys Phe
50 55 60

Arg Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Asn Thr Ala Tyr
65 70 75 80

```
Met Glu Leu Ser Arg Leu Gly Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Pro Glu Lys Phe Asp Phe Trp Gly Gly Asp Asn Trp Gly
            100                 105                 110

Arg Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ala Val Leu Thr Gln Pro
    130                 135                 140

Ser Ser Val Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr
145                 150                 155                 160

Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Gly Val His Trp Tyr Gln
                165                 170                 175

Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asn Ser Asn
            180                 185                 190

Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr
        195                 200                 205

Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp
    210                 215                 220

Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser Leu Ser Gly Tyr Val Phe Gly
225                 230                 235                 240

Thr Gly Thr Gln Leu Thr Val Leu Ser Ala Ala Ala
                245                 250
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<210> 98
<211> 5
<212> PRT
<213> Homo sapiens

<400> 98
Asp Tyr Tyr Met His
1   5

<210> 99
<211> 17
<212> PRT
<213> Homo sapiens

<400> 99
Trp Ile Asn Pro Tyr Thr Gly Gly Ala Phe Tyr Ala Gln Lys Phe Arg
1 5 10 15

Gly

<210> 100
<211> 12
<212> PRT
<213> Homo sapiens

<400> 100
Glu Pro Glu Lys Phe Asp Phe Trp Gly Gly Asp Asn
1 5 10

<210> 101
<211> 14
<212> PRT
<213> Homo sapiens

<400> 101
Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Gly Val His
1 5 10

<210> 102
<211> 7
<212> PRT
<213> Homo sapiens

<400> 102
Gly Asn Ser Asn Arg Pro Ser
1 5

<210> 103
<211> 11
<212> PRT
<213> Homo sapiens

<400> 103
Gln Ser Tyr Asp Ser Ser Leu Ser Gly Tyr Val
1 5 10

<210> 104
<211> 363
<212> DNA
<213> Homo sapiens

<400> 104
caggtccagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggata caccttcacc gactactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg ggtgggatgg atcaaccctt atactggtgg cgcattctat 180

gcacagaagt ttcggggcag ggtcacaatg accagggaca cgtccatcaa cacagcctac 240

atggagctga gcagactggg atctgacgac acggccgtgt attattgtgc gagagaacct 300

gaaaaattcg atttttgggg gggtgacaac tggggccggg ggacaatggt caccgtctcc 360

tca 363

<210> 105
<211> 336
<212> DNA
<213> Homo sapiens

<400> 105
caggctgtgc tgactcagcc gtcctcagtg tctggggccc cagggcagag ggtcaccatc 60

tcctgcactg ggagcagctc caacatcggg gcaggttatg gtgtacactg gtaccaacag 120

cttccaggaa cagccccccaa actcctcatc tatggtaaca gcaatcggcc ctcaggggtc 180

cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cactgggctc 240

caggctgagg atgaggctga ttattactgc cagtcctatg acagcagcct gagtggttat 300

gtcttcggaa ctgggaccca gctcaccgtc ctaggt 336

<210> 106
<211> 756
<212> DNA
<213> Homo sapiens

<400> 106
caggtccagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggata caccttcacc gactactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg ggtgggatgg atcaaccctt atactggtgg cgcattctat 180

gcacagaagt ttcggggcag ggtcaccatg accagggaca cgtccatcaa cacagcctac 240

atggagctga gcagactggg atctgacgac acggccgtgt attattgtgc gagagaacct 300

gaaaaattcg atttttgggg gggtgacaac tggggccggg ggacaatggt caccgtctcg 360

agtggaggcg gcggttcagg cggaggtggc tctggcggtg gcggaagtgc acaggctgtg 420

ctgactcagc cgtcctcagt gtctggggcc ccagggcaga gggtcaccat ctcctgcact 480

gggagcagct ccaacatcgg ggcaggttat ggtgtacact ggtaccaaca gcttccagga 540

acagccccca aactcctcat ctatggtaac agcaatcggc cctcaggggt ccctgaccga 600

ttctctggct ccaagtctgg cacctcagcc tccctggcca tcactgggct ccaggctgag 660

gatgaggctg attattactg ccagtcctat gacagcagcc tgagtggtta tgtcttcgga 720

actgggaccc agctcaccgt tttaagtgcg gccgca 756

<210> 107
<211> 15
<212> DNA
<213> Homo sapiens

<400> 107
gactactata tgcac 15

<210> 108
<211> 51
<212> DNA
<213> Homo sapiens

<400> 108
tggatcaacc cttatactgg tggcgcattc tatgcacaga agtttcgggg c 51

<210> 109
<211> 36
<212> DNA
<213> Homo sapiens

<400> 109
gaacctgaaa aattcgattt ttgggggggt gacaac 36

<210> 110
<211> 42
<212> DNA
<213> Homo sapiens

<400> 110
actgggagca gctccaacat cggggcaggt tatggtgtac ac 42

<210> 111
<211> 21
<212> DNA
<213> Homo sapiens

<400> 111
ggtaacagca atcggccctc a 21

<210> 112
<211> 33
<212> DNA
<213> Homo sapiens

<400> 112
cagtcctatg acagcagcct gagtggttat gtc 33

<210> 113
<211> 119
<212> PRT
<213> Homo sapiens

<400> 113
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Thr Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Arg Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Ile Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Leu Trp Val Trp Asp Pro Leu Asp Tyr Trp Gly Arg Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 114
<211> 108
<212> PRT
<213> Homo sapiens

<400> 114
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Ile Gly
1 5 10 15

```
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Gly Ile Tyr His Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Lys Ala Ser Ser Leu Ala Ser Gly Ala Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Phe Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Glu Phe Ala Trp
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
            100                 105
```

<210> 115
<211> 246
<212> PRT
<213> Homo sapiens

<400> 115

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Thr Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
            20                  25                  30

Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Arg Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Ile Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Leu Trp Val Trp Asp Pro Leu Asp Tyr Trp Gly Arg Gly
            100                 105                 110
```

```
Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
      115                 120                 125

Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Thr
    130                 135                 140

Leu Ser Ala Ser Ile Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
145                 150                 155                 160

Glu Gly Ile Tyr His Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
                165                 170                 175

Ala Pro Lys Leu Leu Ile Tyr Lys Ala Ser Ser Leu Ala Ser Gly Ala
            180                 185                 190

Pro Ser Arg Phe Ser Gly Ser Gly Phe Gly Thr Asp Phe Thr Leu Thr
        195                 200                 205

Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
    210                 215                 220

Tyr Ser Glu Phe Ala Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
225                 230                 235                 240

Lys Arg Ala Ala Ala His
                245
```

<210> 116
<211> 5
<212> PRT
<213> Homo sapiens

<400> 116
Asp Tyr Tyr Met Ser
1   5

<210> 117
<211> 17
<212> PRT
<213> Homo sapiens

<400> 117
Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1   5   10   15

Gly

<210> 118
<211> 10
<212> PRT
<213> Homo sapiens

<400> 118
Gly Leu Trp Val Trp Asp Pro Leu Asp Tyr
1 5 10

<210> 119
<211> 11
<212> PRT
<213> Homo sapiens

<400> 119
Arg Ala Ser Glu Gly Ile Tyr His Trp Leu Ala
1 5 10

<210> 120
<211> 7
<212> PRT
<213> Homo sapiens

<400> 120
Lys Ala Ser Ser Leu Ala Ser
1 5

<210> 121
<211> 9
<212> PRT
<213> Homo sapiens

<400> 121
Gln Gln Tyr Ser Glu Phe Ala Trp Thr
1 5

<210> 122
<211> 357
<212> DNA
<213> Homo sapiens

<400> 122
gaggtgcagc tggtggagtc tgggggaggc ttggtcacgc ctggagggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt gactactaca tgagctgggt ccgccaggct 120

ccagggaggg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac 180

gcagactccg tgaagggccg gatcaccatc tccagagaca acgccaagaa ctcactgtat 240

ctgcaaatga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagggctt 300

tgggtttggg atcctcttga ctactggggc agaggaaccc tggtcaccgt ctcctca 357

<210> 123
<211> 324
<212> DNA
<213> Homo sapiens

<400> 123
gacatccaga tgacccagtc tccttccacc ctgtctgcat ctattggaga cagagtcacc 60

atcacctgcc gggccagtga gggtatttat cactggttgg cctggtatca gcagaagcca 120

gggaaagccc ctaaactcct gatctataag gcctctagtt tagccagtgg ggccccatca 180

aggttcagcg gcagtggatt tgggaccgat ttcactctca ccatcagcag cctgcagcct 240

gatgattttg caacttatta ctgccaacaa tacagcgagt tcgcctggac cttcggcgga 300

gggaccaagc tggagatcaa acgt 324

<210> 124
<211> 738
<212> DNA
<213> Homo sapiens

<400> 124
gaggtgcagc tggtggagtc tgggggaggc ttggtcacgc ctggagggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt gactactaca tgagctgggt ccgccaggct 120

ccagggaggg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac 180

gcagactccg tgaagggccg gatcaccatc tccagagaca acgccaagaa ctcactgtat 240

ctgcaaatga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagggctt 300

tgggtttggg atcctcttga ctactggggc agaggaaccc tggtcaccgt ctcttcaggt 360

gggggcggtt caggcggagg tggcagcggc ggtggcggat cggacatcca gatgacccag 420

tccccttcca ccctgtctgc atctattgga gacagagtca ccatcacctg ccgggccagt 480

gagggtattt atcactggtt ggcctggtat cagcagaagc cagggaaagc ccctaaactc 540

ctgatctata aggcctctag tttagccagt ggggccccat caaggttcag cggcagtgga 600

tttgggacag atttcactct caccatcagc agcctgcagc ctgatgattt tgcaacttat 660

tactgccaac aatacagcga gttcgcctgg accttcggcg gagggaccaa gctggagatc 720

aaacgtgcgg ccgcacat 738

<210> 125
<211> 15
<212> DNA
<213> Homo sapiens

<400> 125
gactactaca tgagc 15

<210> 126
<211> 51
<212> DNA
<213> Homo sapiens

<400> 126
gctattagtg gtagtggtgg tagcacatac tacgcagact ccgtgaaggg c 51

<210> 127
<211> 30
<212> DNA
<213> Homo sapiens

<400> 127
gggctttggg tttgggatcc tcttgactac 30

<210> 128
<211> 33
<212> DNA
<213> Homo sapiens

<400> 128
cgggccagtg agggtattta tcactggttg gcc 33

<210> 129
<211> 21
<212> DNA
<213> Homo sapiens

<400> 129
aaggcctcta gtttagccag t 21

<210> 130
<211> 27
<212> DNA
<213> Homo sapiens

<400> 130
caacaataca gcgagttcgc ctggacc 27

<210> 131
<211> 119
<212> PRT
<213> Homo sapiens

<400> 131
Gln Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Val Ser Ala Tyr Thr Gly Asn Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Gly Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Gly Tyr Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 132
<211> 108
<212> PRT
<213> Homo sapiens

<400> 132
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Ile Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Gly Ile Tyr His Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Ala Ser Ser Leu Ala Ser Gly Ala Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Phe Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Met Gly Glu Tyr Asn Ala
85 90 95

Thr Ile Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 133
<211> 246
<212> PRT
<213> Homo sapiens

<400> 133
Gln Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Val Ser Ala Tyr Thr Gly Asn Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Gly Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Gly Tyr Tyr Asp Ala Tyr Asp Ile Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
115 120 125

Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Thr
130 135 140

Leu Ser Ala Ser Ile Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
145 150 155 160

Glu Gly Ile Tyr His Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
165 170 175

Ala Pro Lys Leu Leu Ile Tyr Lys Ala Ser Ser Leu Ala Ser Gly Ala
180 185 190

Pro Ser Arg Phe Ser Gly Ser Gly Phe Gly Thr Asp Phe Thr Leu Thr
195 200 205

Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
210 215 220

Met Gly Glu Tyr Asn Ala Thr Ile Gly Gly Gly Thr Lys Leu Glu Ile
225 230 235 240

Lys Arg Ala Ala Ala His
245

<210> 134
<211> 5
<212> PRT
<213> Homo sapiens

<400> 134
Ser Tyr Gly Ile Ser
1 5

<210> 135
<211> 17
<212> PRT
<213> Homo sapiens

<400> 135
Trp Val Ser Ala Tyr Thr Gly Asn Thr Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 136
<211> 10
<212> PRT
<213> Homo sapiens

<400> 136
Asp Arg Gly Tyr Tyr Asp Ala Phe Asp Ile
1 5 10

<210> 137
<211> 11
<212> PRT
<213> Homo sapiens

<400> 137
Arg Ala Ser Glu Gly Ile Tyr His Trp Leu Ala
1 5 10

<210> 138
<211> 7
<212> PRT
<213> Homo sapiens

<400> 138
Lys Ala Ser Ser Leu Ala Ser
1 5

<210> 139
<211> 9
<212> PRT
<213> Homo sapiens

<400> 139
Gln Gln Met Gly Glu Tyr Asn Ala Thr
1 5

<210> 140
<211> 357
<212> DNA
<213> Homo sapiens

<400> 140
caggtgcagc tggtggagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggtta cacctttacc agttatggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg gtcagcgctt acactggtaa cacaaactat 180

gcacagaagt tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240

atggaactga ggggcctgag atctgacgac acggccgtgt attactgtgc gagagatcgt 300

ggatactatg atgcttttga tatctggggc caaggcaccc tggtcaccgt ctcctca 357

<210> 141
<211> 324
<212> DNA
<213> Homo sapiens

<400> 141
gacatccaga tgacccagtc tccttccacc ctgtctgcat ctattggaga cagagtcacc 60

atcacctgcc gggccagtga gggtatttat cactggttgg cctggtatca gcagaagcca 120

gggaaagccc ctaaactcct gatctataag gcctctagtt tagccagtgg ggccccatca 180

aggttcagcg gcagtggatt tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gatgattttg caacttatta ctgccaacaa atgggcgagt acaacgccac catcggcgga 300

gggaccaagc tggagatcaa acgt 324

<210> 142
<211> 738
<212> DNA
<213> Homo sapiens

<400> 142
caggtgcagc tggtggagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggtta cacctttacc agttatggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg gtcagcgctt acactggtaa cacaaactat 180

gcacagaagt tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240

atggaactga ggggcctgag atctgacgac acggccgtgt attactgtgc gagagatcgt 300

ggatactatg atgcttatga tatctggggc caaggcaccc tggtcaccgt ctcctcaggt 360

ggaggcggtt caggcggagg tggcagcggc ggtggcggat cggacatcca gatgacccag 420

tctccttcca ccctgtctgc atctattgga gacagagtca ccatcacctg ccgggccagt 480

gagggtattt atcactggtt ggcctggtat cagcagaagc cagggaaagc ccctaaactc 540

ctgatctata aggcctctag tttagccagt ggggccccat caaggttcag cggcagtgga 600

tttgggacag atttcactct caccatcagc agcctgcagc ctgatgattt tgcaacttat 660

tactgccaac aaatgggcga gtacaacgcc accatcggcg gagggaccaa gctggagatc 720

aaacgtgcgg ccgcacat 738

<210> 143
<211> 15
<212> DNA
<213> Homo sapiens

<400> 143
agttatggta tcagc 15

<210> 144
<211> 51
<212> DNA
<213> Homo sapiens

<400> 144
tgggtcagcg cttacactgg taacacaaac tatgcacaga agttccaggg c 51

<210> 145
<211> 30
<212> DNA
<213> Homo sapiens

<400> 145
gatcgtggat actatgatgc ttttgatatc 30

<210> 146
<211> 33
<212> DNA
<213> Homo sapiens

<400> 146
cgggccagtg agggtattta tcactggttg gcc 33

<210> 147
<211> 21
<212> DNA
<213> Homo sapiens

<400> 147
aaggcctcta gtttagccag t 21

<210> 148
<211> 27
<212> DNA
<213> Homo sapiens

<400> 148
caacaaatgg gcgagtacaa cgccacc 27

<210> 149
<211> 119
<212> PRT
<213> Homo sapiens

<400> 149
Gln Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

```
Gly Trp Ile Ser Ala Tyr Thr Gly Asn Thr Asn Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Arg Gly Tyr Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115
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<210> 150
<211> 108
<212> PRT
<213> Homo sapiens

<400> 150

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Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Ile Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Gly Ile Tyr His Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Lys Ala Ser Ser Leu Ala Ser Gly Ala Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Phe Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Met Gly Glu Trp Lys Ala
                85                  90                  95

Ala Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
            100                 105
```

<210> 151
<211> 246
<212> PRT
<213> Homo sapiens

<400> 151

```
Gln Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                  10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Trp Ile Ser Ala Tyr Thr Gly Asn Thr Asn Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Arg Gly Tyr Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Thr
    130                 135                 140

Leu Ser Ala Ser Ile Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
145                 150                 155                 160

Glu Gly Ile Tyr His Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
                165                 170                 175

Ala Pro Lys Leu Leu Ile Tyr Lys Ala Ser Ser Leu Ala Ser Gly Ala
            180                 185                 190

Pro Ser Arg Phe Ser Gly Ser Gly Phe Gly Thr Asp Phe Thr Leu Thr
        195                 200                 205

Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
    210                 215                 220
```

Met Gly Glu Trp Lys Ala Ala Phe Gly Gly Gly Thr Lys Leu Glu Ile
225 230 235 240

Lys Arg Ala Ala Ala His
245

<210> 152
<211> 5
<212> PRT
<213> Homo sapiens

<400> 152
Ser Tyr Gly Ile Ser
1 5

<210> 153
<211> 17
<212> PRT
<213> Homo sapiens

<400> 153
Trp Ile Ser Ala Tyr Thr Gly Asn Thr Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 154
<211> 10
<212> PRT
<213> Homo sapiens

<400> 154
Asp Arg Gly Tyr Tyr Asp Ala Phe Asp Ile
1 5 10

<210> 155
<211> 11
<212> PRT
<213> Homo sapiens

<400> 155
Arg Ala Ser Glu Gly Ile Tyr His Trp Leu Ala
1 5 10

<210> 156
<211> 7
<212> PRT
<213> Homo sapiens

<400> 156
Lys Ala Ser Ser Leu Ala Ser
1 5

<210> 157
<211> 9
<212> PRT
<213> Homo sapiens

<400> 157
Gln Gln Met Gly Glu Trp Lys Ala Ala
1 5

<210> 158
<211> 357
<212> DNA
<213> Homo sapiens

<400> 158
caggtgcagc tggtggagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggtta cacctttacc agttatggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcagcgctt acactggtaa cacaaactat 180

gcacagaagt tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240

atggaactga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagatcgt 300

ggatactatg atgctttcga tatctggggc caaggcaccc tggtcaccgt ctcctca 357

<210> 159
<211> 324
<212> DNA
<213> Homo sapiens

<400> 159
gacatccaga tgacccagtc tccttccacc ctgtctgcat ctattggaga cagagtcacc 60

atcacctgcc gggccagtga gggtatttat cactggttgg cctggtatca gcagaagcca 120

gggaaagccc ctaaactcct gatctataag gcctctagtt tagccagtgg ggccccatca 180

aggttcagcg gcagtggatt tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gatgattttg caacttatta ctgccaacaa atgggggagt ggaaggcggc cttcggcgga 300

gggaccaagc tggagatcaa acgt 324

<210> 160
<211> 738
<212> DNA
<213> Homo sapiens

<400> 160
caggtgcagc tggtggagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggtta cacctttacc agttatggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcagcgctt acactggtaa cacaaactat 180

gcacagaagt tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240

atggaactga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagatcgt 300

ggatactatg atgctttcga tatctggggc caaggcaccc tggtcaccgt ctcctcaggt 360

gggggcggtt caggcggagg tggcagcggc ggtggcggat cggacatcca gatgacccag 420

tctccttcca ccctgtctgc atctattgga gacagagtca ccatcacctg ccgggccagt 480

gagggtattt atcactggtt ggcctggtat cagcagaagc cagggaaagc ccctaaactc 540

ctgatctata aggcctctag tttagccagt ggggccccat caaggttcag cggcagtgga 600

tttgggacag atttcactct caccatcagc agcctgcagc ctgatgattt tgcaacttat 660

tactgccaac aaatggggga gtggaaggcg gccttcggcg gagggaccaa gctggagatc 720

aaacgtgcgg ccgcacat 738

<210> 161
<211> 15
<212> DNA
<213> Homo sapiens

<400> 161
agttatggta tcagc 15

<210> 162
<211> 51
<212> DNA
<213> Homo sapiens

<400> 162
tggatcagcg cttacactgg taacacaaac tatgcacaga agttccaggg c 51

<210> 163
<211> 30
<212> DNA
<213> Homo sapiens

<400> 163
gatcgtggat actatgatgc tttcgatatc 30

<210> 164
<211> 33
<212> DNA
<213> Homo sapiens

<400> 164
cgggccagtg agggtattta tcactggttg gcc 33

<210> 165
<211> 21
<212> DNA
<213> Homo sapiens

<400> 165
aaggcctcta gtttagccag t 21

<210> 166
<211> 27
<212> DNA
<213> Homo sapiens

<400> 166
caacaaatgg gggagtggaa ggcggcc 27

<210> 167
<211> 5
<212> PRT
<213> Homo sapiens

<400> 167
Asp Tyr Gly Met Asn
1 5

<210> 168
<211> 111
<212> PRT
<213> Homo sapiens

<400> 168
Gln Ala Val Leu Thr Gln Pro Ser Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Ala Ser Gly Asp Val Gly Ala Tyr
20 25 30

Asn Phe Val Ser Trp Tyr Gln Gln His Pro Gly Lys Thr Pro Lys Leu
35 40 45

Ile Ile Tyr Asp Val Asn Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

```
Ser Gly Ser Lys Ser Ser Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Glu Ser Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Thr
                85                  90                  95

Phe Ser Val Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly
            100                 105                 110
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<210> 169
<211> 252
<212> PRT
<213> Homo sapiens

<400> 169

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Arg Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Val Asn Trp Asn Gly Gly Thr Arg Asp Tyr Ala Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Trp Tyr Ser Gly Ala Ala Trp Asn Met Gly Tyr Trp Gly
            100                 105                 110

Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ala Val Leu Thr Gln Pro
    130                 135                 140

Ser Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr
145                 150                 155                 160
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Gly Ala Ser Gly Asp Val Gly Ala Tyr Asn Phe Val Ser Trp Tyr Gln
                165                 170                 175

Gln His Pro Gly Lys Thr Pro Lys Leu Ile Ile Tyr Asp Val Asn Lys
            180                 185                 190

Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Ser Asn
        195                 200                 205

Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ser Asp
    210                 215                 220

Tyr Tyr Cys Ser Ser Tyr Thr Ser Thr Phe Ser Val Val Phe Gly Gly
225                 230                 235                 240

Gly Thr Lys Val Thr Val Leu Gly Ala Ala Ala His
                245                 250
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<210> 170
<211> 5
<212> PRT
<213> Homo sapiens

<400> 170
Asp Tyr Gly Met Asn
1   5

<210> 171
<211> 17
<212> PRT
<213> Homo sapiens

<400> 171
Gly Val Asn Trp Asn Gly Gly Thr Arg Asp Tyr Ala Ala Ser Val Lys
1   5   10   15

Gly

<210> 172
<211> 12
<212> PRT
<213> Homo sapiens

<400> 172
Gly Trp Tyr Ser Gly Ala Ala Trp Asn Met Gly Tyr
1   5   10

<210> 173
<211> 14
<212> PRT
<213> Homo sapiens

<400> 173
Thr Gly Ala Ser Gly Asp Val Gly Ala Tyr Asn Phe Val Ser
1 5 10

<210> 174
<211> 7
<212> PRT
<213> Homo sapiens

<400> 174
Asp Val Asn Lys Arg Pro Ser
1 5

<210> 175
<211> 10
<212> PRT
<213> Homo sapiens

<400> 175
Ser Ser Tyr Thr Ser Thr Phe Ser Val Val
1 5 10

<210> 176
<211> 363
<212> DNA
<213> Homo sapiens

<400> 176
gaggtgcagc tggtggagtc cgggggaggt gtggtacggc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttgac gattatggca tgaactgggt ccgccaagct 120

ccagggaagg ggctggagtg ggtctctggt gttaattgga atggtggtac cagagattat 180

gcagcctccg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240

ctgcaaatga acagtctgag agccgaggac acggccttgt attactgtgc gagaggatgg 300

tatagtgggg ccgcgtggaa catgggctac tggggccgag gaaccctggt caccgtctcc 360

tca 363

<210> 177
<211> 333
<212> DNA
<213> Homo sapiens

<400> 177
caggctgtgc tgactcagcc gtcctccgtg tctgggtctc ctggacagtc gatcaccatc 60

tcctgcactg gagccagcgg tgacgttggt gcttataact ttgtctcctg gtaccaacaa 120

cacccaggca aaacccccaa actcataatt tatgatgtca ataagcggcc ctcaggggtt 180

tctaatcgct tctctggctc caagtctagc aacacggcct ccctgaccat ctctgggctc 240

caggccgagg acgagtctga ttattactgc agctcatata caagcacctt ctctgtggta 300

tttggcggag ggaccaaggt caccgtccta ggt 333

<210> 178
<211> 757
<212> DNA
<213> Homo sapiens

<400> 178
cgaggtgcag ctggtggagt ccgggggagg tgtggtacgg cctgggggggt ccctgagact 60

ctcctgtgca gcctctggat tcacctttga cgattatggc atgaactggg tccgccaagc 120

tccagggaag gggctggagt gggtctctgg tgttaattgg aatggtggta ccagagatta 180

tgcagcctcc gtgaagggcc gattcaccat ctccagagac aacgccaaga actccctgta 240

tctgcaaatg aacagtctga gagccgagga cacggccttg tattactgtg cgagaggatg 300

gtatagtggg gccgcgtgga acatgggcta ctggggccga ggaaccctgg tcaccgtctc 360

gagtggaggc ggcggttcag gcggaggtgg ctctggcggt ggcggaagtg cacaggctgt 420

gctgactcag ccgtcctccg tgtctgggtc tcctggacag tcgatcacca tctcctgcac 480

tggagccagc ggtgacgttg gtgcttataa ctttgtctcc tggtaccaac aacacccagg 540

caaaaccccc aaactcataa tttatgatgt caataagcgg ccctcagggg tttctaatcg 600

cttctctggc tccaagtcta gcaacacggc ctccctgacc atctctgggc tccaggccga 660

ggacgagtct gattattact gcagctcata tacaagcacc ttctctgtgg tatttggcgg 720

agggaccaag gtcaccgtcc taggtgcggc cgcacat 757

<210> 179
<211> 15
<212> DNA
<213> Homo sapiens

<400> 179
gattatggca tgaac 15

<210> 180
<211> 51
<212> DNA
<213> Homo sapiens

<400> 180
ggtgttaatt ggaatggtgg taccagagat tatgcagcct ccgtgaaggg c 51

<210> 181
<211> 36
<212> DNA
<213> Homo sapiens

<400> 181
ggatggtata gtggggccgc gtggaacatg ggctac 36

<210> 182
<211> 42
<212> DNA
<213> Homo sapiens

<400> 182
actggagcca gcggtgacgt tggtgcttat aactttgtct cc 42

<210> 183
<211> 21
<212> DNA
<213> Homo sapiens

<400> 183
gatgtcaata agcggccctc a 21

<210> 184
<211> 30
<212> DNA
<213> Homo sapiens

<400> 184
agctcatata caagcacctt ctctgtggta 30

<210> 185
<211> 121
<212> PRT
<213> Homo sapiens

<400> 185
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Val Asn Trp Asn Gly Gly Thr Arg Asp Tyr Ala Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Arg Gly Trp Tyr Ser Gly Ser Pro Trp Ser Leu Gly His Trp Gly
100 105 110

Arg Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 186
<211> 111
<212> PRT
<213> Homo sapiens

<400> 186
Gln Ala Val Leu Thr Gln Pro Ser Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Val Thr Ile Ser Cys Thr Gly Ala Ser Gly Asp Val Gly Ala Tyr
20 25 30

Asn Phe Val Ser Trp Tyr Gln Gln His Pro Gly Lys Thr Pro Lys Leu
35 40 45

Ile Ile Tyr Asp Val Asn Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Arg Leu
65 70 75 80

Gln Ala Glu Asp Glu Ser Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Arg
85 90 95

Tyr Thr Thr Glu Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly
100 105 110

<210> 187
<211> 271
<212> PRT
<213> Homo sapiens

<400> 187
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Val Asn Trp Asn Gly Gly Thr Arg Asp Tyr Ala Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Arg Gly Trp Tyr Ser Gly Ser Pro Trp Ser Leu Gly His Trp Gly
100 105 110

Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
115 120 125

Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly
130 135 140

Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ala Val Leu
145 150 155 160

Thr Gln Pro Ser Ser Val Ser Gly Ser Pro Gly Gln Ser Val Thr Ile
165 170 175

Ser Cys Thr Gly Ala Ser Gly Asp Val Gly Ala Tyr Asn Phe Val Ser
180 185 190

Trp Tyr Gln Gln His Pro Gly Lys Thr Pro Lys Leu Ile Ile Tyr Asp
195 200 205

```
Val Asn Lys Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys
    210                 215                 220

Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Arg Leu Gln Ala Glu Asp
225                 230                 235                 240

Glu Ser Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Arg Tyr Thr Thr Glu
                245                 250                 255

Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly Ala Ala Ala His
            260                 265                 270
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<210> 188
<211> 5
<212> PRT
<213> Homo sapiens

<400> 188
Asp Tyr Gly Met Asn
1   5

<210> 189
<211> 17
<212> PRT
<213> Homo sapiens

<400> 189
Gly Val Asn Trp Asn Gly Gly Thr Arg Asp Tyr Ala Ala Ser Val Lys
1   5   10   15

Gly

<210> 190
<211> 12
<212> PRT
<213> Homo sapiens

<400> 190
Gly Trp Tyr Ser Gly Ser Pro Trp Ser Leu Gly His
1   5   10

<210> 191
<211> 14
<212> PRT
<213> Homo sapiens

<400> 191
Thr Gly Ala Ser Gly Asp Val Gly Ala Tyr Asn Phe Val Ser
1 5 10

<210> 192
<211> 7
<212> PRT
<213> Homo sapiens

<400> 192
Asp Val Asn Lys Arg Pro Ser
1 5

<210> 193
<211> 10
<212> PRT
<213> Homo sapiens

<400> 193
Ser Ser Tyr Thr Ser Arg Tyr Thr Thr Glu
1 5 10

<210> 194
<211> 363
<212> DNA
<213> Homo sapiens

<400> 194
gaggtgcagc tggtggagtc cgggggaggt gtggtacggc ctgggggGTC cctgagactc 60

tcctgtgcag cctctggatt cacctttgac gattatggca tgaactgggt ccgccaagct 120

ccagggaagg ggctggagtg ggtctctggt gttaattgga atggtggtac cagagattat 180

gcagcctccg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240

ctgcaaatga acagtctgag agccgaggac acggccttgt attactgtgc gagaggatgg 300

tatagtggga gcccgtggtc gctgggccac tggggccgag gaaccctggt caccgtctcc 360

tca 363

<210> 195
<211> 333
<212> DNA
<213> Homo sapiens

<400> 195
caggctgtgc tgactcagcc gtcctccgtg tctgggtctc ctggacagtc ggtcaccatc 60

tcctgcactg gagccagcgg tgacgttggt gcttataact ttgtctcctg gtaccaacaa 120

cacccaggca aaacccccaa actcataatt tatgatgtca ataagcggcc ctcaggggtt 180

tctaatcgct tctctggctc caagtctggc aacacggcct ccctgaccat ctctaggctc 240

caggccgagg acgagtctga ttattactgc agctcatata catcgaggta cacgaccgag 300

tttggcggag ggaccaaggt caccgtccta ggt 333

<210> 196
<211> 813
<212> DNA
<213> Homo sapiens

<400> 196
gaggtgcagc tggtggagtc cgggggaggt gtggtacggc ctgggggGTC cctgagactc 60

tcctgtgcag cctctggatt cacctttgac gattatggca tgaactgggt ccgccaagct 120

ccagggaagg ggctggagtg ggtctctggt gttaattgga atggtggtac cagagattat 180

gcagcctccg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240

ctgcaaatga acagtctgag agccgaggac acggccttgt attactgtgc gagaggatgg 300

tatagtggga gcccgtggtc gctgggccac tggggccgag gaaccctggt caccgtctcg 360

agtggaggcg gcggttcagg cggaggtggc tctggcggta gcggaggtgg ctctggcggt 420

agcggaggtg gctctagcgg aggtggctct ggcggtggcg gaagtgcaca ggctgtgctg 480

actcagccgt cctccgtgtc tgggtctcct ggacagtcgg tcaccatctc ctgcactgga 540

gccagcggtg acgttggtgc ttataacttt gtctcctggt accaacaaca cccaggcaaa 600

acccccaaac tcataattta tgatgtcaat aagcggccct caggggtttc taatcgcttc 660

tctggctcca agtctggcaa cacggcctcc ctgaccatct ctaggctcca ggccgaggac 720

gagtctgatt attactgcag ctcatataca tcgaggtaca cgaccgagtt tggcggaggg 780

accaaggtca ccgtcctagg tgcggccgca cat 813

<210> 197
<211> 15
<212> DNA
<213> Homo sapiens

<400> 197
gattatggca tgaac 15

<210> 198
<211> 51
<212> DNA
<213> Homo sapiens

<400> 198
ggtgttaatt ggaatggtgg taccagagat tatgcagcct ccgtgaaggg c 51

<210> 199
<211> 36
<212> DNA
<213> Homo sapiens

<400> 199
ggatggtata gtgggagccc gtggtcgctg ggccac 36

<210> 200
<211> 42
<212> DNA
<213> Homo sapiens

<400> 200
actggagcca gcggtgacgt tggtgcttat aactttgtct cc 42

<210> 201
<211> 21
<212> DNA
<213> Homo sapiens

<400> 201
gatgtcaata agcggccctc a 21

<210> 202
<211> 30
<212> DNA
<213> Homo sapiens

<400> 202
agctcatata catcgaggta cacgaccgag 30

<210> 203
<211> 121
<212> PRT
<213> Homo sapiens

<400> 203
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Val Asn Trp Asn Gly Gly Thr Arg Asp Tyr Ala Ala Ser Val
50 55 60

```
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Trp Tyr Ser Gly Ala Ala Trp Asn Met Gly Tyr Trp Gly
            100                 105                 110

Arg Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> 204
<211> 111
<212> PRT
<213> Homo sapiens

<400> 204

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Gln Ala Val Leu Thr Gln Pro Ser Ser Val Ser Gly Ser Pro Gly Gln
1               5                   10                  15

Ser Ile Thr Ile Ser Cys Thr Gly Ala Ser Gly Asp Val Gly Ala Tyr
            20                  25                  30

Asn Phe Val Ser Trp Tyr Gln Gln His Pro Gly Lys Thr Pro Lys Leu
        35                  40                  45

Ile Ile Tyr Asp Val Asn Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Glu Ser Asp Tyr Tyr Cys Ala Ser Leu Val Ser Asp
                85                  90                  95

Phe Ser Val Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly
            100                 105                 110
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<210> 205
<211> 266
<212> PRT
<213> Homo sapiens

<400> 205

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Arg Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Val Asn Trp Asn Gly Gly Thr Arg Asp Tyr Ala Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Trp Tyr Ser Gly Ala Ala Trp Asn Met Gly Tyr Trp Gly
            100                 105                 110

Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly
    130                 135                 140

Ser Gly Gly Gly Gly Ser Ala Gln Ala Val Leu Thr Gln Pro Ser Ser
145                 150                 155                 160

Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Ala
                165                 170                 175

Ser Gly Asp Val Gly Ala Tyr Asn Phe Val Ser Trp Tyr Gln Gln His
            180                 185                 190

Pro Gly Lys Thr Pro Lys Leu Ile Ile Tyr Asp Val Asn Lys Arg Pro
        195                 200                 205

Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala
    210                 215                 220
```

Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ser Asp Tyr Tyr
225 230 235 240

Cys Ala Ser Leu Val Ser Asp Phe Ser Val Val Phe Gly Gly Gly Thr
245 250 255

Lys Val Thr Val Leu Gly Ala Ala Ala His
260 265

<210> 206
<211> 5
<212> PRT
<213> Homo sapiens

<400> 206
Asp Tyr Gly Met Asn
1 5

<210> 207
<211> 17
<212> PRT
<213> Homo sapiens

<400> 207
Gly Val Asn Trp Asn Gly Gly Thr Arg Asp Tyr Ala Ala Ser Val Lys
1 5 10 15

Gly

<210> 208
<211> 12
<212> PRT
<213> Homo sapiens

<400> 208
Gly Trp Tyr Ser Gly Ala Ala Trp Asn Met Gly Tyr
1 5 10

<210> 209
<211> 14
<212> PRT
<213> Homo sapiens

<400> 209
Thr Gly Ala Ser Gly Asp Val Gly Ala Tyr Asn Phe Val Ser
1 5 10

<210> 210
<211> 7
<212> PRT
<213> Homo sapiens

<400> 210
Asp Val Asn Lys Arg Pro Ser
1 5

<210> 211
<211> 10
<212> PRT
<213> Homo sapiens

<400> 211
Ala Ser Leu Val Ser Asp Phe Ser Val Val
1 5 10

<210> 212
<211> 363
<212> DNA
<213> Homo sapiens

<400> 212
gaggtgcagc tggtggagtc cgggggaggt gtggtacggc ctggggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttgac gattatggca tgaactgggt ccgccaagct 120

ccagggaagg ggctggagtg ggtctctggt gttaattgga atggtggtac cagagattat 180

gcagcctccg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240

ctgcaaatga acagtctgag agccgaggac acggccttgt attactgtgc gagaggatgg 300

tatagtgggg ccgcgtggaa catgggctac tggggccgag gaaccctggt caccgtctcc 360

tca 363

<210> 213
<211> 333
<212> DNA
<213> Homo sapiens

<400> 213
caggctgtgc tgactcagcc gtcctccgtg tctgggtccc ctggacagtc gatcaccatc 60

tcctgcactg gagccagcgg tgacgttggt gcttataact ttgtctcctg gtaccaacaa 120

cacccaggca aaaccccaa actcataatt tatgatgtca ataagcggcc ctcaggggtt 180

tctaatcgct tctctggctc caagtctggc aacacggcct ccctgaccat ctctgggctc 240

caggccgagg acgagtctga ttattactgc gcctccctcg tctccgactt ctctgtggta 300

tttggcggag ggaccaaggt caccgtccta ggt 333

<210> 214
<211> 798
<212> DNA
<213> Homo sapiens

<400> 214
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tcctgtgcag cctctggatt cacctttgac gattatggca tgaactgggt ccgccaagct 120

ccagggaagg ggctggagtg ggtctctggt gttaattgga atggtggtac cagagattat 180

gcagcctccg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240

ctgcaaatga acagtctgag agccgaggac acggccttgt attactgtgc gagaggatgg 300

tatagtgggg ccgcgtggaa catgggctac tggggccgag gaaccctggt caccgtctcg 360

agtggaggcg gcggttcagg cggaggtggc tctggtggta gcggaggtgg ctctggcggt 420

ggcggaggtg gctctggcgg tggcggaagt gcacaggctg tgctgactca gccgtcctcc 480

gtgtctgggt cccctggaca gtcgatcacc atctcctgca ctggagccag cggtgacgtt 540

ggtgcttata actttgtctc ctggtaccaa caacacccag gcaaaacccc caaactcata 600

atttatgatg tcaataagcg gccctcaggg gtttctaatc gcttctctgg ctccaagtct 660

ggcaacacgg cctccctgac catctctggg ctccaggccg aggacgagtc tgattattac 720

tgcgcctccc tcgtctccga cttctctgtg gtatttggcg gagggaccaa ggtcaccgtc 780

ctaggtgcgg ccgcacat 798

<210> 215
<211> 15
<212> DNA
<213> Homo sapiens

<400> 215
gattatggca tgaac 15

<210> 216
<211> 51
<212> DNA
<213> Homo sapiens

<400> 216
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<210> 217
<211> 36
<212> DNA
<213> Homo sapiens

<400> 217
ggatggtata gtggggccgc gtggaacatg ggctac 36

<210> 218
<211> 42
<212> DNA
<213> Homo sapiens

<400> 218
actggagcca gcggtgacgt tggtgcttat aactttgtct cc 42

<210> 219
<211> 21
<212> DNA
<213> Homo sapiens

<400> 219
gatgtcaata agcggccctc a 21

<210> 220
<211> 30
<212> DNA
<213> Homo sapiens

<400> 220
gcctccctcg tctccgactt ctctgtggta 30

<210> 221
<211> 119
<212> PRT
<213> Homo sapiens

<400> 221
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Gln Ala Ser Gly Tyr Thr Phe Ser Asp Tyr
20 25 30

Tyr Ile His Trp Val Arg Gln Thr Pro Gly Gln Gly Phe Glu Trp Met
35 40 45

Gly Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Trp Val Thr Met Thr Arg Asp Met Ser Asn Thr Thr Ala Tyr
65 70 75 80

Met Glu Leu Pro Arg Leu Arg Asp Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Leu Thr Gly Phe Asp Pro Phe Asp Ile Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 222
<211> 109
<212> PRT
<213> Homo sapiens

<400> 222
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys
1 5 10 15

Thr Ala Thr Ile Thr Cys Gly Gly Asn Asn Phe Arg Asn Lys Arg Val
20 25 30

His Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Arg Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Phe Tyr Cys Gln Val Trp Asp Leu Phe Asn Asp Asn
85 90 95

Gly Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105

<210> 223
<211> 248
<212> PRT
<213> Homo sapiens

<400> 223
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

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Ser Val Lys Val Ser Cys Gln Ala Ser Gly Tyr Thr Phe Ser Asp Tyr
            20                  25                  30

Tyr Ile His Trp Val Arg Gln Thr Pro Gly Gln Gly Phe Glu Trp Met
        35                  40                  45

Gly Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Trp Val Thr Met Thr Arg Asp Met Ser Asn Thr Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Pro Arg Leu Arg Asp Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Leu Thr Gly Phe Asp Pro Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Ala Gln Ser Val Leu Thr Gln Pro Pro Ser
    130                 135                 140

Val Ser Val Ala Pro Gly Lys Thr Ala Thr Ile Thr Cys Gly Gly Asn
145                 150                 155                 160

Asn Phe Arg Asn Lys Arg Val His Trp Tyr Gln Gln Arg Pro Gly Gln
                165                 170                 175

Ala Pro Val Leu Val Ile Tyr Tyr Asp Ser Asp Arg Pro Ser Gly Ile
            180                 185                 190

Pro Glu Arg Phe Ser Gly Ser Arg Ser Gly Asn Thr Ala Thr Leu Thr
        195                 200                 205

Ile Ser Arg Val Glu Ala Gly Asp Glu Ala Asp Phe Tyr Cys Gln Val
    210                 215                 220

Trp Asp Leu Phe Asn Asp Asn Gly Val Phe Gly Gly Gly Thr Lys Leu
225                 230                 235                 240
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Thr Val Leu Gly Ala Ala Ala His
245

<210> 224
<211> 5
<212> PRT
<213> Homo sapiens

<400> 224
Asp Tyr Tyr Ile His
1 5

<210> 225
<211> 17
<212> PRT
<213> Homo sapiens

<400> 225
Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 226
<211> 10
<212> PRT
<213> Homo sapiens

<400> 226
Asp Leu Thr Gly Phe Asp Pro Phe Asp Ile
1 5 10

<210> 227
<211> 11
<212> PRT
<213> Homo sapiens

<400> 227
Gly Gly Asn Asn Phe Arg Asn Lys Arg Val His
1 5 10

<210> 228
<211> 7
<212> PRT
<213> Homo sapiens

<400> 228
Tyr Asp Ser Asp Arg Pro Ser
1 5

<210> 229
<211> 11
<212> PRT
<213> Homo sapiens

<400> 229
Gln Val Trp Asp Leu Phe Asn Asp Asn Gly Val
1 5 10

<210> 230
<211> 357
<212> DNA
<213> Homo sapiens

<400> 230
gaggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgtcagg cttctggata caccttcagc gattactata ttcactgggt gcgacagacc 120

cctggacaag ggtttgagtg gatgggatgg gtcaaccctg acactggtgg cacaagatac 180

gcgcagaagt ttcagggctg ggtcacaatg accagggaca tgtccaacac cacagcctac 240

atggagctgc ccaggctgag agacgacgac acggccgtat attactgtgc gagagatcta 300

actggatttg atccttttga tatctggggc cagggaaccc tggtcaccgt ctcctca 357

<210> 231
<211> 327
<212> DNA
<213> Homo sapiens

<400> 231
cagtctgtgc tgactcagcc accctcagtg tcagtggccc caggaaagac ggccacgatt 60

acctgtgggg gaaacaactt tcgaaataaa agagtacact ggtatcagca gaggccaggc 120

caggcccctg tcctggtcat ctattatgac tcagaccggc cctcagggat ccctgagcga 180

ttctctggct cccgctctgg gaacacggcc accctgacca tcagcagggt cgaggccggg 240

gatgaggccg acttttactg tcaggtgtgg gatctcttca acgacaacgg cgtgttcggc 300

ggagggacca agctgaccgt cctaggt 327

<210> 232
<211> 744
<212> DNA
<213> Homo sapiens

<400> 232
gaagtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgtcagg cttctggata caccttcagc gattactata ttcactgggt gcgacagacc 120

cctggacaag ggtttgagtg gatgggatgg gtcaaccctg acactggtgg cacaagatac 180

gcgcagaagt ttcagggctg ggtcacaatg accagggaca tgtccaacac cacagcctac 240

atggagctgc ccaggctgag agacgacgac acggccgtat attactgtgc gagagatcta 300

actggatttg atccttttga tatctggggc cagggaaccc tggtcaccgt ctcgagtgga 360

ggcggcagtt caggtggagg tggctctggc ggtggcggaa gtgcacagtc tgtgctgact 420

cagccaccct cagtgtcagt ggccccagga aagacggcca cgattacctg tgggggaaac 480

aactttcgaa ataaaagagt acactggtat cagcagaggc caggccaggc ccctgtcctg 540

gtcatctatt atgattcaga ccggccctca gggatccctg agcgattctc tggctcccgc 600

tctgggaaca cggccaccct gaccatcagc agggtcgagg ccggggatga ggccgacttt 660

tactgtcagg tgtgggatct cttcaacgac aacggcgtgt tcggcggagg gaccaagctg 720

accgtcctag gtgcggccgc acat 744

<210> 233
<211> 15
<212> DNA
<213> Homo sapiens

<400> 233
gattactata ttcac 15

<210> 234
<211> 51
<212> DNA
<213> Homo sapiens

<400> 234
tgggtcaacc ctgacactgg tggcacaaga tacgcgcaga agtttcaggg c 51

<210> 235
<211> 30
<212> DNA
<213> Homo sapiens

<400> 235
gatctaactg gatttgatcc ttttgatatc 30

<210> 236
<211> 33
<212> DNA
<213> Homo sapiens

<400> 236
gggggaaaca actttcgaaa taaaagagta cac 33

<210> 237
<211> 21
<212> DNA
<213> Homo sapiens

<400> 237
tatgactcag accggccctc a 21

<210> 238
<211> 33
<212> DNA
<213> Homo sapiens

<400> 238
caggtgtggg atctcttcaa cgacaacggc gtg 33

<210> 239
<211> 119
<212> PRT
<213> Homo sapiens

<400> 239
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Gln Ala Ser Gly Tyr Thr Phe Ser Asp Tyr
20 25 30

Tyr Ile His Trp Val Arg Gln Thr Pro Gly Gln Gly Phe Glu Trp Met
35 40 45

Gly Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Trp Val Thr Met Thr Arg Asp Met Ser Asn Thr Thr Ala Tyr
65 70 75 80

Met Glu Leu Pro Arg Leu Arg Asp Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Leu Thr Gly Phe Asp Pro Phe Asp Ile Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 240
<211> 109
<212> PRT
<213> Homo sapiens

<400> 240
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys
1 5 10 15

Thr Ala Thr Ile Thr Cys Gly Gly Asn Asn Phe Arg Asn Lys Arg Val
20 25 30

His Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Arg Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Phe Tyr Cys Gln Val Trp Asp Phe Leu Thr Asp Ser
85 90 95

Gly Ser Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105

<210> 241
<211> 248
<212> PRT
<213> Homo sapiens

<400> 241
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Gln Ala Ser Gly Tyr Thr Phe Ser Asp Tyr
20 25 30

Tyr Ile His Trp Val Arg Gln Thr Pro Gly Gln Gly Phe Glu Trp Met
35 40 45

Gly Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Trp Val Thr Met Thr Arg Asp Met Ser Asn Thr Thr Ala Tyr
65 70 75 80

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Met Glu Leu Pro Arg Leu Arg Asp Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Leu Thr Gly Phe Asp Pro Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Ala Gln Ser Val Leu Thr Gln Pro Pro Ser
    130                 135                 140

Val Ser Val Ala Pro Gly Lys Thr Ala Thr Ile Thr Cys Gly Gly Asn
145                 150                 155                 160

Asn Phe Arg Asn Lys Arg Val His Trp Tyr Gln Gln Arg Pro Gly Gln
                165                 170                 175

Ala Pro Val Leu Val Ile Tyr Tyr Asp Ser Asp Arg Pro Ser Gly Ile
            180                 185                 190

Pro Glu Arg Phe Ser Gly Ser Arg Ser Gly Asn Thr Ala Thr Leu Thr
        195                 200                 205

Ile Ser Arg Val Glu Ala Gly Asp Glu Ala Asp Phe Tyr Cys Gln Val
    210                 215                 220

Trp Asp Phe Leu Thr Asp Ser Gly Ser Phe Gly Gly Gly Thr Lys Leu
225                 230                 235                 240

Thr Val Leu Gly Ala Ala Ala His
                245
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<210> 242
<211> 5
<212> PRT
<213> Homo sapiens

<400> 242

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Asp Tyr Tyr Ile His
1               5
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<210> 243
<211> 17
<212> PRT
<213> Homo sapiens

<400> 243
Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 244
<211> 10
<212> PRT
<213> Homo sapiens

<400> 244
Asp Leu Thr Gly Phe Asp Pro Phe Asp Ile
1 5 10

<210> 245
<211> 11
<212> PRT
<213> Homo sapiens

<400> 245
Gly Gly Asn Asn Phe Arg Asn Lys Arg Val His
1 5 10

<210> 246
<211> 7
<212> PRT
<213> Homo sapiens

<400> 246
Tyr Asp Ser Asp Arg Pro Ser
1 5

<210> 247
<211> 11
<212> PRT
<213> Homo sapiens

<400> 247
Gln Val Trp Asp Phe Leu Thr Asp Ser Gly Ser
1 5 10

<210> 248
<211> 357
<212> DNA
<213> Homo sapiens

<400> 248
gaggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgtcagg cttctggata caccttcagc gattactata ttcactgggt gcgacagacc 120

cctggacaag ggtttgagtg gatgggatgg gtcaaccctg acactggtgg cacaagatac 180

gcgcagaagt ttcagggctg ggtcacaatg accagggaca tgtccaacac cacagcctac 240

atggagctgc ccaggctgag agacgacgac acggccgtat attactgtgc gagagatcta 300

actggatttg atccttttga tatctggggc cagggaaccc tggtcaccgt ctcctca 357

<210> 249
<211> 327
<212> DNA
<213> Homo sapiens

<400> 249
cagtctgtgc tgactcagcc accctcagtg tcagtggccc caggaaagac ggccacaatt 60

acctgtgggg gaaacaactt tcgaaataaa agagtacact ggtatcagca gaggccaggc 120

caggcgcctg tcctggtcat ctattatgat tcagaccggc cctcagggat ccctgagcga 180

ttctctggct cccgctctgg gaacacggcc accctgacca tcagcagggt cgaggccggg 240

gatgaggccg acttttactg tcaggtgtgg gatttcctca ccgactcggg gtcgttcggc 300

ggagggacca agctgaccgt cctaggt 327

<210> 250
<211> 744
<212> DNA
<213> Homo sapiens

<400> 250
gaagtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgtcagg cttctggata caccttcagc gattactata ttcactgggt gcgacagacc 120

cctggacaag ggtttgagtg gatgggatgg gtcaaccctg acactggtgg cacaagatac 180

gcgcagaagt ttcagggctg ggtcacaatg accagggaca tgtccaacac cacagcctac 240

atggagctgc ccaggctgag agacgacgac acggccgtat attactgtgc gagagatcta 300

actggatttg atccttttga tatctggggc cagggaaccc tggtcaccgt ctcgagtgga 360

ggcggcggtt caggcggagg tggctctggc ggtggcggaa gtgcacagtc tgtgctgact 420

cagccaccct cagtgtcagt ggccccagga aagacggcca caattacctg tggggaaac 480

aactttcgaa ataaaagagt acactggtat cagcagaggc caggccaggc gcctgtcctg 540

gtcatctatt atgattcaga ccggccctca gggatccctg agcgattctc tggctcccgc 600

tctgggaaca cggccaccct gaccatcagc agggtcgagg ccggggatga ggccgacttt 660

tactgtcagg tgtgggattt cctcaccgac tcggggtcgt tcggcggagg gaccaagctg 720

accgtcctag gtgcggccgc acat 744

<210> 251
<211> 15
<212> DNA
<213> Homo sapiens

<400> 251
gattactata ttcac 15

<210> 252
<211> 51
<212> DNA
<213> Homo sapiens

<400> 252
tgggtcaacc ctgacactgg tggcacaaga tacgcgcaga agtttcaggg c 51

<210> 253
<211> 30
<212> DNA
<213> Homo sapiens

<400> 253
gatctaactg gatttgatcc ttttgatatc 30

<210> 254
<211> 33
<212> DNA
<213> Homo sapiens

<400> 254
gggggaaaca actttcgaaa taaaagagta cac 33

<210> 255
<211> 21
<212> DNA
<213> Homo sapiens

<400> 255
tatgattcag accggccctc a 21

<210> 256
<211> 33
<212> DNA
<213> Homo sapiens

<400> 256
caggtgtggg atttcctcac cgactcgggg tcg 33

<210> 257
<211> 119
<212> PRT
<213> Homo sapiens

<400> 257
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Gln Ala Ser Gly Tyr Thr Phe Ser Asp Tyr
20 25 30

Tyr Ile His Trp Val Arg Gln Thr Pro Gly Gln Gly Phe Glu Trp Met
35 40 45

Gly Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Trp Val Thr Met Thr Arg Asp Met Ser Asn Thr Thr Ala Tyr
65 70 75 80

Met Glu Leu Pro Arg Leu Arg Asp Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Leu Thr Gly Tyr Asp Tyr Tyr Asp Arg Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 258
<211> 108
<212> PRT
<213> Homo sapiens

<400> 258
Gln Ser Val Leu Thr Gln Pro Pro Ser Met Ser Val Ala Pro Gly Lys
1 5 10 15

Thr Ala Thr Ile Thr Cys Gly Gly Asn Asn Phe Arg Asn Lys Arg Val
20 25 30

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His Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60

Arg Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65                  70                  75                  80

Asp Glu Ala Asp Phe Tyr Cys Gln Val Trp Asp Phe Leu Ala Asp Glu
                85                  90                  95

Ala Met Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105
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<210> 259
<211> 262
<212> PRT
<213> Homo sapiens

<400> 259

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Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Gln Ala Ser Gly Tyr Thr Phe Ser Asp Tyr
            20                  25                  30

Tyr Ile His Trp Val Arg Gln Thr Pro Gly Gln Gly Phe Glu Trp Met
        35                  40                  45

Gly Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Trp Val Thr Met Thr Arg Asp Met Ser Asn Thr Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Pro Arg Leu Arg Asp Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Leu Thr Gly Tyr Asp Tyr Tyr Asp Arg Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125
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Ser Gly Gly Gly Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly Ser Gly
    130                 135                 140

Gly Gly Gly Ser Ala Gln Ser Val Leu Thr Gln Pro Pro Ser Met Ser
145                 150                 155                 160

Val Ala Pro Gly Lys Thr Ala Thr Ile Thr Cys Gly Gly Asn Asn Phe
                165                 170                 175

Arg Asn Lys Arg Val His Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro
            180                 185                 190

Val Leu Val Ile Tyr Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu
        195                 200                 205

Arg Phe Ser Gly Ser Arg Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser
    210                 215                 220

Arg Val Glu Ala Gly Asp Glu Ala Asp Phe Tyr Cys Gln Val Trp Asp
225                 230                 235                 240

Phe Leu Ala Asp Glu Ala Met Phe Gly Gly Gly Thr Lys Leu Thr Val
                245                 250                 255

Leu Gly Ala Ala Ala His
            260
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<210> 260
<211> 5
<212> PRT
<213> Homo sapiens

<400> 260
Asp Tyr Tyr Ile His
1   5

<210> 261
<211> 17
<212> PRT
<213> Homo sapiens

<400> 261
Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe Gln
1   5   10   15

Gly

<210> 262
<211> 10
<212> PRT
<213> Homo sapiens

<400> 262
Asp Leu Thr Gly Tyr Asp Tyr Tyr Asp Arg
1 5 10

<210> 263
<211> 11
<212> PRT
<213> Homo sapiens

<400> 263
Gly Gly Asn Asn Phe Arg Asn Lys Arg Val His
1 5 10

<210> 264
<211> 7
<212> PRT
<213> Homo sapiens

<400> 264
Tyr Asp Ser Asp Arg Pro Ser
1 5

<210> 265
<211> 11
<212> PRT
<213> Homo sapiens

<400> 265
Gln Val Trp Asp Phe Leu Ala Asp Glu Ala Met
1 5 10

<210> 266
<211> 357
<212> DNA
<213> Homo sapiens

<400> 266
gaggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgtcagg cttctggata caccttcagc gattactata ttcactgggt gcgacagacc 120

cctggacaag ggtttgagtg gatgggatgg gtcaaccctg acactggtgg cacaagatac 180

gcgcagaagt ttcagggctg ggtcacaatg accagggaca tgtccaacac cacagcctac 240

atggagctgc ccaggctgag agacgacgac acggccgtat attactgtgc gagagatcta 300

actggatacg actactacga ccggtggggc cagggaaccc tggtcaccgt ctcctca 357

<210> 267
<211> 327
<212> DNA
<213> Homo sapiens

<400> 267
cagtctgtgc tgactcagcc gccctcaatg tcagtggccc caggaaagac ggccacgatt 60

acctgtgggg gaaacaactt tcgaaataaa agagtacact ggtatcagca gaggccaggc 120

caggcccctg tcctggtcat ctattatgat tcagaccggc cctcagggat ccctgagcga 180

ttctctggct cccgctctgg gaacacggcc accctgacca tcagcagggt cgaggccggg 240

gatgaggccg acttttactg tcaggtgtgg gatttcctcg ccgacgaggc gatgttcggc 300

ggagggacca agctgaccgt cctaggt 327

<210> 268
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<212> DNA
<213> Homo sapiens

<400> 268
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cctggacaag ggtttgagtg gatgggatgg gtcaaccctg acactggtgg cacaagatac 180

gcgcagaagt ttcagggctg ggtcacaatg accagggaca tgtccaacac cacagcctac 240

atggagctgc ccaggctgag agacgacgac acggccgtat attactgtgc gagagatcta 300

actggatacg actactacga ccggtggggc cagggaaccc tggtcaccgt ctcgagtgga 360

ggcggcggtt caggcggagg tggctctggc ggtggtggag gtggctctgg cggtggcgga 420

ggtggctctg gcggtggcgg aagtgcacag tctgtgctga ctcagccgcc ctcaatgtca 480

gtggccccag gaaagacggc cacgattacc tgtgggggaa acaactttcg aaataaaaga 540

gtacactggt atcagcagag gccaggccag gcccctgtcc tggtcatcta ttatgattca 600

gaccggccct cagggatccc tgagcgattc tctggctccc gctctgggaa cacggccacc 660

ctgaccatca gcagggtcga ggccggggat gaggccgact tttactgtca ggtgtgggat 720

ttcctcgccg acgaggcgat gttcggcgga gggaccaagc tgaccgtcct aggtgcggcc 780

gcacat 786

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<212> DNA
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<400> 269
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<210> 270
<211> 51
<212> DNA
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<400> 270
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<210> 271
<211> 30
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<213> Homo sapiens

<400> 271
gatctaactg gatacgacta ctacgaccgg 30

<210> 272
<211> 33
<212> DNA
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<400> 272
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<210> 273
<211> 21
<212> DNA
<213> Homo sapiens

<400> 273
tatgattcag accggccctc a 21

<210> 274
<211> 33
<212> DNA
<213> Homo sapiens

<400> 274
caggtgtggg atttcctcgc cgacgaggcg atg 33

<210> 275
<211> 119
<212> PRT
<213> Homo sapiens

<400> 275
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Gln Ala Ser Gly Tyr Thr Phe Ser Asp Tyr
20 25 30

Tyr Ile His Trp Val Arg Gln Thr Pro Gly Gln Gly Phe Glu Trp Met
35 40 45

Gly Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Trp Val Thr Met Thr Arg Asp Met Ser Asn Thr Thr Ala Tyr
65 70 75 80

Met Glu Leu Pro Gly Leu Arg Asp Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Leu Thr Gly Tyr Asp Gln Tyr Thr Ala Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 276
<211> 109
<212> PRT
<213> Homo sapiens

<400> 276
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys
1 5 10 15

Thr Ala Thr Ile Thr Cys Gly Gly Asn Asn Phe Arg Asn Lys Arg Val
20 25 30

His Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Arg Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Phe Tyr Cys Ser Thr Phe Asp Pro Phe Thr Asp Arg
85 90 95

Pro Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105

<210> 277
<211> 248
<212> PRT
<213> Homo sapiens

<400> 277
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Gln Ala Ser Gly Tyr Thr Phe Ser Asp Tyr
20 25 30

Tyr Ile His Trp Val Arg Gln Thr Pro Gly Gln Gly Phe Glu Trp Met
35 40 45

Gly Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Trp Val Thr Met Thr Arg Asp Met Ser Asn Thr Thr Ala Tyr
65 70 75 80

Met Glu Leu Pro Gly Leu Arg Asp Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Leu Thr Gly Tyr Asp Gln Tyr Thr Ala Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
115 120 125

Ser Gly Gly Gly Gly Gly Ser Ala Gln Ser Val Leu Thr Gln Pro Pro Ser
130 135 140

Val Ser Val Ala Pro Gly Lys Thr Ala Thr Ile Thr Cys Gly Gly Asn
145 150 155 160

Asn Phe Arg Asn Lys Arg Val His Trp Tyr Gln Gln Arg Pro Gly Gln
165 170 175

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Ala Pro Val Leu Val Ile Tyr Tyr Asp Ser Asp Arg Pro Ser Gly Ile
            180                 185                 190

Pro Glu Arg Phe Ser Gly Ser Arg Ser Gly Asn Thr Ala Thr Leu Thr
        195                 200                 205

Ile Ser Arg Val Glu Ala Gly Asp Glu Ala Asp Phe Tyr Cys Ser Thr
    210                 215                 220

Phe Asp Pro Phe Thr Asp Arg Pro Leu Phe Gly Gly Gly Thr Lys Leu
225                 230                 235                 240

Thr Val Leu Gly Ala Ala Ala His
                245
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<210> 278
<211> 5
<212> PRT
<213> Homo sapiens

<400> 278
Asp Tyr Tyr Ile His
1   5

<210> 279
<211> 17
<212> PRT
<213> Homo sapiens

<400> 279
Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe Gln
1   5   10   15

Gly

<210> 280
<211> 10
<212> PRT
<213> Homo sapiens

<400> 280
Asp Leu Thr Gly Tyr Asp Gln Tyr Thr Ala
1   5   10

<210> 281
<211> 11
<212> PRT
<213> Homo sapiens

<400> 281
Gly Gly Asn Asn Phe Arg Asn Lys Arg Val His
1 5 10

<210> 282
<211> 7
<212> PRT
<213> Homo sapiens

<400> 282
Tyr Asp Ser Asp Arg Pro Ser
1 5

<210> 283
<211> 11
<212> PRT
<213> Homo sapiens

<400> 283
Ser Thr Phe Asp Pro Phe Thr Asp Arg Pro Leu
1 5 10

<210> 284
<211> 357
<212> DNA
<213> Homo sapiens

<400> 284
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tcctgtcagg cttctggata caccttcagc gattactata ttcactgggt gcgacagacc 120

ccaggacaag ggtttgagtg gatgggatgg gtcaaccctg acactggtgg cacgagatac 180

gcgcagaagt ttcagggctg ggtcacaatg accagggaca tgtccaacac cacagcctac 240

atggagctgc ccgggctgag agacgacgac acggccgtat attactgtgc gagagatcta 300

actgggtacg accagtacac ggcctggggc cagggaaccc tggtcaccgt ctcctca 357

<210> 285
<211> 327
<212> DNA
<213> Homo sapiens

<400> 285
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acctgtgggg gaaacaactt tcgaaataaa agagtacact ggtatcagca gaggccaggc 120

caggcccctg tcctggtcat ctattatgat tcagaccggc cctcagggat ccctgagcga 180

ttctctggct cccgctctgg gaacacggcc accctgacca tcagcagggt cgaggccggg 240

gatgaggccg acttttactg tagcaccttc gacccccttca ctgatcgtcc gctgttcggc 300

ggagggacca agctgaccgt cctaggt 327

<210> 286
<211> 744
<212> DNA
<213> Homo sapiens

<400> 286
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tcctgtcagg cttctggata caccttcagc gattactata ttcactgggt gcgacagacc 120

ccaggacaag ggtttgagtg gatgggatgg gtcaaccctg acactggtgg cacgagatac 180

gcgcagaagt ttcagggctg ggtcacaatg accagggaca tgtccaacac cacagcctac 240

atggagctgc ccgggctgag agacgacgac acggccgtat attactgtgc gagagatcta 300

actgggtacg accagtacac ggcctggggc cagggaaccc tggtcaccgt ctcgagtgga 360

ggcggcggtt caggcggagg tggctctggc ggtggcggaa gtgcacagtc tgtgctgact 420

cagccaccct cagtgtcagt ggccccagga aagacggcca cgattacctg tgggggaaac 480

aactttcgaa ataaaagagt acactggtat cagcagaggc caggccaggc ccctgtcctg 540

gtcatctatt atgattcaga ccggccctca gggatccctg agcgattctc tggctcccgc 600

tctgggaaca cggccaccct gaccatcagc agggtcgagg ccggggatga ggccgacttt 660

tactgtagca ccttcgaccc cttcactgat cgtccgctgt tcggcggagg gaccaagctg 720

accgtcctag gtgcggccgc acat 744

<210> 287
<211> 15
<212> DNA
<213> Homo sapiens

<400> 287
gattactata ttcac 15

<210> 288
<211> 51
<212> DNA
<213> Homo sapiens

<400> 288
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<210> 289
<211> 30
<212> DNA
<213> Homo sapiens

<400> 289
gatctaactg ggtacgacca gtacacggcc 30

<210> 290
<211> 33
<212> DNA
<213> Homo sapiens

<400> 290
gggggaaaca actttcgaaa taaaagagta cac 33

<210> 291
<211> 21
<212> DNA
<213> Homo sapiens

<400> 291
tatgattcag accggccctc a 21

<210> 292
<211> 33
<212> DNA
<213> Homo sapiens

<400> 292
agcaccttcg acccccttcac tgatcgtccg ctg 33

<210> 293
<211> 120
<212> PRT
<213> Homo sapiens

<400> 293
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Lys Lys Pro Gly Ala Ser
1 5 10 15

Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr Tyr
20 25 30

Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val Gly
35 40 45

Trp Ile Asn Pro Tyr Thr Gly Gly Ala Phe Tyr Ala Gln Lys Phe Arg
50 55 60

Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Asn Thr Ala Tyr Met
65 70 75 80

Glu Leu Ser Arg Leu Gly Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Glu Pro Glu Arg Phe Gly Asp Ser Thr Gly Gln Val Trp Gly Arg
100 105 110

Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 294
<211> 113
<212> PRT
<213> Homo sapiens

<400> 294
Gln Ala Val Leu Thr Gln Pro Ser Ser Val Ser Gly Ala Pro Arg Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Gly Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Tyr His Trp Asp Lys Glu
85 90 95

Gln Ser Gly Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr Val Leu Ser
100 105 110

Ala

<210> 295
<211> 249
<212> PRT
<213> Homo sapiens

<400> 295

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Lys Lys Pro Gly Ala Ser
1               5                   10                  15

Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr Tyr
            20                  25                  30

Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val Gly
        35                  40                  45

Trp Ile Asn Pro Tyr Thr Gly Gly Ala Phe Tyr Ala Gln Lys Phe Arg
    50                  55                  60

Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Asn Thr Ala Tyr Met
65                  70                  75                  80

Glu Leu Ser Arg Leu Gly Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Arg Glu Pro Glu Arg Phe Gly Asp Ser Thr Gly Gln Val Trp Gly Arg
            100                 105                 110

Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
        115                 120                 125

Gly Ser Gly Gly Ser Arg Ser Ala Gln Ala Val Leu Thr Gln Pro Ser
    130                 135                 140

Ser Val Ser Gly Ala Pro Arg Gln Arg Val Thr Ile Ser Cys Thr Gly
145                 150                 155                 160

Ser Ser Ser Asn Ile Gly Ala Gly Tyr Gly Val His Trp Tyr Gln Gln
                165                 170                 175

Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asn Ser Asn Arg
            180                 185                 190

Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser
        195                 200                 205
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Ala Ser Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr
210 215 220

Tyr Cys Tyr His Trp Asp Lys Glu Gln Ser Gly Tyr Val Phe Gly Thr
225 230 235 240

Gly Thr Gln Leu Thr Val Leu Ser Ala
245

<210> 296
<211> 5
<212> PRT
<213> Homo sapiens

<400> 296
Asp Tyr Tyr Met His
1 5

<210> 297
<211> 17
<212> PRT
<213> Homo sapiens

<400> 297
Trp Ile Asn Pro Tyr Thr Gly Gly Ala Phe Tyr Ala Gln Lys Phe Arg
1 5 10 15

Gly

<210> 298
<211> 12
<212> PRT
<213> Homo sapiens

<400> 298
Glu Pro Glu Arg Phe Gly Asp Ser Thr Gly Gln Val
1 5 10

<210> 299
<211> 14
<212> PRT
<213> Homo sapiens

<400> 299
Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Gly Val His
1 5 10

<210> 300
<211> 7
<212> PRT
<213> Homo sapiens

<400> 300
Gly Asn Ser Asn Arg Pro Ser
1 5

<210> 301
<211> 11
<212> PRT
<213> Homo sapiens

<400> 301
Tyr His Trp Asp Lys Glu Gln Ser Gly Tyr Val
1 5 10

<210> 302
<211> 363
<212> DNA
<213> Homo sapiens

<400> 302
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tcctgcaagg cttctggata caccttcacc gactactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg ggtgggatgg atcaaccctt atactggtgg cgcattctat 180

gcacagaagt ttcggggcag ggtcacaatg accagggaca cgtccatcaa cacagcctac 240

atggagctaa gcagactggg atctgacgac acggccgtgt attattgtgc gagagaacct 300

gaaagattcg gcgactccac ggggcaggtc tggggccggg ggacaatggt caccgtctcg 360

agt 363

<210> 303
<211> 339
<212> DNA
<213> Homo sapiens

<400> 303
caggctgtgc tgactcagcc gtcctcagtg tctggggccc caaggcagag ggtcaccatc 60

tcctgcactg ggagcagctc caacatcggg gcaggttatg gtgtacactg gtaccaacag 120

cttccaggaa cagccccaa actcctcatc tatggtaaca gcaatcggcc ctcaggggtc 180

cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cactgggctc 240

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gtcttcggaa ctgggaccca gctcaccgtt ttaagtgcg 339

<210> 304
<211> 750
<212> DNA
<213> Homo sapiens

<400> 304
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tcctgcaagg cttctggata caccttcacc gactactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg ggtgggatgg atcaaccctt atactggtgg cgcattctat 180

gcacagaagt ttcggggcag ggtcacaatg accagggaca cgtccatcaa cacagcctac 240

atggagctaa gcagactggg atctgacgac acggccgtgt attattgtgc gagagaacct 300

gaaagattcg gcgactccac ggggcaggtc tggggccggg ggacaatggt caccgtctcg 360

agtgggggcg gcggttcagg cggaggtggc tctggcggta gcagaagtgc acaggctgtg 420

ctgactcagc cgtcctcagt gtctggggcc ccaaggcaga gggtcaccat ctcctgcact 480

gggagcagct ccaacatcgg ggcaggttat ggtgtacact ggtaccaaca gcttccagga 540

acagccccca aactcctcat ctatggtaac agcaatcggc cctcaggggt ccctgaccga 600

ttctctggct ccaagtctgg cacctcagcc tccctggcca tcactgggct ccaggctgag 660

gatgaggctg attattactg ctaccactgg gacaaggagc agagtggtta tgtcttcgga 720

actgggaccc agctcaccgt tttaagtgcg 750

<210> 305
<211> 15
<212> DNA
<213> Homo sapiens

<400> 305
gactactata tgcac 15

<210> 306
<211> 51
<212> DNA
<213> Homo sapiens

<400> 306
tggatcaacc cttatactgg tggcgcattc tatgcacaga agtttcgggg c 51

<210> 307
<211> 36
<212> DNA
<213> Homo sapiens

<400> 307
gaacctgaaa gattcggcga ctccacgggg caggtc 36

<210> 308
<211> 42
<212> DNA
<213> Homo sapiens

<400> 308
actgggagca gctccaacat cggggcaggt tatggtgtac ac 42

<210> 309
<211> 21
<212> DNA
<213> Homo sapiens

<400> 309
ggtaacagca atcggccctc a 21

<210> 310
<211> 33
<212> DNA
<213> Homo sapiens

<400> 310
taccactggg acaaggagca gagtggttat gtc 33

<210> 311
<211> 121
<212> PRT
<213> Homo sapiens

<400> 311
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Gln Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45

Gly Trp Ile Asn Pro Tyr Thr Gly Ser Ala Phe Tyr Ala Gln Lys Phe
50 55 60

Arg Gly Arg Ala Thr Met Thr Arg Asn Thr Ser Ile Asn Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Gly Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Pro Glu Lys Phe Gly Glu Ser Ser Gly Gln Leu Trp Gly
100 105 110

Arg Gly Thr Met Val Thr Ile Ser Ser
115 120

<210> 312
<211> 113
<212> PRT
<213> Homo sapiens

<400> 312
Gln Ala Val Leu Thr Gln Pro Ser Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Pro Gly
20 25 30

Tyr Gly Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Gly Asp Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Gly
85 90 95

Leu Ser Gly Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr Val Leu Ser
100 105 110

Ala

<210> 313
<211> 250
<212> PRT
<213> Homo sapiens

<400> 313
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

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Ser Val Lys Val Ser Cys Gln Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
        35                  40                  45

Gly Trp Ile Asn Pro Tyr Thr Gly Ser Ala Phe Tyr Ala Gln Lys Phe
    50                  55                  60

Arg Gly Arg Ala Thr Met Thr Arg Asn Thr Ser Ile Asn Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Arg Leu Gly Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Pro Glu Lys Phe Gly Glu Ser Ser Gly Gln Leu Trp Gly
            100                 105                 110

Arg Gly Thr Met Val Thr Ile Ser Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gly Gly Ser Gly Ser Ala Gln Ala Val Leu Thr Gln Pro
    130                 135                 140

Ser Ser Val Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr
145                 150                 155                 160

Gly Ser Ser Ser Asn Ile Gly Pro Gly Tyr Gly Val His Trp Tyr Gln
                165                 170                 175

Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asp Ser Asn
            180                 185                 190

Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr
        195                 200                 205

Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp
    210                 215                 220

Tyr Tyr Cys Gln Ser Tyr Asp Ser Gly Leu Ser Gly Tyr Val Phe Gly
225                 230                 235                 240
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Thr Gly Thr Gln Leu Thr Val Leu Ser Ala
245 250

<210> 314
<211> 5
<212> PRT
<213> Homo sapiens

<400> 314
Asp Tyr Tyr Met His
1 5

<210> 315
<211> 17
<212> PRT
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<400> 315
Trp Ile Asn Pro Tyr Thr Gly Ser Ala Phe Tyr Ala Gln Lys Phe Arg
1 5 10 15

Gly

<210> 316
<211> 12
<212> PRT
<213> Homo sapiens

<400> 316
Glu Pro Glu Lys Phe Gly Glu Ser Ser Gly Gln Leu
1 5 10

<210> 317
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<212> PRT
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Thr Gly Ser Ser Ser Asn Ile Gly Pro Gly Tyr Gly Val His
1 5 10

<210> 318
<211> 7
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<400> 318
Gly Asp Ser Asn Arg Pro Ser
1 5

<210> 319
<211> 11
<212> PRT
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<400> 319
Gln Ser Tyr Asp Ser Gly Leu Ser Gly Tyr Val
1 5 10

<210> 320
<211> 363
<212> DNA
<213> Homo sapiens

<400> 320
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tcctgtcagg cttctggata caccttcacc gactactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg ggtggggtgg atcaaccctt atactggtag cgcattctat 180

gcacagaagt ttcggggcag ggccacaatg accaggaaca cgtccatcaa cacagcctac 240

atggagctga gcagactggg atctgacgac acggccgtgt attattgtgc gagagaacct 300

gaaaaattcg gcgagtccag cggccagttg tggggccggg ggacaatggt caccatctcg 360

agt 363

<210> 321
<211> 339
<212> DNA
<213> Homo sapiens

<400> 321
caggctgtgc tgactcagcc gtcctcagtg tctggggccc agggcagag ggtcaccatc 60

tcctgcactg ggagcagctc caacatcggg gcaggttatg gtgtacactg gtaccaacag 120

cttccaggaa cagcccccaa actcctcatc tatggtgaca gcaatcggcc ctcaggggtc 180

cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cactgggctc 240

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gtcttcggaa ctgggaccca gctcaccgtt ttaagtgcg 339

<210> 322
<211> 750
<212> DNA
<213> Homo sapiens

<400> 322
gaagtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgtcagg cttctggata caccttcacc gactactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg ggtggggtgg atcaaccctt atactggtag cgcattctat 180

gcacagaagt ttcggggcag ggccacaatg accaggaaca cgtccatcaa cacagcctac 240

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agtggaggcg gcggttcagg cggaggtggc tctggcggta gcggaagtgc acaggctgtg 420

ctgactcagc cgtcctcagt gtctggggcc ccagggcaga gggtcaccat ctcctgcact 480

gggagcagct ccaacatcgg ggcaggttat ggtgtacact ggtaccaaca gcttccagga 540

acagccccca aactcctcat ctatggtgac agcaatcggc cctcaggggt ccctgaccga 600

ttctctggct ccaagtctgg cacctcagcc tccctggcca tcactgggct ccaggccgag 660

gatgaggctg attattactg ccagtcctat gacagcggcc tgagtggtta tgtcttcgga 720

actgggaccc agctcaccgt tttaagtgcg 750

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<400> 326
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<210> 328
<211> 33
<212> DNA
<213> Homo sapiens

<400> 328
cagtcctatg acagcggcct gagtggttat gtc 33

<210> 329
<211> 121
<212> PRT
<213> Homo sapiens

<400> 329

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Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	His	Tyr
			20					25					30		
Tyr	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Val
		35					40					45			
Gly	Trp	Ile	Asn	Pro	Tyr	Thr	Gly	Gly	Ala	Phe	Tyr	Ala	Gln	Lys	Phe
	50					55					60				
Gln	Gly	Arg	Val	Thr	Met	Thr	Arg	Asp	Thr	Ser	Ile	Asn	Thr	Ala	Tyr
65					70					75					80
Met	Glu	Leu	Ser	Arg	Leu	Gly	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Glu	Pro	Glu	Lys	Phe	Asp	Ser	Pro	Asn	Ala	Glu	Ile	Trp	Gly
			100					105					110		
Arg	Gly	Thr	Met	Val	Thr	Ile	Ser	Ser							
		115					120								

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<212> PRT
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<400> 330
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Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Gly Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
85 90 95

Leu Ser Gly Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr Val Leu Ser
100 105 110

Ala

<210> 331
<211> 250
<212> PRT
<213> Homo sapiens

<400> 331
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr His Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45

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Gly Trp Ile Asn Pro Tyr Thr Gly Gly Ala Phe Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Asn Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Arg Leu Gly Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Pro Glu Lys Phe Asp Ser Pro Asn Ala Glu Ile Trp Gly
            100                 105                 110

Arg Gly Thr Met Val Thr Ile Ser Ser Glu Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gly Gly Ser Gly Ser Ala Gln Ala Val Leu Thr Gln Pro
    130                 135                 140

Ser Ser Val Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr
145                 150                 155                 160

Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Gly Val His Trp Tyr Gln
                165                 170                 175

Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asn Ser Asn
            180                 185                 190

Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr
        195                 200                 205

Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp
    210                 215                 220

Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser Leu Ser Gly Tyr Val Phe Gly
225                 230                 235                 240

Thr Gly Thr Gln Leu Thr Val Leu Ser Ala
                245                 250
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<211> 5
<212> PRT
<213> Homo sapiens

<400> 332
His Tyr Tyr Met His
1 5

<210> 333
<211> 17
<212> PRT
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<400> 333
Trp Ile Asn Pro Tyr Thr Gly Gly Ala Phe Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 334
<211> 12
<212> PRT
<213> Homo sapiens

<400> 334
Glu Pro Glu Lys Phe Asp Ser Pro Asn Ala Glu Ile
1 5 10

<210> 335
<211> 14
<212> PRT
<213> Homo sapiens

<400> 335
Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Gly Val His
1 5 10

<210> 336
<211> 7
<212> PRT
<213> Homo sapiens

<400> 336
Gly Asn Ser Asn Arg Pro Ser
1 5

<210> 337
<211> 11
<212> PRT
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<400> 337
Gln Ser Tyr Asp Ser Ser Leu Ser Gly Tyr Val
1 5 10

<210> 338
<211> 363
<212> DNA
<213> Homo sapiens

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cctggacaag ggcttgagtg ggtgggatgg atcaaccctt atactggtgg cgcattctat 180

gcacagaagt ttcagggcag ggtcacaatg accagggaca cgtccatcaa cacagcctac 240

atggagctga gcagactggg atctgacgac acggccgtgt attattgtgc gagagaacct 300

gaaaaattcg actcgccgaa cgccgagatc tggggccggg ggacaatggt caccatctcg 360

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<400> 339
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cttccaggaa cagccccaa actcctcatc tatggtaaca gcaatcggcc ctcaggggtc 180

cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cactgggctc 240

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gtcttcggaa ccgggaccca gctcaccgtt ttaagtgcg 339

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<211> 750
<212> DNA
<213> Homo sapiens

<400> 340
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tcctgcaagg cttctggata caccttcacc cactactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg ggtgggatgg atcaaccctt atactggtgg cgcattctat 180

gcacagaagt ttcagggcag ggtcacaatg accagggaca cgtccatcaa cacagcctac 240

atggagctga gcagactggg atctgacgac acggccgtgt attattgtgc gagagaacct 300

gaaaaattcg actcgccgaa cgccgagatc tggggccggg ggacaatggt caccatctcg 360

agtgaaggcg gcggttcagg cggaggtggc tctggcggta gcggaagtgc acaggctgtg 420

ctgactcagc cgtcctcagt gtctggggcc ccagggcaga gggtcaccat ctcctgcact 480

gggagcagct ccaacatcgg ggcaggttat ggtgtacact ggtaccaaca gcttccagga 540

acagccccca aactcctcat ctatggtaac agcaatcggc cctcaggggt ccctgaccga 600

ttctctggct ccaagtctgg cacctcagcc tccctggcca tcactgggct ccaggctgag 660

gatgaggctg attattactg ccagtcctat gacagcagcc tgagtggtta tgtcttcgga 720

accgggaccc agctcaccgt tttaagtgcg 750

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<400> 341
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<210> 342
<211> 51
<212> DNA
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<210> 343
<211> 36
<212> DNA
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<400> 343
gaacctgaaa aattcgactc gccgaacgcc gagatc 36

<210> 344
<211> 42
<212> DNA
<213> Homo sapiens

<400> 344
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<210> 345
<211> 21
<212> DNA
<213> Homo sapiens

<400> 345
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<210> 346
<211> 33
<212> DNA
<213> Homo sapiens

<400> 346
cagtcctatg acagcagcct gagtggttat gtc 33

<210> 347
<211> 121
<212> PRT
<213> Homo sapiens

<400> 347
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45

Gly Trp Ile Asn Pro Tyr Thr Gly Ser Ala Phe Tyr Ala Gln Lys Phe
50 55 60

Arg Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Asn Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Gly Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Pro Glu Lys Phe Asp Ser Asp Asp Ser Asp Val Trp Gly
100 105 110

Arg Gly Thr Met Val Thr Val Ser Gly
115 120

<210> 348
<211> 112
<212> PRT
<213> Homo sapiens

<400> 348
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1 5 10 15

Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr
20 25 30

Gly Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Ile
35 40 45

Ile Tyr Gly Asp Ser Ser Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65 70 75 80

Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Asn Ser Leu
85 90 95

Ser Gly Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr Val Leu Ser Ala
100 105 110

<210> 349
<211> 249
<212> PRT
<213> Homo sapiens

<400> 349
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45

Gly Trp Ile Asn Pro Tyr Thr Gly Ser Ala Phe Tyr Ala Gln Lys Phe
50 55 60

Arg Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Asn Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Gly Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

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Ala Arg Glu Pro Glu Lys Phe Asp Ser Asp Asp Ser Asp Val Trp Gly
            100                 105                 110

Arg Gly Thr Met Val Thr Val Ser Gly Gly Gly Gly Ser Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gly Gly Ser Gly Ser Ala Gln Ala Val Leu Thr Pro Pro
    130                 135                 140

Ser Val Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr Gly
145                 150                 155                 160

Ser Ser Ser Asn Ile Gly Ala Gly Tyr Gly Val His Trp Tyr Gln Gln
                165                 170                 175

Leu Pro Gly Thr Ala Pro Lys Leu Ile Ile Tyr Gly Asp Ser Ser Arg
            180                 185                 190

Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser
        195                 200                 205

Ala Ser Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr
    210                 215                 220

Tyr Cys Gln Ser Tyr Asp Asn Ser Leu Ser Gly Tyr Val Phe Gly Thr
225                 230                 235                 240

Gly Thr Gln Leu Thr Val Leu Ser Ala
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<212> PRT
<213> Homo sapiens

<400> 350
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1   5

<210> 351
<211> 17
<212> PRT
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<400> 351
Trp Ile Asn Pro Tyr Thr Gly Ser Ala Phe Tyr Ala Gln Lys Phe Arg
1 5 10 15

Gly

<210> 352
<211> 12
<212> PRT
<213> Homo sapiens

<400> 352
Glu Pro Glu Lys Phe Asp Ser Asp Asp Ser Asp Val
1 5 10

<210> 353
<211> 14
<212> PRT
<213> Homo sapiens

<400> 353
Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Gly Val His
1 5 10

<210> 354
<211> 8
<212> PRT
<213> Homo sapiens

<400> 354
Gly Asp Ser Ser Arg Pro Ser Gly
1 5

<210> 355
<211> 11
<212> PRT
<213> Homo sapiens

<400> 355
Gln Ser Tyr Asp Asn Ser Leu Ser Gly Tyr Val
1 5 10

<210> 356
<211> 363
<212> DNA
<213> Homo sapiens

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tcctgcaagg cttctggata caccttcacc aactactata tgcactgggt gcgacaggcc 120

cctggacagg ggcttgagtg ggtgggatgg atcaaccctt atactggtag cgcattctat 180

gcacagaagt ttcggggcag ggttacaatg accagggaca cgtccatcaa cacagcctac 240

atggagctga gcagactggg atctgacgac acggccgtgt attattgtgc gagagaacct 300

gaaaaattcg actccgacga ctccgacgtc tggggccgcg ggacaatggt caccgtctcg 360

ggt 363

<210> 357
<211> 339
<212> DNA
<213> Homo sapiens

<400> 357
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tcctgcactg ggagcagctc caacatcggg gcaggttatg gtgtacactg gtaccaacag 120

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cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cactgggctc 240

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gtcttcggaa ctgggaccca gctcaccgtt ttaagtgcg 339

<210> 358
<211> 750
<212> DNA
<213> Homo sapiens

<400> 358
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tcctgcaagg cttctggata caccttcacc aactactata tgcactgggt gcgacaggcc 120

cctggacagg ggcttgagtg ggtgggatgg atcaaccctt atactggtag cgcattctat 180

gcacagaagt ttcggggcag ggttacaatg accagggaca cgtccatcaa cacagcctac 240

atggagctga gcagactggg atctgacgac acggccgtgt attattgtgc gagagaacct 300

gaaaaattcg actccgacga ctccgacgtc tggggccgcg ggacaatggt caccgtctcg 360

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gggagcagct ccaacatcgg ggcaggttat ggtgtacact ggtaccaaca gcttccagga 540

acagccccca aactcatcat ctatggtgac agcagtcggc cctcaggggt ccctgaccga 600

ttctctggct ccaagtctgg cacctcagcc tccctggcca tcactgggct ccaggctgag 660

gatgaggctg attattactg ccagtcctat gacaacagcc tgagcggtta tgtcttcgga 720

actgggaccc agctcaccgt tttaagtgcg 750

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<211> 15
<212> DNA
<213> Homo sapiens

<400> 359
aactactata tgcac 15

<210> 360
<211> 51
<212> DNA
<213> Homo sapiens

<400> 360
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<210> 361
<211> 36
<212> DNA
<213> Homo sapiens

<400> 361
gaacctgaaa aattcgactc cgacgactcc gacgtc 36

<210> 362
<211> 42
<212> DNA
<213> Homo sapiens

<400> 362
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<210> 363
<211> 24
<212> DNA
<213> Homo sapiens

<400> 363
ggtgacagca gtcggccctc aggg 24

<210> 364
<211> 33
<212> DNA
<213> Homo sapiens

<400> 364
cagtcctatg acaacagcct gagcggttat gtc 33

<210> 365
<211> 119
<212> PRT
<213> Homo sapiens

<400> 365
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Ile Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Leu Trp Val Trp Asp Pro Leu Asp Tyr Trp Gly Arg Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 366
<211> 108
<212> PRT
<213> Homo sapiens

<400> 366
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Gly Ile Tyr His Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Ala Ser Ser Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Asn Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 367
<211> 243
<212> PRT
<213> Homo sapiens

<400> 367
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Ile Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Leu Trp Val Trp Asp Pro Leu Asp Tyr Trp Gly Arg Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
115 120 125

Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Thr
130 135 140

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
145 150 155 160

Glu Gly Ile Tyr His Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
165 170 175

Ala Pro Lys Leu Leu Ile Tyr Lys Ala Ser Ser Leu Ala Ser Gly Val
180 185 190

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
195 200 205

Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
210 215 220

Tyr Ser Asn Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
225 230 235 240

Lys Arg Ala

<210> 368
<211> 5
<212> PRT
<213> Homo sapiens

<400> 368
Asp Tyr Tyr Met Ser
1 5

<210> 369
<211> 17
<212> PRT
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<400> 369
Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 370
<211> 10
<212> PRT
<213> Homo sapiens

<400> 370
Gly Leu Trp Val Trp Asp Pro Leu Asp Tyr
1 5 10

<210> 371
<211> 11
<212> PRT
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<400> 371
Arg Ala Ser Glu Gly Ile Tyr His Trp Leu Ala
1 5 10

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<212> PRT
<213> Homo sapiens

<400> 372
Lys Ala Ser Ser Leu Ala Ser
1 5

<210> 373
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<400> 373
Gln Gln Tyr Ser Asn Tyr Pro Leu Thr
1 5

<210> 374
<211> 357
<212> DNA
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<400> 374
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tcctgtgcag cctctggatt caccttcagt gactactaca tgagctggat ccgccaggct 120

ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac 180

gcagactccg tgaagggccg gatcaccatc tccagagaca acgccaagaa ctcactgtat 240

ctgcaaatga acagcctgag agctgaggac acggccgtgt attactgtgc gagagggctt 300

tgggtttggg atcctcttga ctactggggc agaggaaccc tggtcaccgt ctcttca 357

<210> 375
<211> 324
<212> DNA
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<400> 375
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atcacctgcc gggccagtga gggtatttat cactggttgg cctggtatca gcagaagcca 120

gggaaagccc ctaaactcct gatctataag gcctctagtt tagccagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagag ttcactctca ccatcagcag cctgcagcct 240

gatgattttg caacttatta ctgccaacaa tatagtaatt atccgctcac tttcggcgga 300

gggaccaagg tggagatcaa acgt 324

<210> 376
<211> 729
<212> DNA
<213> Homo sapiens

<400> 376
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tcctgtgcag cctctggatt caccttcagt gactactaca tgagctggat ccgccaggct 120

ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac 180

gcagactccg tgaagggccg gatcaccatc tccagagaca acgccaagaa ctcactgtat 240

ctgcaaatga acagcctgag agctgaggac acggccgtgt attactgtgc gagagggctt 300

tgggtttggg atcctcttga ctactggggc agaggaaccc tggtcaccgt ctcttcaggt 360

ggaggcggtt caggcggagg tggcagcggc ggtggcggat cggacatcca gatgacccag 420

tctccttcca ccctgtctgc atctgttgga gacagagtca ccatcacctg ccgggccagt 480

gagggtattt atcactggtt ggcctggtat cagcagaagc cagggaaagc ccctaaactc 540

ctgatctata aggcctctag tttagccagt ggggtcccat caaggttcag cggcagtgga 600

tctgggacag atttcactct caccatcagc agcctgcagc ctgatgattt tgcaacttat 660

tactgccaac aatatagtaa ttatccgctc actttcggcg gagggaccaa ggtggagatc 720

aaacgtgcg 729

<210> 377
<211> 15
<212> DNA
<213> Homo sapiens

<400> 377
gactactaca tgagc 15

<210> 378
<211> 51
<212> DNA
<213> Homo sapiens

<400> 378
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<210> 379
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<400> 379
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<400> 380
cgggccagtg agggtattta tcactggttg gcc 33

<210> 381
<211> 21
<212> DNA
<213> Homo sapiens

<400> 381
aaggcctcta gtttagccag t 21

<210> 382
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<400> 382
caacaatata gtaattatcc gctcact 27

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<211> 5
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<400> 383
Ser Tyr Gly Ile Ser
1 5

<210> 384
<211> 108
<212> PRT
<213> Homo sapiens

<400> 384
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Gly Ile Tyr His Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Ala Ser Ser Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Asn Tyr Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
100 105

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<211> 243
<212> PRT
<213> Homo sapiens

<400> 385
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Ala Tyr Thr Gly Asn Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Gly Tyr Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
115 120 125

Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Thr
130 135 140

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
145 150 155 160

Glu Gly Ile Tyr His Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
165 170 175

Ala Pro Lys Leu Leu Ile Tyr Lys Ala Ser Ser Leu Ala Ser Gly Val
180 185 190

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
195 200 205

Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
210 215 220

Tyr Ser Asn Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
225 230 235 240

Lys Arg Ala

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<212> PRT
<213> Homo sapiens

<400> 386
Ser Tyr Gly Ile Ser
1 5

<210> 387
<211> 17
<212> PRT
<213> Homo sapiens

<400> 387
Trp Ile Ser Ala Tyr Thr Gly Asn Thr Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 388
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<212> PRT
<213> Homo sapiens

<400> 388
Asp Arg Gly Tyr Tyr Asp Ala Phe Asp Ile
1 5 10

<210> 389
<211> 11
<212> PRT
<213> Homo sapiens

<400> 389
Arg Ala Ser Glu Gly Ile Tyr His Trp Leu Ala
1 5 10

<210> 390
<211> 7
<212> PRT
<213> Homo sapiens

<400> 390
Lys Ala Ser Ser Leu Ala Ser
1 5

<210> 391
<211> 9
<212> PRT
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<400> 391
Gln Gln Tyr Ser Asn Tyr Pro Leu Thr
1 5

<210> 392
<211> 357
<212> DNA
<213> Homo sapiens

<400> 392
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tcctgcaagg cttctggtta cacctttacc agttatggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcagcgctt acactggtaa cacaaactat 180

gcacagaagt tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240

atggaactga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagatcgt 300

ggatactatg atgcttttga tatctggggc caaggcaccc tggtcaccgt ctcctca 357

<210> 393
<211> 324
<212> DNA
<213> Homo sapiens

<400> 393
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atcacctgcc gggccagtga gggtatttat cactggttgg cctggtatca gcagaagcca 120

gggaaagccc ctaaactcct gatctataag gcctctagtt tagccagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagag ttcactctca ccatcagcag cctgcagcct 240

gatgattttg caacttatta ctgccaacaa tatagtaatt atccgctcac tttcggcgga 300

gggaccaagg tggagatcaa acgt 324

<210> 394
<211> 729
<212> DNA
<213> Homo sapiens

<400> 394
caggtgcagc tggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggtta cacctttacc agttatggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcagcgctt acactggtaa cacaaactat 180

gcacagaagt tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240

atggaactga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagatcgt 300

ggatactatg atgcttttga tatctggggc caaggcaccc tggtcaccgt ctcctcaggt 360

ggaggcggtt caggcggagg tggcagcggc ggtggcggat cggacatcca gatgacccag 420

tctccttcca ccctgtctgc atctgttgga gacagagtca ccatcacctg ccgggccagt 480

gagggtattt atcactggtt ggcctggtat cagcagaagc cagggaaagc ccctaaactc 540

ctgatctata aggcctctag tttagccagt ggggtcccat caaggttcag cggcagtgga 600

tctgggacag agttcactct caccatcagc agcctgcagc ctgatgattt tgcaacttat 660

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aaacgtgcg 729

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<400> 395
agttatggta tcagc 15

<210> 396
<211> 51
<212> DNA
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<400> 396
tggatcagcg cttacactgg taacacaaac tatgcacaga agttccaggg c 51

<210> 397
<211> 30
<212> DNA
<213> Homo sapiens

<400> 397
gatcgtggat actatgatgc ttttgatatc 30

<210> 398
<211> 33
<212> DNA
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<400> 398
cgggccagtg agggtattta tcactggttg gcc 33

<210> 399
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<212> DNA
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<400> 399
aaggcctcta gtttagccag t 21

<210> 400
<211> 27
<212> DNA
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<400> 400
caacaatata gtaattatcc gctcact 27

<210> 401
<211> 119
<212> PRT
<213> Homo sapiens

<400> 401
Gln Met Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Gly Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala His Ile Trp Tyr Asp Gly Ser Asn Glu Lys Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Met Thr Val Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Glu Gln His Trp Ile Thr Ala Phe Asp Ile Trp Gly Lys Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 402
<211> 111
<212> PRT
<213> Homo sapiens

<400> 402
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Glu Gly Ser Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Thr Arg
85 90 95

Ser Thr Arg Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 403
<211> 246
<212> PRT
<213> Homo sapiens

<400> 403
Gln Met Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Gly Met Tyr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala His Ile Trp Tyr Asp Gly Ser Asn Glu Lys Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Met Thr Val Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Glu Gln His Trp Ile Thr Ala Phe Asp Ile Trp Gly Lys Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Ala Gly Gly
115 120 125

Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu Thr Gln Pro Ala Ser Val
130 135 140

Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser
145 150 155 160

Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser Trp Tyr Gln Gln His Pro
165 170 175

Gly Lys Ala Pro Lys Leu Met Ile Tyr Glu Gly Ser Lys Arg Pro Ser
180 185 190

Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser
195 200 205

Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys
210 215 220

Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val Phe Gly Gly Gly Thr Lys
225 230 235 240

Leu Thr Val Leu Gly Ala
245

<210> 404
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<212> PRT
<213> Homo sapiens

<400> 404
Asn Tyr Gly Met Tyr
1 5

<210> 405
<211> 17
<212> PRT
<213> Homo sapiens

<400> 405
His Ile Trp Tyr Asp Gly Ser Asn Glu Lys Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 406
<211> 10
<212> PRT
<213> Homo sapiens

<400> 406
Glu Gln His Trp Ile Thr Ala Phe Asp Ile
1 5 10

<210> 407
<211> 14
<212> PRT
<213> Homo sapiens

<400> 407
Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> 408
<211> 7
<212> PRT
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<400> 408
Glu Gly Ser Lys Arg Pro Ser
1 5

<210> 409
<211> 10
<212> PRT
<213> Homo sapiens

<400> 409
Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val
1 5 10

<210> 410
<211> 357
<212> DNA
<213> Homo sapiens

<400> 410
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tcctgtgcag cctctggatt caccttcagt aactatggca tgtactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcacat atttggtatg atggaagtaa tgaaaagtat 180

gcagactccg tgaagggccg aatgaccgtc tccagagaca attccaagaa cacgttgtat 240

ttgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gacagagcaa 300

cactggatta ctgcttttga tatctggggc aaaggaaccc tggtcaccgt ctcctca 357

<210> 411
<211> 333
<212> DNA
<213> Homo sapiens

<400> 411
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tcctgcactg gaaccagcag tgacgttggt ggttataact atgtctcctg gtaccaacaa 120

cacccaggca aagccccaa actcatgatt tatgagggca gtaagcggcc ctcaggggtt 180

tctaatcgct tctctggctc caagtctggc aacacggcct ccctgacaat ctctgggctc 240

caggctgagg acgaggctga ttactactgc agctcatata caaccaggag cactcgagtt 300

ttcggcggag ggaccaagct gaccgtccta ggt 333

<210> 412
<211> 738
<212> DNA
<213> Homo sapiens

<400> 412
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tcctgtgcag cctctggatt caccttcagt aactatggca tgtactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcacat atttggtatg atggaagtaa tgaaaagtat 180

gcagactccg tgaagggccg aatgaccgtc tccagagaca attccaagaa cacgttgtat 240

ttgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gacagagcaa 300

cactggatta ctgcttttga tatctggggc aaaggcaccc tggtcaccgt ctcctcaggt 360

ggaggcggtt caggcgcagg tggcagcggc ggtggcggat cacagtctgc gctgactcag 420

cctgcctccg tgtctgggtc tcctggacag tcgatcacca tctcctgcac tggaaccagc 480

agtgacgttg gtggttataa ctatgtctcc tggtaccaac aacacccagg caaagccccc 540

aaactcatga tttatgaggg cagtaagcgg ccctcagggg tttctaatcg cttctctggc 600

tccaagtctg gcaacacggc ctccctgaca atctctgggc tccaggctga ggacgaggct 660

gattattact gcagctcata tacaaccagg agcactcgag ttttcggcgg agggaccaag 720

ctgaccgtcc taggtgcg 738

<210> 413
<211> 15
<212> DNA
<213> Homo sapiens

<400> 413
aactatggca tgtac 15

<210> 414
<211> 51
<212> DNA
<213> Homo sapiens

<400> 414
catatttggt atgatggaag taatgaaaag tatgcagact ccgtgaaggg c 51

<210> 415
<211> 30
<212> DNA
<213> Homo sapiens

<400> 415
gagcaacact ggattactgc ttttgatatc 30

<210> 416
<211> 42
<212> DNA
<213> Homo sapiens

<400> 416
actggaacca gcagtgacgt tggtggttat aactatgtct cc 42

<210> 417
<211> 21
<212> DNA
<213> Homo sapiens

<400> 417
gagggcagta agcggccctc a 21

<210> 418
<211> 30
<212> DNA
<213> Homo sapiens

<400> 418
agctcatata caaccaggag cactcgagtt 30

<210> 419
<211> 121
<212> PRT
<213> Homo sapiens

<400> 419
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Val Asn Trp Asn Gly Gly Thr Arg Asp Tyr Ala Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr His Cys
85 90 95

Ala Arg Gly Trp Tyr Ser Gly Ser Phe Tyr Tyr Phe Gly Tyr Trp Gly
100 105 110

Arg Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 420
<211> 111
<212> PRT
<213> Homo sapiens

<400> 420
Gln Ala Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Ala Ser Gly Asp Val Gly Ala Tyr
20 25 30

Asn Phe Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Ile Ile Tyr Asp Val Asn Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Thr
85 90 95

Phe Ser Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 421
<211> 249
<212> PRT
<213> Homo sapiens

<400> 421
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Val Asn Trp Asn Gly Gly Thr Arg Asp Tyr Ala Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr His Cys
85 90 95

Ala Arg Gly Trp Tyr Ser Gly Ser Phe Tyr Tyr Phe Gly Tyr Trp Gly
100 105 110

Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ala Ala Leu Thr Gln Pro
130 135 140

Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr
145 150 155 160

Gly Ala Ser Gly Asp Val Gly Ala Tyr Asn Phe Val Ser Trp Tyr Gln
165 170 175

Gln His Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp Val Asn Lys
180 185 190

Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn
195 200 205

Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp
210 215 220

Tyr Tyr Cys Ser Ser Tyr Thr Ser Thr Phe Ser Val Val Phe Gly Gly
225 230 235 240

Gly Thr Lys Leu Thr Val Leu Gly Ala
245

<210> 422
<211> 5
<212> PRT
<213> Homo sapiens

<400> 422
Asp Tyr Gly Met Asn
1 5

<210> 423
<211> 17
<212> PRT
<213> Homo sapiens

<400> 423
Gly Val Asn Trp Asn Gly Gly Thr Arg Asp Tyr Ala Ala Ser Val Lys
1 5 10 15

Gly

<210> 424
<211> 12
<212> PRT
<213> Homo sapiens

<400> 424
Gly Trp Tyr Ser Gly Ser Phe Tyr Tyr Phe Gly Tyr
1 5 10

<210> 425
<211> 14
<212> PRT
<213> Homo sapiens

<400> 425
Thr Gly Ala Ser Gly Asp Val Gly Ala Tyr Asn Phe Val Ser
1 5 10

<210> 426
<211> 7
<212> PRT
<213> Homo sapiens

<400> 426
Asp Val Asn Lys Arg Pro Ser
1 5

<210> 427
<211> 10
<212> PRT
<213> Homo sapiens

<400> 427
Ser Ser Tyr Thr Ser Thr Phe Ser Val Val
1 5 10

<210> 428
<211> 363
<212> DNA
<213> Homo sapiens

<400> 428
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tcctgtgcag cctctggatt cacctttgac gattatggca tgaactgggt ccgccaagct 120

ccagggaagg ggctggagtg ggtctctggt gttaattgga atggtggtac cagagattat 180

gcagcctccg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240

ctgcaaatga acagtctgag agccgaggac acggccttgt atcactgtgc gagaggatgg 300

tatagtggga gcttctacta ctttggctac tggggccgag gaaccctggt caccgtctcc 360

tca 363

<210> 429
<211> 333
<212> DNA
<213> Homo sapiens

<400> 429
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tcctgcactg gagccagcgg tgacgttggt gcttataact ttgtctcctg gtaccaacaa 120

cacccaggca aagcccccaa actcataatt tatgatgtca ataagcggcc ctcaggggtt 180

tctaatcgct tctctggctc caagtctggc aacacggcct ccctgaccat ctctgggctc 240

caggccgagg acgaggctga ttattactgc agctcatata caagcacctt ctctgtggta 300

tttggcggag ggaccaagct gaccgtccta ggt 333

<210> 430
<211> 747
<212> DNA
<213> Homo sapiens

<400> 430
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tcctgtgcag cctctggatt cacctttgac gattatggca tgaactgggt ccgccaagct 120

ccagggaagg ggctggagtg ggtctctggt gttaattgga atggtggtac cagagattat 180

gcagcctccg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240

ctgcaaatga acagtctgag agccgaggac acggccttgt atcactgtgc gagaggatgg 300

tatagtggga gcttctacta ctttggctac tggggccgag gaaccctggt caccgtctcg 360

agtggaggcg gcggttcagg cggaggtggc tctggcggtg gcggaagtgc acaggctgcg 420

ctgactcagc cggcctccgt gtctgggtct cctggacagt cgatcaccat ctcctgcact 480

ggagccagcg gtgacgttgg tgcttataac tttgtctcct ggtaccaaca acacccaggc 540

aaagccccca aactcataat ttatgatgtc aataagcggc cctcaggggt ttctaatcgc 600

ttctctggct ccaagtctgg caacacggcc tccctgacca tctctgggct ccaggccgag 660

gacgaggctg attattactg cagctcatat acaagcacct tctctgtggt atttggcgga 720

gggaccaagc tcaccgtcct aggtgcg 747

<210> 431
<211> 15
<212> DNA
<213> Homo sapiens

<400> 431
gattatggca tgaac 15

<210> 432
<211> 51
<212> DNA
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<400> 432
ggtgttaatt ggaatggtgg taccagagat tatgcagcct ccgtgaaggg c 51

<210> 433
<211> 36
<212> DNA
<213> Homo sapiens

<400> 433
ggatggtata gtgggagctt ctactacttt ggctac 36

<210> 434
<211> 42
<212> DNA
<213> Homo sapiens

<400> 434
actggagcca gcggtgacgt tggtgcttat aactttgtct cc 42

<210> 435
<211> 21
<212> DNA
<213> Homo sapiens

<400> 435
gatgtcaata agcggccctc a 21

<210> 436
<211> 30
<212> DNA
<213> Homo sapiens

<400> 436
agctcatata caagcacctt ctctgtggta 30

<210> 437
<211> 119
<212> PRT
<213> Homo sapiens

<400> 437
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asp Tyr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe
50 55 60

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Gln Gly Arg Val Thr Met Thr Arg Asp Met Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Leu Thr Gly Phe Asp Pro Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115
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<210> 438
<211> 109
<212> PRT
<213> Homo sapiens

<400> 438

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Ser Ser Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys
1               5                   10                  15

Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Phe Arg Asn Lys Arg Val
            20                  25                  30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60

Arg Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65                  70                  75                  80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Ser Ser Thr Asp Arg
                85                  90                  95

Pro Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105
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<210> 439
<211> 245
<212> PRT
<213> Homo sapiens

<400> 439

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asp Tyr
            20                  25                  30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Met Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Leu Thr Gly Phe Asp Pro Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Ala Ser Ser Val Leu Thr Gln Pro Pro Ser
    130                 135                 140

Val Ser Val Ala Pro Gly Lys Thr Ala Arg Ile Thr Cys Gly Gly Asn
145                 150                 155                 160

Asn Phe Arg Asn Lys Arg Val His Trp Tyr Gln Gln Lys Pro Gly Gln
                165                 170                 175

Ala Pro Val Leu Val Ile Tyr Tyr Asp Ser Asp Arg Pro Ser Gly Ile
            180                 185                 190

Pro Glu Arg Phe Ser Gly Ser Arg Ser Gly Asn Thr Ala Thr Leu Thr
        195                 200                 205

Ile Ser Arg Val Glu Ala Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val
    210                 215                 220

Trp Asp Ser Ser Thr Asp Arg Pro Leu Phe Gly Gly Gly Thr Lys Leu
225                 230                 235                 240
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Thr Val Leu Gly Ala
245

<210> 440
<211> 5
<212> PRT
<213> Homo sapiens

<400> 440
Asp Tyr Tyr Ile His
1 5

<210> 441
<211> 17
<212> PRT
<213> Homo sapiens

<400> 441
Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 442
<211> 10
<212> PRT
<213> Homo sapiens

<400> 442
Asp Leu Thr Gly Phe Asp Pro Phe Asp Ile
1 5 10

<210> 443
<211> 11
<212> PRT
<213> Homo sapiens

<400> 443
Gly Gly Asn Asn Phe Arg Asn Lys Arg Val His
1 5 10

<210> 444
<211> 7
<212> PRT
<213> Homo sapiens

<400> 444
Tyr Asp Ser Asp Arg Pro Ser
1 5

<210> 445
<211> 11
<212> PRT
<213> Homo sapiens

<400> 445
Gln Val Trp Asp Ser Ser Thr Asp Arg Pro Leu
1 5 10

<210> 446
<211> 357
<212> DNA
<213> Homo sapiens

<400> 446
caggtccagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgtaagg cttctggata caccttcagc gattactata ttcactgggt gcgacaggcc 120

cctggacaag ggttggagtg gatgggatgg gtcaaccctg acactggtgg cacaagatac 180

gcgcagaagt ttcagggccg ggtcacaatg accagggaca tgtccatctc cacagcctac 240

atggagctgt ccaggctgag aagcgacgac acggccgtat attactgtgc gagagatcta 300

actggatttg atccttttga tatctggggc cagggaaccc tggtcaccgt ctcctca 357

<210> 447
<211> 327
<212> DNA
<213> Homo sapiens

<400> 447
tcgtctgtgc tgactcagcc accctcagtg tcagtggccc caggaaagac ggcccgcatt 60

acctgtgggg gaaacaactt tcgaaataaa agagtacact ggtatcagca gaagccaggc 120

caggcccctg tcctggtcat ctattatgat tcagaccggc cctcagggat ccctgagcga 180

ttctctggct cccgctctgg gaacacggcc accctgacca tcagcagggt cgaggccggg 240

gatgaggccg actattactg tcaggtgtgg gatagtagta ctgatcgtcc gctgttcggc 300

ggagggacca agctgaccgt cctaggt 327

<210> 448
<211> 735
<212> DNA
<213> Homo sapiens

<400> 448
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tcctgtaagg cttctggata caccttcagc gattactata ttcactgggt gcgacaggcc 120

cctggacaag ggttggagtg gatgggatgg gtcaaccctg acactggtgg cacaagatac 180

gcgcagaagt ttcagggccg ggtcacaatg accagggaca tgtccatctc cacagcctac 240

atggagctgt ccaggctgag aagcgacgac acggccgtat attactgtgc gagagatcta 300

actggatttg atccttttga tatctggggc cagggaaccc tggtcaccgt ctcgagtgga 360

ggcggcggtt caggcggagg tggctctggc ggtggcggaa gtgcatcgtc tgtgctgact 420

cagccaccct cagtgtcagt ggccccagga aagacggccc gcattacctg tgggggaaac 480

aactttcgaa ataaaagagt acactggtat cagcagaagc caggccaggc ccctgtcctg 540

gtcatctatt atgattcaga ccggccctca gggatccctg agcgattctc tggctcccgc 600

tctgggaaca cggccaccct gaccatcagc agggtcgagg ccggggatga ggccgactat 660

tactgtcagg tgtgggatag tagtactgat cgtccgctgt tcggcggagg gaccaagctg 720

accgtcctag gtgcg 735

<210> 449
<211> 15
<212> DNA
<213> Homo sapiens

<400> 449
gattactata ttcac 15

<210> 450
<211> 51
<212> DNA
<213> Homo sapiens

<400> 450
tgggtcaacc ctgacactgg tggcacaaga tacgcgcaga agtttcaggg c 51

<210> 451
<211> 30
<212> DNA
<213> Homo sapiens

<400> 451
gatctaactg gatttgatcc ttttgatatc 30

<210> 452
<211> 33
<212> DNA
<213> Homo sapiens

<400> 452
gggggaaaca actttcgaaa taaaagagta cac 33

<210> 453
<211> 21
<212> DNA
<213> Homo sapiens

<400> 453
tatgattcag accggccctc a 21

<210> 454
<211> 33
<212> DNA
<213> Homo sapiens

<400> 454
caggtgtggg atagtagtac tgatcgtccg ctg 33

<210> 455
<211> 121
<212> PRT
<213> Homo sapiens

<400> 455

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
1				5					10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Asp	Tyr
			20					25					30		
Tyr	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Val
		35					40					45			
Gly	Trp	Ile	Asn	Pro	Tyr	Thr	Gly	Gly	Ala	Phe	Tyr	Ala	Gln	Lys	Phe
	50					55					60				
Arg	Gly	Arg	Val	Thr	Met	Thr	Arg	Asp	Thr	Ser	Ile	Ser	Thr	Ala	Tyr
65					70					75					80
Met	Glu	Leu	Ser	Arg	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Glu	Pro	Glu	Lys	Phe	Asp	Phe	Trp	Gly	Gly	Asp	Asn	Trp	Gly
			100					105					110		
Arg	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser							
		115					120								

<210> 456
<211> 112
<212> PRT
<213> Homo sapiens

<400> 456
Gln Ala Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Gly Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
85 90 95

Leu Ser Gly Tyr Val Phe Gly Gly Gly Thr Gln Leu Thr Val Leu Gly
100 105 110

<210> 457
<211> 250
<212> PRT
<213> Homo sapiens

<400> 457
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45

Gly Trp Ile Asn Pro Tyr Thr Gly Gly Ala Phe Tyr Ala Gln Lys Phe
50 55 60

Arg Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

```
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Pro Glu Lys Phe Asp Phe Trp Gly Gly Asp Asn Trp Gly
            100                 105                 110

Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ala Val Leu Thr Gln Pro
    130                 135                 140

Pro Ser Val Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr
145                 150                 155                 160

Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Gly Val His Trp Tyr Gln
                165                 170                 175

Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asn Ser Asn
            180                 185                 190

Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr
        195                 200                 205

Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp
    210                 215                 220

Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser Leu Ser Gly Tyr Val Phe Gly
225                 230                 235                 240

Gly Gly Thr Gln Leu Thr Val Leu Ser Ala
                245                 250
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<210> 458
<211> 5
<212> PRT
<213> Homo sapiens

<400> 458
Asp Tyr Tyr Met His
1   5

<210> 459
<211> 17
<212> PRT
<213> Homo sapiens

<400> 459
Trp Ile Asn Pro Tyr Thr Gly Gly Ala Phe Tyr Ala Gln Lys Phe Arg
1 5 10 15

Gly

<210> 460
<211> 12
<212> PRT
<213> Homo sapiens

<400> 460
Glu Pro Glu Lys Phe Asp Phe Trp Gly Gly Asp Asn
1 5 10

<210> 461
<211> 14
<212> PRT
<213> Homo sapiens

<400> 461
Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Gly Val His
1 5 10

<210> 462
<211> 7
<212> PRT
<213> Homo sapiens

<400> 462
Gly Asn Ser Asn Arg Pro Ser
1 5

<210> 463
<211> 11
<212> PRT
<213> Homo sapiens

<400> 463
Gln Ser Tyr Asp Ser Ser Leu Ser Gly Tyr Val
1 5 10

<210> 464
<211> 363
<212> DNA
<213> Homo sapiens

<400> 464
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tcctgcaagg cttctggata caccttcacc gactactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg ggtgggatgg atcaaccctt atactggtgg cgcattctat 180

gcacagaagt ttcggggcag ggtcacaatg accagggaca cgtccatcag cacagcctac 240

atggagctga gcagactgag atctgacgac acggccgtgt attattgtgc gagagaacct 300

gaaaaattcg atttttgggg gggtgacaac tggggccggg ggacattggt caccgtctcc 360

tca 363

<210> 465
<211> 336
<212> DNA
<213> Homo sapiens

<400> 465
caggctgtgc tgactcagcc gccgtcagtg tctggggccc cagggcagag ggtcaccatc 60

tcctgcactg ggagcagctc caacatcggg gcaggttatg gtgtacactg gtaccaacag 120

cttccaggaa cagccccaa actcctcatc tatggtaaca gcaatcggcc ctcaggggtc 180

cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cactgggctc 240

caggctgagg atgaggctga ttattactgc cagtcctatg acagcagcct gagtggttat 300

gtcttcggag gtgggaccca gctcaccgtc ctaggt 336

<210> 466
<211> 750
<212> DNA
<213> Homo sapiens

<400> 466
caggtccagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggata caccttcacc gactactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg ggtgggatgg atcaaccctt atactggtgg cgcattctat 180

gcacagaagt ttcggggcag ggtcacaatg accagggaca cgtccatcag cacagcctac 240

atggagctga gcagactgag atctgacgac acggccgtgt attattgtgc gagagaacct 300

gaaaaattcg atttttgggg gggtgacaac tggggccggg ggacattggt caccgtctcg 360

agtggaggcg gcggttcagg cggaggtggc tctggcggtg gcggaagtgc acaggctgtg 420

ctgactcagc cgccgtcagt gtctggggcc ccagggcaga gggtcaccat ctcctgcact 480

gggagcagct ccaacatcgg ggcaggttat ggtgtacact ggtaccaaca gcttccagga 540

acagccccca aactcctcat ctatggtaac agcaatcggc cctcaggggt ccctgaccga 600

ttctctggct ccaagtctgg cacctcagcc tccctggcca tcactgggct ccaggctgag 660

gatgaggctg attattactg ccagtcctat gacagcagcc tgagtggtta tgtcttcgga 720

ggtgggaccc agctcaccgt tttaagtgcg 750

<210> 467
<211> 15
<212> DNA
<213> Homo sapiens

<400> 467
gactactata tgcac 15

<210> 468
<211> 51
<212> DNA
<213> Homo sapiens

<400> 468
tggatcaacc cttatactgg tggcgcattc tatgcacaga agtttcgggg c 51

<210> 469
<211> 36
<212> DNA
<213> Homo sapiens

<400> 469
gaacctgaaa aattcgattt ttgggggggt gacaac 36

<210> 470
<211> 42
<212> DNA
<213> Homo sapiens

<400> 470
actgggagca gctccaacat cggggcaggt tatggtgtac ac 42

<210> 471
<211> 21
<212> DNA
<213> Homo sapiens

<400> 471
ggtaacagca atcggccctc a 21

<210> 472
<211> 33
<212> DNA
<213> Homo sapiens

<400> 472
cagtcctatg acagcagcct gagtggttat gtc 33

<210> 473
<211> 119
<212> PRT
<213> Homo sapiens

<400> 473
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Val Ser Ala Tyr Thr Gly Asn Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Gly Tyr Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 474
<211> 108
<212> PRT
<213> Homo sapiens

<400> 474
Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Gly Ile Tyr His Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Ala Ser Ser Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Met Gly Glu Tyr Asn Ala
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> 475
<211> 242
<212> PRT
<213> Homo sapiens

<400> 475
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Val Ser Ala Tyr Thr Gly Asn Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Gly Tyr Tyr Asp Ala Phe Asp Ile Trp Gly Gln Gly
100 105 110

```
Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Thr
    130                 135                 140

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
145                 150                 155                 160

Glu Gly Ile Tyr His Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
                165                 170                 175

Ala Pro Lys Leu Leu Ile Tyr Lys Ala Ser Ser Leu Ala Ser Gly Val
            180                 185                 190

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
        195                 200                 205

Ile Ser Ser Leu Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
    210                 215                 220

Met Gly Glu Tyr Asn Ala Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
225                 230                 235                 240

Lys Arg
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<210> 476
<211> 5
<212> PRT
<213> Homo sapiens

<400> 476

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Ser Tyr Gly Ile Ser
1               5
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<210> 477
<211> 17
<212> PRT
<213> Homo sapiens

<400> 477

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Trp Val Ser Ala Tyr Thr Gly Asn Thr Asn Tyr Ala Gln Lys Phe Gln
1               5                   10                  15

Gly
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<210> 478
<211> 10
<212> PRT
<213> Homo sapiens

<400> 478
Asp Arg Gly Tyr Tyr Asp Ala Phe Asp Ile
1 5 10

<210> 479
<211> 11
<212> PRT
<213> Homo sapiens

<400> 479
Arg Ala Ser Glu Gly Ile Tyr His Trp Leu Ala
1 5 10

<210> 480
<211> 7
<212> PRT
<213> Homo sapiens

<400> 480
Lys Ala Ser Ser Leu Ala Ser
1 5

<210> 481
<211> 9
<212> PRT
<213> Homo sapiens

<400> 481
Gln Gln Met Gly Glu Tyr Asn Ala Thr
1 5

<210> 482
<211> 357
<212> DNA
<213> Homo sapiens

<400> 482
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tcctgcaagg cttctggtta cacctttacc agttatggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg gtcagcgctt acactggtaa cacaaactat 180

gcacagaagt tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240

atggaactga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagatcgt 300

ggatactatg atgcttttga tatctggggc caaggcaccc tggtcaccgt ctcctca 357

<210> 483
<211> 324
<212> DNA
<213> Homo sapiens

<400> 483
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atcacctgcc gggccagtga gggtatttat cactggttgg cctggtatca gcagaagcca 120

gggaaagccc ctaaactcct gatctataag gcctctagtt tagccagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagag ttcactctca ccatcagcag cctgcagcct 240

gatgattttg caacttatta ctgccaacaa atgggcgagt acaacgccac cttcggcgga 300

gggaccaagg tggagatcaa acgt 324

<210> 484
<211> 726
<212> DNA
<213> Homo sapiens

<400> 484
caggtgcagc tggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggtta cacctttacc agttatggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg gtcagcgctt acactggtaa cacaaactat 180

gcacagaagt tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240

atggaactga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagatcgt 300

ggatactatg atgcttttga tatctggggc caaggcaccc tggtcaccgt ctcctcaggt 360

ggaggcggtt caggcggagg tggcagcggc ggtggcggat cggacatcca gatgacccag 420

tctccttcca ccctgtctgc atctgttgga gacagagtca ccatcacctg ccgggccagt 480

gagggtattt atcactggtt ggcctggtat cagcagaagc cagggaaagc ccctaaactc 540

ctgatctata aggcctctag tttagccagt ggggtcccat caaggttcag cggcagtgga 600

tctgggacag agttcactct caccatcagc agcctgcagc ctgatgattt tgcaacttat 660

tactgccaac aaatgggcga gtacaacgcc accttcggcg gagggaccaa ggtggagatc 720

aaacgt 726

<210> 485
<211> 15
<212> DNA
<213> Homo sapiens

<400> 485
agttatggta tcagc 15

<210> 486
<211> 51
<212> DNA
<213> Homo sapiens

<400> 486
tgggtcagcg cttacactgg taacacaaac tatgcacaga agttccaggg c 51

<210> 487
<211> 30
<212> DNA
<213> Homo sapiens

<400> 487
gatcgtggat actatgatgc ttttgatatc 30

<210> 488
<211> 33
<212> DNA
<213> Homo sapiens

<400> 488
cgggccagtg agggtattta tcactggttg gcc 33

<210> 489
<211> 21
<212> DNA
<213> Homo sapiens

<400> 489
aaggcctcta gtttagccag t 21

<210> 490
<211> 27
<212> DNA
<213> Homo sapiens

<400> 490
caacaaatgg gcgagtacaa cgccacc 27

<210> 491
<211> 121
<212> PRT
<213> Homo sapiens

<400> 491
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Val Asn Trp Asn Gly Gly Thr Arg Asp Tyr Ala Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr His Cys
85 90 95

Ala Arg Gly Trp Tyr Ser Gly Ala Ala Trp Asn Met Gly Tyr Trp Gly
100 105 110

Arg Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 492
<211> 111
<212> PRT
<213> Homo sapiens

<400> 492
Gln Ala Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15

Ser Ile Thr Ile Ser Cys Thr Gly Ala Ser Gly Asp Val Gly Ala Tyr
20 25 30

Asn Phe Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Ile Ile Tyr Asp Val Asn Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Thr Ser Thr
85 90 95

Phe Ser Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105 110

<210> 493
<211> 248
<212> PRT
<213> Homo sapiens

<400> 493
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Arg Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Val Asn Trp Asn Gly Gly Thr Arg Asp Tyr Ala Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr His Cys
85 90 95

Ala Arg Gly Trp Tyr Ser Gly Ala Ala Trp Asn Met Gly Tyr Trp Gly
100 105 110

Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
115 120 125

Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ala Ala Leu Thr Gln Pro
130 135 140

Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr
145 150 155 160

Gly Ala Ser Gly Asp Val Gly Ala Tyr Asn Phe Val Ser Trp Tyr Gln
165 170 175

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Gln His Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp Val Asn Lys
           180                 185                 190

Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn
        195                 200                 205

Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp
    210                 215                 220

Tyr Tyr Cys Ser Ser Tyr Thr Ser Thr Phe Ser Val Val Phe Gly Gly
225                 230                 235                 240

Gly Thr Lys Leu Thr Val Leu Gly
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<213> Homo sapiens

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Asp Tyr Gly Met Asn
1   5

<210> 495
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<400> 495
Gly Val Asn Trp Asn Gly Gly Thr Arg Asp Tyr Ala Ala Ser Val Lys
1   5   10   15

Gly

<210> 496
<211> 12
<212> PRT
<213> Homo sapiens

<400> 496
Gly Trp Tyr Ser Gly Ala Ala Trp Asn Met Gly Tyr
1   5   10

<210> 497
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<213> Homo sapiens

<400> 497
Thr Gly Ala Ser Gly Asp Val Gly Ala Tyr Asn Phe Val Ser
1 5 10

<210> 498
<211> 7
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<213> Homo sapiens

<400> 498
Asp Val Asn Lys Arg Pro Ser
1 5

<210> 499
<211> 10
<212> PRT
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<400> 499
Ser Ser Tyr Thr Ser Thr Phe Ser Val Val
1 5 10

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<211> 363
<212> DNA
<213> Homo sapiens

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tcctgtgcag cctctggatt cacctttgac gattatggca tgaactgggt ccgccaagct 120

ccagggaagg ggctggagtg ggtctctggt gttaattgga atggtggtac cagagattat 180

gcagcctccg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240

ctgcaaatga acagtctgag agccgaggac acggccttgt atcactgtgc gagaggatgg 300

tatagtgggg ccgcgtggaa catgggctac tggggccgag gaaccctggt caccgtctcc 360

tca 363

<210> 501
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<212> DNA
<213> Homo sapiens

<400> 501
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tcctgcactg gagccagcgg tgacgttggt gcttataact ttgtctcctg gtaccaacaa 120

cacccaggca aagcccccaa actcataatt tatgatgtca ataagcggcc ctcaggggtt 180

tctaatcgct tctctggctc caagtctggc aacacggcct ccctgaccat ctctgggctc 240

caggccgagg acgaggctga ttattactgc agctcatata caagcacctt ctctgtggta 300

tttggcggag ggaccaagct gaccgtccta ggt 333

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<211> 744
<212> DNA
<213> Homo sapiens

<400> 502
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tcctgtgcag cctctggatt cacctttgac gattatggca tgaactgggt ccgccaagct 120

ccagggaagg ggctggagtg ggtctctggt gttaattgga atggtggtac cagagattat 180

gcagcctccg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240

ctgcaaatga acagtctgag agccgaggac acggccttgt atcactgtgc gagaggatgg 300

tatagtgggg ccgcgtggaa catgggctac tggggccgag gaaccctggt caccgtctcc 360

tcaggaggcg gcggttcagg cggaggtggc tctggcggtg gcggaagtgc acaggctgcg 420

ctgactcagc cggcctccgt gtctgggtct cctggacagt cgatcaccat ctcctgcact 480

ggagccagcg gtgacgttgg tgcttataac tttgtctcct ggtaccaaca acacccaggc 540

aaagccccca aactcataat ttatgatgtc aataagcggc cctcaggggt ttctaatcgc 600

ttctctggct ccaagtctgg caacacggcc tccctgacca tctctgggct ccaggccgag 660

gacgaggctg attattactg cagctcatat acaagcacct tctctgtggt atttggcgga 720

gggaccaagc tgaccgtcct aggt 744

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<213> Homo sapiens

<400> 503
gattatggca tgaac 15

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<212> DNA
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<212> DNA
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<211> 42
<212> DNA
<213> Homo sapiens

<400> 506
actggagcca gcggtgacgt tggtgcttat aactttgtct cc 42

<210> 507
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<212> DNA
<213> Homo sapiens

<400> 507
gatgtcaata agcggccctc a 21

<210> 508
<211> 30
<212> DNA
<213> Homo sapiens

<400> 508
agctcatata caagcacctt ctctgtggta 30

<210> 509
<211> 119
<212> PRT
<213> Homo sapiens

<400> 509
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asp Tyr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

```
Gly Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Met Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Leu Thr Gly Phe Asp Pro Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115
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<210> 510
<211> 109
<212> PRT
<213> Homo sapiens

<400> 510

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Ser Ser Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys
1               5                   10                  15

Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Phe Arg Asn Lys Arg Val
            20                  25                  30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60

Arg Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65                  70                  75                  80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Leu Phe Asn Asp Asn
                85                  90                  95

Gly Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105
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<210> 511
<211> 244
<212> PRT
<213> Homo sapiens

<400> 511

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                  10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asp Tyr
            20                  25                  30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Met Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Leu Thr Gly Phe Asp Pro Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Ala Ser Ser Val Leu Thr Gln Pro Pro Ser
    130                 135                 140

Val Ser Val Ala Pro Gly Lys Thr Ala Arg Ile Thr Cys Gly Gly Asn
145                 150                 155                 160

Asn Phe Arg Asn Lys Arg Val His Trp Tyr Gln Gln Lys Pro Gly Gln
                165                 170                 175

Ala Pro Val Leu Val Ile Tyr Tyr Asp Ser Asp Arg Pro Ser Gly Ile
            180                 185                 190

Pro Glu Arg Phe Ser Gly Ser Arg Ser Gly Asn Thr Ala Thr Leu Thr
        195                 200                 205
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Ile Ser Arg Val Glu Ala Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val
210 215 220

Trp Asp Leu Phe Asn Asp Asn Gly Val Phe Gly Gly Gly Thr Lys Leu
225 230 235 240

Thr Val Leu Gly

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<211> 5
<212> PRT
<213> Homo sapiens

<400> 512
Asp Tyr Tyr Ile His
1 5

<210> 513
<211> 17
<212> PRT
<213> Homo sapiens

<400> 513
Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 514
<211> 10
<212> PRT
<213> Homo sapiens

<400> 514
Asp Leu Thr Gly Phe Asp Pro Phe Asp Ile
1 5 10

<210> 515
<211> 11
<212> PRT
<213> Homo sapiens

<400> 515
Gly Gly Asn Asn Phe Arg Asn Lys Arg Val His
1 5 10

<210> 516
<211> 7
<212> PRT
<213> Homo sapiens

<400> 516
Tyr Asp Ser Asp Arg Pro Ser
1 5

<210> 517
<211> 11
<212> PRT
<213> Homo sapiens

<400> 517
Gln Val Trp Asp Leu Phe Asn Asp Asn Gly Val
1 5 10

<210> 518
<211> 357
<212> DNA
<213> Homo sapiens

<400> 518
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tcctgtaagg cttctggata caccttcagc gattactata ttcactgggt gcgacaggcc 120

cctggacaag ggttggagtg gatgggatgg gtcaaccctg acactggtgg cacaagatac 180

gcgcagaagt ttcagggccg ggtcacaatg accagggaca tgtccatctc cacagcctac 240

atggagctgt ccaggctgag aagcgacgac acggccgtat attactgtgc gagagatcta 300

actggatttg atccttttga tatctggggc cagggaaccc tggtcaccgt ctcctca 357

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<211> 327
<212> DNA
<213> Homo sapiens

<400> 519
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acctgtgggg gaaacaactt tcgaaataaa agagtacact ggtatcagca gaagccaggc 120

caggcccctg tcctggtcat ctattatgat tcagaccggc cctcagggat ccctgagcga 180

ttctctggct cccgctctgg gaacacggcc accctgacca tcagcagggt cgaggccggg 240

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ggagggacca agctgaccgt cctaggt 327

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<211> 732
<212> DNA
<213> Homo sapiens

<400> 520
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tcctgtaagg cttctggata caccttcagc gattactata ttcactgggt gcgacaggcc 120

cctggacaag ggttggagtg gatgggatgg gtcaaccctg acactggtgg cacaagatac 180

gcgcagaagt ttcagggccg ggtcacaatg accagggaca tgtccatctc cacagcctac 240

atggagctgt ccaggctgag aagcgacgac acggccgtat attactgtgc gagagatcta 300

actggatttg atccttttga tatctggggc cagggaaccc tggtcaccgt ctcctcagga 360

ggcggcagtt caggtggagg tggctctggc ggtggcggaa gtgcatcgtc tgtgctgact 420

cagccaccct cagtgtcagt ggccccagga aagacggccc gcattacctg tgggggaaac 480

aactttcgaa ataaaagagt acactggtat cagcagaagc caggccaggc ccctgtcctg 540

gtcatctatt atgattcaga ccggccctca gggatccctg agcgattctc tggctcccgc 600

tctgggaaca cggccaccct gaccatcagc agggtcgagg ccggggatga ggccgactat 660

tactgtcagg tgtgggatct cttcaacgac aacggcgtgt tcggcggagg gaccaagctg 720

accgtcctag gt 732

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<211> 15
<212> DNA
<213> Homo sapiens

<400> 521
gattactata ttcac 15

<210> 522
<211> 51
<212> DNA
<213> Homo sapiens

<400> 522
tgggtcaacc ctgacactgg tggcacaaga tacgcgcaga agtttcaggg c 51

<210> 523
<211> 30
<212> DNA
<213> Homo sapiens

<400> 523
gatctaactg gatttgatcc ttttgatatc 30

<210> 524
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<212> DNA
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<400> 524
gggggaaaca actttcgaaa taaaagagta cac 33

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<212> DNA
<213> Homo sapiens

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<210> 526
<211> 33
<212> DNA
<213> Homo sapiens

<400> 526
caggtgtggg atctcttcaa cgacaacggc gtg 33

<210> 527
<211> 119
<212> PRT
<213> Homo sapiens

<400> 527

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
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Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Ser	Asp	Tyr
			20					25					30		
Tyr	Ile	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
		35					40					45			
Gly	Trp	Val	Asn	Pro	Asp	Thr	Gly	Gly	Thr	Arg	Tyr	Ala	Gln	Lys	Phe
	50					55					60				
Gln	Gly	Arg	Val	Thr	Met	Thr	Arg	Asp	Met	Ser	Ile	Ser	Thr	Ala	Tyr
65					70					75					80
Met	Glu	Leu	Ser	Arg	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	

Ala Arg Asp Leu Thr Gly Phe Asp Pro Phe Asp Ile Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> 528
<211> 109
<212> PRT
<213> Homo sapiens

<400> 528
Ser Ser Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys
1 5 10 15

Thr Ala Arg Ile Thr Cys Gly Gly Asn Asn Phe Arg Asn Lys Arg Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Tyr Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Arg Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Arg Val Glu Ala Gly
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Val Trp Asp Phe Leu Thr Asp Ser
85 90 95

Gly Ser Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105

<210> 529
<211> 244
<212> PRT
<213> Homo sapiens

<400> 529
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asp Tyr
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Met Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Leu Thr Gly Phe Asp Pro Phe Asp Ile Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
115 120 125

Ser Gly Gly Gly Gly Ser Ala Ser Ser Val Leu Thr Gln Pro Pro Ser
130 135 140

Val Ser Val Ala Pro Gly Lys Thr Ala Arg Ile Thr Cys Gly Gly Asn
145 150 155 160

Asn Phe Arg Asn Lys Arg Val His Trp Tyr Gln Gln Lys Pro Gly Gln
165 170 175

Ala Pro Val Leu Val Ile Tyr Tyr Asp Ser Asp Arg Pro Ser Gly Ile
180 185 190

Pro Glu Arg Phe Ser Gly Ser Arg Ser Gly Asn Thr Ala Thr Leu Thr
195 200 205

Ile Ser Arg Val Glu Ala Gly Asp Glu Ala Asp Tyr Tyr Cys Gln Val
210 215 220

Trp Asp Phe Leu Thr Asp Ser Gly Ser Phe Gly Gly Gly Thr Lys Leu
225 230 235 240

Thr Val Leu Gly

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<212> PRT
<213> Homo sapiens

<400> 530
Asp Tyr Tyr Ile His
1 5

<210> 531
<211> 17
<212> PRT
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<400> 531
Trp Val Asn Pro Asp Thr Gly Gly Thr Arg Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 532
<211> 10
<212> PRT
<213> Homo sapiens

<400> 532
Asp Leu Thr Gly Phe Asp Pro Phe Asp Ile
1 5 10

<210> 533
<211> 11
<212> PRT
<213> Homo sapiens

<400> 533
Gly Gly Asn Asn Phe Arg Asn Lys Arg Val His
1 5 10

<210> 534
<211> 7
<212> PRT
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<400> 534
Tyr Asp Ser Asp Arg Pro Ser
1 5

<210> 535
<211> 11
<212> PRT
<213> Homo sapiens

<400> 535
Gln Val Trp Asp Phe Leu Thr Asp Ser Gly Ser
1 5 10

<210> 536
<211> 357
<212> DNA
<213> Homo sapiens

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tcctgtaagg cttctggata caccttcagc gattactata ttcactgggt gcgacaggcc 120

cctggacaag ggttggagtg gatgggatgg gtcaaccctg acactggtgg cacaagatac 180

gcgcagaagt ttcagggccg ggtcacaatg accagggaca tgtccatctc cacagcctac 240

atggagctgt ccaggctgag aagcgacgac acggccgtat attactgtgc gagagatcta 300

actggatttg atccttttga tatctggggc cagggaaccc tggtcaccgt ctcctca 357

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<211> 327
<212> DNA
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caggcccctg tcctggtcat ctattatgat tcagaccggc cctcagggat ccctgagcga 180

ttctctggct cccgctctgg gaacacggcc accctgacca tcagcagggt cgaggccggg 240

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ggagggacca agctgaccgt cctaggt 327

<210> 538
<211> 732
<212> DNA
<213> Homo sapiens

<400> 538
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tcctgtaagg cttctggata caccttcagc gattactata ttcactgggt gcgacaggcc 120

cctggacaag ggttggagtg gatgggatgg gtcaaccctg acactggtgg cacaagatac 180

gcgcagaagt ttcagggccg ggtcacaatg accagggaca tgtccatctc cacagcctac 240

atggagctgt ccaggctgag aagcgacgac acggccgtat attactgtgc gagagatcta 300

actggatttg atccttttga tatctggggc cagggaaccc tggtcaccgt ctcctcagga 360

ggcggcggtt caggcggagg tggctctggc ggtggcggaa gtgcatcgtc tgtgctgact 420

cagccaccct cagtgtcagt ggccccagga aagacggccc gcattacctg tgggggaaac 480

aactttcgaa ataaaagagt acactggtat cagcagaagc caggccaggc ccctgtcctg 540

gtcatctatt atgattcaga ccggccctca gggatccctg agcgattctc tggctcccgc 600

tctgggaaca cggccaccct gaccatcagc agggtcgagg ccggggatga ggccgactat 660

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accgtcctag gt 732

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<212> DNA
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<400> 539
gattactata ttcac 15

<210> 540
<211> 51
<212> DNA
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<400> 540
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<210> 541
<211> 30
<212> DNA
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<400> 541
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<210> 542
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<212> DNA
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gggggaaaca actttcgaaa taaaagagta cac 33

<210> 543
<211> 21
<212> DNA
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<400> 543
tatgattcag accggccctc a 21

<210> 544
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<212> DNA
<213> Homo sapiens

<400> 544
caggtgtggg atttcctcac cgactcgggg tcg 33

<210> 545
<211> 121
<212> PRT
<213> Homo sapiens

<400> 545

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
1				5				10				15			
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Asp	Tyr
			20					25				30			
Tyr	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Val
		35					40					45			
Gly	Trp	Ile	Asn	Pro	Tyr	Thr	Gly	Gly	Ala	Phe	Tyr	Ala	Gln	Lys	Phe
	50					55					60				
Arg	Gly	Arg	Val	Thr	Met	Thr	Arg	Asp	Thr	Ser	Ile	Ser	Thr	Ala	Tyr
65					70					75					80
Met	Glu	Leu	Ser	Arg	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85					90					95	
Ala	Arg	Glu	Pro	Glu	Arg	Phe	Gly	Asp	Ser	Thr	Gly	Gln	Val	Trp	Gly
			100					105					110		
Arg	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser							
		115					120								

<210> 546
<211> 112
<212> PRT
<213> Homo sapiens

<400> 546
Gln Ala Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Gly Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Tyr His Trp Asp Lys Glu
85 90 95

Gln Ser Gly Tyr Val Phe Gly Gly Gly Thr Gln Leu Thr Val Leu Gly
100 105 110

<210> 547
<211> 249
<212> PRT
<213> Homo sapiens

<400> 547
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45

Gly Trp Ile Asn Pro Tyr Thr Gly Gly Ala Phe Tyr Ala Gln Lys Phe
50 55 60

Arg Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Pro Glu Arg Phe Gly Asp Ser Thr Gly Gln Val Trp Gly
            100                 105                 110

Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gly Gly Ser Arg Ser Ala Gln Ala Val Leu Thr Gln Pro
    130                 135                 140

Pro Ser Val Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr
145                 150                 155                 160

Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Gly Val His Trp Tyr Gln
                165                 170                 175

Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asn Ser Asn
            180                 185                 190

Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr
        195                 200                 205

Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp
    210                 215                 220

Tyr Tyr Cys Tyr His Trp Asp Lys Glu Gln Ser Gly Tyr Val Phe Gly
225                 230                 235                 240

Gly Gly Thr Gln Leu Thr Val Leu Gly
                245
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<210> 548
<211> 5
<212> PRT
<213> Homo sapiens

<400> 548
Asp Tyr Tyr Met His
1   5

<210> 549
<211> 17
<212> PRT
<213> Homo sapiens

<400> 549
Trp Ile Asn Pro Tyr Thr Gly Gly Ala Phe Tyr Ala Gln Lys Phe Arg
1 5 10 15

Gly

<210> 550
<211> 12
<212> PRT
<213> Homo sapiens

<400> 550
Glu Pro Glu Arg Phe Gly Asp Ser Thr Gly Gln Val
1 5 10

<210> 551
<211> 14
<212> PRT
<213> Homo sapiens

<400> 551
Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Gly Val His
1 5 10

<210> 552
<211> 7
<212> PRT
<213> Homo sapiens

<400> 552
Gly Asn Ser Asn Arg Pro Ser
1 5

<210> 553
<211> 11
<212> PRT
<213> Homo sapiens

<400> 553
Tyr His Trp Asp Lys Glu Gln Ser Gly Tyr Val
1 5 10

<210> 554
<211> 363
<212> DNA
<213> Homo sapiens

<400> 554
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggata caccttcacc gactactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg ggtgggatgg atcaaccctt atactggtgg cgcattctat 180

gcacagaagt ttcggggcag ggtcacaatg accagggaca cgtccatcag cacagcctac 240

atggagctga gcagactgag atctgacgac acggccgtgt attattgtgc gagagaacct 300

gaaagattcg gcgactccac ggggcaggtc tggggccggg ggacattggt caccgtctcc 360

tca 363

<210> 555
<211> 336
<212> DNA
<213> Homo sapiens

<400> 555
caggctgtgc tgactcagcc gccgtcagtg tctggggccc cagggcagag ggtcaccatc 60

tcctgcactg ggagcagctc caacatcggg gcaggttatg gtgtacactg gtaccaacag 120

cttccaggaa cagccccaa actcctcatc tatggtaaca gcaatcggcc ctcaggggtc 180

cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cactgggctc 240

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gtcttcggag gtgggaccca gctcaccgtc ctaggt 336

<210> 556
<211> 747
<212> DNA
<213> Homo sapiens

<400> 556
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tcctgcaagg cttctggata caccttcacc gactactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg ggtgggatgg atcaaccctt atactggtgg cgcattctat 180

gcacagaagt ttcggggcag ggtcacaatg accagggaca cgtccatcag cacagcctac 240

atggagctga gcagactgag atctgacgac acggccgtgt attattgtgc gagagaacct 300

gaaagattcg gcgactccac ggggcaggtc tggggccggg ggacattggt caccgtctcc 360

tcaggggcg gcggttcagg cggaggtggc tctggcggta gcagaagtgc acaggctgtg 420

ctgactcagc cgccgtcagt gtctggggcc ccagggcaga gggtcaccat ctcctgcact 480

gggagcagct ccaacatcgg ggcaggttat ggtgtacact ggtaccaaca gcttccagga 540

acagccccca aactcctcat ctatggtaac agcaatcggc cctcaggggt ccctgaccga 600

ttctctggct ccaagtctgg cacctcagcc tccctggcca tcactgggct ccaggctgag 660

gatgaggctg attattactg ctaccactgg gacaaggagc agagtggtta tgtcttcgga 720

ggtgggaccc agctcaccgt cctaggt 747

<210> 557
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<212> DNA
<213> Homo sapiens

<400> 557
gactactata tgcac 15

<210> 558
<211> 51
<212> DNA
<213> Homo sapiens

<400> 558
tggatcaacc cttatactgg tggcgcattc tatgcacaga agtttcgggg c 51

<210> 559
<211> 36
<212> DNA
<213> Homo sapiens

<400> 559
gaacctgaaa gattcggcga ctccacgggg caggtc 36

<210> 560
<211> 42
<212> DNA
<213> Homo sapiens

<400> 560
actgggagca gctccaacat cggggcaggt tatggtgtac ac 42

<210> 561
<211> 21
<212> DNA
<213> Homo sapiens

<400> 561
ggtaacagca atcggccctc a 21

<210> 562
<211> 33
<212> DNA
<213> Homo sapiens

<400> 562
taccactggg acaaggagca gagtggttat gtc 33

<210> 563
<211> 121
<212> PRT
<213> Homo sapiens

<400> 563
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45

Gly Trp Ile Asn Pro Tyr Thr Gly Ser Ala Phe Tyr Ala Gln Lys Phe
50 55 60

Arg Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Pro Glu Lys Phe Gly Glu Ser Ser Gly Gln Leu Trp Gly
100 105 110

Arg Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 564
<211> 112
<212> PRT
<213> Homo sapiens

<400> 564
Gln Ala Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Gly Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Gly Asp Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Gly
85 90 95

Leu Ser Gly Tyr Val Phe Gly Gly Gly Thr Gln Leu Thr Val Leu Gly
100 105 110

<210> 565
<211> 249
<212> PRT
<213> Homo sapiens

<400> 565
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45

Gly Trp Ile Asn Pro Tyr Thr Gly Ser Ala Phe Tyr Ala Gln Lys Phe
50 55 60

Arg Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Pro Glu Lys Phe Gly Glu Ser Ser Gly Gln Leu Trp Gly
100 105 110

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Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gly Gly Ser Gly Ser Ala Gln Ala Val Leu Thr Gln Pro
    130                 135                 140

Pro Ser Val Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr
145                 150                 155                 160

Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Gly Val His Trp Tyr Gln
                165                 170                 175

Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asp Ser Asn
            180                 185                 190

Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr
        195                 200                 205

Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp
    210                 215                 220

Tyr Tyr Cys Gln Ser Tyr Asp Ser Gly Leu Ser Gly Tyr Val Phe Gly
225                 230                 235                 240

Gly Gly Thr Gln Leu Thr Val Leu Gly
                245
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<210> 566
<211> 5
<212> PRT
<213> Homo sapiens

<400> 566
Asp Tyr Tyr Met His
1   5

<210> 567
<211> 17
<212> PRT
<213> Homo sapiens

<400> 567
Trp Ile Asn Pro Tyr Thr Gly Ser Ala Phe Tyr Ala Gln Lys Phe Arg
1   5   10   15

Gly

<210> 568
<211> 12
<212> PRT
<213> Homo sapiens

<400> 568
Glu Pro Glu Lys Phe Gly Glu Ser Ser Gly Gln Leu
1 5 10

<210> 569
<211> 14
<212> PRT
<213> Homo sapiens

<400> 569
Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Gly Val His
1 5 10

<210> 570
<211> 7
<212> PRT
<213> Homo sapiens

<400> 570
Gly Asp Ser Asn Arg Pro Ser
1 5

<210> 571
<211> 11
<212> PRT
<213> Homo sapiens

<400> 571
Gln Ser Tyr Asp Ser Gly Leu Ser Gly Tyr Val
1 5 10

<210> 572
<211> 363
<212> DNA
<213> Homo sapiens

<400> 572
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggata caccttcacc gactactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg ggtgggatgg atcaaccctt atactggtag cgctttctat 180

gcacagaagt ttcggggcag ggtcacaatg accagggaca cgtccatcag cacagcctac 240

atggagctga gcagactgag atctgacgac acggccgtgt attattgtgc gagagaacct 300

gaaaaattcg gcgagtccag cggccagttg tggggccggg ggacattggt caccgtctcc 360

tca 363

<210> 573
<211> 336
<212> DNA
<213> Homo sapiens

<400> 573
caggctgtgc tgactcagcc gccgtcagtg tctggggccc cagggcagag ggtcaccatc 60

tcctgcactg ggagcagctc caacatcggg gcaggttatg gtgtacactg gtaccaacag 120

cttccaggaa cagccccaa actcctcatc tatggtgaca gcaatcggcc ctcaggggtc 180

cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cactgggctc 240

caggctgagg atgaggctga ttattactgc cagtcctatg acagcggcct gagtggttat 300

gtcttcggag gtgggaccca gctcaccgtc ctaggt 336

<210> 574
<211> 747
<212> DNA
<213> Homo sapiens

<400> 574
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tcctgcaagg cttctggata caccttcacc gactactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg ggtgggatgg atcaaccctt atactggtag cgctttctat 180

gcacagaagt ttcggggcag ggtcacaatg accagggaca cgtccatcag cacagcctac 240

atggagctga gcagactgag atctgacgac acggccgtgt attattgtgc gagagaacct 300

gaaaaattcg gcgagtccag cggccagttg tggggccggg ggacattggt caccgtctcc 360

tcaggaggcg gcggttcagg cggaggtggc tctggcggta gcggaagtgc acaggctgtg 420

ctgactcagc cgccgtcagt gtctggggcc ccagggcaga gggtcaccat ctcctgcact 480

gggagcagct ccaacatcgg ggcaggttat ggtgtacact ggtaccaaca gcttccagga 540

acagccccca aactcctcat ctatggtgac agcaatcggc cctcaggggt ccctgaccga 600

ttctctggct ccaagtctgg cacctcagcc tccctggcca tcactgggct ccaggctgag 660

gatgaggctg attattactg ccagtcctat gacagcggcc tgagtggtta tgtcttcgga 720

ggtgggaccc agctcaccgt cctaggt 747

<210> 575
<211> 15
<212> DNA
<213> Homo sapiens

<400> 575
gactactata tgcac 15

<210> 576
<211> 51
<212> DNA
<213> Homo sapiens

<400> 576
tggatcaacc cttatactgg tagcgctttc tatgcacaga agtttcgggg c 51

<210> 577
<211> 36
<212> DNA
<213> Homo sapiens

<400> 577
gaacctgaaa aattcggcga gtccagcggc cagttg 36

<210> 578
<211> 42
<212> DNA
<213> Homo sapiens

<400> 578
actgggagca gctccaacat cggggcaggt tatggtgtac ac 42

<210> 579
<211> 21
<212> DNA
<213> Homo sapiens

<400> 579
ggtgacagca atcggccctc a 21

<210> 580
<211> 33
<212> DNA
<213> Homo sapiens

<400> 580
cagtcctatg acagcggcct gagtggttat gtc 33

<210> 581
<211> 121
<212> PRT
<213> Homo sapiens

<400> 581
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr His Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45

Gly Trp Ile Asn Pro Tyr Thr Gly Gly Ala Phe Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Pro Glu Lys Phe Asp Ser Pro Asn Ala Glu Ile Trp Gly
100 105 110

Arg Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 582
<211> 112
<212> PRT
<213> Homo sapiens

<400> 582
Gln Ala Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

Tyr Gly Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
85 90 95

Leu Ser Gly Tyr Val Phe Gly Gly Gly Thr Gln Leu Thr Val Leu Gly
100 105 110

<210> 583
<211> 249
<212> PRT
<213> Homo sapiens

<400> 583
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr His Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45

Gly Trp Ile Asn Pro Tyr Thr Gly Gly Ala Phe Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Pro Glu Lys Phe Asp Ser Pro Asn Ala Glu Ile Trp Gly
100 105 110

Arg Gly Thr Leu Val Thr Val Ser Ser Glu Gly Gly Gly Ser Gly Gly
115 120 125

Gly Gly Ser Gly Gly Ser Gly Ser Ala Gln Ala Val Leu Thr Gln Pro
130 135 140

Pro Ser Val Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr
145 150 155 160

Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Gly Val His Trp Tyr Gln
165 170 175

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Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asn Ser Asn
            180                 185                 190

Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr
        195                 200                 205

Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp
    210                 215                 220

Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser Leu Ser Gly Tyr Val Phe Gly
225                 230                 235                 240

Gly Gly Thr Gln Leu Thr Val Leu Gly
                245
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<210> 584
<211> 5
<212> PRT
<213> Homo sapiens

<400> 584
His Tyr Tyr Met His
1   5

<210> 585
<211> 17
<212> PRT
<213> Homo sapiens

<400> 585
Trp Ile Asn Pro Tyr Thr Gly Gly Ala Phe Tyr Ala Gln Lys Phe Gln
1   5   10   15

Gly

<210> 586
<211> 12
<212> PRT
<213> Homo sapiens

<400> 586
Glu Pro Glu Lys Phe Asp Ser Pro Asn Ala Glu Ile
1   5   10

<210> 587
<211> 14
<212> PRT
<213> Homo sapiens

<400> 587
Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Gly Val His
1 5 10

<210> 588
<211> 7
<212> PRT
<213> Homo sapiens

<400> 588
Gly Asn Ser Asn Arg Pro Ser
1 5

<210> 589
<211> 11
<212> PRT
<213> Homo sapiens

<400> 589
Gln Ser Tyr Asp Ser Ser Leu Ser Gly Tyr Val
1 5 10

<210> 590
<211> 363
<212> DNA
<213> Homo sapiens

<400> 590
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggata caccttcacc cactactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg ggtgggatgg atcaaccctt atactggtgg cgcattctat 180

gcacagaagt ttcagggcag ggtcacaatg accagggaca cgtccatcag cacagcctac 240

atggagctga gcagactgag atctgacgac acggccgtgt attattgtgc gagagaacct 300

gaaaaattcg actcgccgaa cgccgagatc tggggccggg ggacattggt caccgtctcc 360

tca 363

<210> 591
<211> 336
<212> DNA
<213> Homo sapiens

<400> 591
caggctgtgc tgactcagcc gccgtcagtg tctggggccc agggcagag ggtcaccatc 60

tcctgcactg ggagcagctc caacatcggg gcaggttatg gtgtacactg gtaccaacag 120

cttccaggaa cagcccccaa actcctcatc tatggtaaca gcaatcggcc ctcaggggtc 180

cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cactgggctc 240

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gtcttcggag gtgggaccca gctcaccgtc ctaggt 336

<210> 592
<211> 747
<212> DNA
<213> Homo sapiens

<400> 592
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggata caccttcacc cactactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg ggtgggatgg atcaaccctt atactggtgg cgcattctat 180

gcacagaagt ttcagggcag ggtcacaatg accagggaca cgtccatcag cacagcctac 240

atggagctga gcagactgag atctgacgac acggccgtgt attattgtgc gagagaacct 300

gaaaaattcg actcgccgaa cgccgagatc tggggccggg ggacattggt caccgtctcc 360

tcagaaggcg gcggttcagg cggaggtggc tctggcggta gcggaagtgc acaggctgtg 420

ctgactcagc cgccgtcagt gtctggggcc ccagggcaga gggtcaccat ctcctgcact 480

gggagcagct ccaacatcgg ggcaggttat ggtgtacact ggtaccaaca gcttccagga 540

acagccccca aactcctcat ctatggtaac agcaatcggc cctcaggggt ccctgaccga 600

ttctctggct ccaagtctgg cacctcagcc tccctggcca tcactgggct ccaggctgag 660

gatgaggctg attattactg ccagtcctat gacagcagcc tgagtggtta tgtcttcgga 720

ggtgggaccc agctcaccgt cctaggt 747

<210> 593
<211> 15
<212> DNA
<213> Homo sapiens

<400> 593
cactactata tgcac 15

<210> 594
<211> 51
<212> DNA
<213> Homo sapiens

<400> 594
tggatcaacc cttatactgg tggcgcattc tatgcacaga agtttcaggg c 51

<210> 595
<211> 36
<212> DNA
<213> Homo sapiens

<400> 595
gaacctgaaa aattcgactc gccgaacgcc gagatc 36

<210> 596
<211> 42
<212> DNA
<213> Homo sapiens

<400> 596
actgggagca gctccaacat cggggcaggt tatggtgtac ac 42

<210> 597
<211> 21
<212> DNA
<213> Homo sapiens

<400> 597
ggtaacagca atcggccctc a 21

<210> 598
<211> 33
<212> DNA
<213> Homo sapiens

<400> 598
cagtcctatg acagcagcct gagtggttat gtc 33

<210> 599
<211> 121
<212> PRT
<213> Homo sapiens

<400> 599
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
35 40 45

```
Gly Trp Ile Asn Pro Tyr Thr Gly Ser Ala Phe Tyr Ala Gln Lys Phe
    50                  55                  60

Arg Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Pro Glu Lys Phe Asp Ser Asp Asp Ser Asp Val Trp Gly
            100                 105                 110

Arg Gly Thr Leu Val Thr Val Ser Ser
        115                 120
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<210> 600
<211> 112
<212> PRT
<213> Homo sapiens

<400> 600

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Gln Ala Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30

Tyr Gly Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Gly Asp Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Asn Ser
                85                  90                  95

Leu Ser Gly Tyr Val Phe Gly Gly Gly Thr Gln Leu Thr Val Leu Gly
            100                 105                 110
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<210> 601
<211> 249
<212> PRT
<213> Homo sapiens

<400> 601

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                  10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20                  25                  30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Val
        35                  40                  45

Gly Trp Ile Asn Pro Tyr Thr Gly Ser Ala Phe Tyr Ala Gln Lys Phe
    50                  55                  60

Arg Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Pro Glu Lys Phe Asp Ser Asp Asp Ser Asp Val Trp Gly
            100                 105                 110

Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Ser Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gly Gly Ser Gly Ser Ala Gln Ala Val Leu Thr Gln Pro
    130                 135                 140

Pro Ser Val Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser Cys Thr
145                 150                 155                 160

Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Gly Val His Trp Tyr Gln
                165                 170                 175

Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asp Ser Asn
            180                 185                 190

Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr
        195                 200                 205
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Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp
210 215 220

Tyr Tyr Cys Gln Ser Tyr Asp Asn Ser Leu Ser Gly Tyr Val Phe Gly
225 230 235 240

Gly Gly Thr Gln Leu Thr Val Leu Gly
245

<210> 602
<211> 5
<212> PRT
<213> Homo sapiens

<400> 602
Asn Tyr Tyr Met His
1 5

<210> 603
<211> 17
<212> PRT
<213> Homo sapiens

<400> 603
Trp Ile Asn Pro Tyr Thr Gly Ser Ala Phe Tyr Ala Gln Lys Phe Arg
1 5 10 15

Gly

<210> 604
<211> 12
<212> PRT
<213> Homo sapiens

<400> 604
Glu Pro Glu Lys Phe Asp Ser Asp Asp Ser Asp Val
1 5 10

<210> 605
<211> 14
<212> PRT
<213> Homo sapiens

<400> 605
Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Gly Val His
1 5 10

<210> 606
<211> 7
<212> PRT
<213> Homo sapiens

<400> 606
Gly Asp Ser Asn Arg Pro Ser
1 5

<210> 607
<211> 11
<212> PRT
<213> Homo sapiens

<400> 607
Gln Ser Tyr Asp Asn Ser Leu Ser Gly Tyr Val
1 5 10

<210> 608
<211> 363
<212> DNA
<213> Homo sapiens

<400> 608
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggata caccttcacc aactactata tgcactgggt gcgacaggcc 120

cctggacaag ggcttgagtg ggtgggatgg atcaaccctt atactggtag cgcattctat 180

gcacagaagt ttcggggcag ggtcacaatg accagggaca cgtccatcag cacagcctac 240

atggagctga gcagactgag atctgacgac acggccgtgt attattgtgc gagagaacct 300

gaaaaattcg actccgacga ctccgacgtc tggggccgcg ggacattggt caccgtctcc 360

tca 363

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cttccaggaa cagcccccaa actcctcatc tatggtgaca gcaatcggcc ctcaggggtc 180

cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cactgggctc 240

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gtcttcggag gtgggaccca gctcaccgtc ctaggt 336

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<212> DNA
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cctggacaag ggcttgagtg ggtgggatgg atcaaccctt atactggtag cgcattctat 180

gcacagaagt ttcggggcag ggtcacaatg accagggaca cgtccatcag cacagcctac 240

atggagctga gcagactgag atctgacgac acggccgtgt attattgtgc gagagaacct 300

gaaaaattcg actccgacga ctccgacgtc tggggccgcg ggacattggt caccgtctcc 360

tcaggaggcg gcagttcagg cggaggtggc tctggcggta gcggaagtgc acaggctgtg 420

ctgactcagc cgccgtcagt gtctggggcc ccagggcaga gggtcaccat ctcctgcact 480

gggagcagct ccaacatcgg ggcaggttat ggtgtacact ggtaccaaca gcttccagga 540

acagccccca aactcctcat ctatggtgac agcaatcggc cctcaggggt ccctgaccga 600

ttctctggct ccaagtctgg cacctcagcc tccctggcca tcactgggct ccaggctgag 660

gatgaggctg attattactg ccagtcctat gacaacagcc tgagcggtta tgtcttcgga 720

ggtgggaccc agctcaccgt cctaggt 747

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<212> DNA
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<400> 613
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<212> DNA
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<400> 614
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<210> 615
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<212> DNA
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<400> 615
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<210> 616
<211> 33
<212> DNA
<213> Homo sapiens

<400> 616
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<210> 617
<211> 121
<212> PRT
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<400> 617
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Val Asn Trp Asn Gly Gly Thr Arg Asp Tyr Ala Ala Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr His Cys
85 90 95

Ala Arg Gly Trp Tyr Ser Gly Ala Ala Trp Asn Met Gly Tyr Trp Gly
100 105 110

Arg Gly Thr Leu Val Thr Val Ser Ser
115 120

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<211> 110
<212> PRT
<213> Homo sapiens

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Ser Ile Thr Ile Ser Cys Thr Gly Ala Ser Gly Asp Val Gly Ala Tyr
20 25 30

Asn Phe Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Ile Ile Tyr Asp Val Asn Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Leu Val Ser Asp
85 90 95

Phe Ser Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 619
<211> 261
<212> PRT
<213> Homo sapiens

<400> 619
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

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Ser Gly Val Asn Trp Asn Gly Gly Thr Arg Asp Tyr Ala Ala Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr His Cys
                85                  90                  95

Ala Arg Gly Trp Tyr Ser Gly Ala Ala Trp Asn Met Gly Tyr Trp Gly
            100                 105                 110

Arg Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Gly Gly
    130                 135                 140

Ser Gly Gly Gly Gly Ser Ala Gln Ala Ala Leu Thr Gln Pro Ala Ser
145                 150                 155                 160

Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Ala
                165                 170                 175

Ser Gly Asp Val Gly Ala Tyr Asn Phe Val Ser Trp Tyr Gln Gln His
            180                 185                 190

Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp Val Asn Lys Arg Pro
        195                 200                 205

Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala
    210                 215                 220

Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr
225                 230                 235                 240

Cys Ala Ser Leu Val Ser Asp Phe Ser Val Val Phe Gly Gly Gly Thr
                245                 250                 255
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Lys Leu Thr Val Leu
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<400> 620
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<210> 621
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<212> PRT
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<400> 621
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Gly

<210> 622
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<212> PRT
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<400> 622
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<212> PRT
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<400> 623
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<210> 624
<211> 7
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<213> Homo sapiens

<400> 624
Asp Val Asn Lys Arg Pro Ser
1 5

<210> 625
<211> 10
<212> PRT
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<400> 625
Ala Ser Leu Val Ser Asp Phe Ser Val Val
1 5 10

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<212> DNA
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gccgcctctg tgaagggcag attcaccatc agccgggaca acgccaagaa cagcctgtac 240

ctgcagatga acagcctgag agccgaggac accgccctgt accactgcgc cagaggctgg 300

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agc 363

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<212> DNA
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<400> 627
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caccccggca aggcccccaa gctgatcatc tacgacgtga acaagagacc cagcggcgtg 180

tccaacagat tcagcggcag caagagcggc aacaccgcca gcctgaccat cagcggactg 240

caggccgagg acgaggccga ctactactgc gccagcctgg tgtccgactt cagcgtggtg 300

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<212> DNA
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gccgcctctg tgaagggcag attcaccatc agccgggaca acgccaagaa cagcctgtac 240

ctgcagatga acagcctgag agccgaggac accgccctgt accactgcgc cagaggctgg 300

tacagcggag ccgcctggaa catgggctac tggggcagag gcaccctggt gaccgtgtcc 360

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ggcggaggtg gctctggcgg tggcggaagt gcacaggccg ccctgaccca gcccgccagc 480

gtgtctggca gcccaggcca gagcatcacc atcagctgca ccggcgccag cggcgatgtg 540

ggcgcctaca acttcgtgtc ctggtatcag cagcaccccg gcaaggcccc caagctgatc 600

atctacgacg tgaacaagag acccagcggc gtgtccaaca gattcagcgg cagcaagagc 660

ggcaacaccg ccagcctgac catcagcgga ctgcaggccg aggacgaggc cgactactac 720

tgcgccagcc tggtgtccga cttcagcgtg gtgttcggcg gaggcaccaa gctgaccgtg 780

ctg 783

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<212> DNA
<213> Homo sapiens

<400> 629
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<210> 630
<211> 51
<212> DNA
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<400> 630
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<210> 631
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<212> DNA
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<400> 631
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<210> 632
<211> 42
<212> DNA
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<400> 632
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<210> 633
<211> 21
<212> DNA
<213> Homo sapiens

<400> 633
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<210> 634
<211> 30
<212> DNA
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<400> 634
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