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DESCRIPTION

Field of the invention

[0001] The present invention is related to human antibodies and antigen-binding fragments of human antibodies that specifically bind human proprotein convertase subtilisin/kexin type 9 (PCSK9), and therapeutic methods of using those antibodies.

Statement of Related Art

[0002] Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a proprotein convertase belonging to the proteinase K subfamily of the secretory subtilase family. The encoded protein is synthesized as a soluble zymogen that undergoes autocatalytic intramolecular processing in the endoplasmic reticulum. Evidence suggest that PCSK9 increases plasma LDL cholesterol by promoting degradation of the LDL receptor, which mediates LDL endocytosis in the liver, the major route of LDL clearance from circulation. The structure of PCSK9 protein shows that it has a signal sequence, followed by a prodomain, a catalytic domain that contains a conserved triad of residues (D186, H226 and S386), and a C-terminal domain. It is synthesized as a soluble 74-kDa precursor that undergoes autocatalytic cleavage in the ER, generating a 14-kDa prodomain and 60-kDa catalytic fragment. The autocatalytic activity has been shown to be required for secretion. After cleavage the prodomain remains tightly associated with the catalytic domain.

[0003] Antibodies to PCSK9 are described in, for example, WO 2008/057457, WO 2008/057458, WO 2008/057459, WO 2008/063382, WO 2008/125623, and US 2008/0008697.

BRIEF SUMMARY OF THE INVENTION

[0004] In a first aspect, the invention provides fully human monoclonal antibodies (mAbs) and antigen-binding fragments thereof as defined in the claims that specifically bind and neutralize human PCSK9 (hPCSK9) activity.

[0005] Specifically, the invention provides a human antibody or antigen-binding fragment of a human antibody that specifically binds human proprotein convertase subtilisin/kexin type 9 (hPCSK9) comprising a HCVR of SEQ ID NO:90 and a LCVR of SEQ ID NO: 92.

[0006] Described herein are antibodies or antigen-binding fragments of antibodies that specifically bind hPCSK9 and are characterized by at least one of:

1. (i) capable of reducing serum total cholesterol at least about 25-35% and sustaining the

reduction over at least a 24 day period relative to a predose level, preferably the reduction in serum total cholesterol is at least about 30-40%;

2. (ii) capable of reducing serum LDL cholesterol at least about 65-80% and sustaining the reduction over at least a 24 day period relative to a predose level or capable of reducing serum LDL cholesterol at least about 40-70% and sustaining the reduction over at least a 60 to 90 day period relative to a predose level;
3. (iii) capable of reducing serum triglyceride at least about 25-40% relative to predose level;

[0007] The antibody may achieve one or more of (i) - (iii) without reducing serum HDL cholesterol or reducing serum HDL cholesterol no more than 5% relative to predose level; with little or no measurable effect on liver function, as determined by ALT and AST measurements.

[0008] In one embodiment, the antibody or fragment thereof is characterized as binding an epitope comprising amino acid residue 238 of hPCSK9 (SEQ ID NO:755). In a more specific embodiment, the antibody or fragment thereof binds an epitope comprising one or more of amino acid residue 238, 153, 159 and 343 of hPCSK9 (SEQ ID NO:755). In a more specific embodiment, the antibody or fragment thereof is characterized as binding an epitope which does not comprise an amino acid residue at position 192, 194, 197 and/or 237 of SEQ ID NO:755.

[0009] Also described herein is an antibody or fragment thereof characterized as binding an epitope comprising amino acid residue 366 of hPCSK9 (SEQ ID NO:755). Described herein is an antibody fragment thereof which binds an epitope comprising one or more of amino acid residue at position 147, 366 and 380 of SEQ ID NO:755. More specifically, the antibody or fragment thereof may be characterized as binding an epitope which does not comprise an amino acid residue at position 215 and/or 238 of SEQ ID NO:755.

[0010] In one embodiment, the antibody or fragment thereof is characterized as exhibiting an enhanced binding affinity (K_D) for hPCSK9 at pH 5.5 relative to the K_D at pH 7.4, as measured by plasmon surface resonance. In a specific embodiment, the antibody or fragment thereof exhibits at least a 20-fold, at least a 40-fold or at least a 50-fold enhanced affinity for PCSK9 at an acidic pH relative to a neutral pH, as measured by surface plasmon resonance.

[0011] Described herein are antibodies or fragments thereof characterized as not exhibiting an enhanced binding affinity for PCSK9 at an acidic pH relative to a neutral pH, as measured by surface plasmon resonance. The binding at an acidic pH may be less and the $T_{1/2}$ shorter than at neutral pH.

[0012] In another embodiment, the antibody or antigen-binding fragment binds human, human GOF mutation D374Y, cynomolgus monkey, rhesus monkey, mouse, rat and hamster PCSK9.

[0013] Described herein are antibodies or antigen-binding fragments that bind human and monkey PCSK9, but do not bind mouse, rat or hamster PCSK9

[0014] The mAbs can be full-length (e.g., an IgG1 or IgG4 antibody) or may comprise only an antigen-binding portion (e.g., a Fab, F(ab')₂ or scFv fragment), and may be modified to affect functionality, e.g., to eliminate residual effector functions (Reddy et al. (2000) J. Immunol. 164:1925-1933).

[0015] Described herein is an antibody or antigen-binding fragment of an antibody comprising a heavy chain variable region (HCVR) selected from the group consisting of SEQ ID NO:2, 18, 22, 26, 42, 46, 50, 66, 70, 74, 90, 94, 98, 114, 118, 122, 138, 142, 146, 162, 166, 170, 186, 190, 194, 210, 214, 218, 234, 238, 242, 258, 262, 266, 282, 286, 290, 306, 310, 314, 330, 334, 338, 354, 358, 362, 378, 382, 386, 402, 406, 410, 426, 430, 434, 450, 454, 458, 474, 478, 482, 498, 502, 506, 522, 526, 530, 546, 550, 554, 570, 574, 578, 594, 598, 602, 618, 622, 626, 642, 646, 650, 666, 670, 674, 690, 694, 698, 714, 718, 722, 738 and 742, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity. The HCVR may have an amino acid sequence selected from the group consisting of SEQ ID NO:50, 66, 70, 74, 90, 94, 122, 138, 142, 218, 234, 238, 242, 258, 262, 314, 330 and 334. In the claimed invention, the HCVR comprises SEQ ID NO:90.

[0016] The antibody or fragment thereof as described herein may further comprise a light chain variable region (LCVR) selected from the group consisting of SEQ ID NO:10, 20, 24, 34, 44, 48, 58, 68, 72, 82, 92, 96, 106, 116, 120, 130, 140, 144, 154, 164, 168, 178, 188, 192, 202, 212, 216, 226, 236, 240, 250, 260, 264, 274, 284, 288, 298, 308, 312, 322, 332, 336, 346, 356, 360, 370, 380, 384, 394, 404, 408, 418, 428, 432, 442, 452, 456, 466, 476, 480, 490, 500, 504, 514, 524, 528, 538, 548, 552, 562, 572, 576, 586, 596, 600, 610, 620, 624, 634, 644, 648, 658, 668, 672, 682, 692, 696, 706, 716, 720, 730, 740 and 744, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity. The LCVR may have an amino acid sequence selected from the group consisting of SEQ ID NO: 58, 68, 72, 82, 92, 96, 130, 140, 144, 226, 236, 240, 250, 260, 264, 322, 332 and 336. In the claimed invention, the LCVR comprises SEQ ID NO:92.

[0017] The antibody or fragment thereof described herein may comprise a HCVR and LCVR (HCVR/LCVR) sequence pair selected from the group consisting of SEQ ID NO: 2/10, 18/20, 22/24, 26/34, 42/44, 46/48, 50/58, 66/68, 70/72, 74/82, 90/92, 94/96, 98/106, 114/116, 118/120, 122/130, 138/140, 142/144, 146/154, 162/164, 166/168, 170/178, 186/188, 190/192, 194/202, 210/212, 214/216, 218/226, 234/236, 238/240, 242/250, 258/260, 262/264, 266/274, 282/284, 286/288, 290/298, 306/308, 310/312, 314/322, 330/332, 334/336, 338/346, 354/356, 358/360, 362/370, 378/380, 382/384, 386/394, 402/404, 406/408, 410/418, 426/428, 430/432, 434/442, 450/452, 454/456, 458/466, 474/476, 478/480, 482/490, 498/500, 502/504, 506/514, 522/524, 526/528, 530/538, 546/548, 550/552, 554/562, 570/572, 574/576, 578/586, 594/596, 598/600, 602/610, 618/620, 622/624, 626/634, 642/644, 646/648, 650/658, 666/668, 670/672, 674/682, 690/692, 694/696, 698/706, 714/716, 718/720, 722/730, 738/740 and 742/744. The HCVR and LCVR may be selected from the amino acid sequence pairs of SEQ ID NO: 50/58,

66/68, 70/72, 74/82, 90/92, 94/96, 122/130, 138/140, 142/144, 218/226, 234/236, 238/240, 242/250, 258/260, 262/264, 314/322, 330/332 and 334/336. In the claimed invention the HCVR/LCVR pair comprises SEQ ID NO:90/92.

[0018] Also described herein is an antibody or antigen-binding fragment of an antibody comprising a heavy chain CDR3 (HCDR3) domain selected from the group consisting of SEQ ID NO:8, 32, 56, 80, 104, 128, 152, 176, 200, 224, 248, 272, 296, 320, 344, 368, 392, 416, 440, 464, 488, 512, 536, 560, 584, 608, 632, 656, 680, 704 and 728, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a light chain CDR3 (LCDR3) domain selected from the group consisting of SEQ ID NO:16, 40, 64, 88, 112, 136, 160, 184, 208, 232, 256, 280, 304, 328, 352, 376, 400, 424, 448, 472, 496, 520, 544, 568, 592, 616, 640, 664, 688, 712 and 736, or substantially similar sequences thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity. The HCDR3/LCDR3 sequence pairs may be SEQ ID NO:56/64, 80/88, 128/136, 224/232, 248/256 or 320/328. The HCDR3/LCDR3 may comprise SEQ ID NO:80/88 or 224/232.

[0019] Also described herein is an antibody or fragment thereof further comprising a heavy chain CDR1 (HCDR1) domain selected from the group consisting of SEQ ID NO:4, 28, 52, 76, 100, 124, 148, 172, 196, 220, 244, 268, 292, 316, 340, 364, 388, 412, 436, 460, 484, 508, 532, 556, 580, 604, 628, 652, 676, 700 and 724, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a heavy chain CDR2 (HCDR2) domain selected from the group consisting of SEQ ID NO:6, 30, 54, 78, 102, 126, 150, 174, 198, 222, 246, 270, 294, 318, 342, 366, 390, 414, 438, 462, 486, 510, 534, 558, 582, 606, 630, 654, 678, 702 and 726, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a light chain CDR1 (LCDR1) domain selected from the group consisting of SEQ ID NO:12, 36, 60, 84, 108, 132, 156, 180, 204, 228, 252, 276, 300, 324, 348, 372, 396, 420, 444, 468, 492, 516, 540, 564, 588, 612, 636, 660, 684, 708 and 732, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a light chain CDR2 (LCDR2) domain selected from the group consisting of SEQ ID NO:14, 38, 62, 86, 110, 134, 158, 182, 206, 230, 254, 278, 302, 326, 350, 374, 398, 422, 446, 470, 494, 518, 542, 566, 590, 614, 638, 662, 686, 710 and 734, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity. The heavy and light chain CDR sequences may be SEQ ID NO:52, 54, 56, 60, 62, 64; 76, 78, 80, 84, 86, 88; 124, 126, 128, 132, 134, 136; 220, 222, 224, 228, 230, 232; 244, 246, 248, 252, 254, 256; and 316, 318, 320, 324, 326, 328. The heavy and light chain CDR sequences may be SEQ ID NO: 76, 78, 80, 84, 86, 88; or 220, 222, 224, 228, 230, 232.

[0020] Also described herein is an antibody or antigen-binding fragment of an antibody which specifically binds hPCSK9, wherein the antibody or fragment comprises heavy and light chain CDR domains contained within heavy and light chain sequence pairs selected from the group consisting of SEQ ID NO: 2/10, 18/20, 22/24, 26/34, 42/44, 46/48, 50/58, 66/68, 70/72, 74/82, 90/92, 94/96, 98/106, 114/116, 118/120, 122/130, 138/140, 142/144, 146/154, 162/164,

166/168, 170/178, 186/188, 190/192, 194/202, 210/212, 214/216, 218/226, 234/236, 238/240, 242/250, 258/260, 262/264, 266/274, 282/284, 286/288, 290/298, 306/308, 310/312, 314/322, 330/332, 334/336, 338/346, 354/356, 358/360, 362/370, 378/380, 382/384, 386/394, 402/404, 406/408, 410/418, 426/428, 430/432, 434/442, 450/452, 454/456, 458/466, 474/476, 478/480, 482/490, 498/500, 502/504, 506/514, 522/524, 526/528, 530/538, 546/548, 550/552, 554/562, 570/572, 574/576, 578/586, 594/596, 598/600, 602/610, 618/620, 622/624, 626/634, 642/644, 646/648, 650/658, 666/668, 670/672, 674/682, 690/692, 694/696, 698/706, 714/716, 718/720, 722/730, 738/740 and 742/744. The CDR sequences contained within HCVR and LCVR may be selected from the amino acid sequence pairs of SEQ ID NO: 50/58, 66/68, 70/72, 74/82, 90/92, 94/96, 122/130, 138/140, 142/144, 218/226, 234/236, 238/240, 242/250, 258/260, 262/264, 314/322, 330/332 and 334/336. In specific embodiments, the CDR sequences contained within HCVR and LCVR selected from the amino acid sequence pairs of SEQ ID NO: 90/92.

[0021] Also described herein is a fully human monoclonal antibody or antigen-binding fragment thereof that specifically binds neutralizes hPCSK9 activity, wherein the antibody or fragment thereof exhibits one or more of the following characteristics:

1. (i) capable of reducing serum total cholesterol at least about 25-35% and sustaining the reduction over at least a 24 day period relative to a predose level, preferably the reduction in serum total cholesterol is at least about 30-40%;
2. (ii) capable of reducing serum LDL cholesterol at least about 65-80% and sustaining the reduction over at least a 24 day period relative to a predose level;
3. (iii) capable of reducing serum triglyceride at least about 25-40% relative to predose level;
4. (iv) does not reduce serum HDL cholesterol or reduces serum HDL cholesterol no more than 5% relative to predose level;
5. (v) binds an epitope comprising amino acid residue 238 of hPCSK9 (SEQ ID NO:755);
6. (vi) exhibits an enhanced binding affinity (K_D) for hPCSK9 at pH 5.5 relative to the K_D at pH 7.4, as measured by plasmon surface resonance, wherein the enhanced affinity is at least about a 20- to 50-fold increase in affinity;
7. (vii) binds human, human GOF mutation D374Y, cynomolgus monkey, rhesus monkey, mouse, rat and hamster PCSK9;
8. (viii) comprises heavy and light chain CDR3 sequences comprising SEQ ID NO:80 and 88;
9. (ix) comprises CDR sequences from SEQ ID NO:90 and 92.

[0022] Also described herein is a fully human monoclonal antibody or antigen-binding fragment thereof that specifically binds and neutralizes hPCSK9 activity, wherein the antibody or fragment thereof exhibits one or more of the following characteristics:

1. (i) capable of reducing serum LDL cholesterol at least about 40-70% and sustaining the reduction over at least a 60 or 90 day period relative to a predose level;

2. (ii) capable of reducing serum triglyceride at least about 25-40% relative to predose level;
3. (iii) does not reduce serum HDL cholesterol or reduces serum HDL cholesterol no more than 5% relative to predose level;
4. (iv) binds an epitope comprising amino acid residue 366 of hPCSK9 (SEQ ID NO:755);
5. (v) does not exhibit an enhanced binding affinity for PCSK9 at an acidic pH relative to a neutral pH, as measured by surface plasmon resonance;
6. (vi) binds human and monkey PCSK9, but does not bind mouse, rat or hamster PCSK9;
7. (vii) comprises heavy and light chain CDR3 sequences comprising SEQ ID NO:224 and 232; and
8. (viii) comprises CDR sequences from SEQ ID NO:218 and 226.

[0023] In a third aspect, the invention provides nucleic acid molecules encoding anti-PCSK9 antibodies or fragments thereof. Recombinant expression vectors carrying the nucleic acids of the invention, and host cells into which such vectors have been introduced, are also encompassed by the invention. Also described are methods of producing the antibodies by culturing the host cells under conditions permitting production of the antibodies, and recovering the antibodies produced.

[0024] Also described herein is an antibody or fragment thereof comprising a HCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 1, 17, 21, 25, 41, 45, 49, 65, 69, 73, 89, 93, 97, 113, 117, 121, 137, 141, 145, 161, 165, 169, 185, 189, 193, 209, 213, 217, 233, 237, 241, 257, 261, 265, 281, 285, 289, 305, 309, 313, 329, 333, 337, 353, 357, 361, 377, 381, 385, 401, 405, 409, 425, 429, 433, 449, 453, 457, 473, 477, 481, 497, 501, 505, 521, 525, 529, 545, 549, 553, 569, 573, 577, 593, 597, 601, 617, 621, 625, 641, 645, 649, 665, 669, 673, 689, 693, 697, 713, 717, 721, 737 and 741, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof. The HCVR may be encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 49, 65, 69, 73, 89, 93, 121, 137, 141, 217, 233, 237, 241, 257, 261, 313, 329 and 333. The HCVR may be encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 89 and 217.

[0025] The antibody or fragment thereof may further comprise a LCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 9, 19, 23, 33, 43, 47, 57, 67, 71, 81, 91, 95, 105, 115, 119, 129, 139, 143, 153, 163, 167, 177, 187, 191, 201, 211, 215, 225, 235, 239, 249, 259, 263, 273, 283, 287, 297, 307, 311, 321, 331, 335, 345, 355, 359, 369, 379, 383, 393, 403, 407, 417, 427, 431, 441, 451, 455, 465, 475, 479, 489, 499, 503, 513, 523, 527, 537, 547, 551, 561, 571, 575, 585, 595, 599, 609, 619, 623, 633, 643, 647, 657, 667, 671, 681, 691, 695, 705, 715, 719, 729, 739 and 743, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof. The LCVR may be encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 57, 67, 71, 81, 91, 95, 129, 139, 143, 225, 235, 239, 249, 259, 263, 321, 331 and

335. The LCVR may be encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 91 and 225.

[0026] Also described herein is an antibody or antigen-binding fragment of an antibody comprising a HCDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 7, 31, 55, 79, 103, 127, 151, 175, 199, 223, 247, 271, 295, 319, 343, 367, 391, 415, 439, 463, 487, 511, 535, 559, 583, 607, 631, 655, 679, 703 and 727, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof; and a LCDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 15, 39, 63, 87, 111, 135, 159, 183, 207, 231, 255, 279, 303, 327, 351, 375, 399, 423, 447, 471, 495, 519, 543, 567, 591, 615, 639, 663, 687, 711 and 735, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof. The HCDR3 and LCDR3 sequences may be encoded by the nucleic acid sequence of SEQ ID NO: 55/63, 79/87, 127/135, 223/231, 247/255 and 319/327, respectively. The HCDR3 and LCDR3 sequence pair may be encoded by the nucleic acid sequence of SEQ ID NO: 79/87 and 223/231.

[0027] The antibody or fragment thereof may further comprise, a HCDR1 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 3, 27, 51, 75, 99, 123, 147, 171, 195, 219, 243, 267, 291, 315, 339, 363, 387, 411, 435, 459, 483, 507, 531, 555, 579, 603, 627, 651, 675, 699 and 723, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof; a HCDR2 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 5, 29, 53, 77, 101, 125, 149, 173, 197, 221, 245, 269, 293, 317, 341, 365, 389, 413, 437, 461, 485, 509, 533, 557, 581, 605, 629, 653, 677, 701 and 725, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof; a LCDR1 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 11, 35, 59, 83, 107, 131, 155, 179, 203, 227, 251, 275, 299, 323, 347, 371, 395, 419, 443, 467, 491, 515, 539, 563, 587, 611, 635, 659, 683, 707 and 731, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof; and a LCDR2 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 13, 37, 61, 85, 109, 133, 157, 181, 205, 229, 253, 277, 301, 325, 349, 373, 397, 421, 445, 469, 493, 517, 541, 565, 589, 613, 637, 661, 685, 709 and 733, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof. The heavy and light chain CDR sequences may be encoded by the nucleic acid sequences of SEQ ID NO: 51, 53, 55, 59, 61, 63; 75, 77, 79, 83, 85, 87; 123, 125, 127, 131, 133, 135; 219, 221, 223, 227, 229, 231; 243, 245, 247, 251, 253, 255; and 315, 317, 319, 323, 325, 327. The heavy and light chain CDR sequences may be encoded by the nucleic acid sequences of SEQ ID NO: 75, 77, 79, 83, 85, 87; and 219, 221, 223, 227, 229, 231.

[0028] Also described herein is an isolated antibody or antigen-binding fragment of an antibody that specifically binds hPCSK9, comprising a HCDR3 and a LCDR3, wherein the HCDR3 comprises an amino acid sequence of the formula $X^1 - X^2 - X^3 - X^4 - X^5 - X^6 - X^7 - X^8 - X^9 - X^{10} - X^{11} - X^{12} - X^{13} - X^{14} - X^{15} - X^{16} - X^{17} - X^{18} - X^{19} - X^{20}$ (SEQ ID NO: 747) wherein X^1 is

Ala, X² is Arg or Lys, X³ is Asp, X⁴ is Ser or Ile, X⁵ is Asn or Val, X⁶ is Leu or Trp, X⁷ is Gly or Met, X⁸ is Asn or Val, X⁹ is Phe or Tyr, X¹⁰ is Asp, X¹¹ is Leu or Met, X¹² is Asp or absent, X¹³ is Tyr or absent, X¹⁴ is Tyr or absent, X¹⁵ is Tyr or absent, X¹⁶ is Tyr or absent, X¹⁷ is Gly or absent, X¹⁸ is Met or absent, X¹⁹ is Asp or absent, and X²⁰ is Val or absent; and the LCDR3 comprises an amino acid sequence of the formula X¹ - X² - X³ - X⁴ - X⁵ - X⁶ - X⁷ - X⁸ - X⁹ (SEQ ID NO:750) wherein X¹ is Gin or Met, X² is Gin, X³ is Tyr or Thr, X⁴ is Tyr or Leu, X⁵ is Thr or Gin, X⁶ is Thr, X⁷ is Pro, X⁸ is Tyr or Leu, and X⁹ is Thr.

[0029] The antibody or fragment thereof may further comprise a HCDR1 sequence of the formula X¹ - X² - X³ - X⁴ - X⁵ - X⁶ - X⁷ - X⁸ (SEQ ID NO:745), wherein X¹ is Gly, X² is Phe, X³ is Thr, X⁴ is Phe, X⁵ is Ser or Asn, X⁶ is Ser or Asn, X⁷ is Tyr or His, and X⁸ is Ala or Trp; a HCDR2 sequence of the formula X¹ - X² - X³ - X⁴ - X⁵ - X⁶ - X⁷ - X⁸ (SEQ ID NO:746), wherein X¹ is Ile, X² is Ser or Asn, X³ is Gly or Gin, X⁴ is Asp or Ser, X⁵ is Gly, X⁶ is Ser or Gly, X⁷ is Thr or Glu, and X⁸ is Thr or Lys; a LCDR1 sequence of the formula X¹ - X² - X³ - X⁴ - X⁵ - X⁶ - X⁷ - X⁸ - X⁹ - X¹⁰ - X¹¹ - X¹² (SEQ ID NO:748) wherein X¹ is Gin, X² is Ser, X³ is Val or Leu, X⁴ is Leu, X⁵ is His or Tyr, X⁶ is Arg or Ser, X⁷ is Ser or Asn, X⁸ is Asn or Gly, X⁹ is Asn, X¹⁰ is Arg or Asn, X¹¹ is Asn or Tyr, and X¹² is Phe or absent; a LCDR2 sequence of the formula X¹ - X² - X³ (SEQ ID NO:749) wherein X¹ is Trp or Leu, X² is Ala or Gly, and X³ is Ser. Fig. 1 shows the sequence alignment of heavy and light chain variable regions for 316P and 300N mAbs.

[0030] Also described herein is a human anti-PCSK9 antibody or antigen-binding fragment of an antibody comprising a heavy chain variable region (HCVR) encoded by nucleotide sequence segments derived from V_H, D_H and J_H germline sequences, and a light chain variable region (LCVR) encoded by nucleotide sequence segments derived from V_K and J_K germline sequences, wherein the germline sequences are (a) V_H gene segment 3-23, D_H gene segment 7-27, J_H gene segment 2, V_K gene segment 4-1 and J_K gene segment 2; or (b) V_H gene segment 3-7, D_H gene segment 2-8, J_H gene segment 6, V_K gene segment 2-28 and J_K gene segment 4.

[0031] In some embodiments, the antibody or antigen-binding fragment thereof binds to a PCSK9 protein of SEQ ID NO:755, wherein the binding of the antibody or fragment thereof to a variant PCSK9 protein is less than 50% of the binding between the antibody or fragment thereof and the PCSK9 protein of SEQ ID NO:755. In specific embodiment, the antibody or fragment thereof binds to the variant PCSK9 protein with a binding affinity (K_D) which is less than about 50%, less than about 60%, less than about 70%, less than about 80%, less than about 90% or less than about 95% compared to the binding to PCSK9 (SEQ ID NO:755).

[0032] In one embodiment, the variant PCSK9 protein comprises at least one mutation at position 238 of SEQ ID NO:755. In a more specific embodiment, the mutation is D238R. In one

embodiment, the antibody or antibody fragment binding affinity for the variant PCSK9 protein is at least 90% less relative to the wildtype protein of SEQ ID NO:755, wherein the variant protein comprises a mutation at residue 238. In one embodiment, the antibody or antibody fragment binding affinity for the variant PCSK9 protein is at least 80% less relative to the wildtype protein of SEQ ID NO:755, wherein the variant protein comprises a mutation at one or more of residue 153, 159, 238 and 343. In a more specific embodiment, the mutation is one of S153R, E159R, D238R and D343R.

[0033] Also described herein, the variant PCSK9 protein comprises at least one mutation at position 366 of SEQ ID NO:755. The mutation may be E366K. The antibody or antibody fragment binding affinity for the variant PCSK9 protein may be at least 95% less relative to the wildtype protein of SEQ ID NO:755, wherein the variant protein comprises a mutation at residue 366. The antibody or antibody fragment binding affinity for the variant PCSK9 protein may be at least 70%, 80% or 90% less relative to the wildtype protein of SEQ ID NO:755, wherein the variant protein comprises a mutation at one or more of residue 147, 366 and/or 380. The mutation may be one of S147F, E366K and V380M.

[0034] The invention encompasses anti-PCSK9 antibodies having a modified glycosylation pattern. In some applications, modification to remove undesirable glycosylation sites may be useful, or e.g., removal of a fucose moiety to increase antibody dependent cellular cytotoxicity (ADCC) function (see Shield et al. (2002) JBC 277:26733). In other applications, modification of galactosylation can be made in order to modify complement dependent cytotoxicity (CDC).

[0035] In a further aspect, the invention features a pharmaceutical composition comprising a recombinant human antibody or fragment thereof as defined in the claims which specifically binds hPCSK9 and a pharmaceutically acceptable carrier. In one embodiment, the invention features a composition which is a combination of an antibody or antigen-binding fragment of an antibody of the invention, and a second therapeutic agent. The second therapeutic agent may be any agent that is advantageously combined with the antibody or fragment thereof of the invention, for example, an agent capable of inducing a cellular depletion of cholesterol synthesis by inhibiting 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A (CoA) reductase, such as, for example, cerivastatin, atorvastatin, simvastatin, pitavastatin, rosuvastatin, fluvastatin, lovastatin, pravastatin, etc.; capable of inhibiting cholesterol uptake and or bile acid reabsorption; capable of increasing lipoprotein catabolism (such as niacin); and/or activators of the LXR transcription factor that plays a role in cholesterol elimination such as 22-hydroxycholesterol.

[0036] Also described herein are methods for inhibiting hPCSK9 activity using the anti-PCSK9 antibody or antigen-binding portion of the antibody of the invention, wherein the therapeutic methods comprise administering a therapeutically effective amount of a pharmaceutical composition comprising an antibody or antigen-binding fragment of an antibody of the invention. The disorder treated is any disease or condition which is improved, ameliorated, inhibited or prevented by removal, inhibition or reduction of PCSK9 activity. Specific populations treatable by the therapeutic methods include subjects indicated for LDL apheresis, subjects

with PCSK9-activating mutations (gain of function mutations, "GOF"), subjects with heterozygous Familial Hypercholesterolemia (heFH); subjects with primary hypercholesterolemia who are statin intolerant or statin uncontrolled; and subjects at risk for developing hypercholesterolemia who may be preventably treated. Other indications include dyslipidemia associated with secondary causes such as Type 2 diabetes mellitus, cholestatic liver diseases (primary biliary cirrhosis), nephrotic syndrome, hypothyroidism, obesity; and the prevention and treatment of atherosclerosis and cardiovascular diseases.

[0037] The anti-hPCSK9 antibody or antibody fragment of the invention may be useful to reduce elevated total cholesterol, non-HDL cholesterol, LDL cholesterol, and/or apolipoprotein B (apolipoprotein B100).

[0038] The antibody or antigen-binding fragment of the invention may be used alone or in combination with a second agent, for example, an HMG-CoA reductase inhibitor and/or other lipid lowering drugs.

[0039] Further embodiments include an antibody or antigen-binding fragment of an antibody as defined above for use to attenuate or inhibit a PCSK9-mediated disease or condition.

[0040] The disclosure encompasses the use of an antibody or antigen-binding fragment of an antibody as defined above in the manufacture of a medicament for use to attenuate or inhibit a PCSK9-mediated disease or condition. In specific embodiments, wherein the PCSK9-mediated disease or condition is hypercholesterolemia, hyperlipidemia, LDL apheresis, heterozygous for Familial Hypercholesterolemia, statin intolerant, statin uncontrolled, risk for developing hypercholesterolemia, dyslipidemia, cholestatic liver disease, nephrotic syndrome, hypothyroidism, obesity, atherosclerosis and cardiovascular diseases.

[0041] Other embodiments will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURE

[0042]

Fig. 1. Sequence comparison tables of heavy chain (A) and light chain (B) variable regions and CDRs of antibodies H1H316P and H1M300N.

Fig. 2. Antibody concentrations in serum over time. 316P 5 mg/kg (□); 300N 5 mg/kg (□); 316P 15 mg/kg (v); 300N 15 mg/kg (●).

Fig. 3. Serum total cholesterol level as a percentage of change over buffer control. Control (T); 316P 5 mg/kg (v); 300N 5 mg/kg (σ); 316P 15 mg/kg (□); 300N 15 mg/kg (Δ).

Fig. 4. Serum LDL cholesterol level as a percentage of change over buffer control. Control (T);

316P 5 mg/kg (v); 300N 5 mg/kg (σ); 316P 15 mg/kg ($\square$); 300N 15 mg/kg (Δ).

Fig. 5. Serum LDL cholesterol level normalized to buffer control. Buffer control (T); 316P 5 mg/kg (v); 300N 5 mg/kg (σ); 316P 15 mg/kg ($\square$); 300N 15 mg/kg (Δ).

Fig. 6. Serum HDL cholesterol level as a percentage of change over buffer control. Control (T); 316P 5 mg/kg (v); 300N 5 mg/kg (σ); 316P 15 mg/kg ($\square$); 300N 15 mg/kg (Δ).

Fig. 7. Serum triglyceride level as a percentage of change over buffer control. Buffer control (T); 316P 5 mg/kg (v); 300N 5 mg/kg (σ); 316P 15 mg/kg ($\square$); 300N 15 mg/kg (Δ).

Fig. 8. Serum LDL cholesterol level expressed as a percentage of change over baseline following a single dose subcutaneous administration. 316P 5 mg/kg (v); 300N 5 mg/kg ($\bullet$).

Fig. 9. Antibody concentrations in serum over time following a single dose subcutaneous administration. 316P 5 mg/kg ($\bullet$); 300N 5 mg/kg (σ).

Fig. 10. Western blot for mouse LDL receptor of total liver homogenates. Samples were taken 24 hours after PBS (lanes 1-3), 5 mg/kg 316P (lanes 4-6), or 5 mg/kg of non-hPCSK9 specific mAb (lanes 7-8) administration and 4 hours after 1.2 mg/kg hPCSK9-mmh (all lanes).

Fig. 11. Effects of 316P on serum LDL cholesterol level in *PCSK9^{hu/hu}* mice. Buffer control (); 316P 1 mg/kg (); 316P 5 mg/kg (); 316P 10 mg/kg ().

Fig. 12. Anti-hPCSK9 mAb serum pharmacokinetic profile in C57BL/6 mice. Single dose of Control I mAb (λ) at 10 mg/kg; 316P (σ) at 10 mg/kg and 300N (v) at 10 mg/kg.

Fig. 13. Anti-hPCSK9 mAb serum pharmacokinetic profile in hPCSK9 heterozygous mice: single dose at 10 mg/kg: Control I mAb (λ); 316P (σ) and 300N (v).

Fig. 14. Effect of 316P on serum LDL cholesterol levels in Syrian Hamster fed a normal diet. Buffer control ($\bullet$); 316P 1 mg/kg (v); 316P 3 mg/kg (σ); 316P 5 mg/kg (τ).

DETAILED DESCRIPTION

[0043] Before the present methods are described, it is to be understood that this invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the

purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0044] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, preferred methods and materials are now described.

Definitions

[0045] The term "human proprotein convertase subtilisin/kexin type 9" or "hPCSK9", as used herein, refers to hPCSK9 having the nucleic acid sequence shown in SEQ ID NO:754 and the amino acid sequence of SEQ ID NO:755, or a biologically active fragment thereof.

[0046] The term "antibody", as used herein, is intended to refer to immunoglobulin molecules comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains interconnected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region ("HCVR" or "VH") and a heavy chain constant region (comprised of domains CH1, CH2 and CH3). Each light chain is comprised of a light chain variable region ("LCVR" or "VL") and a light chain constant region (CL). The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4.

[0047] Substitution of one or more CDR residues or omission of one or more CDRs is also possible. Antibodies have been described in the scientific literature in which one or two CDRs can be dispensed with for binding. Padlan et al. (1995 FASEB J. 9:133-139) analyzed the contact regions between antibodies and their antigens, based on published crystal structures, and concluded that only about one fifth to one third of CDR residues actually contact the antigen. Padlan also found many antibodies in which one or two CDRs had no amino acids in contact with an antigen (see also, Vajdos et al. 2002 J Mol Biol 320:415-428).

[0048] CDR residues not contacting antigen can be identified based on previous studies (for example residues H60-H65 in CDRH2 are often not required), from regions of Kabat CDRs lying outside Chothia CDRs, by molecular modeling and/or empirically. If a CDR or residue(s) thereof is omitted, it is usually substituted with an amino acid occupying the corresponding position in another human antibody sequence or a consensus of such sequences. Positions for substitution within CDRs and amino acids to substitute can also be selected empirically. Empirical substitutions can be conservative or non-conservative substitutions.

[0049] The term "human antibody", as used herein, is intended to include antibodies having

variable and constant regions derived from human germline immunoglobulin sequences. The human mAbs 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. However, the term "human antibody", as used herein, is not intended to include mAbs in which CDR sequences derived from the germline of another mammalian species (e.g., mouse), have been grafted onto human FR sequences.

[0050] The term "specifically binds," or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Specific binding can be characterized by an equilibrium dissociation constant of at least about 1×10^{-6} M or less (e.g., a smaller K_D denotes a tighter binding). Methods for determining whether two molecules specifically bind are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. An isolated antibody that specifically binds hPCSK9 may, however, exhibit cross-reactivity to other antigens such as PCSK9 molecules from other species. Moreover, multi-specific antibodies (e.g., bispecifics) that bind to hPCSK9 and one or more additional antigens are nonetheless considered antibodies that "specifically bind" hPCSK9, as used herein.

[0051] The term "high affinity" antibody refers to those mAbs having a binding affinity to hPCSK9 of at least 10^{-10} M; preferably 10^{-11} M; even more preferably 10^{-12} M, as measured by surface plasmon resonance, e.g., BIACORE™ or solution-affinity ELISA.

[0052] By the term "slow off rate", "Koff" or "kd" is meant an antibody that dissociates from hPCSK9 with a rate constant of $1 \times 10^{-3} \text{ s}^{-1}$ or less, preferably $1 \times 10^{-4} \text{ s}^{-1}$ or less, as determined by surface plasmon resonance, e.g., BIACORE™.

[0053] The term "antigen-binding portion" of an antibody (or simply "antibody fragment"), as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to hPCSK9. An antibody fragment may include a Fab fragment, a $F(ab')_2$ fragment, a Fv fragment, a dAb fragment, a fragment containing a CDR, or an isolated CDR.

[0054] The specific embodiments, antibody or antibody fragments of the invention may be conjugated to a therapeutic moiety ("immunoconjugate"), such as a cytotoxin, a chemotherapeutic drug, an immunosuppressant or a radioisotope.

[0055] An "isolated antibody", as used herein, is intended to refer to an antibody that is substantially free of other mAbs having different antigenic specificities (e.g., an isolated antibody that specifically binds hPCSK9 is substantially free of mAbs that specifically bind antigens other than hPCSK9). An isolated antibody that specifically binds hPCSK9 may, however, have cross-reactivity to other antigens, such as PCSK9 molecules from other species.

[0056] A "neutralizing antibody", as used herein (or an "antibody that neutralizes PCSK9 activity"), is intended to refer to an antibody whose binding to hPCSK9 results in inhibition of at least one biological activity of PCSK9. This inhibition of the biological activity of PCSK9 can be assessed by measuring one or more indicators of PCSK9 biological activity by one or more of several standard *in vitro* or *in vivo* assays known in the art (see examples below).

[0057] The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIACORE™ system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, NJ).

[0058] The term " K_D ", as used herein, is intended to refer to the equilibrium dissociation constant of a particular antibody-antigen interaction.

[0059] The term "epitope" is a region of an antigen that is bound by an antibody. Epitopes may be defined as structural or functional. Functional epitopes are generally a subset of the structural epitopes and have those residues that directly contribute to the affinity of the interaction. Epitopes may also be conformational, that is, composed of non-linear amino acids. In certain embodiments, epitopes may include determinants that are chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl groups, or sulfonyl groups, and, in certain embodiments, may have specific three-dimensional structural characteristics, and/or specific charge characteristics.

[0060] The term "substantial identity" or "substantially identical," when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 90%, and more preferably at least about 95%, 96%, 97%, 98% or 99% of the nucleotide bases, as measured by any well-known algorithm of sequence identity, such as FASTA, BLAST or GAP, as discussed below.

[0061] As applied to polypeptides, the term "substantial similarity" or "substantially similar" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 90% sequence identity, even more preferably at least 95%, 98% or 99% sequence identity. Preferably, residue positions which are not identical differ by conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well known to those of skill in the art. See, e.g., Pearson (1994) *Methods Mol. Biol.* 24: 307-331. Examples of groups of amino acids that have side chains with similar

chemical properties include 1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; 2) aliphatic-hydroxyl side chains: serine and threonine; 3) amide-containing side chains: asparagine and glutamine; 4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; 5) basic side chains: lysine, arginine, and histidine; 6) acidic side chains: aspartate and glutamate, and 7) sulfur-containing side chains: cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet et al. (1992) *Science* 256: 1443-45. A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

[0062] Sequence similarity for polypeptides is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions. For instance, GCG software contains programs such as GAP and BESTFIT which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from different species of organisms or between a wild type protein and a mutein thereof. See, e.g., GCG Version 6.1. Polypeptide sequences also can be compared using FASTA with default or recommended parameters; a program in GCG Version 6.1. FASTA (e.g., FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson (2000) *supra*). Another preferred algorithm when comparing a sequence of the invention to a database containing a large number of sequences from different organisms is the computer program BLAST, especially BLASTP or TBLASTN, using default parameters. See, e.g., Altschul et al. (1990) *J. Mol. Biol.* 215: 403-410 and (1997) *Nucleic Acids Res.* 25:3389-402.

[0063] In specific embodiments, the antibody or antibody fragment for use in the method of the invention may be monospecific, bispecific, or multispecific. Multispecific antibodies may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for epitopes of more than one target polypeptide. An exemplary bi-specific antibody format that can be used in the context of the present invention involves the use of a first immunoglobulin (Ig) CH3 domain and a second Ig CH3 domain, wherein the first and second Ig CH3 domains differ from one another by at least one amino acid, and wherein at least one amino acid difference reduces binding of the bispecific antibody to Protein A as compared to a bi-specific antibody lacking the amino acid difference. In one embodiment, the first Ig CH3 domain binds Protein A and the second Ig CH3 domain contains a mutation that reduces or abolishes Protein A binding such as an H95R modification (by IMGT exon numbering; H435R by EU numbering). The second CH3 may further comprise an Y96F modification (by IMGT; Y436F by EU). Further modifications that may be found within the second CH3 include: D16E, L18M, N44S, K52N, V57M, and V82I (by IMGT; D356E, L358M, N384S, K392N, V397M, and V422I by EU) in the case of IgG1 mAbs; N44S, K52N, and V82I (IMGT; N384S, K392N, and V422I by EU) in the case of IgG2 mAbs; and Q15R, N44S, K52N,

V57M, R69K, E79Q, and V82I (by IMGT; Q355R, N384S, K392N, V397M, R409K, E419Q, and V422I by EU) in the case of IgG4 mAbs. Variations on the bi-specific antibody format described above are contemplated within the scope of the present invention.

[0064] By the phrase "therapeutically effective amount" is meant an amount that produces the desired effect for which it is administered. The exact amount will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, for example, Lloyd (1999) *The Art, Science and Technology of Pharmaceutical Compounding*).

Preparation of Human Antibodies

[0065] Methods for generating human antibodies in transgenic mice are known (see for example, US 6,596,541, Regeneron Pharmaceuticals, VELOCIMMUNE™). The VELOCIMMUNE™ technology involves generation of a transgenic mouse having a genome comprising human heavy and light chain variable regions operably linked to endogenous mouse constant region loci such that the mouse produces an antibody comprising a human variable region and a mouse constant region in response to antigenic stimulation. The DNA encoding the variable regions of the heavy and light chains of the antibody are isolated and operably linked to DNA encoding the human heavy and light chain constant regions. The DNA is then expressed in a cell capable of expressing the fully human antibody. In specific embodiment, the cell is a CHO cell.

[0066] Antibodies may be therapeutically useful in blocking a ligand-receptor interaction or inhibiting receptor component interaction, rather than by killing cells through fixation of complement and participation in complement-dependent cytotoxicity (CDC), or killing cells through antibody-dependent cell-mediated cytotoxicity (ADCC). The constant region of an antibody is thus important in the ability of an antibody to fix complement and mediate cell-dependent cytotoxicity. Thus, the isotype of an antibody may be selected on the basis of whether it is desirable for the antibody to mediate cytotoxicity.

[0067] Human antibodies can exist in two forms that are associated with hinge heterogeneity. In one form, an antibody molecule comprises a stable four-chain construct of approximately 150-160 kDa in which the dimers are held together by an interchain heavy chain disulfide bond. In a second form, the dimers are not linked via inter-chain disulfide bonds and a molecule of about 75-80 kDa is formed composed of a covalently coupled light and heavy chain (half-antibody). These forms have been extremely difficult to separate, even after affinity purification.

[0068] The frequency of appearance of the second form in various intact IgG isotypes is due to, but not limited to, structural differences associated with the hinge region isotype of the antibody. A single amino acid substitution in the hinge region of the human IgG4 hinge can significantly reduce the appearance of the second form (Angal et al. (1993) *Molecular*

Immunology 30:105) to levels typically observed using a human IgG1 hinge. The instant invention encompasses antibodies having one or more mutations in the hinge, CH2 or CH3 region which may be desirable, for example, in production, to improve the yield of the desired antibody form.

[0069] Generally, a VELOCIMMUNE™ mouse is challenged with the antigen of interest, and lymphatic cells (such as B-cells) are recovered from the mice that express antibodies. The lymphatic cells may be fused with a myeloma cell line to prepare immortal hybridoma cell lines, and such hybridoma cell lines are screened and selected to identify hybridoma cell lines that produce antibodies specific to the antigen of interest. DNA encoding the variable regions of the heavy chain and light chain may be isolated and linked to desirable isotypic constant regions of the heavy chain and light chain. Such an antibody protein may be produced in a cell, such as a CHO cell. Alternatively, DNA encoding the antigen-specific chimeric antibodies or the variable domains of the light and heavy chains may be isolated directly from antigen-specific lymphocytes.

[0070] Initially, high affinity chimeric antibodies are isolated having a human variable region and a mouse constant region. As described below, the antibodies are characterized and selected for desirable characteristics, including affinity, selectivity, epitope, etc. The mouse constant regions are replaced with a desired human constant region to generate the fully human antibody of the invention, for example wild-type or modified IgG1 or IgG4 (for example, SEQ ID NO:751, 752, 753). While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

Epitope Mapping and Related Technologies

[0071] To screen for antibodies that bind to a particular epitope (e.g., those which block binding of IgE to its high affinity receptor), a routine cross-blocking assay such as that described Antibodies, Harlow and Lane (Cold Spring Harbor Press, Cold Spring Harb., NY) can be performed. Other methods include alanine scanning mutants, peptide blots (Reineke (2004) Methods Mol Biol 248:443-63), or peptide cleavage analysis. In addition, methods such as epitope excision, epitope extraction and chemical modification of antigens can be employed (Tomer (2000) Protein Science 9: 487-496).

[0072] The term "epitope" refers to a site on an antigen to which B and/or T cells respond. B-cell epitopes can be formed both from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents, whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation.

[0073] Modification-Assisted Profiling (MAP), also known as Antigen Structure-based Antibody Profiling (ASAP) is a method that categorizes large numbers of monoclonal antibodies (mAbs) directed against the same antigen according to the similarities of the binding profile of each antibody to chemically or enzymatically modified antigen surfaces (US 2004/0101920). Each category may reflect a unique epitope either distinctly different from or partially overlapping with epitope represented by another category. This technology allows rapid filtering of genetically identical mAbs, such that characterization can be focused on genetically distinct mAbs. When applied to hybridoma screening, MAP may facilitate identification of rare hybridoma clones that produce mAbs having the desired characteristics. MAP may be used to sort the anti-PCSK9 mAbs of the invention into groups of mAbs binding different epitopes.

[0074] Described herein are anti-hPCSK9 antibodies or antigen-binding fragments which bind an epitope within the catalytic domain, which is about 153 to 425 of SEQ ID NO:755); more specifically, an epitope from about 153 to about 250 or from about 250 to about 425; more specifically, the antibody or antibody fragment binds an epitope within the fragment from about 153 to about 208, from about 200 to about 260, from about 250 to about 300, from about 275 to about 325, from about 300 to about 360, from about 350 to about 400, and/or from about 375 to about 425.

[0075] The anti-hPCSK9 antibody or antigen-binding fragment of an antibody described herein may bind an epitope within the propeptide domain (residues 31 to 152 of SEQ ID NO:755); more specifically, an epitope from about residue 31 to about residue 90 or from about residue 90 to about residue 152; more specifically, the antibody or antibody fragment binds an epitope within the fragment from about residue 31 to about residue 60, from about residue 60 to about residue 90, from about residue 85 to about residue 110, from about residue 100 to about residue 130, from about residue 125 to about residue 150, from about residue 135 to about residue 152, and/or from about residue 140 to about residue 152.

[0076] The anti-hPCSK9 antibody or antigen-binding fragment of an antibody may bind an epitope within the C-terminal domain, (residues 426 to 692 of SEQ ID NO:755); more specifically, an epitope from about residue 426 to about residue 570 or from about residue 570 to about residue 692; more specifically, the antibody or antibody fragment may bind an epitope within the fragment from about residue 450 to about residue 500, from about residue 500 to about residue 550, from about residue 550 to about residue 600, and/or from about residue 600 to about residue 692.

[0077] The antibody or antibody fragment may bind an epitope which includes more than one of the enumerated epitopes within the catalytic, propeptide or C-terminal domain, and/or within two or three different domains (for example, epitopes within the catalytic and C-terminal domains, or within the propeptide and catalytic domains, or within the propeptide, catalytic and C-terminal domains).

[0078] In some embodiments, the antibody or antigen-binding fragment binds an epitope on hPCSK9 comprising amino acid residue 238 of hPCSK9 (SEQ ID NO:755). Experimental

results (Table 27) show that when D238 was mutated, the K_D of mAb 316P exhibited >400-fold reduction in binding affinity ($\sim 1 \times 10^{-9}$ M to $\sim 410 \times 10^{-9}$ M) and $T_{1/2}$ decreased >30-fold (from -37 to -1 min). In a specific embodiment, the mutation was D238R. In specific embodiments, the antibody or antigen-binding fragment of the invention binds an epitope of hPCSK9 comprising two or more of amino acid residues at positions 153, 159, 238 and 343.

[0079] As shown below, a mutation in amino acid residue 153, 159 or 343 resulted in about a 5- to 10-fold decrease in affinity or similar shortening in $T_{1/2}$. In specific embodiments, the mutation was S153R, E159R and/or D343R.

[0080] Antibody or antigen-binding fragments described herein may bind an epitope on hPCSK9 comprising amino acid residue 366 of hPCSK9 (SEQ ID NO:755). Experimental results (Table 27) show that when E366 was mutated, the affinity of mAb 300N exhibited about 50-fold decrease (-0.7×10^{-9} M to -36×10^{-9} M) and a similar shortening in $T_{1/2}$ (from -120 to -2 min). In a specific embodiment, the mutation is E366K.

[0081] Described herein are anti-PCSK9 antibodies that bind to the same epitope as any of the specific exemplary antibodies described herein. Also described herein are anti-PCSK9 antibodies that compete for binding to PCSK9 or a PCSK9 fragment with any of the specific exemplary antibodies described herein.

[0082] One can easily determine whether an antibody binds to the same epitope as, or competes for binding with, a reference anti-PCSK9 antibody by using routine methods known in the art. For example, to determine if a test antibody binds to the same epitope as a reference anti-PCSK9 antibody of the invention, the reference antibody is allowed to bind to a PCSK9 protein or peptide under saturating conditions. Next, the ability of a test antibody to bind to the PCSK9 molecule is assessed. If the test antibody is able to bind to PCSK9 following saturation binding with the reference anti-PCSK9 antibody, it can be concluded that the test antibody binds to a different epitope than the reference anti-PCSK9 antibody. On the other hand, if the test antibody is not able to bind to the PCSK9 molecule following saturation binding with the reference anti-PCSK9 antibody, then the test antibody may bind to the same epitope as the epitope bound by the reference anti-PCSK9 antibody of the invention.

[0083] To determine if an antibody competes for binding with a reference anti-PCSK9 antibody, the above-described binding methodology is performed in two orientations: In a first orientation, the reference antibody is allowed to bind to a PCSK9 molecule under saturating conditions followed by assessment of binding of the test antibody to the PCSK9 molecule. In a second orientation, the test antibody is allowed to bind to a PCSK9 molecule under saturating conditions followed by assessment of binding of the reference antibody to the PCSK9 molecule. If, in both orientations, only the first (saturating) antibody is capable of binding to the PCSK9 molecule, then it is concluded that the test antibody and the reference antibody compete for binding to PCSK9. As will be appreciated by a person of ordinary skill in the art, an antibody that competes for binding with a reference antibody may not necessarily bind to the

identical epitope as the reference antibody, but may sterically block binding of the reference antibody by binding an overlapping or adjacent epitope.

[0084] Two antibodies bind to the same or overlapping epitope if each competitively inhibits (blocks) binding of the other to the antigen. That is, a 1-, 5-, 10-, 20- or 100-fold excess of one antibody inhibits binding of the other by at least 50% but preferably 75%, 90% or even 99% as measured in a competitive binding assay (see, e.g., Junghans et al., Cancer Res. 1990 50: 1495-1502). Alternatively, two antibodies have the same epitope if essentially all amino acid mutations in the antigen that reduce or eliminate binding of one antibody reduce or eliminate binding of the other. Two antibodies have overlapping epitopes if some amino acid mutations that reduce or eliminate binding of one antibody reduce or eliminate binding of the other.

[0085] Additional routine experimentation (e.g., peptide mutation and binding analyses) can then be carried out to confirm whether the observed lack of binding of the test antibody is in fact due to binding to the same epitope as the reference antibody or if steric blocking (or another phenomenon) is responsible for the lack of observed binding. Experiments of this sort can be performed using ELISA, RIA, surface plasmon resonance, flow cytometry or any other quantitative or qualitative antibody-binding assay available in the art.

[0086] In a specific embodiment, the invention comprises an anti-PCSK9 antibody or antigen binding fragment of an antibody that binds an PCSK9 protein of SEQ ID NO:755, wherein the binding between the antibody or fragment thereof to PCSK9 and a variant PCSK9 protein is less than 50% of the binding between the antibody or fragment and the PCSK9 protein of SEQ ID NO:755. In one specific embodiment, the variant PCSK9 protein comprises at least one mutation of a residue at a position selected from the group consisting of 153, 159, 238 and 343. In a more specific embodiment, the at least one mutation is S153R, E159R, D238R and D343R. The variant PCSK9 protein may comprise at least one mutation of a residue at a position selected from the group consisting of 366. The variant PCSK9 protein may comprise at least one mutation of a residue at a position selected from the group consisting of 147, 366 and 380. The mutation may be S147F, E366K and/or V380M.

Immunoconjugates

[0087] The invention encompasses a human anti-PCSK9 monoclonal antibody conjugated to a therapeutic moiety ("immunoconjugate"), such as a cytotoxin, a chemotherapeutic drug, an immunosuppressant or a radioisotope. Cytotoxin agents include any agent that is detrimental to cells. Examples of suitable cytotoxin agents and chemotherapeutic agents for forming immunoconjugates are known in the art, see for example, WO 05/103081.

Bispecifics

[0088] The antibodies of the present invention may be monospecific, bispecific, or multispecific. Multispecific mAbs may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for more than one target polypeptide. See, e.g., Tutt et al. (1991) J. Immunol. 147:60-69. The human anti-PCSK9 mAbs can be linked to or co-expressed with another functional molecule, e.g., another peptide or protein. For example, an antibody or fragment thereof can be functionally linked (e.g., by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody or antibody fragment, to produce a bispecific or a multispecific antibody with a second binding specificity.

[0089] An exemplary bi-specific antibody format that can be used in the context of the present invention involves the use of a first immunoglobulin (Ig) CH3 domain and a second Ig CH3 domain, wherein the first and second Ig CH3 domains differ from one another by at least one amino acid, and wherein at least one amino acid difference reduces binding of the bispecific antibody to Protein A as compared to a bi-specific antibody lacking the amino acid difference. In one embodiment, the first Ig CH3 domain binds Protein A and the second Ig CH3 domain contains a mutation that reduces or abolishes Protein A binding such as an H95R modification (by IMGT exon numbering; H435R by EU numbering). The second CH3 may further comprise a Y96F modification (by IMGT; Y436F by EU). Further modifications that may be found within the second CH3 include: D16E, L18M, N44S, K52N, V57M, and V82I (by IMGT; D356E, L358M, N384S, K392N, V397M, and V422I by EU) in the case of IgG1 antibodies; N44S, K52N, and V82I (IMGT; N384S, K392N, and V422I by EU) in the case of IgG2 antibodies; and Q15R, N44S, K52N, V57M, R69K, E79Q, and V82I (by IMGT; Q355R, N384S, K392N, V397M, R409K, E419Q, and V422I by EU) in the case of IgG4 antibodies. Variations on the bi-specific antibody format described above are contemplated within the scope of the present invention.

Bioequivalents

[0090] The anti-PCSK9 antibodies and antibody fragments of the present invention encompass proteins having amino acid sequences that vary from those of the described mAbs, but that retain the ability to bind human PCSK9. Such variant mAbs and antibody fragments comprise one or more additions, deletions, or substitutions of amino acids when compared to parent sequence, but exhibit biological activity that is essentially equivalent to that of the described mAbs. Likewise, the anti-PCSK9 antibody-encoding DNA sequences of the present invention encompass sequences that comprise one or more additions, deletions, or substitutions of nucleotides when compared to the disclosed sequence, but that encode an anti-PCSK9 antibody or antibody fragment that is essentially bioequivalent to an anti-PCSK9 antibody or antibody fragment of the invention. Examples of such variant amino acid and DNA sequences are discussed above.

[0091] Two antigen-binding proteins, or antibodies, are considered bioequivalent if, for example, they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar

dose under similar experimental conditions, either single dose or multiple dose. Some antibodies will be considered equivalents or pharmaceutical alternatives if they are equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on, e.g., chronic use, and are considered medically insignificant for the particular drug product studied. In one embodiment, two antigen-binding proteins are bioequivalent if there are no clinically meaningful differences in their safety, purity, and potency.

[0092] In one embodiment, two antigen-binding proteins are bioequivalent if a patient can be switched one or more times between the reference product and the biological product without an expected increase in the risk of adverse effects, including a clinically significant change in immunogenicity, or diminished effectiveness, as compared to continued therapy without such switching.

[0093] In one embodiment, two antigen-binding proteins are bioequivalent if they both act by a common mechanism or mechanisms of action for the condition or conditions of use, to the extent that such mechanisms are known.

[0094] Bioequivalence may be demonstrated by *in vivo* and *in vitro* methods. Bioequivalence measures include, e.g., (a) an *in vivo* test in humans or other mammals, in which the concentration of the antibody or its metabolites is measured in blood, plasma, serum, or other biological fluid as a function of time; (b) an *in vitro* test that has been correlated with and is reasonably predictive of human *in vivo* bioavailability data; (c) an *in vivo* test in humans or other mammals in which the appropriate acute pharmacological effect of the antibody (or its target) is measured as a function of time; and (d) in a well-controlled clinical trial that establishes safety, efficacy, or bioavailability or bioequivalence of an antibody.

[0095] Bioequivalent variants of anti-PCSK9 antibodies of the invention may be constructed by, for example, making various substitutions of residues or sequences or deleting terminal or internal residues or sequences not needed for biological activity. For example, cysteine residues not essential for biological activity can be deleted or replaced with other amino acids to prevent formation of unnecessary or incorrect intramolecular disulfide bridges upon renaturation.

Treatment Population

[0096] The invention relates to therapeutic methods for treating a human patient in need of a composition of the invention. While modifications in lifestyle and conventional drug treatment are often successful in reducing cholesterol levels, not all patients are able to achieve the recommended target cholesterol levels with such approaches. Various conditions, such as familial hypercholesterolemia (FH), appear to be resistant to lowering of LDL-C levels in spite of aggressive use of conventional therapy. Homozygous and heterozygous familial

hypercholesterolemia (hoFH, heFH) is a condition associated with premature atherosclerotic vascular disease. However, patients diagnosed with hoFH are largely unresponsive to conventional drug therapy and have limited treatment options. Specifically, treatment with statins, which reduce LDL-C by inhibiting cholesterol synthesis and upregulating the hepatic LDL receptor, may have little effect in patients whose LDL receptors are non-existent or defective. A mean LDL-C reduction of only less than about 20% has been recently reported in patients with genotype-confirmed hoFH treated with the maximal dose of statins. The addition of ezetimibe 10 mg/day to this regimen resulted in a total reduction of LDL-C levels of 27%, which is still far from optimal. Likewise, many patients are statin non-responsive, poorly controlled with statin therapy, or cannot tolerate statin therapy; in general, these patients are unable to achieve cholesterol control with alternative treatments. There is a large unmet medical need for new treatments that can address the short-comings of current treatment options.

[0097] Specific populations treatable by the therapeutic methods include patients indicated for LDL apheresis, subjects with PCSK9-activating (GOF) mutations, heterozygous Familial Hypercholesterolemia (heFH); subjects with primary hypercholesterolemia who are statin intolerant or statin uncontrolled; and subjects at risk for developing hypercholesterolemia who may be preventably treated.

Therapeutic Administration and Formulations

[0098] The invention provides therapeutic compositions comprising the anti-PCSK9 antibodies or antigen-binding fragments thereof of the present invention. The administration of therapeutic compositions in accordance with the invention will be administered with suitable carriers, excipients, and other agents that are incorporated into formulations to provide improved transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTIN™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. See also Powell et al. "Compendium of excipients for parenteral formulations" PDA (1998) J Pharm Sci Technol 52:238-311.

[0099] The dose may vary depending upon the age and the size of a subject to be administered, target disease, conditions, route of administration, and the like. When the antibody of the present invention is used for treating various conditions and diseases associated with PCSK9, including hypercholesterolemia, disorders associated with LDL and apolipoprotein B, and lipid metabolism disorders, and the like, in an adult patient, it is advantageous to intravenously administer the antibody of the present invention normally at a

single dose of about 0.01 to about 20 mg/kg body weight, more preferably about 0.02 to about 7, about 0.03 to about 5, or about 0.05 to about 3 mg/kg body weight. Depending on the severity of the condition, the frequency and the duration of the treatment can be adjusted.

[0100] Various delivery systems are known and can be used to administer the pharmaceutical composition of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the mutant viruses, receptor mediated endocytosis (see, e.g., Wu et al. (1987) J. Biol. Chem. 262:4429-4432). Methods of introduction include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The composition may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local.

[0101] The pharmaceutical composition can be also delivered in a vesicle, in particular a liposome (see Langer (1990) Science 249:1527-1533; Treat et al. (1989) in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez Berestein and Fidler (eds.), Liss, New York, pp. 353-365; Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*).

[0102] In certain situations, the pharmaceutical composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Sefton (1987) CRC Crit. Ref. Biomed. Eng. 14:201). In another embodiment, polymeric materials can be used; see, Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974). In yet another embodiment, a controlled release system can be placed in proximity of the composition's target, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138, 1984).

[0103] The injectable preparations may include dosage forms for intravenous, subcutaneous, intracutaneous and intramuscular injections, drip infusions, etc. These injectable preparations may be prepared by methods publicly known. For example, the injectable preparations may be prepared, e.g., by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there are employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared is preferably filled in an appropriate ampoule. A pharmaceutical composition of the present invention can be delivered subcutaneously or intravenously with a standard needle and syringe. In addition, with respect to subcutaneous delivery, a pen delivery device readily has applications in delivering a pharmaceutical composition of the present invention. Such a pen

delivery device can be reusable or disposable. A reusable pen delivery device generally utilizes a replaceable cartridge that contains a pharmaceutical composition. Once all of the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can readily be discarded and replaced with a new cartridge that contains the pharmaceutical composition. The pen delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes prefilled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the composition, the entire device is discarded.

[0104] Numerous reusable pen and autoinjection delivery devices have applications in the subcutaneous delivery of a pharmaceutical composition of the present invention. Examples include, but certainly are not limited to AUTOPEN[™] (Owen Mumford, Inc., Woodstock, UK), DISETRONIC[™] pen (Disetronic Medical Systems, Burghdorf, Switzerland), HUMALOG MIX 75/25[™] pen, HUMALOG[™] pen, HUMALIN 70/30[™] pen (Eli Lilly and Co., Indianapolis, IN), NOVOPEN[™] I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIOR[™] (Novo Nordisk, Copenhagen, Denmark), BD[™] pen (Becton Dickinson, Franklin Lakes, NJ), OPTIPEN[™], OPTIPEN PRO[™], OPTIPEN STARLET[™], and OPTICLIK[™] (sanofi-aventis, Frankfurt, Germany), to name only a few. Examples of disposable pen delivery devices having applications in subcutaneous delivery of a pharmaceutical composition of the present invention include, but certainly are not limited to the SOLOSTAR[™] pen (sanofi-aventis), the FLEXPEN[™] (Novo Nordisk), and the KWIKPEN[™] (Eli Lilly).

[0105] Advantageously, the pharmaceutical compositions for oral or parenteral use described above are prepared into dosage forms in a unit dose suited to fit a dose of the active ingredients. Such dosage forms in a unit dose include, for example, tablets, pills, capsules, injections (ampoules), suppositories, etc. The amount of the aforesaid antibody contained is generally about 5 to about 500 mg per dosage form in a unit dose; especially in the form of injection, it is preferred that the aforesaid antibody is contained in about 5 to about 100 mg and in about 10 to about 250 mg for the other dosage forms.

[0106] The invention relates to therapeutic methods in which the antibody or antibody fragment of the invention is useful to treat hypercholesterolemia associated with a variety of conditions involving hPCSK9. The anti-PCSK9 antibodies or antibody fragments of the invention are particularly useful for the treatment of hypercholesterolemia and the like. Combination therapies may include the anti-PCSK9 antibody of the invention with, for example, one or more of any agent that (1) induces a cellular depletion of cholesterol synthesis by inhibiting 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A (CoA) reductase, such as cerivastatin, atorvastatin, simvastatin, pitavastatin, rosuvastatin, fluvastatin, lovastatin, pravastatin; (2) inhibits cholesterol uptake and or bile acid re-absorption; (3) increase lipoprotein catabolism (such as niacin); and activators of the LXR transcription factor that plays a role in cholesterol elimination such as 22-hydroxycholesterol or fixed combinations such as ezetimibe plus simvastatin; a statin with a bile resin (e.g., cholestyramine, colestipol,

colesevelam), a fixed combination of niacin plus a statin (e.g., niacin with lovastatin); or with other lipid lowering agents such as omega-3-fatty acid ethyl esters (for example, omacor).

EXAMPLES

[0107] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used but some experimental errors and deviations should be accounted for. Unless indicated otherwise, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1: Generation of Human Antibodies to Human PCSK9

[0108] VELOCIMMUNE™ mice were immunized with human PCSK9, and the antibody immune response monitored by antigen-specific immunoassay using serum obtained from these mice. Anti-hPCSK9 expressing B cells were harvested from the spleens of immunized mice shown to have elevated anti-hPCSK9 antibody titers were fused with mouse myeloma cells to form hybridomas. The hybridomas were screened and selected to identify cell lines expressing hPCSK9-specific antibodies using assays as described below. The assays identified several cell lines that produced chimeric anti-hPCSK9 antibodies designated as H1M300, H1M504, H1M505, H1M500, H1M497, H1M498, H1M494, H1M309, H1M312, H1M499, H1M493, H1M496, H1M503, H1M502, H1M508, H 1 M495 and H1M492.

[0109] Human PCSK9-specific antibodies were also isolated directly from antigen-immunized B cells without fusion to myeloma cells, as described in U.S. 2007/0280945A1. Heavy and light chain variable regions were cloned to generate fully human anti-hPCSK9 antibodies designated as H1H313, H1H314, H1H315, H1H316, H1H317, H1H318, H1H320, H1H321 and H1H334. Stable recombinant antibody-expressing CHO cell lines expressing these antibodies were established.

Example 2. Gene Utilization Analysis

[0110] To analyze the structure of the mAbs produced, the nucleic acids encoding antibody variable regions were cloned and sequenced. The predicted amino acid sequences of the variable regions were confirmed by N-terminal amino acid sequencing. From the nucleic acid sequence and predicted amino acid sequence of the mAbs, gene usage was identified for each antibody chain.

Table 1

Antibody	Heavy Chain Variable Region			Light Chain Variable Region	
	VH	D	JH	VK	JK
H1H313	3-13	1-26	4	3-15	3
H1H314	3-33	3-3	4	1-5	2
H1H315	3-33	3-3	4	4-1	1
H1H316	3-23	7-27	2	4-1	2
H1H317	3-13	1-26	4	1-6	1
H1H318	4-59	3-10	6	1-9	1
H1H320	1-18	2-2	6	2-30	1
H1H321	2-5	1-7	6	2-28	4
H1H334	2-5	6-6	6	2-28	4
H1M300	3-7	2-8	6	2-28	4
H1M504	3-30	2-8	6	2-28	4
H1M505	3-30	2-8	6	2-28	4
H1M500	2-5	5-5	6	2-28	4
H1M497	1-18	2-2	6	2-30	2
H1M498	3-21	2-2	4	1-5	2
H1M494	3-11	5-12	6	3-20	4
H1M309	3-21	6-13	4	1-5	1
H1M312	3-21	6-13	4	1-5	1
H1M499	3-21	6-13	4	1-5	1
H1M493	3-21	6-13	4	1-5	1
H1M496	3-13	6-19	4	3-15	3
H1M503	1-18	2-2	6	2-28	1
H1M502	3-13	6-13	4	3-15	3
H1M508	3-13	6-13	4	3-15	3
H1M495	3-9	4-17	6	1-9	3
H1M492	3-23	3-3	2	3-20	4

Example 3. Antigen Binding Affinity Determination

[0111] Equilibrium dissociation constants (K_D) for hPCSK9 binding to mAbs generated by hybridoma cell lines described above were determined by surface kinetics in a real-time biosensor surface plasmon resonance assay (BIAcore™ T100). Each antibody was captured

at a flow rate of 4 $\mu\text{l}/\text{min}$ for 90 sec on a goat anti-mouse IgG polyclonal antibody surface created through direct chemical coupling to a BIACORE™ chip to form a captured antibody surface. hPCSK9-myc-myc-his (hPCSK9-mmh) at a concentration of 50 nM or 12.5 nM was injected over the captured antibody surfaces at a flowrate of 50 $\mu\text{l}/\text{min}$ for 300 sec, and antigen-antibody dissociation was monitored for 15 min at either 25°C or 37°C (K_D = pM; $T_{1/2}$ = min).

Table 2

Antibody	25°C		37°C	
	K_D	$T_{1/2}$	K_D	$T_{1/2}$
H1M300	399	170	1510	32
H1M309	29.9	7461	537	326
H1M312	0.225	15568	432	392
H1M493	46.5	4921	522	341
H1M494	870	114	2350	30
H1M495	440	222	7500	19
H1M496	254	257	421	118
H1M497	20.1	5801	480	290
H1M498	6400	30	7500	14
H1M499	106	2253	582	316
H1M500	1400	91	6010	15
H1M502	78.3	958	411	151
H1M503	510	118	1880	30
H1M504	3470	35	11200	6
H1M505	2740	42	9200	6
H1M508	138	572	442	139
H1M510	1070	68	3960	10

[0112] Equilibrium dissociation constants (K_D) for hPCSK9 binding to mAbs generated via direct isolation of splenocytes were determined by surface kinetics in a real-time biosensor surface plasmon resonance assay (BIACORE™ T100). Each selected antibody was captured at a flowrate of 2 $\mu\text{l}/\text{min}$ for 6 min on a goat anti-human IgG polyclonal antibody surface created through direct chemical coupling to a BIACORE™ chip to form a captured antibody surface. Human PCSK9-mmh at a concentration of 50 nM or 12.5 nM was injected over the captured antibody surface at a flowrate of 70 $\mu\text{l}/\text{min}$ for 5 min, and antigen-antibody dissociation was monitored for 15 min at either 25°C or 37°C (K_D = pM; $T_{1/2}$ = min).

Table 3

Antibody	25°C		37°C	
	K _D	T _{1/2}	K _D	T _{1/2}
H1H313P	244	230	780	60
H1H314P	3990	65	3560	43
H1H315P	129	151	413	35
H1H316P	377	42	1080	11
H1H317P	30400	137	18600	70
H1H318P	972	59	1690	28
H1H320P	771	28	1930	8
H1H321P	865	106	3360	23
H1H334P	3750	46	15900	8

[0113] Dissociation rate (kd) of selected mAbs for tagged rhesus monkey (*Macaca mulata*) PCSK9 (mmPCSK9; SEQ ID NO:756) (mmPCSK9-mmh) at 25°C was determined as described above.

Table 4

Antibody	kd (1/s)	T _{1/2} (min)
H1H313P	2.92×10^{-5}	396
H1H318P	3.69×10^{-3}	3
H1H334P	8.06×10^{-3}	1
H1H315P	2.29×10^{-4}	51
H1H316P	2.29×10^{-4}	51
H1H320P	3.17×10^{-4}	36
H1M300	1.52×10^{-4}	76
H1M504	5.04×10^{-4}	23
H1M497	6.60×10^{-5}	175
H1M503	8.73×10^{-5}	132
H1M496	4.45×10^{-5}	260

Example 4. Effect of pH on Antigen Binding Affinity

[0114] The effects of pH on antigen binding affinity for CHO cell-produced fully human anti-hPCSK9 mAbs was assessed as described above. The mAbs tested are fully human versions

of H1H316P ("316P") (HCVR/LCVR SEQ ID NO: 90/92; CDR sequences SEQ ID NO: 76/78/80 and 84/86/88) and H1M300N ("300N") (HCVR/LCVR SEQ ID NO: 218/226; CDR sequences SEQ ID NO:220/222/224 and 228/230/232). hPCSK9-mmh was captured on an anti-myc mAb surface either at a high density (about 35 to 45 resonance units) (RU) or at a low density (about 5 to 14 RU). Each antibody, at 50 nM in HBST (pH 7.4 or pH 5.5) was injected over the captured hPCSK9 surface at a flow rate of 100 μ l/min for 1.5 min at 25°C and antigen-antibody dissociation was monitored for 10 min. Control I: anti-hPCSK9 mAb SEQ ID NO:79/101 (WO 2008/063382) (K_D = pM; $T_{1/2}$ = min).

Table 5

Antibody	High hPCSK9 Density Surface				Low hPCSK9 Density Surface			
	pH 7.4		pH 5.5		pH 7.4		pH 5.5	
	K_D	$T_{1/2}$	K_D	$T_{1/2}$	K_D	$T_{1/2}$	K_D	$T_{1/2}$
316P	191	74	144	83	339	45	188	58
300N	65	507	1180	26	310	119	1380	13
Control I	20000	29	ND	ND	ND	ND	ND	ND

[0115] The antigen binding properties of 316P and 300N at pH 7.4 or pH 5.5 were determined by a modified BIACORE™ assay as described above. Briefly, mAbs were immobilized onto BIACORE™ CM5 sensor chips via amine coupling. Varying concentrations of myc-myc-his tagged hPCSK9, mouse PCSK9 (mPCSK9, SEQ ID NO:757), hPCSK9 with a gain of function (GOF) point mutation of D374Y (hPCSK9(D374Y)), cynomolgus monkey (*Macaca fascicularis*) PCSK9 (mfPCSK9, SEQ ID NO:761) (mfPCSK9), rat (*Rattus norvegicus*) PCSK9 (rPCSK9, SEQ ID NO:763) and his-tagged Syrian golden hamster (*Mesocricetus auratus*) PCSK9 (maPCSK9, SEQ ID NO:762) (maPCSK9), ranging from 11 to 100 nM, were injected over the antibody surface at the flow rate of 100 μ l/min for 1.5 min and antigen-antibody dissociation was monitored in real time for 5 min at either 25°C (Table 6) or 37°C (Table 7). Control II: anti-hPCSK9 mAbs SEQ ID NO:67/12 (WO 2009/026558). NB: no binding was observed under the experimental condition (K_D = pM; $T_{1/2}$ = min).

Table 6. pH Effect at 25°C

Antigen	316P			
	pH 7.4		pH 5.5	
	K_D	$T_{1/2}$	K_D	$T_{1/2}$
hPCSK9-mmh	1260	36	22	39
mPCSK9-mmh	4460	10	63	11
hPCSK9(D347Y)-mmh	2490	15	166	13
mfPCSK9-mmh	1420	42	8	23
maPCSK9-h	8350	8	87	8
rPCSK9-mmh	24100	2	349	5

Antigen	316P			
	pH 7.4		pH 5.5	
	K _D	T _{1/2}	K _D	T _{1/2}
	300N			
hPCSK9-mmh	1100	76	3100	5
mPCSK9-mmh	NB	NB	NB	NB
hPCSK9(D347Y)-mmh	1310	46	9030	3
mfPCSK9-mmh	2170	31	38500	.4
maPCSK9-h	NB	NB	NB	NB
rPCSK9-mmh	NB	NB	NB	NB
	Control I			
hPCSK9-mmh	33100	14	1740	31
mPCSK9-mmh	NB	NB	NB	NB
hPCSK9(D347Y)-mmh	71000	11	7320	30
mfPCSK9-mmh	362000	0.2	67200	3
maPCSK9-h	NB	NB	NB	NB
rPCSK9-mmh	NB	NB	NB	NB
	Control II			
hPCSK9-mmh	143	266	2	212
mPCSK9-mmh	3500	11	33	12
hPCSK9(D347Y)-mmh	191	155	49	56
mfPCSK9-mmh	102	262	12	63
maPCSK9-h	6500	3	ND	ND
rPCSK9-mmh	22400	2	106	5

Table 7. pH Effect at 37°C

Antigen	316P			
	pH 7.4		pH 5.5	
	K _D	T _{1/2}	K _D	T _{1/2}
hPCSK9-mmh	4000	9	142	11
mPCSK9-mmh	12200	3	13600	3
hPCSK9(D347Y)-mmh	6660	4	1560	5
mfPCSK9-mmh	3770	11	44	5
maPCSK9-h	21700	2	ND	ND
rPCSK9-mmh	55100	2	399	1
	300N			

Antigen	316P			
	pH 7.4		pH 5.5	
	K _D	T _{1/2}	K _D	T _{1/2}
hPCSK9-mmh	2470	20	11900	1
mPCSK9-mmh	NB	NB	NB	NB
hPCSK9(D347Y)-mmh	2610	14	28000	1
mfPCSK9-mmh	2170	31	38500	0.4
maPCSK9-h	NB	NB	NB	NB
rPCSK9-mmh	NB	NB	NB	NB
	Control I			
hPCSK9-mmh	45900	0.1	11300	3
mPCSK9-mmh	NB	NB	NB	NB
hPCSK9(D347Y)-mmh	169000	0.4	27000	3
mfPCSK9-mmh	500000	0.6	5360	0.3
maPCSK9-h	NB	NB	NB	NB
rPCSK9-mmh	NB	NB	NB	NB
	Control II			
hPCSK9-mmh	284	87	20	44
mPCSK9-mmh	8680	3	89	3
hPCSK9(D347Y)-mmh	251	57	483	26
mfPCSK9-mmh	180	127	214	65
maPCSK9-h	8830	0.5	ND	ND
rPCSK9-mmh	30200	1	233	1

Example 5. Anti-hPCSK9 mAbs Binding to hPCSK9 with Point Mutation D374Y

[0116] The binding affinity of selected anti-hPCSK9 mAbs to hPCSK9 with a gain of function (GOF) point mutation of D374Y (hPCSK9(D374Y)-mmh) was determined as described above. Each antibody was captured at a flowrate of 40 μ l/min for 8-30 sec on a goat anti-human IgG polyclonal antibody surface created through direct chemical coupling to a BIACORE™ chip to form a captured antibody surface. hPCSK9(D374Y)-mmh at varying concentrations of 1.78 nM to 100 nM was injected over the captured antibody surface at a flowrate of 50 μ l/min for 5 min, and the dissociation of hPCSK9(D374Y)-mmh and antibody was monitored for 15 min at 25°C. Control III: anti-hPCSK9 mAbs SEQ ID NO:49/23 (WO 2009/026558) (K_D = pM; T_{1/2} = min).

Table 8

Antibody	K_D	$T_{1/2}$
316P	1780	14
300N	1060	49
Control I	23600	25
Control II	66	216
Control III	1020	126

Example 6. Binding Specificity of Anti-hPCSK9 mAbs

[0117] 316P, 300N, and Control I anti-hPCSK9 mAbs were captured on an amine-coupled anti-hFc CM5 chip on BIACORE™2000. Tagged (myc-myc-his) human PCSK9, human PCSK1 (hPCSK1) (SEQ ID NO:759), human PCSK7 (hPCSK7) (SEQ ID NO:760), or mouse PCSK9 were injected (100 nM) over the captured mAb surface and allowed to bind at 25°C for 5 min. Changes in RU were recorded. Results: 300N and Control I bound only to hPCSK9, and 316P bound both hPCSK9 and mPCSK9.

[0118] The binding specificities of anti-hPCSK9 mAbs were determined by ELISA. Briefly, anti-hPCSK9 antibody was coated on a 96-well plate. Human PCSK9-mmh, mPCSK9-mmh, maPCSK9-h, hPCSK1-mmh, or hPCSK7-mmh, at 1.2 nM, were added to antibody-coated plates and incubated at RT for 1 hr. Plate-bound PCSK protein was then detected by HRP-conjugated anti-His antibody. Results show that 316P binds human, mouse, and hamster PCSK9, whereas 300N and Control I only bound hPCSK9. None of the anti-hPCSK9 mAbs exhibited significant binding to hPCSK1 or hPCSK7.

Example 7. Cross-Reactivity of Anti-hPCSK9 mAbs

[0119] Cross-reactivity of anti-hPCSK9 mAbs with mmPCSK9, mfPCSK9, mPCSK9, maPCSK9, or rPCSK9 was determined using BIACORE™3000. Anti-hPCSK9 mAbs were captured on an anti-hFc surface created through direct chemical coupling to a BIACORE™ chip. Purified tagged hPCSK9, hPCSK9(D374Y), mmPCSK9, mfPCSK9, mPCSK9, maPCSK9, or rPCSK9, each at 1.56 nM to 50 nM, was injected over the antibody surface at either 25°C or 37°C. Binding between 316P, 300N, Control I, Control II, or Control III and the PCSK9 proteins was determined (K_D = pM; $T_{1/2}$ = min).

Table 9. 316P mAb

Antigen	37°C		25°C	
	K_D	$T_{1/2}$	K_D	$T_{1/2}$
hPCSK9-mmh	1800	9	580	36

Antigen	37°C		25°C	
	K _D	T _{1/2}	K _D	T _{1/2}
hPCSK9(D374Y)-mmh	4200	4	1690	15
mmPCSK9-mmh	1800	21	550	92
mfPCSK9-mmh	1800	11	520	60
mPCSK9-mmh	4700	3	2300	11
maPCSK9-h	19000	1	6810	5
rPCSK9-mmh	37500	1	14500	2

Table 10. 300N mAb

Antigen	37°C		25°C	
	K _D	T _{1/2}	K _D	T _{1/2}
hPCSK9-mmh	2400	22	740	110
hPCSK9(D374Y)-mmh	2200	14	900	65
mmPCSK9-mmh	1600	26	610	79
mfPCSK9-mmh	3800	11	1500	45
mPCSK9-mmh	NB	NB	NB	NB
maPCSK9-h	NB	NB	NB	NB
rPCSK9-mmh	NB	NB	NB	NB

Table 11. Control I mAb

Antigen	37°C		25°C	
	K _D	T _{1/2}	K _D	T _{1/2}
hPCSK9-mmh	226000	2	27500	16
hPCSK9(D374Y)-mmh	ND	ND	23600	25
mmPCSK9-mmh	420000	3	291000	2
mfPCSK9-mmh	14300	10	24900	14
mPCSK9-mmh	NB	NB	NB	NB
maPCSK9-h	NB	NB	NB	NB
rPCSK9-mmh	NB	NB	NB	NB

Table 12. Control II mAb

Antigen	37°C		25°C	
	K _D	T _{1/2}	K _D	T _{1/2}
hPCSK9-mmh	91	162	61	372
hPCSK9(D374Y)-mmh	93	90	66	216
mfPCSK9-mmh	33	252	26	546
mPCSK9-mmh	4700	3	2300	11

Antigen	37°C		25°C	
	K _D	T _{1/2}	K _D	T _{1/2}
maPCSK9-h	60800	0.4	25000	2
rPCSK9-mmh	14100	1	6900	3

Table 13. Control III mAb

Antigen	37°C		25°C	
	K _D	T _{1/2}	K _D	T _{1/2}
hPCSK9-mmh	380	378	490	450
hPCSK9(D374Y)-mmh	130	660	1000	126
mfPCSK9-mmh	110	750	340	396
mPCSK9-mmh	33500	1	10900	4
maPCSK9-h	780	107	2100	67
rPCSK9-mmh	NB	NB	33200	2

Example 8. Inhibition of Binding Between hPCSK9 and hLDLR Domains

[0120] The ability of selected anti-hPCSK9 mAbs to block hPCSK9 binding to human LDLR full length extracellular domain (hLDLR-ecto SEQ ID NO:758), hLDLR EGF-A domain (amino acids 313-355 of SEQ ID NO:758), or hLDLR EGF-AB domains (amino acids of 314-393 of SEQ ID NO:758) (LDLR Genbank number NM_000527) was evaluated using BIACORE™ 3000. Briefly, hLDLR-ecto, EGF-A-hFc, or EGF-AB-hFc protein was amine-coupled on a CM5 chip to create a receptor or receptor fragment surface. Selected anti-hPCSK9 mAbs, at 62.5 nM (2.5 fold excess over antigen), were premixed with 25 nM of hPCSK9-mmh, followed by 40 min incubation at 25°C to allow antibody-antigen binding to reach equilibrium to form equilibrated solutions. The equilibrated solutions were injected over the receptor or receptor fragment surfaces at 2 µl/min for 40 min at 25°C. Changes in RU due to the binding of the anti-hPCSK9 mAbs to hLDLR-ecto, EGF-A-hFc, or EGF-AB-hFc were determined. Results show that H1H316P and H1M300N blocked the binding of hPCSK9-mmh to hLDLR-ecto, hLDLR EGF-A domain, and hLDLR EGF-AB domains; H1H320P blocked the binding of hPCSK9-mmh to hLDLR-ecto and hLDLR EGF-A domain; and H1 H321 P blocked the binding of hPCSK9-mmh to hLDLR EGF-A domain.

[0121] The ability of the mAbs to block hPCSK9 binding to hLDLR-ecto, hLDLR EGF-A domain, or hLDLR EGF-AB domains was also evaluated with an ELISA-based immunoassay. Briefly, hLDLR-ecto, hLDLR EGF-A-hFc or hLDLR EGF-AB-hFc, each at 2 µg/ml, was coated on a 96-well plate in PBS buffer overnight at 4°C, and nonspecific binding sites blocked with BSA. This plate was used to measure free hPCSK9-mmh in a PCSK9-mmh solution pre-equilibrated with varying concentrations of anti-hPCSK9 mAbs. A constant amount of hPCSK9-mmh (500 pM)

was pre-mixed with varied amounts of antibody, ranging from 0 to -50 nM in serial dilutions, followed by 1 hr incubation at room temperature (RT) to allow antibody-antigen binding to reach equilibrium. The equilibrated sample solutions were transferred to receptor or receptor fragment coated plates. After 1 hour of binding, the plates were washed and bound hPCSK9-mmh detected using HRP conjugated anti-myc antibody. IC₅₀ values (in pM) were determined as the amount of antibody required to achieve 50% reduction of hPCSK9-mmh bound to the plate-coated receptor or receptor fragment. The results show that specific mAbs functionally block PCSK9 from binding the three receptors at both neutral pH (7.2) and acidic pH (5.5).

Table 14

Ab	pH 7.2			pH 5.5		
	Plate Coating Surface					
	hLDLR-ecto	EGF-A	EGF-AB	hLDLR-ecto	EGF-A	EGF-AB
316P	<125	<125	<125	<125	<125	<125
300N	144	146	<125	1492	538	447
Control I	-	>100,000	>100,000	-	>100,000	>100,000
Control II	288	510	274	411	528	508
Control III	303	635	391	742	787	1073

[0122] The ability of the mAbs to block hPCSK9 GOF mutant hPCSK9(D374Y)-mmh binding to hLDLR EGF-A domain or hLDLR EGF-AB domain (IC₅₀ values in pM) was also evaluated with the ELISA-based immunoassay described above using a constant amount of 0.05 nM hPCSK9(D374Y)-mmh.

Table 15

	pH 7.2		pH 5.5	
	Plate Coating Surface			
	EGF-A	EGF-AB	EGF-A	EGF-AB
316P	203	139	1123	1139
300N	135	142	3463	3935
Control I	>100,000	>100,000	>100,000	>100,000
Control II	72	57	129	118
Control III	537	427	803	692

[0123] The ability of the mAbs to block either mmPCSK9 or mPCSK9 binding to hLDLR-ecto domain, hLDLR EGF-A domain, or hLDLR EGF-AB domain (IC₅₀ values in pM) was evaluated at neutral pH (7.2) with the ELISA-based immunoassay describe above using a constant amount of 1 nM of mmh-tagged mmPCSK9 or 1 nM of mPCSK9.

Table 16

	1 nM mmPCSK9-mmh			1 nM mPCSK9-mmh	
	hLDLR-ecto	EGF-A	EGF-AB	EGF-A	EGF-AB
316P	<250	<250	<250	<250	<250
300N	255	256	290	>33000	>33000

[0124] The ability of the mAbs to block hPCSK9, mmPCSK9, rPCSK9, maPCSK9, mfPCSK9, or mPCSK9 binding to hLDLR EGF-A domain (IC₅₀ values in pM) was evaluated at neutral pH (7.2) (Table 17) or acidic pH (5.5, Table 18) with the ELISA-based immunoassay described above using a constant amount of 0.5 nM of hPCSK9-mmh, 1 nM of mmPCSK9-mmh, 1 nM of rPCSK9-mmh, 1 nM of maPCSK9-h, 0.3 nM of mfPCSK9-mmh, or 1 nM of mPCSK9-mmh.

Table 17

	hPCSK9	mmPCSK9	rPCSK9	maPCSK9	mfPCSK9	mPCSK9
316P	<125	<250	2662	349	75	305
300N	182	460	>100000	>100000	473	>100000
Control I	-	>100000	>100000	>100000	>100000	>100000
Control II	146	83	2572	2038	361	855
Control III	249	293	>100000	245	572	>100000

Table 18

	hPCSK9	mmPCSK9	rPCSK9	maPCSK9	mPCSK9
316P	<125	<250	42880	1299	991
300N	223	3704	>100000	>100000	>100000
Control I	>10000	>100000	>100000	>100000	>100000
Control II	154	<250	11640	8339	2826
Control III	390	376	>100000	414	>100000

[0125] The ability of 316P and Control I to block hPCSK9 binding to hLDLR was also determined. Briefly, either recombinant hLDLR or hLDLR-EGFA-mFc was immobilized onto BIACORE™ CM5 chips via amine coupling. An antigen-antibody mixture of 100 nM hPCSK9-mmh and 316P, Control I mAb, or a non-hPCSK9 specific mAb (each at 250 nM) was incubated at RT for 1 hr, and then injected over the hLDLR or hLDLR-EGFA surface at the flow rate of 10 µl/min for 15 min at 25°C. Changes in RU due to the binding between the free hPCSK9-mmh in the mixture to either hLDLR or hLDLR-EGFA were recorded. The binding of hPCSK9 to either hLDLR or hLDLR-EGFA was completely blocked by 316P and 300N but not by Control I mAb.

Example 9. Epitope Mapping

[0126] In order to determine epitope-binding specificity, three chimeric PCSK9-mmh proteins were generated in which specific human PCSK9 domains were substituted with mouse PCSK9 domains. Chimeric protein #1 consists of a mouse PCSK9 pro-domain (amino acid residues 1-155 of SEQ ID NO:757) followed by a human PCSK9 catalytic domain (residues 153-425 of SEQ ID NO:755) and a mouse PCSK9 C-terminal domain (residues 429-694 SEQ ID NO:757) (mPro-hCat-mC-term-mmh). Chimeric protein #2 consists of a human PCSK9 pro-domain (residues 1-152 of SEQ ID NO:755) followed by a mouse PCSK9 catalytic domain (residues 156-428 of SEQ ID NO:757) and a mouse PCSK9 C-terminal (hPro-mCat-mC-term-mmh). Chimeric protein #3 consists of mouse PCSK9 pro-domain and a mouse PCSK9 catalytic domain followed by a human PCSK9 C-terminal domain (residues 426-692 of SEQ ID NO:755) (mPro-mCat-hC-term-mmh). In addition, hPCSK9 with a point mutation of D374Y (hPCSK9(D374Y)-mmh) was generated.

[0127] Binding specificity of mAbs to test proteins hPCSK9-mmh, mouse PCSK9-mmh, chimeric proteins #1, #2, and #3, and hPCSK9(D374Y)-mmh were tested as follows: the mAbs were coated on a 96-well plate overnight at 4°C, then each test protein (1.2 nM) was added to the plate. After 1 hr binding at RT, the plate was washed and bound test protein detected using HRP-conjugated anti-myc polyclonal antibody (++ = OD>1.0; + = OD 0.4 - 1.0; - = OD < 0.4).

Table 19

Antibody	hPCSK9	mPCSK9	Chimeric Protein			hPCSK9(D374Y)
			#1	#2	#3	
H1M300	++	-	++	+	-	++
H1M309	++	-	-	-	++	++
H1M312	++	-	-	-	++	++
H1M492	++	-	-	-	-	+
H1M493	++	-	-	-	++	++
H1M494	++	-	-	+	++	++
H1M495	++	-	-	-	++	++
H1M496	++	-	-	-	++	++
H1M497	++	-	-	++	+	++
H1M498	++	-	-	-	+	++
H1M499	++	-	-	-	++	++
H1M500	++	-	++	-	-	++
H1M502	++	-	-	-	++	++
H1M503	++	-	-	++	-	++
H1M504	++	-	-	-	-	+
H1M505	++	-	++	+	-	++
H1M508	++	-	-	-	++	++
H1H318P	++	-	++	-	-	++

Antibody	hPCSK9	mPCSK9	Chimeric Protein			hPCSK9(D374Y)
			#1	#2	#3	
H1H334P	++	-	++	-	-	++
H1H316P	++	++	++	++	++	++
H1H320P	++	-	-	++	-	++
Control I	++	-	-	-	++	++

[0128] Binding specificity of 316P, 300N and control anti-hPCSK9 mAbs to hPCSK9-mmh, mPCSK9-mmh, mmPCSK9-mmh, mfPCSK9-mmh, rPCSK9-mmh, chimeric proteins #1, #2, and #3, and hPCSK9(D374Y)-mmh were tested as described above except that the protein concentration is 1.7 nM (- = OD < 0.7; + = OD 0.7 - 1.5; ++ = OD > 1.5).

Table 20

	316P	300N	Control I	Control II	Control III
hPCSK9-mmh	++	++	++	++	++
mPCSK9-mmh	++	-	-	++	++
mmPCSK9-mmh	++	++	++	++	++
mfPCSK9-mmh	++	++	++	++	++
rPCSK9-mmh	++	-	-	++	+
Chimeric Protein #1	++	++	-	++	++
Chimeric Protein #2	++	++	-	++	++
Chimeric Protein #3	++	+	++	++	++
hPCSK9(D374Y)	++	++	++	++	++

[0129] Similar results for selected mAbs were obtained by BIACORE™ binding assay. Briefly, 316P, 300N, or Control I mAb was captured on an amine-coupled anti-hFc CM5 chip and 100 nM of each protein injected over the mAb-captured surface. Changes in RU due to the binding of each protein to the mAb surface was determined.

Table 21

Antibody	hPCSK9	mPCSK9	Chimeric Protein		
			#1	#2	#3
316P	500	505	529	451	467
300N	320	13	243	76	10
Control I	65	7	4	3	69

[0130] To further assess the binding specificity of 316P, which cross-reacts with mPCSK9-

mmh, a cross-competition ELISA assay was developed to determine binding domain specificity. Briefly, mAbs specific for chimeric protein #1, #2, or #3, were first coated on a 96-well plate overnight at 1 µg/ml. Human PCSK9-mmh (2 µg/ml) was then added to each well followed by 1 hr incubation at RT. 316P (1 µg/ml) was added and incubated for another hour at RT. Plate-bound 316P was detected using HRP-conjugated anti-hFc polyclonal antibody. Although 316P binding to hPCSK9-mmh was not affected by the presence of mAbs specific for either chimeric protein #2 or chimeric protein #3, 316P binding to hPCSK9-mmh was greatly reduced by the presence of antibody specific for chimeric protein #1.

Example 10. BIACORE™-Based Antigen Binding Profile Assessment

[0131] Antibody binding profiles were also established for 316P, 300N, Control I, II, and III mAbs using BIACORE™ 1000. Briefly, hPCSK9-mmh was captured on an anti-myc surface. A first anti-hPCSK9 mAb (50 µg/ml) was injected over the PCSK9-bound surface for 10 min, at a flow rate of 10 µl/min at 25°C. A second anti-hPCSK9 mAb (50 µg/ml) was then injected over the first mAb-bound surface for 10 min, at a flow rate of 10 µl/min at 25°C. Ability of the first mAb to block binding of the second mAb was measured and is expressed as percent inhibition.

Table 22

First mAb	Second mAb				
	316P	300N	Control I	Control II	Control III
316P	100	101	27	99	101
300N	77	100	12	82	-2
Controll	6	12	100	6	9
Control II	91	102	-6	100	3
Control III	73	10	-12	1	100

Example 11. Increase of LDL Uptake by Anti-hPCSK9 Antibodies

[0132] The ability of anti-hPCSK9 mAbs to increase LDL uptake *in vitro* was determined using a human hepatocellular liver carcinoma cell line (HepG2). HepG2 cells were seeded onto 96-well plates at 9×10^4 cells/well in DMEM complete media and incubated at 37°C, 5% CO₂, for 6 hr to form HepG2 monolayers. Human PCSK9-mmh, at 50 nM in lipoprotein deficient medium (LPDS), and a test mAb was added in various concentrations from 500 nM to 0.98 nM in LPDS medium. Data are expressed as IC₅₀ values for each experiment (IC₅₀ = antibody concentration at which increases LDL uptake by 50%). In addition, the experiment also showed that both 316P and 300N were able to completely reverse the inhibitory effect of hPCSK9 on LDL uptake, while Control I mAb or H1M508 anti-hPCSK9 mAb reversed the inhibitory effect by about 50%.

Table 23

Antibody	IC ₅₀ (nM)
316P	21.30
300N	22.12
Control I	>250
H1M508	>250

[0133] The ability of anti-hPCSK9 mAbs to reverse the inhibitory effect on LDL uptake by PCSK9 protein from different mammalian species was also tested in a HepG2 cell line as described above. Briefly, HepG2 cells were incubated overnight with serial dilutions of antibody in LPDS medium (beginning with 500 nM) and 50 nM of hPCSK9-mmh, mfPCSK9-mmh, mPCSK9-mmh, rPCSK9-mmh, or maPCSK9-h. HepG2 cells were also incubated overnight with serial dilutions of antibody in LPDS (beginning with 50 nM) and 1 nM hPCSK9(D374Y). As shown in Table 24, while 316P was able to completely reverse the inhibitory effect on LDL by all PCSK9 proteins tested, 300N was only able to reverse the inhibitory effect on LDL uptake by hPCSK9, hPCSK9(D374Y), and mfPCSK9. Values are expressed as nM IC₅₀.

Table 24

	316P	300N	Control I	Control II	Control III
hPCSK9-mmh	14.1	12.6	>500	13.4	12.4
hPCSK9(D374Y)-mmh	2.1	1.1	>50	0.7	0.6
mfPCSK9-mmh	14.7	13.4	>500	14.2	13.6
mPCSK9-mmh	21.2	>500	>500	19	>500
rPCSK9-mmh	27.7	>500	>500	21.9	>500
maPCSK9-h	14.4	>500	>500	29.5	12.7

Example 12. Neutralization of Biological Effect of hPCSK9 *In Vivo*

[0134] To assess the biological effect of neutralizing PCSK9, hPCSK9 was over-expressed in C57BL/6 mice by hydrodynamic delivery (HDD) of DNA constructs encoding full-length hPCSK9-mmh. 4 mice (C57BL/6) were injected with empty vector/saline (control), and 16 mice were injected with a 50 µg hPCSK9-mmh-DNA/saline mixture in the tail vein equal to 10% of their body weight. At day 7 after HDD, delivery of hPCSK9 resulted in a 1.6-fold elevation of total cholesterol, 3.4-fold elevation in LDL-cholesterol (LDL-C) and a 1.9-fold elevation in non-HDL cholesterol (relative to control). Serum hPCSK9 levels on day 7 were all greater than 1 µg/ml, as assessed by quantitative ELISA.

[0135] Administration of H1M300N on day 6 after HDD to 3 experimental groups (1, 5 or 10

mg/kg) (n=4 per group) via intraperitoneal (i.p.) injection resulted in a significant attenuation of serum cholesterol levels. At 18 hours after administration, total cholesterol was reduced by 9.8%, 26.3% and 26.8%, LDL-C was reduced by 5.1%, 52.3% and 56.7%, and non-HDL cholesterol was reduced by 7.4%, 33.8% and 28.6% in the 1, 5 or 10 mg/kg H1M300N treated groups, respectively.

Example 13. Pharmacokinetic and Serum Chemistry Study in Monkeys

[0136] A pharmacokinetic (PK) study was conducted in naïve male cynomolgus monkeys (*Macaca fascicularis*) with a body weight range between 5-7 kg and aged between 3-5 years.

[0137] *Group assignments.* The monkeys were assigned into 5 treatment groups: Treatment Group 1 (n=3) received control buffer (10 mM sodium phosphate, pH 6, 1 ml/kg); Treatment Group 2 (n=3) received 1 ml/kg of 316P (5 mg/ml); Treatment Group 3 (n=3) received 1 ml/kg 300N (5 mg/ml); Treatment Group 4 (n=3) received 1 ml/kg 316P (15 mg/ml); and Treatment Group 5 (n=3) received 1 ml/kg 300N (15 mg/ml). All treatments were administered by IV bolus followed by a 1 ml saline flush. Total dose volume (ml) was calculated on the most recent body weight (each animal was weighed twice during acclimation and once weekly throughout the study). A single dose of test mAb or buffer control was administered on Day 1.

[0138] *Animal care.* Animals were housed in a temperature- and humidity-monitored environment. The targeted range of temperature and relative humidity was between 18-29°C and 30-70%, respectively. An automatic lighting system provided a 12-hour diurnal cycle. The dark cycle could be interrupted for study- or facility-related activities. The animals were individually housed in cages that comply with the Animal Welfare Act and recommendations set forth in The Guide for the Care and Use of Laboratory Animals (National Research Council 1996).

[0139] *Diet and Feeding.* Animals were fed twice per day according to SNBL USA SOPs. Animals were fasted when required by specific procedures (e.g., prior to blood draws for serum chemistry, urine collection, or when procedures involving sedation are performed). The diet was routinely analyzed for contaminants and found to be within manufacturer's specifications.

[0140] *Experimental Design.* An appropriate number of animals were selected from SNBL USA stock. Animals were examined for health by veterinary staff, and had undergone serum chemistry, hematology, and coagulation screening. 16 males, confirmed healthy, were assigned to the study. 15 males were assigned to specific study groups and the remaining animal was available as a spare. A stratified randomization scheme incorporating serum cholesterol level (based on the average of two draws in acclimation) was used to assign animals to study groups.

[0141] *Acclimation Period.* Previously quarantined animals were acclimated to the study room for a minimum of 14 days prior to initiation of dosing. Acclimation phase data was collected

from all animals, including the spare. All animals were assessed for behavioral abnormalities that could affect performance on study. The spare animal was returned to stock after day 1.

[0142] *Blood collection.* Blood was collected by venipuncture from a peripheral vein from restrained, conscious animals. Whenever possible, blood was collected via a single draw and then divided appropriately.

[0143] *PK Study.* Blood samples (1.5 ml) were collected at pre-dose, 2 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, 8 hr, 12 hr, 24 hr, and subsequently once every 24 hr in serum separator tubes (SST). Specimen storage serum is transferred to 2 vials and stored at -60°C or below.

[0144] Serum samples were analyzed using an optimized ELISA (enzyme-linked immunosorbant assay) procedure. Briefly, a microtiter plate was first coated with hPCSK9-mmh. Test mAb 316P or 300N was then captured on the hPCSK9-mmh plate. The captured 316P or 300N was detected using a biotinylated mouse anti-hIgG4 followed by binding to NeutrAvidin-HRP. Varying concentrations of 316P or 300N, ranging from 100 to 1.56 ng/ml, were used as standards. One percent monkey serum (assay matrix) in the absence of 316P or 300N was used as the zero (0 ng/ml) standard. The results, shown in Fig. 2, indicate a dose-dependent increase in serum 316P and 300N levels. PK parameters were analyzed using WinNonlin software (Noncompartmental analysis, Model 201- IV bolus administration).

Table 25

PK Parameter	316P		300N	
	5 mg/kg	15 mg/kg	5 mg/kg	15 mg/kg
T _{max} (h)	0.428	0.105	4.02	0.428
C _{max} (µg/ml)	184	527	226	1223
T _{1/2} (h)	83	184	215	366

[0145] *Serum Chemistry.* Blood samples were collected at pre-dose, 12 hr, 48 hr, and subsequently once every 48 hr, for clinical chemistry analysis, in particular lipid profiles (i.e. cholesterol, LDL-C, HDL-C, triglycerides). With the exception of the 12 hr post-dose sample, all animals were subject to an overnight fast prior to sample collection. The sample volume was approximately 1 ml. Chemistry parameters were determined using an Olympus automated analyzer. Parameters measured (Xybion code): Albumin (ALB); Alkaline Phosphatase (ALP); Alanine Aminotransferase (ALT); Aspartate Transaminase (AST); Total Bilirubin (TBIL); Calcium (Ca); Total Cholesterol (TCho); Creatine Kinase (CK); Creatinine (CRN); Gamma Glutamyltransaminase (GGT); Glucose (GLU); Inorganic Phosphorus (IP); Total Protein (TP); Triglyceride (TRIG); Blood Urea Nitrogen (BUN); Globulin (GLOB); Albumin/Globulin Ratio (A/G); Chloride (Cl); Potassium (K); Sodium (Na); LDL and HDL cholesterol. Residual serum was stored at -20°C or below and disposed of no sooner than one week after analysis.

[0146] Results from samples through Day 105 post-dose time point are shown in Figs. 3-7.

There was a reduction in total cholesterol and LDL-C in animals receiving 316P and 300N, regardless of dose, within 24 hours of the first dose. Serum total cholesterol reduced rapidly and robustly (~ 35%, Fig. 3). A robust decrease of ~80% was seen in LDL-C (Figs. 4-5) by day 6. In animals that received a 15 mg/kg dose of 300N, the reduction in both total cholesterol (~10-15% reduction) and LDL-C (~40% reduction) continued to at least day 80 of the study. In addition, HDL-C was elevated in animals that received 316P at 15 mg/kg (Fig. 6). Animals that received a higher dose (15 mg/kg) of either 316P or 300N also showed a reduction in triglycerides during the course of study (Fig. 7). 316P exhibited maximal suppression of LDL-C levels of up to 80% relative to baseline. The length of this suppression was dose-dependent with at least 60% suppression (relative to baseline LDL-C levels) lasting approximately 18 days (5 mg/kg dose) and approximately 45 days (15 mg/kg dose). 300N exhibits a distinct pharmacodynamic profile from 316P. LDL-C suppression by 300N was sustained for a much longer period of time at comparable doses (50% LDL-C suppression for 28 days following a 5 mg/kg dose and 50% LDL-C suppression for approximately 90 days following a 15 mg/kg dose). There was little or no measurable change in liver function as determined by ALT and AST measurements. All animals receiving an anti-PCSK9 antibody in the study exhibited a rapid suppression of LDL-C and total cholesterol.

[0147] A similar LDL-C lowering effect of 316P and 300N was also observed in cynomolgous monkeys that received a single subcutaneous (SC) administration of either 5 mg/kg 316P or 5 mg/kg 300N (Fig. 8). Both 316P and 300N dramatically suppressed the LDL-C levels and maintained an LDL-C lowering effect for approximately 15 and 30 days, respectively (Fig. 8). The pharmacodynamic effect (approximately 40% LDL-C suppression) appears to approximately correlate with functional antibody levels in monkey serum (Fig. 9). As antibody levels decrease below 10 µg/ml, LDL-C suppression appeared to diminish as well. In addition, 300N demonstrated a substantially longer circulating half-life than 316P and hence a longer observed LDL-C suppression.

Table 26

PK Parameter	316P	300N
T _{max} (h)	60	84
C _{max} (µg/ml)	46	63
T _{1/2} (h)	64	286

Example 14. Attenuation of LDL Receptor Degradation by Anti-hPCSK9 Antibodies

[0148] To assess the biological effect of PCSK9 on hepatic LDL receptor levels and subsequent effects on serum LDL-C levels, hPCSK9 was administered to mice expressing hPCSK9 but not mPCSK9 (*PCSK9^{hu/hu}* mice) by intravenous injection. Specifically, *PCSK9^{hu/hu}* mice were injected with PBS (control), or 1.2 mg/kg hPCSK9-mmh via the tail vein. Six hours after delivery of hPCSK9, a 1.4-fold elevation (relative to baseline level) in total cholesterol and

a 2.3-fold elevation in LDL-C) in serum were observed. Analysis of hepatic LDL receptor levels in a separate cohort (n=3) of animals 4 hours after hPCSK9 administration revealed a significant reduction in detectable LDL receptor in liver homogenates.

[0149] To assess the biological effect of anti-hPCSK9 on hepatic LDL receptor levels and subsequent effects on serum LDL-C levels, 316P and a non-hPCSK9 specific mAb were administered to *PCSK9^{hulhu}* mice at equivalent dose (5 mg/kg i.p.) 20 hours prior to the hPCSK9-mmh protein injection described above. Four hours after the hPCSK9 administration, mice were sacrificed and a total of eight tissues (liver, brain, lung, kidney, heart, ileum, adrenal, and pancreas) were collected and levels of LDL receptor were determined by Western blot. Changes in LDL receptor levels were only observed in liver. In comparison to PBS control dosing, administration of 316P significantly blocked the PCSK9-mediated increases in total cholesterol and LDL cholesterol (LDL-C = 2.49 mg/dl at baseline and 3.1 mg/dl 6 hours after PCSK9; a 25% increase compared to 135% with vehicle). Prior administration of the non-hPCSK9 specific mAb blocked LDL-C increases by approximately 27% from PBS alone (LDL-C = 4.1 mg/dl compared to PBS 5.6 mg/dl). Analysis of LDL receptor levels in a separate cohort of mice (n=3 per group) revealed a significant reduction in LDL receptor levels with PCSK9 administration, which was blocked by 316P but not by the non-hPCSK9 specific mAb (Fig. 10).

[0150] Effect of different doses of 316P was also evaluated in *PCSK9^{hulhu}* mice with both elevated LDL-C and elevated hPCSK9 levels. *PCSK9^{hulhu}* mice were first placed on a high carbohydrate diet for 8 weeks, resulting in a ~2-fold elevation in both LDL-C and hPCSK9 levels. Either 316P or a non-hPCSK9 specific mAb, each at 1 mg/kg, 5 mg/kg, or 10 mg/kg, were administered to the mice. Sera were collected 24 hours later and LDL-C levels were analyzed. 316P was effective in decreasing LDL-C levels in a dose-dependent manner (Fig. 11). In addition, 316P administered at a dose of 10 mg/kg, rapidly reduced LDL-C levels back to original (pre-diet) values within 24 hours (data not shown).

Example 15. Mouse PK Studies

[0151] A PK study was conducted in 6-week-old C57BL/6 mice and 11-15 week old hPCSK9 heterozygous mice. A single injection of Control I, 316P, or 300N, each at 10 mg/kg, was administered SC. Serum bleeds were measured for hIgG levels at 0 hr (pre-bleed), 6 hr, day 1, 3, 6, 10, 14, 21, 28, 35, 42 and 56, for a total of 12 time points, using an anti-hFc capture and anti-hFc detection sandwich ELISA (Figs. 12 and 13). All mAbs achieved their T_{max} at approximately 3 days with corresponding C_{max} levels of approximately 47-115 μ g/ml for C57BL/6 mice and 55-196 μ g/ml for hPCSK9 heterozygous mice. At Day 56, Control I mAb levels were about 12 μ g/ml and 300N levels were about 11 μ g/ml whereas 316P levels were about less than 0.02 μ g/ml in C57BL/6 mice. At Day 56 in hPCSK9 heterozygous mice, Control I mAb levels were about 29 μ g/ml, while both 300N and 316P levels were below the quantifiable limit (BQL) of 0.02 μ g/ml.

Example 16. Anti-hPCSK9 Antibody Binding to Mutant/Variant hPCSK9

[0152] To further assess binding between hPCSK9 and anti-hPCSK9 mAbs, 21 variant hPCSK9 proteins in which each variant contained a single point mutation and two variant hPCSK9 proteins each contained a double mutation were generated. Each selected antibody was captured on a F(ab')₂ anti-hIgG surface created through direct chemical coupling to a BIACORE™ chip to form a captured antibody surface. Each mmh-tagged variant hPCSK9 at varying concentrations from 100 nM to 25 nM was then injected over the captured antibody surface at a flowrate of 60 µl/min for 240 sec, and the dissociation of variant hPCSK9 and antibody was monitored in real time for 20 min at 25°C. nb: no binding was observed under these experimental conditions ($K_D = M \times 10^{-9}$; $T_{1/2} = \text{min}$; WT = wildtype).

Table 27

	316P		300N		Control I		Control II		Control III	
	K_D	$T_{1/2}$	K_D	$T_{1/2}$	K_D	$T_{1/2}$	K_D	$T_{1/2}$	K_D	$T_{1/2}$
WT	1.00	37	0.69	120	30.6	16	0.10	333	0.60	481
P70A	1.42	32	1.68	80	19.0	16	0.24	168	0.90	325
S127R	2.40	36	1.87	110	25.0	18	0.26	288	0.55	550
D129G	1.27	36	1.40	88	22.9	18	0.19	257	0.75	445
S147F	1.29	32	9.07	24	21.1	15	0.22	178	0.23	1468
S153R	5.64	4	0.56	141	36.6	17	0.09	322	3.33	60
E159R	6.96	5	0.82	94	31.7	16	0.08	350	2.97	68
T162R	0.98	43	0.58	140	29.0	17	0.09	322	0.48	362
D192R	1.35	28	0.75	119	30.2	15	0.09	326	nb	nb
R194E	0.38	71	0.65	129	31.4	16	0.07	389	nb	nb
E197R	1.42	27	0.67	115	30.2	17	0.09	339	nb	nb
R215H	0.86	41	1.03	98	37.8	17	0.65	49	0.74	272
R215E	0.90	43	1.81	77	44.0	16	4.48	12	0.78	276
F216L	1.83	32	0.99	121	21.2	15	1.35	39	0.33	880
R237E	2.48	15	1.03	109	29.6	15	0.07	481	5.89	43
D238R	410	1	0.78	123	25.9	19	0.24	144	0.14	1273
A341 R	1.54	21	0.34	190	28.7	18	0.08	340	0.88	200
D343R	7.88	6	1.18	89	27.0	16	0.08	402	4.13	66
R357H	6.26	30	6.53	66	26.4	13	0.63	165	1.91	896
E366K	2.92	13	36.0	2	28.8	18	0.46	69	0.38	808
D374Y	2.04	15	0.66	83	25.0	17	0.08	285	1.02	161
V380M	0.48	63	2.82	28	25.9	17	0.15	177	0.35	711

	316P		300N		Control I		Control II		Control III	
	K _D	T _{1/2}	K _D	T _{1/2}	K _D	T _{1/2}	K _D	T _{1/2}	K _D	T _{1/2}
P70A,S147F	1.18	34	7.87	24	23.5	18	0.23	164	0.79	348
E366K,V380M	3.33	12	78.3	1	25.5	18	0.59	60	0.52	551

[0153] The results show that when residue D238 was mutated, the binding affinity of 316P for hPCSK9 was reduced >400-fold, from a K_D of 1×10^{-9} M to 410×10^{-9} M; and T_{1/2} shortened about 30-fold, from 37 to 1 min, indicating that 316P binds an epitope on hPCSK9 comprising D238 of hPCSK9 (SEQ ID NO:755). Additionally, the BIACORE™ assays show that 316P binding affinity and T_{1/2} were reduced about 5- to 10-fold when a residue at 153, 159 or 343 was mutated. Specifically, K_D was reduced from about 1×10^{-9} M to between about $5 - 8 \times 10^{-9}$ M when any one of S153, E159 or D343 were mutated; while T_{1/2} was decreased from about 37 min to between about 4 - 6 min.

[0154] 300N binding to hPCSK9 was reduced about 50-fold when the residue at position 366 was mutated, resulting in a decreased K_D of from about 0.7×10^{-9} M to about 36×10^{-9} M and a shorter T_{1/2} from about 120 to 2 min. These results indicate that 300N binds an epitope on hPCSK9 comprising E366 of hPCSK9 (SEQ ID NO:755). Additionally, the BIACORE™ assays show that 300N binding affinity and T_{1/2} were reduced between 2- to >10-fold when a residue at 147 or 380 was mutated. Specifically, K_D was reduced from about 0.69×10^{-9} M to between about $2 - 9 \times 10^{-9}$ M when any of S147 or V380 were mutated; while T_{1/2} was shortened from about 120 min to between about 24 - 66 min. Compared to 316P, 300N binding to hPCSK9 was not reduced by a mutation at residue 238.

[0155] In contrast, Control I antibody did not exhibit an altered binding affinity or T_{1/2} in response to any of the positional mutations tested; Control II antibody exhibited a 40-fold decreased affinity when residue 215 was mutated (R215E) (from $\sim 0.1 \times 10^{-9}$ to $\sim 4.5 \times 10^{-9}$), and T_{1/2} was about 27-fold shorter (from -333 to 12 min); while Control III antibody exhibited a decreased affinity when residue 237 was mutated (K_D decreased from $\sim 0.6 \times 10^{-9}$ to $\sim 5.9 \times 10^{-9}$, and T_{1/2} decreased from -481 to -43 min).

[0156] Binding specificity of 316P, 300N, and control anti-hPCSK9 mAbs to hPCSK9 variants was tested using an ELISA-based immunoassay. Anti-PCSK9 mAbs were coated on a 96-well plate overnight at 4°C. Each mmh-tagged variant hPCSK9 in CHO-k1 transient transfection lysate supernatants was added to the antibody-coated plate at various concentrations ranging from 0 to 5 nM. After 1 hr binding at RT, the plate was washed and bound variant hPCSK9 was detected using HRP-conjugated anti-myc polyclonal antibody (- = OD < 0.7; + = OD 0.7 - 1.5; ++ = OD > 1.5).

Table 28

hPCSK9 or Variant	316P	300N	Control I	Control II	Control III
hPCSK9(WT)	++	++	++	++	++
hPCSK9(S127R)	++	++	++	++	++
hPCSK9(D129G)	++	++	++	++	++
hPCSK9(S153R)	++	++	++	++	++
hPCSK9(R215H)	++	++	++	++	++
hPCSK9(F216L)	++	++	++	++	++
hPCSK9(R237E)	++	++	++	++	++
hPCSK9(D238R)	-	++	++	++	++
hPCSK9(A341 R)	++	++	++	++	++
hPCSK9(D343R)	++	++	++	++	++
hPCSK9(R357H)	++	++	++	++	++
hPCSK9(E159R)	++	++	++	++	++
hPCSK9(T162R)	++	++	++	++	++
hPCSK9(D192R)	++	++	++	++	-
hPCSK9(R194E)	++	++	++	++	-
hPCSK9(E197R)	++	++	++	++	-
hPCSK9(R215E)	++	++	++	++	++
hPCSK9(P70A)	++	++	++	++	++
hPCSK9(S147F)	++	++	++	++	++
hPCSK9(E366K)	++	+	++	++	++
hPCSK9(V380M)	++	++	++	++	++
hPCSK9(P70A, S147F)	++	++	++	++	++
hPCSK9(E366K, V380M)	++	+	++	++	++

Example 17. Effect of 316P on Normolipemic and Hyperlipemic Hamster

[0157] The ability of anti-PCSK9 mAb 316P to reduce serum LDL-C was tested in normolipemic or hyperlipemic Gold Syrian hamsters (*Mesocricetus auratus*). Male Syrian Hamsters, age 6-8 weeks, weighing between 80-100 grams, were allowed to acclimate for a period of 7 days before entry into the study. All animals were placed on either a standard chow diet or a hyperlipemic diet of chow supplemented with 0.1% cholesterol and 10% coconut oil. The 316P mAb was delivered to hamsters by a single subcutaneous injection at doses of 1, 3, or 10 mg/kg for normolipemic hamsters and at doses of 3, 10, or 30 mg/kg for hyperlipemic hamsters. Serum samples were taken from all groups at 24 hr and 7, 14, and 22 days post

injection, at which time serum lipid levels were assessed and compared to baseline levels taken 7 days prior to the administration of the mAbs. Circulating total cholesterol and LDL-C in normolipemic hamsters was significantly reduced in a dose-dependent manner compared to vehicle injection. As shown in Fig. 14, administration of 316P effectively reduced LDL-C levels by up to 60% seven days post injection at the highest dose (10 mg/kg) tested. Similar cholesterol reducing effect of 316P was not observed in hyperlipemic hamsters. determined by ALT and AST measurements.

SEQUENCE LISTING

[0158]

<110> Regeneron Pharmaceuticals, Inc.

<120> High Affinity Human Antibodies to PCSK9

<130> 7000A-WO

<140> To be assigned

<141> Filed Herewith

<150> 61/261,776

<151> 2009-11-17

<150> 61/249,135

<151> 2009-10-06

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<151> 2009-06-18

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gaagattttg cattttatct ctgtcagcag tataataact ggctccatt cactttcggc 300
cctgggacca aggtggagat caaacga 327

```

<210> 10

<211> 109

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 10

```

Asp Ile Gln Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1             5             10             15
Glu Arg Ala Ala Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
 20             25             30
Leu Ala Trp Tyr His Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35             40             45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50             55             60
Ile Gly Ser Gly Thr Glu Phe Thr Leu Ile Ile Ser Ser Leu Gln Ser
 65             70             75             80
Glu Asp Phe Ala Phe Tyr Phe Cys Gln Gln Tyr Asn Asn Trp Pro Pro
 85             90             95
Phe Thr Phe Gly Pro Gly Thr Lys Val Glu Ile Lys Arg
100             105

```

<210> 11

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 11

```

cagagtgtta gcagcaac 18

```

<210> 12

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 12

Gln Ser Val Ser Ser Asn
1 5

<210> 13

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 13

ggtgcatcc 9

<210> 14

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 14

Gly Ala Ser
1

<210> 15

<211> 30

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 15

cagcagtata ataactggcc tccattcact 30

<210> 16

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 16

Gln Gln Tyr Asn Asn Trp Pro Pro Phe Thr
 1 5 10

<210> 17

<211> 351

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 17

gaggtgcagc tgggtggagtc tgggggaggc ttggtacagc ctgggggggc cctgagactc 60
 tcctgtgcag cctctggatt tactctaagt agttacgaca tgcactgggt ccgccaatct 120
 acaggaaaag gtctggagtg ggtctcagct attggttcta ccggtgacac atactatcca 180
 ggctccgtga agggccgatt caccatcacc agagaaaaag ccaagaactc cgtgtatctt 240
 caaatgaaca gcctgagagc cggggacacg gctgtgtatt actgtgtaag agaggggtgg 300
 gaggtaccct ttgactactg gggccaggga accctgggtca ccgtctcctc a 351

<210> 18

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 18

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Ser Tyr
 20 25 30
 Asp Met His Trp Val Arg Gln Ser Thr Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Gly Ser Thr Gly Asp Thr Tyr Tyr Pro Gly Ser Val Lys
 50 55 60
 Gly Arg Phe Thr Ile Thr Arg Glu Lys Ala Lys Asn Ser Val Tyr Leu
 65 70 75 80
 Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys Val
 85 90 95
 Arg Glu Gly Trp Glu Val Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu
 100 105 110
 Val Thr Val Ser Ser
 115

<210> 19

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 19

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccgcc 60

```

ctctcctgca gggccagtca gagtgttagc agcaacttag cctggtacca ccagaaacct 120
ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc 180
aggttcagtg gcattgggtc tgggacagag ttcactctca ttatcagcag cctgcagtct 240
gaagattttt cattttatct ctgtcagcag tataataact ggctccatt cactttcggc 300
cctgggacca aagtggatat caaa 324

```

<210> 20

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 20

```

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1             5             10             15
Glu Arg Ala Ala Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
      20             25             30
Leu Ala Trp Tyr His Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
      35             40             45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
      50             55             60
Ile Gly Ser Gly Thr Glu Phe Thr Leu Ile Ile Ser Ser Leu Gln Ser
      65             70             75             80
Glu Asp Phe Ala Phe Tyr Phe Cys Gln Gln Tyr Asn Asn Trp Pro Pro
      85             90             95
Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
      100             105

```

<210> 21

<211> 351

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 21

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gaggtgcagc tgggtggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt tactctaagt agttacgaca tgcactgggt ccgccaagct 120
acaggaaaag gtctggagtg ggtctcagct attggttcta ccggtgacac atactatcca 180
ggctccgtga agggccgatt caccatctcc agagaaaatg ccaagaactc ctgtatctt 240
caaatgaaca gcctgagagc cggggacacg gctgtgtatt actgtgtaag agaggggtgg 300
gaggtaccct ttgactactg gggccaggga accctggtea ccgtctctc a 351

```

<210> 22

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 22

```

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1             5             10             15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Ser Tyr
      20             25             30

```

```

      20      25      30
Asp Met His Trp Val Arg Gln Ala Thr Gly Lys Gly Leu Glu Trp Val
      35      40      45
Ser Ala Ile Gly Ser Thr Gly Asp Thr Tyr Tyr Pro Gly Ser Val Lys

      50      55      60
Gly Arg Phe Thr Ile Ser Arg Glu Asn Ala Lys Asn Ser Leu Tyr Leu
      65      70      75      80
Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys Val
      85      90      95
Arg Glu Gly Trp Glu Val Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu
      100      105      110
Val Thr Val Ser Ser
      115

```

<210> 23

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 23

```

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
ctctcctgca gggccagtc gagtggttagc agcaacttag cctggtagca gcagaaacct 120
ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc 180
aggttcagtg gcagtggtgc tgggacagag ttcactctca ccatcagcag cctgcagtct 240
gaagattttg cagtttatta ctgtcagcag tataataaact ggccctccatt cactttcggc 300
cctgggacca aagtggatat caaa 324

```

<210> 24

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 24

```

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1      5      10      15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
      20      25      30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
      35      40      45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
      50      55      60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
      65      70      75      80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Pro
      85      90      95
Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
      100      105

```

<210> 25

<211> 342

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 25

cagggtgcagc tgggtgcagtc tgggggagggc gtgggtccagc ctggggaggtc cctgagactc 60
 tectgtgcag cgtctggatt cacccttcagt agctatggca tgcactgggt ccgccaggct 120

ccaggcaagg cgctggagtg ggtggcgttt ataggatttg atggaagtaa tatacattat 180
 ggagactccg tgagggggccg aatcatcata tccagagaca attccgagaa cacgttgat 240
 ctggaaatga acagcctgag agccgaggac acggcaatgt actattgtgc gagagagaag 300
 ggttttagact ggggccaggg aaccacggtc accgtctcct ca 342

<210> 26

<211> 114

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 26

Gln	Val	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	Ser	Tyr
			20					25					30		
Gly	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
	35					40						45			
Ala	Phe	Ile	Gly	Phe	Asp	Gly	Ser	Asn	Ile	His	Tyr	Gly	Asp	Ser	Val
	50					55				60					
Arg	Gly	Arg	Ile	Ile	Ile	Ser	Arg	Asp	Asn	Ser	Glu	Asn	Thr	Leu	Tyr
65					70				75					80	
Leu	Glu	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
			85					90					95		
Ala	Arg	Glu	Lys	Gly	Leu	Asp	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val
			100					105					110		
Ser	Ser														

<210> 27

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 27

ggattcacct tcagtagcta tggc 24

<210> 28

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 28
Gly Phe Thr Phe Ser Ser Tyr Gly
1 5

<210> 29
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 29
ataggatttg atggaagtaa tata 24

<210> 30
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 30
Ile Gly Phe Asp Gly Ser Asn Ile
1 5

<210> 31
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 31
gcgagagaga agggtttaga c 21

<210> 32
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 32
Ala Arg Glu Lys Gly Leu Asp
1 5

<210> 33

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 33

```

gccatccaga tgaccagtc tccctccacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtc gagtattagt agctgggttg cctgggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctataag gcgtctagtt tagaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcaactctca ccatcagcag cctgcagcct 240
gatgatattg caacttatta ctgccaacag tataatagtt attacacttt tggccagggg 300
accaaggtgg aaatcaaacg a                                     321

```

<210> 34

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 34

```

Ala 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 Gln Ser Ile Ser Ser 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 Glu 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 Asn Ser Tyr Tyr Thr
 85          90          95
Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100          105

```

<210> 35

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 35

cagagtatta gtagctgg 18

<210> 36

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 36

Gln	Ser	Ile	Ser	Ser	Trp
1				5	

<210> 37

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 37

aaggcgtct	9
-----------	---

<210> 38

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 38

Lys	Ala	Ser
1		

<210> 39

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 39

caacagtata atagttatta cact	24
----------------------------	----

<210> 40

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 40

Gln	Gln	Met	Leu	Gln	Met	Met	Met
-----	-----	-----	-----	-----	-----	-----	-----

Gln Gln Tyr Asn Ser Tyr Tyr Thr
1 5

<210> 41

<211> 342

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 41

```
cagggtgcagc tgggtggagtc tggggggagggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt cacccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcggtt ataggatttg atggaagtaa tatacattat 180
ggagactccg tgaggggccc aatcatcata tccagagaca attccgagaa cacgttgat 240
ctggaaatga acagcctgag agccgaggac acggcaatgt actattgtgc gagagagaag 300
ggttttagact ggggccaggg aaccctggtc accgtctcct ca 342
```

<210> 42

<211> 114

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 42

```
Gln Val 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 Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Phe Ile Gly Phe Asp Gly Ser Asn Ile His Tyr Gly Asp Ser Val
50 55 60
Arg Gly Arg Ile Ile Ile Ser Arg Asp Asn Ser Glu Asn Thr Leu Tyr
65 70 75 80

Leu Glu Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Glu Lys Gly Leu Asp Trp Gly Gln Gly Thr Leu Val Thr Val
100 105 110
Ser Ser
```

<210> 43

<211> 318

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 43

```
gacatccaga tgaccagtc tccttcacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtc gagtattagt agctggttg cctggatatc gcagaaacca 120
gggaaagccc ctaagctcct gatctataag gcgtctagtt tagaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct 240
ctatctttta cactttatta ctgcccagc tataatgatt attacatttt tggcccaggg 300
```

gagcattctt caattcttct cgtccacatg catacatagt attacattct tggccagggg 300
accaagctgg agatcaaa 318

<210> 44

<211> 106

<212> PRT

<213> Artificial Sequence

$\langle 220 \rangle$

<223> Synthetic

<400> 44

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	Gln	Ser	Ile	Ser	Ser	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	Glu	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	Asn	Ser	Tyr	Tyr	Thr
			85						90					95	
Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys						
			100					105							

<210> 45

$\langle 211 \rangle$ 342

<212> DNA

<213> Artificial Sequence

$\langle 220 \rangle$

<223> Synthetic

<400> 45

caggtgcagc	tggtggaatc	tgggggaggc	gtggtccagc	ctgggaggtc	cctgagactc	60
tcctgtgcag	cctctggatt	caaccttcagt	agcttatggca	tgcactgggt	cgcgaaggct	120
ccaggccagg	ggcttggagt	ggtggcagtt	ataggatttc	atggaagtaa	tatatactat	180
cgagactcgg	tgaaggggccg	attcaccatc	tcccagagaca	attccaagaa	cacgctgtat	240
ctgcaaatga	acagccttag	agctgaggac	accgctgtgt	attactgtgc	gagagaagaag	300

ggttttagact ggggccaggg aacctgggc accgtctcct ca 342

<210> 46

<211> 114

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 46

Gln	Val	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	Ser	Tyr
			20					25					30		
Gly	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val

```

      35      40      45
Ala Val Ile Gly Phe Asp Gly Ser Asn Ile Tyr Tyr Ala Asp Ser Val
   50      55      60
Lys Gly Arg Phe Thr Ile 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 Arg Glu Lys Gly Leu Asp Trp Gly Gln Gly Thr Leu Val Thr Val
      100      105      110
Ser Ser

```

<210> 47

<211> 319

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 47

```

gacatccaga tgacccagtc tccttcacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtc gagtattagt agctggttg cctggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctataag gcgtctagtt tagaaagtgg ggtcccatca 180
aggttcagcg gcagtggtatc tgggacagaa ttcactctca ccatcagcag cctgcagcct 240
gatgattttg caacttatta ctgccaacag tataatagtt attacacttt tggccagggg 300
accaagctgg agatcaaac                                     319

```

<210> 48

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 48

```

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 Gln Ser Ile Ser Ser 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 Glu 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 Asn Ser Tyr Tyr Thr
      85      90      95
Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
      100      105

```

<210> 49

<211> 342

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 49

```

cagggtgcagc tgcaggagtc tgggggagggc gtgggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt caccctcagc agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcggtt ataggatttg atggaagtaa tatatattat 180
ggagactccg tgaggggccc aatcatcata tccagagaca attccgagaa cacgttggtat 240
ctggaaatga acagcctgag agccgaggac acggcagtggt attattgtgc gagagagaag 300
ggtttagact ggggccaggg aaccctgggc actgtctcct ca 342

```

<210> 50

<211> 114

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 50

```

Gln Val Gln Leu Gln 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 Ser Tyr
 20           25           30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35           40           45
Ala Phe Ile Gly Phe Asp Gly Ser Asn Ile Tyr Tyr Gly Asp Ser Val
 50           55           60
Arg Gly Arg Ile Ile Ile Ser Arg Asp Asn Ser Glu Asn Thr Leu Tyr
 65           70           75           80
Leu Glu Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85           90           95
Ala Arg Glu Lys Gly Leu Asp Trp Gly Gln Gly Thr Leu Val Thr Val
100           105           110
Ser Ser

```

<210> 51

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 51

```

ggattcacct tcagtagcta tggc 24

```

<210> 52

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 52

```

Gly Phe Thr Phe Ser Ser Tyr Gly
 1           5

```

<210> 53
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 53
ataggatttg atggaagtaa tata 24

<210> 54
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 54
Ile Gly Phe Asp Gly Ser Asn Ile
1 5

<210> 55
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 55
gcgagagaga agggtttaga c 21

<210> 56
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 56
Ala Arg Glu Lys Gly Leu Asp
1 5

<210> 57
<211> 342
<212> DNA
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 57

```

gccatccaga tgacccagtc tccagactcc ctggetgtgt ctctgggcga gagggccacc 60
atcaactgca agtccagcca gagtgttttt cacacctcca acaataagaa ctacttagtt 120
tggtatcagc agaaaccagg acagcctect aagttgctcc ttactgggc ctctaccgg 180
gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240
atcagcagcc tgcaggctga agatgtggca aattattact gtcaccaata ttacagtatt 300
ccgtggacgt tcggccaagg gaccaagggtg gagatcaaac ga 342

```

<210> 58

<211> 114

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 58

```

Ala Ile Gln Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1      5      10      15
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Phe His Thr
20     25     30
Ser Asn Asn Lys Asn Tyr Leu Val Trp Tyr Gln Gln Lys Pro Gly Gln
35     40     45
Pro Pro Lys Leu Leu Leu Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50     55     60
Pro Asp Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65     70     75     80
Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Asn Tyr Tyr Cys His Gln
85     90     95
Tyr Tyr Ser Ile Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100    105    110
Lys Arg

```

<210> 59

<211> 36

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 59

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cagagtgttt ttcacacctc caacaataag aactac 36

```

<210> 60

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 60

Gln Ser Val Phe His Thr Ser Asn Asn Lys Asn Tyr
 1 5 10

<210> 61

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 61

tgggcctct 9

<210> 62

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 62

Trp Ala Ser
 1

<210> 63

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 63

caccaatatt acagtattcc gtggacg 27

<210> 64

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 64

His Gln Tyr Tyr Ser Ile Pro Trp Thr
 1 5

<210> 65

<211> 342

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 65

```

cagggtgcagc tgggtggagtc tgggggagggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cgtctggatt cacccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcgttt ataggatttg atggaagtaa tatatattat 180
ggagactccg tgagggggccg aatcatcata tccagagaca attccgagaa cacgttggtat 240
ctggaaatga acagcctgag agccgaggac acggcagtggt attattgtgc gagagagaag 300
ggttttagact ggggccaggg aaccctggtc accgtctcct ca 342

```

<210> 66

<211> 114

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 66

```

Gln Val 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 Ser Tyr
 20          25          30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35          40          45
Ala Phe Ile Gly Phe Asp Gly Ser Asn Ile Tyr Tyr Gly Asp Ser Val
 50          55          60
Arg Gly Arg Ile Ile Ile Ser Arg Asp Asn Ser Glu Asn Thr Leu Tyr
 65          70          75          80
Leu Glu Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85          90          95
Ala Arg Glu Lys Gly Leu Asp Trp Gly Gln Gly Thr Leu Val Thr Val
100          105          110
Ser Ser

```

<210> 67

<211> 339

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 67

```

gacatcgtagc tgaccacagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc 60
atcaactgca agtccagcca gagtggtttt cacacctcca acaataagaa ctacttagtt 120
tggtatcagc agaaaccagg acagcctcct aagttgctcc tttactgggc ctctaccggg 180
gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240
atcagcagcc tgcaggctga agatgtggca aattattact gtcaccaata ttacagtatt 300
ccgtggacgt tcggccaagg gaccaagggt gaaatcaaa 339

```

<210> 68

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 68

```

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
 1             5             10             15
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Phe His Thr
                20             25             30
Ser Asn Asn Lys Asn Tyr Leu Val Trp Tyr Gln Gln Lys Pro Gly Gln
        35             40             45
Pro Pro Lys Leu Leu Leu Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
        50             55             60
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65             70             75             80

```

```

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Asn Tyr Tyr Cys His Gln
                85             90             95
Tyr Tyr Ser Ile Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
        100             105             110
Lys

```

<210> 69

<211> 342

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 69

```

cagggtgcagc tgggtggagtc tggggggaggc gtggtccagc ctggggaggtc cctgagactc 60
tccctgtgcag cctctgggatt cacccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt ataggatttg atggaagtaa tatatactat 180
gcagactccg tgaaggggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gagagagaag 300
gggttagact ggggccaggg aaccctggtc accgtctcct ca 342

```

<210> 70

<211> 114

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 70

```

Gln Val 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 Ser Tyr
        20             25             30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35             40             45
Ala Val Ile Gly Phe Asp Gly Ser Asn Ile Tyr Tyr Ala Asp Ser Val
        50             55             60
Lys Gly Arg Phe Thr Ile 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 Arg Glu Lys Gly Leu Asp Trp Gly Gln Gly Thr Leu Val Thr Val
 100 105 110
 Ser Ser

<210> 71

<211> 339

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 71

gacatcgtga tgaccacagtc tccagactcc ctggctgtgt ctctggggcga gagggccacc 60
 atcaactgca agtccagcca gagtggtttt cacacctcca acaataagaa ctacttagct 120
 tggtagcagc agaaaccagg acagcctcct aagctgctca tttactgggc ctctaccggg 180

gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240
 atcagcagcc tgcaggctga agatgtggca gtttattact gtcaccaata ttacagtatt 300
 ccgtggacgt tcggccaagg gaccaagggt gaaatcaaa 339

<210> 72

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 72

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
 1 5 10 15
 Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Phe His Thr
 20 25 30
 Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45
 Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
 50 55 60
 Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80
 Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys His Gln
 85 90 95
 Tyr Tyr Ser Ile Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
 100 105 110
 Lys

<210> 73

<211> 354

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 73

gaactacagg taatatacgc taagggaagg ttaatacagg ctagggaagc cctgaagtc 60

```

tcctgtgcag cctctggatt cacctttaac aactatgcc aactatgggt ccgccaggct 120
ccaggaaagg gactggactg ggtctcaact attagtggta gcggtgggtac tacaaactac 180
gcagactccg tgaaggccg tttcattatt tcccgagaca gtccaaaca cacgctgtat 240
ctgcaaataa acagcctgag agccgaggac acggccgtat attactgtgc gaaagattct 300
aactggggaa atttcgatct ctggggccgt ggcaccacgg tcactgtctc ctca 354

```

<210> 74

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 74

```

Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1      5      10      15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Asn Tyr
20      25      30
Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Asp Trp Val
35      40      45
Ser Thr Ile Ser Gly Ser Gly Gly Thr Thr Asn Tyr Ala Asp Ser Val

50      55      60
Lys Gly Arg Phe Ile Ile Ser Arg Asp Ser Ser Lys His 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 Lys Asp Ser Asn Trp Gly Asn Phe Asp Leu Trp Gly Arg Gly Thr
100     105     110
Thr Val Thr Val Ser Ser
115

```

<210> 75

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 75

ggattcacct ttaacaacta tgcc 24

<210> 76

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 76

```

Gly Phe Thr Phe Asn Asn Tyr Ala
1      5

```

<210> 77
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 77
attagtggta gcggtggtac taca 24

<210> 78
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 78
Ile Ser Gly Ser Gly Gly Thr Thr
1 . 5

<210> 79
<211> 33
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 79
gcgaaagatt ctaactgggg aaatttcgat ctc 33

<210> 80
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 80
Ala Lys Asp Ser Asn Trp Gly Asn Phe Asp Leu
1 5 10

<210> 81
<211> 342
<212> DNA
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 81

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gacatccaga tgaccagtc tccagactcc ctggetgtgt ctctgggcga gagggccacc 60
atcaactgca agtcagcca gagtgtttta tacaggcca acaataggaa cttcttaggt 120
tggtaccagc agaaaccagg gcagcctcct aatctactca tttactgggc atctaccgg 180
gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240
atcagcagcc tgcaggctga agatgtggca gtttattact gtcaacaata ttatactact 300
ccgtacactt ttggccaggg gaccaagggt gaaatcaaac ga 342

```

<210> 82

<211> 114

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 82

```

Asp Ile Gln Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
 1           5           10           15
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Arg
          20           25           30
Ser Asn Asn Arg Asn Phe Leu Gly Trp Tyr Gln Gln Lys Pro Gly Gln
          35           40           45
Pro Pro Asn Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
          50           55           60
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
          65           70           75           80
Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
          85           90           95
Tyr Tyr Thr Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
          100          105          110
Lys Arg

```

<210> 83

<211> 36

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 83

```

cagagtgttt tatacaggct caacaatagg aacttc 36

```

<210> 84

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 84

Gln Ser Val Leu Tyr Arg Ser Asn Asn Arg Asn Phe
1 5 10

<210> 85

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 85

tgggcatct 9

<210> 86

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 86

Trp Ala Ser
1

<210> 87

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 87

caacaatatt atactactcc gtacact 27

<210> 88

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 88

Gln Gln Tyr Tyr Thr Thr Pro Tyr Thr
1 5

<210> 89

<211> 354

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 89

```

gaggtgcagc tgggtggagtc tgggggaggc ttggtacagc ctgggggggc cctgagactc 60
tcctgtgcag cctctggatt cacccttaac aactatgcc aactatgggt ccgccaggct 120
ccaggaaagg gactggactg ggtctcaact attagtggta gcggtgggtac tacaaaactac 180
gcagactccg tgaaggcccg ttccattatt tcccgagaca gttccaaaca cacgtgttat 240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagattct 300
aactggggaa atttcgatct ctggggccgt ggcaccctgg tcactgtctc ctca 354

```

<210> 90

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 90

```

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1           5           10           15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Asn Tyr
 20           25           30
Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Asp Trp Val
 35           40           45
Ser Thr Ile Ser Gly Ser Gly Gly Thr Thr Asn Tyr Ala Asp Ser Val
 50           55           60
Lys Gly Arg Phe Ile Ile Ser Arg Asp Ser Ser Lys His 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 Lys Asp Ser Asn Trp Gly Asn Phe Asp Leu Trp Gly Arg Gly Thr
100          105          110
Leu Val Thr Val Ser Ser
115

```

<210> 91

<211> 339

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 91

```

gacatcgtga tgaccagtc tccagactcc ctggtgtgtgt ctctgggcga gagggccacc 60
atcaactgca agtccagcca gagtgtttta tacaggcca acaataggaa cttcttaggt 120

```

```

tgggtaccagc agaaaccagg gcagcctect aatctactca ttactgggc atctaccgg 180
gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240
atcagcagcc tgcaggctga agatgtggca gtttattact gtcaacaata ttatactact 300
ccgtacactt ttggccaggg gaccaagctg gagatcaaa 339

```

<210> 92
 <211> 113
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 92
 Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
 1 5 10 15
 Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Arg
 20 25 30
 Ser Asn Asn Arg Asn Phe Leu Gly Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45
 Pro Pro Asn Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
 50 55 60
 Pro Asp Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80
 Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
 85 90 95
 Tyr Tyr Thr Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
 100 105 110
 Lys

<210> 93
 <211> 354
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 93
 gaggtgcagc tgggtggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60
 tccgtgtgcag cctctggatt cacctttaac aactatgcc a tgagctgggt ccgccaggct 120
 ccagggaagg ggctggagtg ggtctcagct attagtggta gcggtgggtac tacatactac 180
 gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
 ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagattct 300
 aactggggaa atttcgatct ctggggccgt ggcaccctgg tcactgtctc ctca 354

<210> 94
 <211> 118
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 94
 Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Asn Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

```

Ser Ala Ile Ser Gly Ser Gly Gly Thr Thr Tyr Tyr Ala Asp Ser Val
 50          55          60
Lys Gly Arg Phe Thr Ile 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 Lys Asp Ser Asn Trp Gly Asn Phe Asp Leu Trp Gly Arg Gly Thr
          100          105          110
Leu Val Thr Val Ser Ser
          115

```

<210> 95

<211> 339

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 95

```

gacatcgtga tgaccacgtc tccagactcc ctggctgtgt ctctgggcga gagggccacc 60
atcaactgca agtccagcca gagtggttta tacagggtcca acaataggaa cttcttagct 120
tggtaccagc agaaaccagg acagcctcct aagctgctca ttactgggc atctaccgg 180
gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240
atcagcagcc tgcaggctga agatgtggca gtttattact gtcaacaata ttatactact 300
ccgtacactt ttggccaggg gaccaagctg gagatcaaa 339

```

<210> 96

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 96

```

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
 1          5          10          15
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Arg
          20          25          30
Ser Asn Asn Arg Asn Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
          35          40          45
Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
          50          55          60
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
          65          70          75          80
Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
          85          90          95
Tyr Tyr Thr Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
          100          105          110
Lys

```

<210> 97

<211> 351

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 97

```

cagggtgcagc tgggtgcagtc tgggggagggc ttggtacagc ctgggggggtc cctgagactc 60
tcctgtgcag tctctggatt caccctcagt agctacgata tgcaactgggt ccgccaacct 120
acaggaaaag gtctggagtg ggtctcagct attggttcta ctggtgacac atactatcca 180
ggctccgtga agggccgatt caccatctcc agagaaaatg ccaagaactc ctgtatctt 240
caaatgaaca gcctgagagc cggggacacg gctgtgtatt actgtgcaag agagggatgg 300
gacgtacctt ttgacttctg gggccaggga accctgggtca ccgtctcttc a 351

```

<210> 98

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 98

```

Gln Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1      5      10      15
Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Leu Ser Ser Tyr
20     25     30
Asp Met His Trp Val Arg Gln Pro Thr Gly Lys Gly Leu Glu Trp Val
35     40     45
Ser Ala Ile Gly Ser Thr Gly Asp Thr Tyr Tyr Pro Gly Ser Val Lys
50     55     60
Gly Arg Phe Thr Ile Ser Arg Glu Asn Ala Lys Asn Ser Leu Tyr Leu
65     70     75     80
Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys Ala
85     90     95
Arg Glu Gly Trp Asp Val Pro Phe Asp Phe Trp Gly Gln Gly Thr Leu
100    105    110
Val Thr Val Ser Ser
115

```

<210> 99

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 99

```

ggattcaccc ttagtagcta cgat      24

```

<210> 100

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 100

```

Glv Phe Thr Leu Ser Ser Tyr Asp

```

1 5

<210> 101

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 101

attggttcta ctggtgacac a 21

<210> 102

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 102

Ile Gly Ser Thr Gly Asp Thr
1 5

<210> 103

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 103

gcaagagagg gatgggacgt accctttgac ttc 33

<210> 104

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 104

Ala Arg Glu Gly Trp Asp Val Pro Phe Asp Phe
1 5 10

<210> 105

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 105

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gccatccagt tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca ggacattaga aatgatttag gctgggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tacaaagtgg ggtcccatca 180
cgggttcagcg gcagtggatc tggcacagat ttcactotca ccatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacaa gattacaatt acccgtggac gttcggccaa 300
gggaccaagg tggagatcaa acga                                     324

```

<210> 106

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 106

```

Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1      5      10      15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Arg Asn Asp
20     25     30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35     40     45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50     55     60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65     70     75     80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Asp Tyr Asn Tyr Pro Trp
85     90     95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100    105

```

<210> 107

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 107

```

caggacatta gaaatgat      18

```

<210> 108

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 108

Gln Asp Ile Arg Asn Asp
1 5

<210> 109

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 109

gctgcatcc 9

<210> 110

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 110

Ala Ala Ser
1

<210> 111

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 111

ctacaagatt acaattaccc gtggacg 27

<210> 112

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 112

Leu Gln Asp Tyr Asn Tyr Pro Trp Thr
1 5

<210> 113

<211> 351

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 113

```

gagggtgcagc tgggtggagtc tgggggagggc ttggtacagc ctgggggggtc cctgagactc 60
tcctgtgcag tctctggatt caccctcagt agctacgata tgcactgggt cgcgcaacct 120
acaggaaaag gtctggagtg ggtctcagct attggttcta ctggtgacac atactatcca 180
ggctccgtga agggccgatt caccatctcc agagaaaatg ccaagaactc cttgtatctt 240
caaatgaaca gcctgagagc cggggacacg gctgtgtatt actgtgcaag agagggatgg 300
gacgtaccct ttgacttctg gggccaggga accctggtea ccgtctctc a 351

```

<210> 114

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 114

```

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1           5           10           15
Ser Leu Arg Leu Ser Cys Ala Val Ser Gly Phe Thr Leu Ser Ser Tyr
 20           25           30
Asp Met His Trp Val Arg Gln Pro Thr Gly Lys Gly Leu Glu Trp Val
 35           40           45
Ser Ala Ile Gly Ser Thr Gly Asp Thr Tyr Tyr Pro Gly Ser Val Lys

 50           55           60
Gly Arg Phe Thr Ile Ser Arg Glu Asn Ala Lys Asn Ser Leu Tyr Leu
 65           70           75           80
Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys Ala
 85           90           95
Arg Glu Gly Trp Asp Val Pro Phe Asp Phe Trp Gly Gln Gly Thr Leu
100          105          110
Val Thr Val Ser Ser
115

```

<210> 115

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 115

```

gccatccaga tgaccacagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtcg ggacattaga aatgatttag gctggatatc gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatocagtt tacaaagtgg ggtcccatca 180
cgggttcagc gcagtggatc tggcacagat ttactctca ccatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacaa gattacaatt acccgtggac gttcggccaa 300

```


gggaccaagg tggaaatcaa a

321

<210> 116

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 116

```

Ala Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1           5           10           15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Arg Asn Asp
          20           25           30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
          35           40           45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
          50           55           60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
          65           70           75           80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Asp Tyr Asn Tyr Pro Trp
          85           90           95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
          100          105

```

<210> 117

<211> 351

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 117

```

gagggtgcagc tgggtggagtc tggggggaggc ttggtacagc ctgggggggtc cctgagactc 60
tctgtgcagc cctctggatt caccctcagt agctacgata tgcactgggt ccgccaagct 120

```

```

acaggaaaag gtctggagtg ggtctcagct attggttcta ctggtgacac atactatcca 180
ggctccgtga agggccgatt caccatctcc agagaaaatg ccaagaactc cttgtatctt 240
caaatgaaca gcctgagagc cggggacacg gctgtgtatt actgtgcaag agaggggatgg 300
gacgtaccct ttgacttctg gggccaggga accctggta cgtctcctc a 351

```

<210> 118

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 118

```

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1           5           10           15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Ser Tyr
          20           25           30
Asp Met His Trp Val Arg Gln Ala Thr Gly Lys Gly Leu Glu Trp Val

```

```

      35              40              45
Ser Ala Ile Gly Ser Thr Gly Asp Thr Tyr Tyr Pro Gly Ser Val Lys
  50              55              60
Gly Arg Phe Thr Ile Ser Arg Glu Asn Ala Lys Asn Ser Leu Tyr Leu
  65              70              75              80
Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys Ala
      85              90              95
Arg Glu Gly Trp Asp Val Pro Phe Asp Phe Trp Gly Gln Gly Thr Leu
    100              105              110
Val Thr Val Ser Ser
    115

```

<210> 119

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 119

```

gccatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca ggacattaga aatgatttag gctgggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tacaaagtgg ggtcccatca 180
agggttcagcg gcagtggtatc tggcacagat ttactctctca ccatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacaa gattacaatt acccgtggac gttcggccaa 300
gggaccaagg tggaatcaa a                                     321

```

<210> 120

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 120

```

Ala Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
  1              5              10              15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Arg Asn Asp
      20              25              30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
    35              40              45

```

```

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
  50              55              60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
  65              70              75              80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Asp Tyr Asn Tyr Pro Trp
      85              90              95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
    100              105

```

<210> 121

<211> 384

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 121

```

cagggtgcagc tgcaggagtc ggggccagga ctggtgaagc ctccggagac cctgtccctc 60
acctgcactg tctctgggga ctccatcaat acttactact ggagctggtt ccggcagccc 120
ccagggaagg gactggagtg gattgggtat atctattata gtggaaccac caactacaac 180
ccctccctca agagtcgagt caccatatca atagacacgc ccaggaacca gttctccctg 240
aagctgatct ctgtgaccgc agcggacacg gccgtgtatt actgtgcgag agagaggatt 300
actatgattc ggggagttac cctctactat tactcctacg gtatggacgt ctggggccaa 360
gggaccacgg tcaccgtctc ctca                                     384

```

<210> 122

<211> 128

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 122

```

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1      5      10      15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asp Ser Ile Asn Thr Tyr
20     25     30
Tyr Trp Ser Trp Phe Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35     40     45
Gly Tyr Ile Tyr Tyr Ser Gly Thr Thr Asn Tyr Asn Pro Ser Leu Lys
50     55     60
Ser Arg Val Thr Ile Ser Ile Asp Thr Pro Arg Asn Gln Phe Ser Leu
65     70     75     80
Lys Leu Ile Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85     90     95
Arg Glu Arg Ile Thr Met Ile Arg Gly Val Thr Leu Tyr Tyr Tyr Ser
100    105    110
Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115    120    125

```

<210> 123

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 123

```

ggggactcca tcaatactta ctac          24

```

<210> 124

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 124

Gly Asp Ser Ile Asn Thr Tyr Tyr
 1 5

<210> 125

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 125

atctattata gtggaaccac c 21

<210> 126

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 126

Ile Tyr Tyr Ser Gly Thr Thr
 1 5

<210> 127

<211> 66

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 127

gcgagagaga ggattactat gattcgggga gttaccctct actattactc ctacgggtatg 60
 gacgtc 66

<210> 128

<211> 22

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 128

Ala Arg Glu Arg Ile Thr Met Ile Arg Gly Val Thr Leu Tyr Tyr Tyr
 1 5 10 15
 Ser Thr Glu Met Asn Val

Ser Tyr Gly Met Asp Val

20

<210> 129

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 129

```

gacatccaga tgaccagtc tccatccttc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgct gggccagtca ggacattagc agttatttag cctgggtatca gcaaaaacca 120
gggatagccc ctaagctcct gatctatgct gcattccactt tgcaaagtgg ggtcccatca 180
aggttcggcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtcaacag cttaatagtt accctcggac gttcggccaa 300
gggaccaagg tggaaatcaa acga                                     324

```

<210> 130

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 130

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
 1           5           10           15
Asp Arg Val Thr Ile Thr Cys Trp Ala Ser Gln Asp Ile Ser Ser Tyr
      20           25           30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Ile Ala Pro Lys Leu Leu Ile
      35           40           45
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Gly Gly
      50           55           60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
      65           70           75           80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Arg
      85           90           95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
      100          105

```

<210> 131

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 131

caggacatta gcagttat 18

<210> 132

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 132

Gln Asp Ile Ser Ser Tyr
1 5

<210> 133

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 133

gctgcatcc 9

<210> 134

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 134

Ala Ala Ser
1

<210> 135

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 135

caacagctta atagttaccc tcggacg 27

<210> 136

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 136

Gln Gln Leu Asn Ser Tyr Pro Arg Thr
 1 5

<210> 137

<211> 384

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 137

cagggtgcagc tgcaggagtc ggggccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctgggga ctccatcaat acttactact ggagctgggt ccggcagccc 120
 ccagggaagg gactggagtg gattgggtat atctattata gtggaaccac caactacaac 180
 cctccctca agagtcgagt caccatatca atagacacgc ccaggaacca gttctccctg 240
 aagctgatct ctgtgaccgc agcggacacg gccgtgtatt actgtgcgag agagaggatt 300
 actatgattc ggggagttac cctctactat tactctacg gtatggacgt ctggggccaa 360
 gggaccacgg tcaccgtctc ctca 384

<210> 138

<211> 128

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 138

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
 1 5 10 15
 Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asp Ser Ile Asn Thr Tyr
 20 25 30
 Tyr Trp Ser Trp Phe Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Tyr Ile Tyr Tyr Ser Gly Thr Thr Asn Tyr Asn Pro Ser Leu Lys
 50 55 60
 Ser Arg Val Thr Ile Ser Ile Asp Thr Pro Arg Asn Gln Phe Ser Leu
 65 70 75 80
 Lys Leu Ile Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
 85 90 95
 Arg Glu Arg Ile Thr Met Ile Arg Gly Val Thr Leu Tyr Tyr Tyr Ser
 100 105 110
 Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> 139

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 139

```

gacatccaga tgacccagtc tccatccttc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgct gggccagtcg ggacattagc agttatttag cctgggtatca gcaaaaacca 120
gggatagccc ctaagctcct gatctatgct gcatccactt tgcaaagtgg ggtcccatca 180
aggttcggcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtcaacag cttaatagtt accctcggac gttcggccaa 300
gggaccaagg tggaaatcaa a 321

```

<210> 140

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 140

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
 1           5           10           15
Asp Arg Val Thr Ile Thr Cys Trp Ala Ser Gln Asp Ile Ser Ser Tyr
      20           25           30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Ile Ala Pro Lys Leu Leu Ile
      35           40           45
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Gly Gly
      50           55           60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
      65           70           75           80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Arg
      85           90           95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
      100          105

```

<210> 141

<211> 384

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 141

```

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60
acctgcactg tctctgggga ctccatcaat acttactact ggagctggat ccggcagccc 120
ccagggaagg gactggagtg gattgggtat atctattata gtggaaccac caactacaac 180
ccctccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240
aagctgagct ctgtgaccgc tgcggacacg gccgtgtatt actgtgcgag agagaggatt 300
actatgattc ggggagttac cctctactat tactcctacg gtatggacgt ctggggccaa 360
gggaccaagg tcacgtctc ctca 384

```

<210> 142

<211> 128

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 142

```

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
 1           5           10           15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asp Ser Ile Asn Thr Tyr
      20           25           30
Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
      35           40           45
Gly Tyr Ile Tyr Tyr Ser Gly Thr Thr Asn Tyr Asn Pro Ser Leu Lys
      50           55           60
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65           70           75           80
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
      85           90           95
Arg Glu Arg Ile Thr Met Ile Arg Gly Val Thr Leu Tyr Tyr Tyr Ser
      100          105          110
Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
      115          120          125

```

<210> 143

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 143

```

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcaagtca ggacattagc agttatttag gctggatatca gcagaaacca 120
gggaaagccc ctaagcgccct gatctatgct gcattccagtt tgcaaagtgg ggtcccataca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtcaacag cttaatatgtt accctcggac gttcggccaa 300
gggaccaagg tggaaatcaa a 321

```

<210> 144

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 144

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1           5           10           15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Ser Tyr
      20           25           30
Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
      35           40           45
Tyr Ala Ala Ser Ser Leu Gln 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
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ser Tyr Pro Arg
      85           90           95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
      100          105

```

<210> 145

<211> 378

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 145

```

cagggtgcagc tgggtgcagtc tggagctgag gtgaagaagc ctgggggcctc agtgaaggtc 60
tcctgcaagg cttctgggta cacctttacc aactatggta tcagctgggt gcgacaggcc 120
cctggacaag gacttgagtt aatgggatgg attagtgggtt acaatggtaa cacaaactat 180
gcacaagaac tccaggccag agtcaccatg accacagaca catccacgag cacagcctac 240
atggagctga ggaacctgag atctgacgac acggccgtat attactgtgc gagagataga 300
gtcgttgtag cagctgctaa ttactacttt tattctatgg acgtctgggg ccaagggacc 360
acggtcaccg tctctctca                               378

```

<210> 146

<211> 126

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 146

```

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
Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Leu Met
          35           40           45
Gly Trp Ile Ser Gly Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Glu Leu
          50           55           60
Gln Ala Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
          65           70           75           80
Met Glu Leu Arg Asn Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
          85           90           95
Ala Arg Asp Arg Val Val Val Ala Ala Ala Asn Tyr Tyr Phe Tyr Ser
          100          105          110
Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
          115          120          125

```

<210> 147

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 147

```

ggttacacct ttaccaacta tgggt          24

```

<210> 148

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 148

Gly Tyr Thr Phe Thr Asn Tyr Gly
1 5

<210> 149

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 149

attagtgggtt acaatggtaa caca 24

<210> 150

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 150

Ile Ser Gly Tyr Asn Gly Asn Thr
1 5

<210> 151

<211> 57

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 151

gcgagagata gagtcgttgt agcagctgct aattactact ttattctat ggacgtc 57

<210> 152

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 152

Ala Arg Asp Arg Val Val Ala Ala Ala Asn Tyr Tyr Phe Tyr Ser
 1 5 10 15
 Met Asp Val

<210> 153

<211> 339

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 153

gccatccaga tgaccacagtc tccactctcc ctgtccgtca cccttggaca gccggcctcc 60
 atctcctgca ggtctagtca aagcctcgta tacagtgatg gagacaccta ctggaattgg 120
 ttccagcaga gccagggcca atctccaagg cgcctaattt ataaggtttc taaccgggac 180
 tctgggggtcc cagacagatt cagcggcagt gggtcaggca ctgctttcac actgaaaatc 240
 agcgggggtgg aggccgagga tgttgggggt tactactgca tgcaagctac acactggcct 300
 cggacgttcg gccaaaggac caaggtggaa atcaaacga 339

<210> 154

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 154

Ala Ile Gln Met Thr Gln Ser Pro Leu Ser Leu Ser Val Thr Leu Gly
 1 5 10 15
 Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
 20 25 30
 Asp Gly Asp Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
 35 40 45
 Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp Ser Gly Val Pro
 50 55 60
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Lys Ile
 65 70 75 80
 Ser Gly Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
 85 90 95

Thr His Trp Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105 110
 Arg

<210> 155

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 155

caaagcctcg tatacagtga tggagacacc tac 33

<210> 156

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 156

Gln Ser Leu Val Tyr Ser Asp Gly Asp Thr Tyr
1 5 10

<210> 157

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 157

aaggtttct 9

<210> 158

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 158

Lys Val Ser
1

<210> 159

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 159

atgcaagcta cacactggcc tcggacg 27

<210> 160

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 160

Met	Gln	Ala	Thr	His	Trp	Pro	Arg	Thr
1				5				

<210> 161

<211> 378

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 161

cagggtcagc	tggtgcagtc	tgagctgag	gtgaagaagc	ctggggcctc	agtgaaggtc	60
tcttgcaagg	cttctgggta	cacctttacc	aactatggta	tcagctgggt	gcgacaggcc	120
cctggacaag	gacttgagtt	aatgggatgg	attagtgggt	acaatggtaa	cacaaactat	180
gcacaagaac	tccaggccag	agtcaccatg	accacagaca	catccacgag	cacagcctac	240
atggagctga	ggaacctgag	atctgacgac	acggccgtat	attactgtgc	gagagataga	300
gtcgttgtag	cagctgctaa	ttactacttt	tattctatgg	acgtctgggg	ccaagggacc	360
acggtcaccg	tctctctca					378

<210> 162

<211> 126

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 162

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		
Gly	Ile	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Leu	Met
		35				40					45				
Gly	Trp	Ile	Ser	Gly	Tyr	Asn	Gly	Asn	Thr	Asn	Tyr	Ala	Gln	Glu	Leu
	50				55				60						
Gln	Ala	Arg	Val	Thr	Met	Thr	Thr	Asp	Thr	Ser	Thr	Ser	Thr	Ala	Tyr
65				70					75					80	
Met	Glu	Leu	Arg	Asn	Leu	Arg	Ser	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
			85				90						95		
Ala	Arg	Asp	Arg	Val	Val	Val	Ala	Ala	Asn	Tyr	Tyr	Phe	Tyr	Ser	
		100					105					110			
Met	Asp	Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser		
	115					120						125			

<210> 163

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 163

```

gatgttgatga tgactcagtc tccactctcc ctgtccgtca cccttggaca gccggcctcc 60
atctcctgca ggtctagtca aagcctcgta tacagtgatg gagacaccta cttgaattgg 120
tttcagcaga gccagggcca atctccaagg cgctaattt ataagggttc taaccgggac 180
tctgggggtcc cagacagatt cagcggcagt gggtcaggca ctgctttcac actgaaaatc 240
agcgggggtgg aggccgagga tgttgggggtt tactactgca tgcaagctac aactggcct 300
cggacgttcg gccaaaggac caaggtggaa atcaaa 336

```

<210> 164

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 164

```

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Ser Val Thr Leu Gly
1          5          10          15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
20          25          30
Asp Gly Asp Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
35          40          45
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp Ser Gly Val Pro
50          55          60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr Leu Lys Ile
65          70          75          80
Ser Gly Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85          90          95
Thr His Trp Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100          105          110

```

<210> 165

<211> 378

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 165

```

caggttcagc tgggtcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctgggta cacccttaac aactatggta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg attagtgggtt acaatggtaa cacaaactat 180
gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagataga 300
gtcgtttagt cagctgctaa ttactacttt tattctatgg acgtctgggg ccaagggacc 360
acggtcaccg tctctca 378

```

<210> 166

<211> 126

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 166

```

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
Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
      35           40           45
Gly Trp Ile Ser Gly Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
      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 Val Val Val Ala Ala Asn Tyr Tyr Phe Tyr Ser
      100          105          110
Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
      115          120          125

```

<210> 167

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 167

```

gatgtttgtga tgactcagtc tccactctcc ctgcccgtca cccttggaca gccggcctcc 60
atctctctgca ggtctagtca aagcctcgta tacagtgatg gagacaccta cttgaattgg 120
tttcagcaga gccaggcca atctccaagg cgcctaattt ataaggtttc taaccgggac 180
tctgggggtcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc 240
agcaggggtgg aggctgagga tgttggggtt tattactgca tgcaagctac acactggcct 300
cggacgttcg gccaagggac caaggtggaa atcaaa 336

```

<210> 168

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 168

```

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
 1           5           10           15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
      20           25           30
Asp Gly Asp Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
      35           40           45
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp Ser Gly Val Pro
      50           55           60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
      65           70           75           80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
      85           90           95
Thr His Trp Pro Arg Thr Phe Glv Gln Glv Thr Lvs Val Glu Ile Lvs

```


----- 100 105 110 -----

<210> 169

<211> 375

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 169

```
cagggtccact tgaaggagtc tgggtcctacg ctggtgaaac ccacacagac cctcacgctg 60
acctgcacct tctctggatt ctcaactcatc actagtggag tgggtgtggg ctggattcgt 120
cagcccccgc gaaaggccct ggagtggctt gcactcattt attggaatgg tgataagcgc 180
tacagcccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccaggtg 240
gtccttaciaa tgaccaacat ggacctgtg gacacagcca catattactg tgcacacagg 300
ataactgaaa ctagttacta cttctactac ggtatggacg tctggggcca agggaccacg 360
gtcaccgctc cctca 375
```

<210> 170

<211> 125

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 170

```
Gln Val His Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
 1          5          10          15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ile Thr Ser
 20          25          30
Gly Val Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
 35          40          45
Trp Leu Ala Leu Ile Tyr Trp Asn Gly Asp Lys Arg Tyr Ser Pro Ser
 50          55          60
Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
 65          70          75          80
Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
 85          90          95
Cys Ala His Arg Ile Thr Glu Thr Ser Tyr Tyr Phe Tyr Tyr Gly Met
100          105          110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115          120          125
```

<210> 171

<211> 30

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 171

```
ggattctcac tcatcactag tggagtgggt 30
```

<210> 172

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 172

Gly	Phe	Ser	Leu	Ile	Thr	Ser	Gly	Val	Gly
1				5					10

<210> 173

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 173

atttattgga atggtgataa g 21

<210> 174

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 174

Ile	Tyr	Trp	Asn	Gly	Asp	Lys
1				5		

<210> 175

<211> 51

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 175

gcacacagga taactgaaac tagttactac ttctactacg gtatggacgt c 51

<210> 176

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 176

Ala His Arg Ile Thr Glu Thr Ser Tyr Tyr Phe Tyr Tyr Gly Met Asp
 1 5 10 15
 Val

<210> 177

<211> 339

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 177

gacatccaga tgaccagtc tccactctcc ctgcccgtea cccctggaga gccggcctcc 60
 atctcctgca ggtctagtc gagcctcctg catagtcatg gatacgacta ttgggattgg 120
 tacctgcaga agccagggca gtctccacag ctctgatct atttgggttc taatcgggcc 180
 .
 tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
 agcagagtgg aggctgagga tgttgggggt tattactgca tgcaagctct acaaactccg 300
 ctcactttcg gccgagggac caaggtggaa atcaaacga 339

<210> 178

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 178

Asp Ile Gln Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
 1 5 10 15
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
 20 25 30
 His Gly Tyr Asp Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45
 Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
 50 55 60
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
 85 90 95
 Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105 110
 Arg

<210> 179

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 179

cagagcctcc tgcatagtca tggatacgac tat 33

<210> 180

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 180

Gln	Ser	Leu	Leu	His	Ser	His	Gly	Tyr	Asp	Tyr
1				5					10	

<210> 181

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 181

ttgggttct 9

<210> 182

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 182

Leu	Gly	Ser
1		

<210> 183

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 183

atgcaagctc tacaaactcc gctcact 27

<210> 184

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 184

```

Met Gln Ala Leu Gln Thr Pro Leu Thr
 1             5

```

<210> 185

<211> 375

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 185

```

cagatcacct tgaaggagtc tggtcctacg ctgggtgaaac ccacacagac cctcacgctg 60
acctgcacct tctctggatt ctcactcadc actagtggag tgggtgtggg ctggattcgt 120
cagcccccgc gaaaggccct ggagtggctt gcactcattt attggaatgg tgataagcgc 180
tacagcccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccaggtg 240
gtccttacaa tgaccaacat ggaccctgtg gacacagcca catattactg tgcacacagg 300
ataactgaaa ctagttacta cttctactac ggtatggacg tctggggcca agggaccacg 360
gtcacccgtct cctca

```

<210> 186

<211> 125

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 186

```

Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
 1             5             10             15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ile Thr Ser
 20             25             30
Gly Val Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
 35             40             45
Trp Leu Ala Leu Ile Tyr Trp Asn Gly Asp Lys Arg Tyr Ser Pro Ser
 50             55             60
Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
 65             70             75             80
Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
 85             90             95
Cys Ala His Arg Ile Thr Glu Thr Ser Tyr Tyr Phe Tyr Tyr Gly Met
100             105             110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115             120             125

```

<210> 187

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 187

```

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
atctcctgca ggtctagtc gagcctcctg catagtcatg gatacgacta tttggattgg 120
tacctgcaga agccagggca gtctccacag ctctgatct atttgggttc taatcgggcc 180
tccggggctc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggctgagga tggtggggtt tattactgca tgcaagcctt acaaactccg 300
ctcactttcg gccgagggac caaggtggag atcaaaa 336

```

<210> 188

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 188

```

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1      5      10      15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20     25     30
His Gly Tyr Asp Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35     40     45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50     55     60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65     70     75     80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85     90     95
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100    105    110

```

<210> 189

<211> 375

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 189

```

cagatcacct tgaaggagtc tggctctacg ctggtgaaac ccacacagac cctcacgctg 60
acctgcacct tctctggatt ctcactcacc actagtggag tgggtgtggg ctggatccgt 120
cagcccccag gaaaggccct ggagtggctt gcactcattt attggaatgg tgataagcgc 180
tacagcccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccagggt 240
gtccttacaa tgaccaacat ggacctgtg gacacagcca catattactg tgcacacagg 300
ataactgaaa ctagttaacta ctctactaac ggtatggacg tctggggcca agggaccacg 360
gtcacccgtc cctca 375

```

<210> 190

<211> 125

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 190

```

Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
 1           5           10           15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ile Thr Ser
          20           25           30
Gly Val Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
      35           40           45
Trp Leu Ala Leu Ile Tyr Trp Asn Gly Asp Lys Arg Tyr Ser Pro Ser
      50           55           60
Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
65           70           75           80
Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
      85           90           95
Cys Ala His Arg Ile Thr Glu Thr Ser Tyr Tyr Phe Tyr Tyr Gly Met
          100          105          110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
      115           120           125

```

<210> 191

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 191

```

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gcgggcctcc 60
atctcctgca ggtctagtca gagectcctg catagtcatg gatacgacta ttgggattgg 120
tacctgcaga agccagggca gtctccacag ctctgatctc atttgggttc taatcggggc 180
tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggctgagga tgttgggggt tattactgca tgcaagctct acaaactccg 300
ctcacttttc gcggagggac caagtgaggag atcaaaa 336

```

<210> 192

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 192

```

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
 1           5           10           15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
          20           25           30
His Gly Tyr Asp Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
      35           40           45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
      50           55           60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65           70           75           80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
      85           90           95
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
          100          105          110

```

<210> 193

<211> 375

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 193

```

cagatcacct tgaaggagtc tggctcact ctggtgaaac cctcacagac cctcacgctg 60
acctgcacct tctctgggtt ctcaactcagc actagtggag tgggtgtggg ctggatccgt 120
cagcccccag gaaaggccct ggagtggctt gcactcattt attggaattc tgataagcgc 180
tacagcccat ctctgaagag caggtccacc atcaccaagg acacctocaa aaaccaggta 240
gtccttacaa tgaccaacat ggacctgtg gacacagcca catattactg tgcacacaga 300
catgacagct cgtctacta cttctactac ggtatggacg tctggggcca agggatcacg 360
gtcacgctct cctca                                     375

```

<210> 194

<211> 125

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 194

```

Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Ser Gln
 1             5             10             15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
      20             25             30
Gly Val Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
 35             40             45
Trp Leu Ala Leu Ile Tyr Trp Asn Ser Asp Lys Arg Tyr Ser Pro Ser
 50             55             60
Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
 65             70             75             80
Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
      85             90             95
Cys Ala His Arg His Asp Ser Ser Ser Tyr Tyr Phe Tyr Tyr Gly Met
      100            105            110
Asp Val Trp Gly Gln Gly Ile Thr Val Thr Val Ser Ser
      115            120            125

```

<210> 195

<211> 30

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 195

```

gggttctcac tcagcactag tggagtgggt          30

```

<210> 196

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 196

Gly	Phe	Ser	Leu	Ser	Thr	Ser	Gly	Val	Gly
1				5					10

<210> 197

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 197

atttattgga attctgataa g 21

<210> 198

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 198

Ile	Tyr	Trp	Asn	Ser	Asp	Lys
1				5		

<210> 199

<211> 51

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 199

gcacacagac atgacagctc gtcctactac ttctactacg gtatggacgt c 51

<210> 200

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 200

Ala	His	Arg	His	Asp	Ser	Ser	Ser	Tyr	Tyr	Phe	Tyr	Tyr	Gly	Met	Asp
1				5				10					15		
Val															

<210> 201

<211> 339

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 201

gacatccaga	tgacccagtc	tcgctctccc	ctgcccgcca	ccctggaga	gccggcctcc	60
atctcctgca	ggctctagtc	gagcctctcc	catagtcatg	gatacaacta	tttggattgg	120
tacctgcaga	agccagggca	gtctccacaa	ctctgatct	atttgggttc	taatcgggcc	180
tcgggggtcc	ctgacaggtt	cagtggcggt	ggatcaggca	cagattttac	actgaaaatc	240
agcagagtgg	aggctgagga	tgttgggatt	tattactgca	tgcaagctct	acagactcct	300
ctcactttcg	gcggagggac	caaggtggag	atcaaacga			339

<210> 202

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 202

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Leu	Ser	Leu	Pro	Val	Thr	Pro	Gly
1				5				10					15		
Glu	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Leu	Leu	His	Ser
		20					25					30			
His	Gly	Tyr	Asn	Tyr	Leu	Asp	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser
		35				40					45				
Pro	Gln	Leu	Leu	Ile	Tyr	Leu	Gly	Ser	Asn	Arg	Ala	Ser	Gly	Val	Pro
		50				55				60					
Asp	Arg	Phe	Ser	Gly	Gly	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile
65				70				75					80		
Ser	Arg	Val	Glu	Ala	Glu	Asp	Val	Gly	Ile	Tyr	Tyr	Cys	Met	Gln	Ala
			85					90					95		
Leu	Gln	Thr	Pro	Leu	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys
			100				105					110			
Arg															

<210> 203

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 203

cagagcctcc tccatagtca tggatacaac tat 33

<210> 204

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 204

Gln	Ser	Leu	Leu	His	Ser	His	Gly	Tyr	Asn	Tyr
1				5					10	

<210> 205

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 205

ttgggttct 9

<210> 206

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 206

Leu	Gly	Ser
1		

<210> 207

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 207

atgcaagctc tacagactcc tctcact 27

<210> 208

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 208

Met Gln Ala Leu Gln Thr Pro Leu Thr
 1 5

<210> 209

<211> 375

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 209

cagatcacct tgaaggagtc tggctcctact ctggtgaaac cctcacagac cctcacgctg 60
 acctgcacct tctctgggtt ctcactcagc actagtggag tgggtgtggg ctggatccgt 120
 cagcccccag gaaaggccct ggagtggctt gcactcattt attggaattc tgataagcgc 180
 tacagcccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccaggta 240
 gtccctacaa tgaccaacat ggaccctgtg gacacagcca catattactg tgcacacaga 300
 catgacagct cgtcctacta cttctactac ggtatggacg tctggggcca agggaccacg 360
 gtcaccgtct cctca 375

<210> 210

<211> 125

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 210

Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Ser Gln
 1 5 10 15
 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
 20 25 30
 Gly Val Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
 35 40 45
 Trp Leu Ala Leu Ile Tyr Trp Asn Ser Asp Lys Arg Tyr Ser Pro Ser
 50 55 60
 Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
 65 70 75 80
 Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
 85 90 95
 Cys Ala His Arg His Asp Ser Ser Ser Tyr Tyr Phe Tyr Tyr Gly Met
 100 105 110
 Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> 211

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 211

```

gatattgtga tgactcagtc tccgctctcc ctgcccgtca cccctggaga gccggcctcc 60
atctcctgca ggtctagtca gagcctcctc catagtcatg gatacaacta tttggattgg 120
tacctgcaga agccagggca gtctccacaa ctctgatct atttgggttc taatcgggcc 180
tccggggtcc ctgacagggt cagtggcggt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggctgagga tggtgggatt tattactgca tgcaagctct acagactcct 300
ctcactttcg gcggaggagac caaggtggag atcaaaa 336

```

<210> 212

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 212

```

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1           5           10           15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20          25          30
His Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35          40          45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50          55          60
Asp Arg Phe Ser Gly Gly Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65          70          75          80
Ser Arg Val Glu Ala Glu Asp Val Gly Ile Tyr Tyr Cys Met Gln Ala
85          90          95
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100         105         110

```

<210> 213

<211> 375

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 213

```

cagatcacct tgaaggagtc tggctctacg ctggtgaaac ccacacagac cctcacgctg 60
acctgcacct tctctgggtt ctcactcagc actagtggag tgggtgtggg ctggatccgt 120
cagcccccag gaaaggccct ggagtggctt gcactcattt attggaattc tgataagcgc 180
tacagcccat ctctgaagag caggctcacc atcaccaagg acacctcaa aaaccagggtg 240
gtccttacaa tgaccaacat ggaccctgtg gacacagcca catattactg tgacacaga 300
catgacagct cgtcctacta cttctactac ggtatggacg tctggggcca agggaccacg 360
gtcacccgtct cctca 375

```

<210> 214

<211> 125

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 214

```

Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
 1           5           10           15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
          20           25           30
Gly Val Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
          35           40           45
Trp Leu Ala Leu Ile Tyr Trp Asn Ser Asp Lys Arg Tyr Ser Pro Ser
          50           55           60
Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
65           70           75           80
Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
          85           90           95
Cys Ala His Arg His Asp Ser Ser Ser Tyr Tyr Phe Tyr Tyr Gly Met
          100           105           110
      Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
          115           120           125

```

<210> 215

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 215

```

gatattgtga tgactcagtc tccactctcc ctgcccggtca cccctggaga gccggcctcc 60
atctcctgca ggtctagtc gagcctcctc catagtcatg gatacaacta tttggattgg 120
tacctgcaga agccagggca gtctccacag ctctgatct atttgggttc taatcgggcc 180
tccgggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg agcctgagga tgttgggggt tattactgca tgcaagctct acagactcct 300
ctcactttcg gccgaggggac caaggtggag atcaaaa 336

```

<210> 216

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 216

```

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
 1           5           10           15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
          20           25           30
His Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
          35           40           45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
          50           55           60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65           70           75           80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
          85           90           95
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
          100           105           110

```

100

105

110

<210> 217

<211> 381

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 217

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gagatgcaac tgggtggagtc tggggggaggc ttgggtccagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttagt agtcaactgga tgaagtgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaatactat 180
gtggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa etcaactgttt 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatatt 300
gtactaatgg tctatgatat ggactactac tactacggta tggacgtctg gggccaaggg 360
accacggta cegtctctc a 381

```

--

<210> 218

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 218

```

Glu Met Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1      5      10      15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser His
20     25     30
Trp Met Lys Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35     40     45
Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50     55     60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
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 Asp Ile Val Leu Met Val Tyr Asp Met Asp Tyr Tyr Tyr Tyr
100    105    110
Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115    120    125

```

<210> 219

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 219

ggattcacct ttagtagtca ctgg

24

<210> 220

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 220

Gly	Phe	Thr	Phe	Ser	Ser	His	Trp
1				5			

<210> 221

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 221

ataaaccaag atggaagtga gaaa 24

<210> 222

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 222

Ile	Asn	Gln	Asp	Gly	Ser	Glu	Lys
1				5			

<210> 223

<211> 60

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 223

gcgagagata ttgtactaat ggtctatgat atggactact actactacgg tatggacgtc 60

<210> 224

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 224

Ala	Arg	Asp	Ile	Val	Leu	Met	Val	Tyr	Asp	Met	Asp	Tyr	Tyr	Tyr	Tyr
1				5				10					15		
Gly	Met	Asp	Val												
			20												

<210> 225

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 225

gatattgtga	tgactcagtc	tcactctctc	ctgcccgtca	cccctggaga	gccggcctcc	60
atctctctgca	ggctctagtc	gagcctcctg	catagtaatg	gaaacaacta	tttggattgg	120
tacctgcaga	agccagggca	gtctccacag	ctcctgatct	atttgggttc	taatcgggcc	180
tccgggggtcc	ctgacaggtt	cagtggcagt	ggatcaggca	cagattttac	actgaaaatc	240
agcagagtgg	aggctgagga	tgttgggggt	tattactgca	tgcaaaactct	acaaactccg	300
ctcacttttcg	gcggagggac	caaggtggag	atcaaaa			336

<210> 226

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 226

Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Leu	Ser	Leu	Pro	Val	Thr	Pro	Gly
1				5				10					15		
Glu	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Leu	Leu	His	Ser
			20				25					30			
Asn	Gly	Asn	Asn	Tyr	Leu	Asp	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser
		35				40					45				
Pro	Gln	Leu	Leu	Ile	Tyr	Leu	Gly	Ser	Asn	Arg	Ala	Ser	Gly	Val	Pro
	50					55				60					
Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile
65				70					75					80	
Ser	Arg	Val	Glu	Ala	Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Met	Gln	Thr
			85					90					95		
Leu	Gln	Thr	Pro	Leu	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys
		100					105						110		

<210> 227

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 227

cagagcctcc tgcatagtaa tggaaacaac tat 33

<210> 228

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 228

Gln Ser Leu Leu His Ser Asn Gly Asn Asn Tyr
1 5 10

<210> 229

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 229

ttgggttct 9

<210> 230

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 230

Leu Gly Ser
1

<210> 231

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 231

atgcaaactc tacaaactcc gctcact 27

<210> 232

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 232

Met	Gln	Thr	Leu	Gln	Thr	Pro	Leu	Thr
1				5				

<210> 233

<211> 381

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 233

gaggtgcagc	tggtggagtc	tgggggaggc	ttggtccagc	ctgggggggc	cctgagactc	60
tcctgtgcag	cctctggatt	caccttagt	agtcactgga	tgaagtgggt	ccgccaggct	120
ccagggaagg	ggctggagtg	ggtggccaac	ataaaccaag	atggaagtga	gaaatactat	180
gtggactctg	tgaagggccg	attcaccatc	tccagagaca	acgccaagaa	ctcactgttt	240
ctgcaaatga	acagcctgag	agccgaggac	acggctgtgt	attactgtgc	gagagatatt	300
gtactaatgg	tctatgatat	ggactactac	tactacggta	tggacgtctg	gggccaaggg	360
accacggtea	ccgtctcctc	a				381

<210> 234

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 234

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1				5					10					15	
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	His
			20					25					30		
Trp	Met	Lys	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
			35				40					45			
Ala	Asn	Ile	Asn	Gln	Asp	Gly	Ser	Glu	Lys	Tyr	Tyr	Val	Asp	Ser	Val
	50				55					60					
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Ser	Leu	Phe
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	Asp	Ile	Val	Leu	Met	Val	Tyr	Asp	Met	Asp	Tyr	Tyr	Tyr	Tyr
			100					105					110		
Gly	Met	Asp	Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	
	115						120					125			

<210> 235

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 235

```

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
atctcctgca ggtctagtc gagcctcctg catagtaatg gaaacaacta ttgggattgg 120
tacctgcaga agccagggca gtctccacag ctctgatct atttgggttc taatcgggcc 180
tccggggctc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggtcgagga tgttgggggt tattactgca tgcaaactct acaaactccg 300
ctcactttcg gcggagggac caaggtggag atcaaa 336

```

<210> 236

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 236

```

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1           5           10          15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20          25          30
Asn Gly Asn Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35          40          45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50          55          60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65          70          75          80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Thr
85          90          95
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100         105         110

```

<210> 237

<211> 381

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 237

```

gagggtgcagc tgggtggagtc tgggggagggc ttgggtccagc ctgggggggtc cctgagactc 60
tctgtgagcag cctctggatt cacccttagt agtcactgga tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtggccaac ataaaccaag atggaagtga gaaatactat 180
gtggactctg tgaaggggcg attcaccatc tccagagaca acgccaagaa ctactgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatatt 300
gtactaatgg tctatgatat ggactactac tactacggta tggacgtctg ggggcaaggg 360

```

accacgggtca ccgtctctctc a

381

<210> 238

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 238

```

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1          5          10          15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser His
          20          25          30
Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
          35          40          45
Ala Asn Ile Asn Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp 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 Val Tyr Tyr Cys
          85          90          95
Ala Arg Asp Ile Val Leu Met Val Tyr Asp Met Asp Tyr Tyr Tyr Tyr
          100          105          110
Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
          115          120          125

```

<210> 239

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 239

```

gatattgtga tgactcagtc tccactctcc ctgcccgta cccctggaga gccggcctcc 60
atctcctgca ggtctagtca gagcctcctg catagtaatg gaaacaacta ttgggattgg 120
taactgcaga agccagggca gtctccacag ctccctgatct atttgggttc taatcgggcc 180
tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggtgagga tgttgggggt tattactgca tgcaaaactct acaaactccg 300
ctcactttcg gcggagggac caaggtggag atcaaaa 336

```

<210> 240

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 240

```

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
 1          5          10          15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
          20          25          30
Asn Gly Asn Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
          35          40          45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
          50          55          60

```

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile

```

65          70          75          80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Thr
          85          90          95
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
          100          105          110

```

<210> 241

<211> 381

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 241

```

cagggtgcagc tgggtggagtc tggggggaggc gtgggtccagc ctgggagggtc cctgagactc 60
tcctgtgcag tctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagct atatcatatg atggaagtaa taaatactat 180
gtagactccg tgaagggccg attcaccatc tccagagaca attccaagaa aacgctgtat 240
ctgcaaatga acagcctgag agctgaggac acggctgtgt ataattgtgc gaaaaatatt 300
gtactagtga tgtatgatat agactatcac tactatggga tggacgtctg gggccaaggg 360
accacgggtca cegtctcctc a 381

```

<210> 242

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 242

```

Gln Val 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 Val Ser Gly Phe Thr Phe Ser Ser Tyr
20          25          30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35          40          45
Ala Ala Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Val Asp Ser Val
50          55          60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Lys Thr Leu Tyr
65          70          75          80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Asn Cys
85          90          95
Ala Lys Asn Ile Val Leu Val Met Tyr Asp Ile Asp Tyr His Tyr Tyr
100          105          110
Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115          120          125

```

<210> 243

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 243

ggattcacct tcagtagcta tggc 24

<210> 244

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 244

Gly Phe Thr Phe Ser Ser Tyr Gly
1 5

<210> 245

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 245

atatcatatg atggaagtaa taaa 24

<210> 246

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 246

Ile Ser Tyr Asp Gly Ser Asn Lys
1 5

<210> 247

<211> 60

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 247

gcgaaaaata ttgtactagt gatgtatgat atagactatc actactatgg gatggacgtc 60

<210> 248

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 248

Ala	Lys	Asn	Ile	Val	Leu	Val	Met	Tyr	Asp	Ile	Asp	Tyr	His	Tyr	Tyr
1				5					10					15	
Gly	Met	Asp	Val												
			20												

<210> 249

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 249

gatattgtga	tgactcagtc	tcactctctc	ctgcccgtca	cccttgaga	gccggcctcc	60
atctctctgca	ggctctagtc	gagcctcctg	catagtaatg	gatacaacta	tttggattgg	120
tacctgcaga	agccagggca	gtctccacaa	ctctgatct	atttgggttt	taatcgggcc	180
tccgggggtcc	ctgacagggt	cagtggcagt	ggatcaggca	cagattttac	actgaaaatc	240
agcagagtgg	aggctgagga	tgttgggggt	tattactgca	tgcaagctct	acaaactcct	300
ctcactttcg	gcggagggac	caaggtggag	atcaga			336

<210> 250

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 250

Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Leu	Ser	Leu	Pro	Val	Thr	Pro	Gly
1				5					10					15	
Glu	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Leu	Leu	His	Ser
			20					25				30			
Asn	Gly	Tyr	Asn	Tyr	Leu	Asp	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser
		35				40					45				
Pro	Gln	Leu	Leu	Ile	Tyr	Leu	Gly	Phe	Asn	Arg	Ala	Ser	Gly	Val	Pro
		50			55					60					
Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile
				70					75					80	
Ser	Arg	Val	Glu	Ala	Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Met	Gln	Ala
			85					90					95		
Leu	Gln	Thr	Pro	Leu	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Arg
			100					105						110	

<210> 251

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 251

cagagcctcc tgcatagtaa tggatacaac tat 33

<210> 252

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 252

Gln	Ser	Leu	Leu	His	Ser	Asn	Gly	Tyr	Asn	Tyr
1				5					10	

<210> 253

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 253

ttgggtttt 9

<210> 254

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 254

Leu	Gly	Phe
1		

<210> 255

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 255

atgcaagctc tacaaactcc tctcact 27

<210> 256

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 256

Met Gln Ala Leu Gln Thr Pro Leu Thr
1 5

<210> 257

<211> 381

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 257

cagggtgcagc tgggtggagtc tggggggaggc gtgggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag tcctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagct atatcatatg atggaagtaa taaatactat 180
gtagactccg tgaaggggccg attcaccatc tccagagaca attccaagaa aacgctgtat 240ctgcaaatga acagcctgag agctgaggac acggctgtgt ataattgtgc gaaaaatatt 300
gtactagtga tgtatgatat agactatcac tactatggga tggacgtctg gggccaaggg 360
accacggtca ccgtctcttc a 381

<210> 258

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 258

Gln Val 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 Val Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ala Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Val Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Lys Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Asn Cys
85 90 95

Ala Lys Asn Ile Val Leu Val Met Tyr Asp Ile Asp Tyr¹⁰⁰ His Tyr Tyr
 100 105 110
 Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> 259

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 259

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
 atctcctgca ggtctagtca gagcctcctg catagtaatg gatacaacta ttgggattgg 120
 tacctgcaga agccagggca gtctccacaa ctctgatct atttgggttt taatcgggcc 180
 tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
 agcagagtgg aggctgagga tgttggggtt tattactgca tgcaagctct acaaactcct 300
 ctcactttcg gcggacggac caaggtggag atcaaaa 336

<210> 260

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 260

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
 1 5 10 15
 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
 20 25 30
 Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35 40 45
 Pro Gln Leu Leu Ile Tyr Leu Gly Phe Asn Arg Ala Ser Gly Val Pro
 50 55 60
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
 85 90 95
 Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105 110

<210> 261

<211> 381

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 261

caggtgcagc tgggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
 tctgtgtcag cctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
 ccaggcaagg ggctggagtg ggtggcagtt atatcatatg atggaagtaa taaatactat 180
 gggactcga tgaagggcga attcaccatc tccagagaca attccaagaa cagcctctat 240

```

gcagactccg tgaagggcgg atccacccc cccagggcga atccacggga cccagggcga 210
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gaaaaatatt 300
gtactagtga tgtatgatat agactatcac tactatggga tggacgtctg ggggcaaggg 360
accacggtca ccgtctcttc a 381

```

<210> 262

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 262

```

Gln Val 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 Ser Tyr
      20             25             30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35             40             45
Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
 50             55             60
Lys Gly Arg Phe Thr Ile 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 Lys Asn Ile Val Leu Val Met Tyr Asp Ile Asp Tyr His Tyr Tyr
 100            105            110
Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115            120            125

```

<210> 263

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 263

```

gatattgtga tgactcagtc tccactctcc ctgcccgcca cccctggaga gccggcctcc 60

```

```

atctcctgca ggtctagtca gagcctcctg catagtaatg gatacaacta ttgggattgg 120
tacctgcaga agccaggggc gtctccacag ctcctgatct atttgggttt taatcggggc 180
tcgggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggctgagga tggtgggttt tattactgca tgcaagctct acaaactcct 300
ctcactttcg gccggaggac caaggtggag atcaaaa 336

```

<210> 264

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 264

```

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

```

```

      10      10      10
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
      20      25      30
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
      35      40      45
Pro Gln Leu Leu Ile Tyr Leu Gly Phe Asn Arg Ala Ser Gly Val Pro
      50      55      60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
      65      70      75      80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
      85      90      95
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
      100      105      110

```

<210> 265

<211> 381

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 265

```

cagggtgcagc tgggtggagtc tggggggaggc gtgggtccagc ctggggaggtc cctgagactc 60
tcctgtgcag tctctggatt cacccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagct atatcatatg atggaagtaa taaatactat 180
gtagactccg tgaaggggccg attcaccatc tccagagaca attccaagaa aacgctgtat 240
ctgcaaatga acagcctgag agctgaggac acggctgtgt ataattgtgc gaaaaatatt 300
gtactagtga tgtatgatat agactatcac tactatggga tggacgtctg gggccaaggg 360
accacgtca cegtcctctc a 381

```

<210> 266

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 266

```

Gln Val 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 Val Ser Gly Phe Thr Phe Ser Ser Tyr
      20      25      30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
      35      40      45

Ala Ala Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Val Asp Ser Val
 50      55      60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Lys Thr Leu Tyr
 65      70      75      80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Asn Cys
      85      90      95
Ala Lys Asn Ile Val Leu Val Met Tyr Asp Ile Asp Tyr His Tyr Tyr
      100      105      110
Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
      115      120      125

```

<210> 267

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 267

ggattcacct tcagtagcta tggc 24

<210> 268

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 268

Gly Phe Thr Phe Ser Ser Tyr Gly
1 5

<210> 269

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 269

atatcatatg atggaagtaa taaa 24

<210> 270

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 270

Ile Ser Tyr Asp Gly Ser Asn Lys
1 5

<210> 271

<211> 60

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 271

gcgaaaaata ttgtactagt gatgtatgat atagactatc actactatgg gatggacgtc 60

<210> 272

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 272

Ala	Lys	Asn	Ile	Val	Leu	Val	Met	Tyr	Asp	Ile	Asp	Tyr	His	Tyr	Tyr
1				5					10				15		
Gly	Met	Asp	Val												
			20												

<210> 273

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 273

gatattgtga	tgactcagtc	tccactctcc	ctgcccgtca	cccctggaga	gcgggcctcc	60
atctcctgca	ggctctagtc	gagcctcctg	catagtaatg	gatacaacta	tttggattgg	120
tacctgcaga	agccaggggca	gtctccacaa	ctcctgatct	atttgggttt	taatcggggc	180
tccgggggtcc	ctgacagggt	cagtggcagt	ggatcaggca	cagattttac	actgaaaatc	240
agcagagtgg	aggctgagga	tggtgggggt	tattactgca	tgcaagctct	acaaactcct	300
ctcactttcc	gcggaggggac	caaggtggag	atcaga			336

<210> 274

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 274

Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Leu	Ser	Leu	Pro	Val	Thr	Pro	Gly
1				5					10				15		
Glu	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Leu	Leu	His	Ser
			20					25					30		
Asn	Gly	Tyr	Asn	Tyr	Leu	Asp	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser
		35				40					45				
Pro	Gln	Leu	Leu	Ile	Tyr	Leu	Gly	Phe	Asn	Arg	Ala	Ser	Gly	Val	Pro
		50				55				60					
Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile
65				70					75				80		
Ser	Arg	Val	Glu	Ala	Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Met	Gln	Ala
			85					90					95		
Leu	Gln	Thr	Pro	Leu	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Arg
		100					105						110		

<210> 275

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 275

cagagcctcc tgcatagtaa tggatacaac tat 33

<210> 276

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 276

Gln	Ser	Leu	Leu	His	Ser	Asn	Gly	Tyr	Asn	Tyr
1				5					10	

<210> 277

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 277

ttgggtttt 9

<210> 278

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 278

Leu	Gly	Phe
1		

<210> 279

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 279

atgcaagctc tacaaactcc tctcact 27

<210> 280

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 280

Met Gln Ala Leu Gln Thr Pro Leu Thr
1 5

<210> 281

<211> 381

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 281

cagggtgcagc tgggtggagtc tggggggaggc gtgggtccagc ctggggaggtc cctgagactc 60
tctgtgtgcag tctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagct atatcatatg atggaagtaa taaatactat 180
gtagactccg tgaagggccg attcaccatc tccagagaca attccaagaa aacgctgtat 240
ctgcaaatga acagcctgag agctgaggac acggctgtgt ataattgtgc gaaaaatatt 300
gtactagtga tgcattgatag agactatcac tactatggga tggacgtctg gggccaaggg 360
accacggtca ccgtctcttc a 381

<210> 282

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 282

Gln Val 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 Val Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ala Ala Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Val Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Lys Thr Leu Tyr
65 70 75 80

```

65      70      75      80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Asn Cys
      85      90      95
Ala Lys Asn Ile Val Leu Val Met Tyr Asp Ile Asp Tyr His Tyr Tyr
      100     105     110
Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
      115     120     125

```

<210> 283

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 283

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gatattgtga tgaactcagtc tccactctccc ctgcccgtaa cccctggaga gccgggctcc 60
atctctctgca ggtctagtcga gagcctcctg catagtaatg gatacaacta tttggattgg 120
tacctgcaga agccaggggca gtctccacaa ctctgatct atttgggttt taatcgggcc 180
tccgggggtcc ctgacagggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggctgagga tgttgggggtt tattactgca tgcaagctct acaaactcct 300
ctcacttttcg gcggaggggac caaggtggag atcaaaa 336

```

<210> 284

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 284

```

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1      5      10      15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
      20      25      30
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
      35      40      45
Pro Gln Leu Leu Ile Tyr Leu Gly Phe Asn Arg Ala Ser Gly Val Pro
      50      55      60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
      65      70      75      80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
      85      90      95
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
      100     105     110

```

<210> 285

<211> 381

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 285

```

cagggtgcagc tgggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

```

```

ccaggcaagg ggctggagtg ggtggcagtt atatcatatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gaaaaatatt 300
gtactagtga tgtatgatat agactatcac tactatggga tggacgtctg ggggcaagg 360
accacggtca ccgtctcttc a 381

```

<210> 286

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 286

```

Gln Val 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 Ser Tyr
      20             25             30

```

```

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
      35             40             45
Ala Val Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
      50             55             60
Lys Gly Arg Phe Thr Ile 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 Lys Asn Ile Val Leu Val Met Tyr Asp Ile Asp Tyr His Tyr Tyr
      100            105            110
Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
      115            120            125

```

<210> 287

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 287

```

gatattgtga tgactcagtc tccactctcc ctgcccgta cccctggaga gccggcctcc 60
atctctctgca ggtctagtca gagcctcctg catagtaatg gatacaacta tttggattgg 120
tacctgcaga agccagggca gtctccacag ctctcgatct atttgggttt taatcggggc 180
tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaac 240
agcagagtgg aggcctgagga tgttgggggt tattactgca tgcaagctct acaaactcct 300
ctcactttcg gccgaggggac caaggtggag atcaaaa 336

```

<210> 288

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 288

```

Ser Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gln

```

```

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
 1           5           10           15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
          20           25           30
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
          35           40           45
Pro Gln Leu Leu Ile Tyr Leu Gly Phe Asn Arg Ala Ser Gly Val Pro
          50           55           60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65           70           75           80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
          85           90           95
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
          100          105          110

```

<210> 289

<211> 372

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 289

```

cagatcacct tgaaggagtc tggctcctacg ctgggtaaaac ccacacagac cctcacgctg 60
acctgcacct tctctgggtt ctcactcagc gctagtggag tgggtgtggg ctggttccgt 120
cagcccccag gaaaggccct ggagtggctt gcactcattt attggaatga tgataagcgt 180
tacagcccat ctctaaagaa cagcctcacc atcaccaagg acacctccaa aaaccagggt 240
gtccttacaa tgaccaacat ggaccctgtg gacacagcca catattactg tgcacacaga 300
atacatctat ggctctactt ctactacggt atggacgtct ggggccaaagg gaccacggtc 360
accgtctctt ca                                     372

```

<210> 290

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 290

```

Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
 1           5           10           15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Ala Ser
          20           25           30
Gly Val Gly Val Gly Trp Phe Arg Gln Pro Pro Gly Lys Ala Leu Glu
          35           40           45
Trp Leu Ala Leu Ile Tyr Trp Asn Asp Asp Lys Arg Tyr Ser Pro Ser
          50           55           60
Leu Lys Asn Ser Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
65           70           75           80
Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
          85           90           95
Cys Ala His Arg Ile His Leu Trp Ser Tyr Phe Tyr Tyr Gly Met Asp
          100          105          110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
          115          120

```

<210> 291

<211> 30

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 291

gggttctcac tcagcgctag tggagtgggt 30

<210> 292

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 292

Gly Phe Ser Leu Ser Ala Ser Gly Val Gly
1 5 10

<210> 293

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 293

atttattgga atgatgataa g 21

<210> 294

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 294

Ile Tyr Trp Asn Asp Asp Lys
1 5

<210> 295

<211> 48

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 295

gcacacagaa tacatctatg gtctacttc tactacggta tggacgtc 48

<210> 296

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 296

Ala	His	Arg	Ile	His	Leu	Trp	Ser	Tyr	Phe	Tyr	Tyr	Gly	Met	Asp	Val
1			5						10					15	

<210> 297

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 297

gatattgtga	tgactcagtc	tccaactctcc	ctgcccgtca	cccctggaga	gccggcctcc	60
atctcctgca	ggctagtc	gactctcctg	catagtaatg	gatacaacta	tttcgattgg	120
tacctgcaga	agccagggca	gtctccacag	ctcctgatct	atttgggttc	taatcggggc	180
tccgggggtcc	ctgacagatt	cagtggcagt	ggatcaggca	cagattttac	actgaaaatc	240
agcagagtgg	aggctgagga	tgttgggaatt	tattactgca	tgcaagctct	acaaactcct	300
ctcacttttcg	gcggagggac	caaggtggag	atcaga			336

<210> 298

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 298

Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Leu	Ser	Leu	Pro	Val	Thr	Pro	Gly
1				5					10					15	
Glu	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Thr	Leu	Leu	His	Ser
			20					25				30			
Asn	Gly	Tyr	Asn	Tyr	Phe	Asp	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser
		35				40					45				
Pro	Gln	Leu	Leu	Ile	Tyr	Leu	Gly	Ser	Asn	Arg	Ala	Ser	Gly	Val	Pro
	50				55					60					
Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile
65				70					75				80		
Ser	Arg	Val	Glu	Ala	Glu	Asp	Val	Gly	Ile	Tyr	Tyr	Cys	Met	Gln	Ala
			85					90					95		
Leu	Gln	Thr	Pro	Leu	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Arg
			100				105						110		

<210> 299

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 299

cagactctcc tgcataagtaa tggatacaac tat 33

<210> 300

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 300

Gln	Thr	Leu	Leu	His	Ser	Asn	Gly	Tyr	Asn	Tyr
1				5					10	

<210> 301

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 301

ttgggttct 9

<210> 302

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 302

Leu	Gly	Ser
1		

<210> 303

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 303

atgcaagctc tacaaactcc tctcact 27

<210> 304

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 304

Met Gln Ala Leu Gln Thr Pro Leu Thr
1 5

<210> 305

<211> 372

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 305

```

cagatcacct tgaaggagtc tggtcctacg ctggtaaaac ccacacagac cctcacgctg 60
acctgcacct tctctgggtt ctcaactcagc gctagtggag tgggtgtggg ctgggttcctg 120
cagcccccag gaaaggccct ggagtggctt gcactcattt attggaatga tgataagcgt 180
tacagcccat ctctaaagaa cagcctcacc atcaccaagg acacctccaa aaaccaggtg 240
gtccttacaa tgaccaacat ggacctgtg gacacagcca catattactg tgcacacaga 300
atacatctat ggtcctactt ctactacggt atggacgtct ggggccaagg gaccacggtc 360
accgtctcct ca 372

```

<210> 306

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 306

```

Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
1 5 10 15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Ala Ser
20 25 30
Gly Val Gly Val Gly Trp Phe Arg Gln Pro Pro Gly Lys Ala Leu Glu

35 40 45
Trp Leu Ala Leu Ile Tyr Trp Asn Asp Asp Lys Arg Tyr Ser Pro Ser
50 55 60
Leu Lys Asn Ser Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
65 70 75 80
Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr

```



```

      85      90      95
Cys Ala His Arg Ile His Leu Trp Ser Tyr Phe Tyr Tyr Gly Met Asp
      100      105      110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
      115      120

```

<210> 307

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 307

```

gatattgtga tgactcagtc tccactctcc ctgcccgta cccctggaga gccggcctcc 60
atctcctgca ggtctagtca gactctcctg catagtaatg gatacaacta ttctgattgg 120
taacctgcaga agccagggca gtctccacag ctctgatct atttgggttc taatcgggcc 180
tccgggggtcc ctgacagatt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggcagagga tgttgggaatt tattactgca tgcaagctct acaaaactct 300
ctcactttcg gcggaggagc caaggtggag atcaaaa 336

```

<210> 308

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 308

```

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
 1      5      10      15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Thr Leu Leu His Ser
 20      25      30
Asn Gly Tyr Asn Tyr Phe Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35      40      45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
 50      55      60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65      70      75      80
Ser Arg Val Glu Ala Glu Asp Val Gly Ile Tyr Tyr Cys Met Gln Ala
 85      90      95
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100      105      110

```

<210> 309

<211> 372

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 309

```

cagatcacct tgaaggagtc tggctctacg ctgggtgaaac ccacacagac cctcacgctg 60
acctgcacct tctctgggtt ctcactcagc gctagtggag tgggtgtggg ctggatccgt 120
cagcccccag gaaaggccct ggagtggctt gcactcattt attggaatga tgataagcgc 180
tacagcccat ctctgaagag caggctcacc atcaccaagg acacctccaa aaaccaggtg 240

```

```

gtccttacaa tgaccaacat ggacctctgt gacacagcca catattactg tgcacacaga 300
atacatctat ggtcctactt ctactacggt atggacgtct gggggcaagg gaccacggtc 360
accgtctcct ca                                     372

```

<210> 310

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 310

```

Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
 1           5           10           15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Ala Ser
      20           25           30
Gly Val Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
      35           40           45
Trp Leu Ala Leu Ile Tyr Trp Asn Asp Asp Lys Arg Tyr Ser Pro Ser
      50           55           60
Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
      65           70           75           80
Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
      85           90           95
Cys Ala His Arg Ile His Leu Trp Ser Tyr Phe Tyr Tyr Gly Met Asp
      100          105          110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
      115          120

```

<210> 311

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 311

```

gataattgtga tgactcagtc tccactctcc ctgcccggtca cccctggaga gccggcctcc 60
atctcctgca ggtctagtca gactctcctg catagtaatg gatacaacta ttgggattgg 120
tacctgcaga agccagggca gtctccacag ctccctgatct atttgggttc taatcgggcc 180
tccgggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggctgagga tgttggggtt tattactgca tgcaagctct acaaactcct 300
ctcactttcg gcggagggac caaggtggag atcaaa                                     336

```

<210> 312

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 312

```

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
 1           5           10           15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Thr Leu Leu His Ser

```

```

      20      25      30
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
      35      40      45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
      50      55      60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
      65      70      75      80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
      85      90      95
Leu Gln Thr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
      100      105      110

```

<210> 313

<211> 381

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 313

```

cagggtcagc tgggtgcagtc tggacctgag gtgaagaacc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctgggta cacctttacc acctatggta tcagttgggt acgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcgggt acaatggtaa aacaaacgat 180
gcacagaagt tccaggacag agtcgccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccatgt attactgttc gagagatcgt 300
ttagtagtac cacctgccct taattattcc tactacgtta tggacgtctg gggccaaggg 360
accacggtca ccgtctcctc a 381

```

<210> 314

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 314

```

Gln Val Gln Leu Val Gln Ser Gly Pro Glu Val Lys Asn Pro Gly Ala
  1      5      10      15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr 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 Gly Tyr Asn Gly Lys Thr Asn Asp Ala Gln Lys Phe
      50      55      60
Gln Asp Arg Val Ala 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 Ile Tyr Tyr Cys
      85      90      95
Ser Arg Asp Arg Leu Val Val Pro Pro Ala Leu Asn Tyr Ser Tyr Tyr
      100      105      110
Val Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
      115      120      125

```

<210> 315

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 315

ggttacacct ttaccaccta tggt 24

<210> 316

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 316

Gly Tyr Thr Phe Thr Thr Tyr Gly
1 5

<210> 317

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 317

atcagcgggtt acaatggtaa aaca 24

<210> 318

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 318

Ile Ser Gly Tyr Asn Gly Lys Thr
1 5

<210> 319

<211> 60

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 319

tcgagagatc gtttagtagt accacctgcc ctttattatt cctactacgt tatggacgtc 60

<210> 320

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 320

Ser	Arg	Asp	Arg	Leu	Val	Val	Pro	Pro	Ala	Leu	Asn	Tyr	Ser	Tyr	Tyr
1				5					10					15	
Val	Met	Asp	Val												
			20												

<210> 321

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 321

gatgttgtga	tgactcagtc	tccactctcc	ctgcccgtca	cccttggaca	gccggcctcc	60
atctcctgca	ggtctagtca	aagcctcgta	tacagtgatg	gaaacaccta	cttgaattgg	120
tctcagcaga	ggccagggtca	atctccaagg	cgcctaattt	ataaggtttc	taaccgggac	180
tctgggggtcc	cagacagatt	cagcggcagt	gggtcaggca	ctgatttcac	actgaaaatc	240
agcaggggtgg	aggctgagga	tgttggggtt	tattactgca	tgcaaggtag	acactggccg	300
tacacttttg	gccaggggac	caagctggag	atcaaaa			336

<210> 322

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 322

Asp	Val	Val	Met	Thr	Gln	Ser	Pro	Leu	Ser	Leu	Pro	Val	Thr	Leu	Gly
1				5					10					15	
Gln	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Leu	Val	Tyr	Ser
			20					25					30		
Asp	Gly	Asn	Thr	Tyr	Leu	Asn	Trp	Ser	Gln	Gln	Arg	Pro	Gly	Gln	Ser
		35				40					45				
Pro	Arg	Arg	Leu	Ile	Tyr	Lys	Val	Ser	Asn	Arg	Asp	Ser	Gly	Val	Pro
		50				55				60					
Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile
65				70					75					80	
Ser	Arg	Val	Glu	Ala	Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Met	Gln	Gly
			85					90					95		
Thr	His	Trp	Pro	Tyr	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys
			100				105						110		

<210> 323

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 323

caaagcctcg tatacagtga tggaaacacc tac 33

<210> 324

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 324

Gln	Ser	Leu	Val	Tyr	Ser	Asp	Gly	Asn	Thr	Tyr
1				5					10	

<210> 325

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 325

aaggtttct 9

<210> 326

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 326

Lys	Val	Ser
1		

<210> 327

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 327

atgcaaggta cacactggcc gtacact 27

<210> 328

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 328

Met Gln Gly Thr His Trp Pro Tyr Thr
1 5

<210> 329

<211> 381

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 329

```

cagggttcagc tgggtgcagtc tggacctgag gtgaagaacc ctgggggcctc agtgaaggtc 60
tcctgcaagg cttctgggta cacctttacc acctatggta tcagttgggt acgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcggtt acaatggtaa aacaaacgat 180
gcacagaagt tccaggacag agtcgccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccattt attactgttc gagagatcgt 300
ttagtagtac cacctgccct taattattcc tactacgtta tggacgtctg gggccaaggg 360
accacgggtca ccgtctctc a 381

```

<210> 330

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 330

```

Gln Val Gln Leu Val Gln Ser Gly Pro Glu Val Lys Asn Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr 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 Gly Tyr Asn Gly Lys Thr Asn Asp Ala Gln Lys Phe
50 55 60
Gln Asp Arg Val Ala 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 Ile Tyr Tyr Cys

```

```

      85      90      95
Ser Arg Asp Arg Leu Val Val Pro Pro Ala Leu Asn Tyr Ser Tyr Tyr
      100      105      110
Val Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
      115      120      125

```

<210> 331

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 331

```

gatgttgatga tgaactcagtc tccactctcc ctgcccgtea ccccttggaaca gcgggectcc 60
atctcctgca ggtctagtca aagcctcgta tacagtgatg gaaacaacta cttgaattgg 120
tctcagcaga ggccagggtca atctccaagg cgcctaattt ataaggtttc taaccggggac 180
tctgggggtcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc 240
agcagggttg aggtcgagga tgttggggtt tattactgca tgcaagggtac acactggccg 300
tacacttttg gccaggggac caagctggag atcaaaa 336

```

<210> 332

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 332

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly

```

      1      5      10      15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
      20      25      30
Asp Gly Asn Thr Tyr Leu Asn Trp Ser Gln Gln Arg Pro Gly Gln Ser
      35      40      45
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp Ser Gly Val Pro
      50      55      60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
      65      70      75      80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
      85      90      95
Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
      100      105      110

```

<210> 333

<211> 381

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 333

```

caggttcagc tgggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60

```



```

tcctgcaagg cttctgggta caccctttaac acctatggta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcgggt acaatggtaa aacaaactat 180
gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgttc gagagatcgt 300
ttagtagtac caccctgcct taattattcc tactacgtta tggacgtctg ggggcaaggg 360
accaaggtca ccgtctcttc a 381

```

<210> 334

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 334

```

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 Thr 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 Gly Tyr Asn Gly Lys Thr Asn Tyr Ala Gln Lys Leu
 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
Ser Arg Asp Arg Leu Val Val Pro Pro Ala Leu Asn Tyr Ser Tyr Tyr
      100            105            110
Val Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
      115            120            125

```

<210> 335

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 335

```

gatgttgtga tgactcagtc tccactctcc ctgcccgta cccctggaca gccggcctcc 60
atctcctgca ggtctagtc aagcctcgta tacagtgatg gaaacaccta cttgaattgg 120
tttcagcaga ggccaggcca atctccaagg cgcctaattt ataaggtttc taacogggac 180
tctggggtcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc 240
agcagggtgg aggctgagga tgttgggggt tattactgca tgcaaggtac aactggccg 300
tacacttttg gccaggggac caagctggag atcaaa 336

```

<210> 336

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 336

```

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly

```

```

1       5       10       15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
20
Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
35
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp Ser Gly Val Pro
50
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
85
Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100

```

<210> 337

<211> 354

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 337

```

gaggtgcagc tgggtggagtc tgggggagggc ctgggtcaagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt cacccttcagt agctatagca tggactgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcatcc attagtagta gtagtagtta catatactac 180
gcagactctg tgaaggggcg attcaccatc tccagagaca ccgccaagaa ctcactgtat 240
ctgcaaatga acagcctgag agacgaggac acggctgttt attactgtgc gagagagggc 300
agtagcagac tttttgacta ctggggccag ggaaccctgg tcaccgtctc ctca 354

```

<210> 338

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 338

```

Glu 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 Ser Tyr
20
Ser Met Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35
Ser Ser Ile Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
50
Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ala Lys Asn Ser Leu Tyr
65
Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85
Ala Arg Glu Gly Ser Ser Arg Leu Phe Asp Tyr Trp Gly Gln Gly Thr
100
Leu Val Thr Val Ser Ser
115

```

<210> 339

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 339

ggattcacct tcagtagcta tagc 24

<210> 340

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 340

Gly Phe Thr Phe Ser Ser Tyr Ser
1 5

<210> 341

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 341

attagtagta gtagtagtta cata 24

<210> 342

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 342

Ile Ser Ser Ser Ser Ser Tyr Ile
1 5

<210> 343

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 343

gcgagagagg gcagtagcag actttttgac tac 33

<210> 344

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 344

Ala	Arg	Glu	Gly	Ser	Ser	Arg	Leu	Phe	Asp	Tyr
1				5						10

<210> 345

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 345

gacatccaga	tgaccagtc	tccttcacc	ctgtctgcat	ctgtaggaga	cagagtcacc	60
atcacttgcc	gggccagtc	gagtattagt	agctgggttg	cctgggtatca	gcagagacca	120
gggaaagccc	ctaagctcct	gatctataag	gcgtctagtt	tagaagggtgg	agtcccatca	180
agggttcagcg	gcagtggtgc	tgggacagaa	ttcactctca	ccatcagcag	cctgcagcct	240
gaggattttg	caacttatta	ctgccaacag	tataatagtt	attggtacac	tttggccag	300
gggaccaagc	tggagatcaa	a				321

<210> 346

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 346

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	Gln	Ser	Ile	Ser	Ser	Trp
		20					25						30		
Leu	Ala	Trp	Tyr	Gln	Gln	Arg	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
		35				40					45				
Tyr	Lys	Ala	Ser	Ser	Leu	Glu	Gly	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	
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	Asn	Ser	Tyr	Trp	Tyr
			85					90						95	

Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys
			100						105	

<210> 347

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 347

cagagtatta gtagctgg 18

<210> 348

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 348

Gln Ser Ile Ser Ser Trp
1 5

<210> 349

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 349

aaggcgtct 9

<210> 350

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 350

Lys Ala Ser
1

<210> 351

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 351

caacagtata atagttattg gtacact 27

<210> 352

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 352

Gln Gln Tyr Asn Ser Tyr Trp Tyr Thr
1 5

<210> 353

<211> 354

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 353

gaggtgcagc tgggtggagtc tgggggaggc ctggtcaagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt agctatagca tggactgggt ccgccaggct 120
ccaggaagg ggctggagtg ggtctcatcc attagtagta gtagtagtta catatactac 180
gcagactctg tgaagggccg attcaccatc tccagagaca ccgccaagaa ctactgtat 240
ctgcaaatga acagcctgag agacgaggac acggctgttt attactgtgc gagagagggc 300
agttagcagac tttttgacta ctggggccag ggaaccctgg tcaccgtctc ctca 354

<210> 354

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 354

Glu 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 Ser Tyr
20 25 30
Ser Met Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ser Ile Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Thr Ala Lys Asn Ser Leu Tyr
65 70 75 80

```

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
      85          90          95
Ala Arg Glu Gly Ser Ser Arg Leu Phe Asp Tyr Trp Gly Gln Gly Thr
      100        105        110
Leu Val Thr Val Ser Ser
      115

```

<210> 355

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 355

```

gacatccaga tgaccagtc tccctccacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtc gagtattagt agctgggtgg cctgggtatca gcagagacca 120
gggaaagccc ctaagctcct gatctataag gcgtctagtt tagaagggtg agtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct 240
gaggattttg caacttatta ctgccaacag tataatagtt attggtacac ttttggccag 300
gggaccaagc tggagatcaa a                                     321

```

<210> 356

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 356

```

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 Gln Ser Ile Ser Ser Trp
20     25     30
Leu Ala Trp Tyr Gln Gln Arg Pro Gly Lys Ala Pro Lys Leu Leu Ile
35     40     45
Tyr Lys Ala Ser Ser Leu Glu Gly 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
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Trp Tyr
85     90     95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100    105

```

<210> 357

<211> 354

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 357

```

gagggtgcagc tgggtggagtc tgggggagggc ctggtcaagc ctgggggggtc cctgagactc 60
tccctgtgcag cctctggatt caccctcagt agctatagca tgaactgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcatcc attagtagta gtagtagtta catatactac 180
ccagcctcag tggagggggc attgagcctc tccagagaga cggggagggc ctgagctatc 240

```

```
gcagactcag tgaagggctg attcaacacc tccagagaca acgccaagaa cccactgcac 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagggc 300
agtagcagac tttttgacta ctggggccaa ggaaccctgg tcaccgtctc ctca 354
```

<210> 358

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 358

```
Glu 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 Ser Tyr
 20             25             30

Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35             40             45
Ser Ser Ile Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp 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 Val Tyr Tyr Cys
 85             90             95
Ala Arg Glu Gly Ser Ser Arg Leu Phe Asp Tyr Trp Gly Gln Gly Thr
100             105             110
Leu Val Thr Val Ser Ser
115
```

<210> 359

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 359

```
gacatccaga tgaccacgac tccttccacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtc gagtattagt agctgggtgg cctgggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctataag gcgtctagtt tagaaagtgg ggtcccatca 180
agggtcagcg gcagtggatc tgggacagaa ttcactctca ccacagcag cctgcagcct 240
gatgattttg caacttatta ctgccaacag tataatagtt attggtacac ttttggccag 300
gggaccaagc tggagatcaa a 321
```

<210> 360

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 360

```
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 Gln Ser Ile Ser Ser 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 Glu 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 Asn Ser Tyr Trp Tyr
      85      90      95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
      100      105

```

<210> 361

<211> 384

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 361

```

cagggtgcacc tgggtggagtc tggggggaggc ttggtcaagc ctggagggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt gaccactaca tgagctggat ccgccaggct 120
ccagggaagg ggctggagtg gatttcatac attagtaatg atgggtgtac caaatactat 180
gtggactctg tggaggggccg attcatcatt tccaggggaca acgccaagaa ctcattgtat 240
ctacatatga acagcctcag agccgacgac acggccgtgt attactgtgc gagagatcag 300
ggatatattg gctacgactc gtattattac tatttctacg gtatggacgt ctgggggcaa 360
gggaccacgg tcaccgtcgc ctca                                     384

```

<210> 362

<211> 128

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 362

```

Gln Val His 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 His
      20      25      30
Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
      35      40      45
Ser Tyr Ile Ser Asn Asp Gly Gly Thr Lys Tyr Tyr Val Asp Ser Val
      50      55      60
Glu Gly Arg Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
      65      70      75      80
Leu His Met Asn Ser Leu Arg Ala Asp Asp Thr Ala Val Tyr Tyr Cys
      85      90      95
Ala Arg Asp Gln Gly Tyr Ile Gly Tyr Asp Ser Tyr Tyr Tyr Tyr Ser
      100      105      110
Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ala Ser
      115      120      125

```

<210> 363

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 363

ggattcacct tcagtgacca ctac 24

<210> 364

$\langle 211 \rangle$ 8

<212> PRT

<213> Artificial Sequence

$\langle 220 \rangle$

<223> Synthetic

<400> 364

Gly Phe Thr Phe Ser Asp His Tyr
1 5

<210> 365

<211> 24

<212> DNA

<213> Artificial Sequence

$\langle 220 \rangle$

<223> Synthetic

<400> 365

attagtaatg atggtggtac caaa 24

<210> 366

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 366

Ile Ser Asn Asp Gly Gly Thr Lys
1 5

<210> 367

<211> 63

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 367

gcgagagatc agggatatat tggctacgac tcgtattatt actattccta cggtatggac 60
ata 63

guc

uu

<210> 368

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 368

Ala	Arg	Asp	Gln	Gly	Tyr	Ile	Gly	Tyr	Asp	Ser	Tyr	Tyr	Tyr	Tyr	Ser
1				5					10					15	
Tyr	Gly	Met	Asp	Val											
			20												

<210> 369

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 369

```

aaaattgtgt tgacgcagtc tccaggcacc ctgcctttgt ttccagggga aagagccacc 60
ctctcctgta gggccagtca gagtgttaac aacaaattct tagcctggta ccagcagaaa 120
tctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
gacaggttca gtggcagtgg gtctgggacc gacttcactc tcaccatcag cggactggag 240
cctgaagatt ttgaagtgtg ttattgtcaa gtatatggta actcactcac tctcggcgga 300
gggaccaagg tggagatcaa g                                     321

```

<210> 370

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 370

Lys	Ile	Val	Leu	Thr	Gln	Ser	Pro	Gly	Thr	Leu	Pro	Leu	Phe	Pro	Gly
1				5					10					15	
Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser	Gln	Ser	Val	Asn	Asn	Lys
			20					25					30		
Phe	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Ser	Gly	Gln	Ala	Pro	Arg	Leu	Leu
		35					40					45			
Ile	Tyr	Gly	Ala	Ser	Ser	Arg	Ala	Thr	Gly	Ile	Pro	Asp	Arg	Phe	Ser
	50					55					60				
Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Gly	Leu	Glu
65					70				75					80	
Pro	Glu	Asp	Phe	Glu	Val	Tyr	Tyr	Cys	Gln	Val	Tyr	Gly	Asn	Ser	Leu
			85					90					95		
Thr	Leu	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys					
			100					105							

<210> 371

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 371

cagagtgtta acaacaaatt c 21

<210> 372

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 372

Gln Ser Val Asn Asn Lys Phe
1 5

<210> 373

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 373

ggtgcatcc 9

<210> 374

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 374

Gly Ala Ser
1

<210> 375

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 375

caagtatatg gtaactcact cact 24

<210> 376

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 376

Gln Val Tyr Gly Asn Ser Leu Thr
1 5

<210> 377

<211> 384

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 377

```

cagggtgcagc tgggtggagtc tggggggaggc ttgggtcaagc ctggagggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt gaccactaca tgagctggat ccgccaggct 120
ccagggaagg ggcctggagt gatttcatac attagtaatg atggtggtac caaatactat 180
gtggactctg tggagggcog attcatcatt tccagggaca acgccaagaa ctcattgtat 240
ctacatatga acagcctcag agccgacgac acggccgtgt attactgtgc gagagatcag 300
ggatatattg gctacgactc gtattattac tatttcctacg gtatggacgt ctggggccaa 360
gggaccacgg tcaccgtctc ctca 384

```

<210> 378

<211> 128

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 378

```

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 His
20 25 30
Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45
Ser Tyr Ile Ser Asn Asp Gly Gly Thr Lys Tyr Tyr Val Asp Ser Val
50 55 60
Glu Gly Arg Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80
Leu His Met Asn Ser Leu Arg Ala Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

```

Ala Arg Asp Gln Gly Tyr Ile Gly Tyr Asp Ser Tyr Tyr Tyr Tyr Ser
 100 105 110
 Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> 379

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 379

```

gaaattgtgt tgacgcagtc tccaggcacc ctgcctttgt ttccagggga aagagccacc 60
ctctcctgta gggccagtc gagtggtaac aacaaattct tagcctggta ccagcagaaa 120
tctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatcca 180
gacaggttca gtggcagtg gtctgggacc gacttcactc tcaccatcag cggactggag 240
cctgaagatt ttgaagtgt ttattgtcaa gtatatggta actcactcac tctcgcgga 300
gggaccaagg tggagatcaa a                                     321

```

<210> 380

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 380

```

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Pro Leu Phe Pro Gly
 1           5           10           15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Asn Asn Lys
          20           25           30
Phe Leu Ala Trp Tyr Gln Gln Lys Ser Gly Gln Ala Pro Arg Leu Leu
          35           40           45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
          50           55           60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Gly Leu Glu
          65           70           75           80
Pro Glu Asp Phe Glu Val Tyr Tyr Cys Gln Val Tyr Gly Asn Ser Leu
          85           90           95
Thr Leu Gly Gly Thr Lys Val Glu Ile Lys
          100           105

```

<210> 381

<211> 384

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 381

```

cagggtgcagc tgggtggagtc tgggggaggo ttgggtcaagc ctggagggtc cctgagactc 60
tctctgtgcag cctctggatt caccttcagt gaccactaca tgagctggat ccgccaggct 120
ccagggaagg ggctggagtg ggtttcatac attagtaatg atggtgtgtac caaatactac 180
gcagactctg tgaagggccg attcaccatc tccagggaca acgccaagaa ctcactgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gagagatcag 300

```

ggatatattg gctacgactc gtattattac tattcctacg gtatggacgt ctgggggcaa 360
 gggaccacgg tcaccgtctc ctca 384

<210> 382

<211> 128

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 382

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	His
			20					25					30		
Tyr	Met	Ser	Trp	Ile	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
		35					40					45			
Ser	Tyr	Ile	Ser	Asn	Asp	Gly	Gly	Thr	Lys	Tyr	Tyr	Ala	Asp	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	Val	Tyr	Tyr	Cys
			85					90					95		
Ala	Arg	Asp	Gln	Gly	Tyr	Ile	Gly	Tyr	Asp	Ser	Tyr	Tyr	Tyr	Tyr	Ser
			100				105					110			
Tyr	Gly	Met	Asp	Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser
		115					120					125			

<210> 383

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 383

gaaattgtgt tgaacgagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
 ctctcctgca gggccagtc gagtggtaac aacaaattct tagcctggta ccagcagaaa 120
 cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatocca 180
 gacaggttca gtggcagtggt gtctgggaca gacttcactc tcaccatcag cagactggag 240
 cctgaagatt ttgcagtgtt ttactgtcaa gtatatggta actcactcac tttcggcgga 300
 gggaccaagg tggagatcaa a 321

<210> 384

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 384

Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Gly	Thr	Leu	Ser	Leu	Ser	Pro	Gly
1				5					10					15	
Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser	Gln	Ser	Val	Asn	Asn	Lys
			20					25				30			
Phe	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu
		25					30				35				

```

      30      40      50
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
  50      55      60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
  65      70      75      80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Val Tyr Gly Asn Ser Leu
      85      90      95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
      100      105

```

<210> 385

<211> 360

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 385

```

gaggtgcaga aggtggagtc tgggggaggc ctggtcaagc cggggggggtc cctgagactc 60
tcctgtacag cctctggatt caccttcagt acttataaca tgaattgggt ccgccaggct 120
ccaggaagg gactggagtg ggtctcatcc attaggagta gtagtaatta catatactac 180
gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagaa ttactgtat 240
ctgcaaatga acagcctgag agccgatgac acggctgtgt attactgtgc gagagatggc 300
agcagttggt acgactactc tgactactgg ggccagggaa ccctggtcac cgtctctca 360

```

<210> 386

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 386

```

Glu Val Gln Lys Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
  1      5      10      15
Ser Leu Arg Leu Ser Cys Thr Ala Ser Gly Phe Thr Phe Ser Thr Tyr
      20      25      30
Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
      35      40      45
Ser Ser Ile Arg Ser Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp 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 Asp Asp Thr Ala Val Tyr Tyr Cys
      85      90      95
Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln
      100      105      110
Gly Thr Leu Val Thr Val Ser Ser
      115      120

```

<210> 387

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 387

ggattcacct tcagtactta taac 24

<210> 388

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 388

Gly Phe Thr Phe Ser Thr Tyr Asn
1 5

<210> 389

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 389

attaggagta gtagtaatta cata 24

<210> 390

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 390

Ile Arg Ser Ser Ser Asn Tyr Ile
1 5

<210> 391

<211> 39

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 391

gcgagagatg gcagcagttg gtacgactac tctgactac 39

<210> 392

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 392

Ala	Arg	Asp	Gly	Ser	Ser	Trp	Tyr	Asp	Tyr	Ser	Asp	Tyr
1				5					10			

<210> 393

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 393

gacatccaga	tgaccacagtc	tocttccacc	ctgtctgcat	ctgtaggaga	cagagtcacc	60
atcacttgcc	gggccagtc	gagtattagt	agctgggttg	cctgggtatca	acagatacca	120
gggaaagccc	ctaaactcct	gatctataag	gcgtctagtt	tagaaaatgg	ggtcccatca	180
aggttcacgc	gcagtggatc	tgggacagaa	ttcactctca	tcatacagcag	cctgcagcct	240
gatgatattg	caacttatta	ctgccaacag	tatattagtt	attctcggac	gttcggccaa	300
gggaccaagg	tggaatcaa	a				321

<210> 394

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 394

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	Gln	Ser	Ile	Ser	Ser	Trp
		20						25				30			
Leu	Ala	Trp	Tyr	Gln	Gln	Ile	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
		35					40				45				
Tyr	Lys	Ala	Ser	Ser	Leu	Glu	Asn	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50				55					60					
Ser	Gly	Ser	Gly	Thr	Glu	Phe	Thr	Leu	Ile	Ile	Ser	Ser	Leu	Gln	Pro
65				70					75					80	
Asp	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	Ile	Ser	Tyr	Ser	Arg
			85					90					95		
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys					
		100						105							

<210> 395

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 395

cagagtatta gtagctgg 18

<210> 396

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 396

Gln Ser Ile Ser Ser Trp
1 5

<210> 397

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 397

aaggcgtct 9

<210> 398

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 398

Lys Ala Ser
1

<210> 399

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 399

caacagtata ttagttattc tcggacg 27

<210> 400

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 400

Gln Gln Tyr Ile Ser Tyr Ser Arg Thr
1 5

<210> 401

<211> 360

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 401

gaggtgcagc tgggtggagtc tggggggaggc ctgggtcaagc cggggggggtc cctgagactc 60
tcctgtacag cctctggatt caccttcagt acttataaca tgaattgggt ccgccaggct 120
ccagggaagg gactggagtg ggtctcatcc attaggagta gtagtaatta catatactac 180
gcagactcag tgaagggccg attcaccatc tccagagaca acgccaaagaa ttcactgtat 240
ctgcaaatga acagcctgag agccgatgac acggctgtgt attactgtgc gagagatggc 300
agcagttggt acgactactc tgactactgg ggccaggga ccttggtcac cgtctcctca 360

<210> 402

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 402

Glu 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 Thr Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30
Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Ser Ile Arg Ser Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp 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 Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln
100 105 110
Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 403

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 403

```

gacatccaga tgacccagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtc gagtattagt agctgggttg cctgggtatca acagatacca 120
gggaaagccc ctaaactcct gatctataag gcgtctagtt tagaaaatgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca tcacagcag cctgcagcct 240
gatgattttg caacttatta ctgccaacag tatattagtt attctcggac gtcgggcaa 300
gggaccaagg tggaaatcaa a 321

```

<210> 404

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 404

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 Gln Ser Ile Ser Ser Trp
20           25           30
Leu Ala Trp Tyr Gln Gln Ile Pro Gly Lys Ala Pro Lys Leu Leu Ile
35           40           45
Tyr Lys Ala Ser Ser Leu Glu Asn Gly Val Pro Ser Arg Phe Ser Gly
50           55           60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Ile Ile Ser Ser Leu Gln Pro
65           70           75           80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ile Ser Tyr Ser Arg
85           90           95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100          105

```

<210> 405

<211> 360

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 405

```

gaggtgcagc tgggtggagtc tgggggaggc ctggtcaagc ctggggggtc cctgagactc 60
tcctgtgcag cctctggatt caocttcagt acttataaca tgaactgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcatcc attaggagta gtagtaatta catatactac 180
gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagaa ctcactgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatggc 300
agcagttggt acgactactc tgactactgg ggccaaggaa cctgggtcac cgtctctca 360

```

<210> 406

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 406

```

Glu 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 Thr Tyr
 20           25           30
Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35           40           45
Ser Ser Ile Arg Ser Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp 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 Val Tyr Tyr Cys
 85           90           95
Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln
100           105           110
Gly Thr Leu Val Thr Val Ser Ser
115           120

```

<210> 407

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 407

```

gacatccaga tgaccagtc tccctccacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtca gaggattagt agctgggtgg cctgggtatca gcagaaacca 120
gggaaagccc ctaagtcct gatctataag gcgtctagtt tagaaagtgg ggtcccatca 180
agggtcagcg gcagtggtatc tgggacagaa ttactctctca ccacagcag cctgcagcct 240
gatgattttg caacttatta ctgccaacag tatattagtt attctcggac gttcggccaa 300
gggaccaagg tggaaatcaa a                                     321

```

<210> 408

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 408

```

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 Gln Ser Ile Ser Ser 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 Glu 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

```

```

      50      100      150      200
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ile Ser Tyr Ser Arg
      85      90      95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
      100      105

```

<210> 409

<211> 360

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 409

```

gaggtgcagc tgggtggagtc tggggggaggc ctgggtcaagc cggggggggtc cctgagactc 60
tcctgtacag cctctggatt caccttcagt acttataaca tgaattgggt ccgccaggct 120
ccagggaagg gactggagtg ggtctcatcc attaggagta gtagtaatta catatactac 180
gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagaa ttcactgtat 240
ctgcaaatga acagcctgag agccgatgac acggctgtgt attactgtgc gagagatggc 300
agcagttggt acgactactc tgactactgg ggccaggga ccttggtcac cgtctcctca 360

```

<210> 410

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 410

```

Glu 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 Thr Ala Ser Gly Phe Thr Phe Ser Thr Tyr
 20      25      30
Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35      40      45
Ser Ser Ile Arg Ser Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp 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 Asp Asp Thr Ala Val Tyr Tyr Cys
 85      90      95
Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln
100      105      110
Gly Thr Leu Val Thr Val Ser Ser
115      120

```

<210> 411

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 411

ggattcacct tcagtactta taac

<210> 412

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 412

Gly Phe Thr Phe Ser Thr Tyr Asn
1 5

<210> 413

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 413

attaggagta gtagtaatta cata 24

<210> 414

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 414

Ile Arg Ser Ser Ser Asn Tyr Ile
1 5

<210> 415

<211> 39

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 415

gcgagagatg gcagcagttg gtacgactac tctgactac 39

<210> 416

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 416

Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr
1 5 10

<210> 417

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 417

gacatccaga tgaccacagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtc gagtattagt agctgggtgg cctgggtatca acagatacca 120
gggaaagccc ctaaaactcct gatctataag gcgtctagtt tagaaaatgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca tcatcagcag cctgcagcct 240
gatgattttg caacttatta ctgccaacag tatattagtt attctcggac gttcggccaa 300
gggaccaagg tggaaatcaa a 321

<210> 418

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 418

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 Gln Ser Ile Ser Ser Trp
20 25 30
Leu Ala Trp Tyr Gln Gln Ile Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Lys Ala Ser Ser Leu Glu Asn Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Ile Ile Ser Ser Leu Gln Pro
65 70 75 80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ile Ser Tyr Ser Arg

85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> 419

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 419

cagagtatta gtagctgg 18

<210> 420

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 420

Gln Ser Ile Ser Ser Trp
1 5

<210> 421

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 421

aaggcgtct 9

<210> 422

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 422

Lys Ala Ser
1

<210> 423

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 423

caacagtata ttagttattc tcggacg 27

<210> 424

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 424

Gln Gln Tyr Ile Ser Tyr Ser Arg Thr
1 5

<210> 425

<211> 360

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 425

gaggtgcagc tgggtggagtc tggggggaggc ctggtcaagc cggggggggtc cctgagactc 60
tcctgtacag cctctggatt caccctcagt acttataaca tgaattgggt ccgccaggct 120
ccagggaagg gactggagtg ggtctcatcc attaggagta gtagtaatta catatactac 180
gcagactcag tgaagggccg attcaccatc tccagagaca acgccaaagaa ttactgttat 240
ctgcaaatga acagcctgag agccgatgac acggctgtgt attactgtgc gagagatggc 300
agcagttggt acgactactc tgactactgg ggccaggga ccttggtcac cgtctctcca 360

<210> 426

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 426

Glu	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	Thr	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Thr	Tyr		
			20					25					30				
Asn	Met	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val		
		35					40					45					
Ser	Ser	Ile	Arg	Ser	Ser	Ser	Asn	Tyr	Ile	Tyr	Tyr	Ala	Asp	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	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys		
			85					90						95			
Ala	Arg	Asp	Gly	Ser	Ser	Trp	Tyr	Asp	Tyr	Ser	Asp	Tyr	Trp	Gly	Gln		
			100					105						110			
Gly	Thr	Leu	Val	Thr	Val	Ser	Ser										
		115					120										

<210> 427

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 427

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gacatccaga tgaccagtc tocttcacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtc gagtattagt agctgggttg cctgggtatc acagatacca 120
gggaaagccc ctaaactcct gatctataag gcgtctagtt tagaaaatgg ggtcccatca 180
agggtcagcg gcagtggatc tgggacagaa ttcactctca tcatcagcag cctgcagcct 240
gatgatattg caacttatta ctgccaacag tatattagtt attctcggac gttcggccaa 300
gggaccaagg tggaatcaa a 321

```

<210> 428

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 428

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
-      5      10      15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
      20      25      30
Leu Ala Trp Tyr Gln Gln Ile Pro Gly Lys Ala Pro Lys Leu Leu Ile
      35      40      45
Tyr Lys Ala Ser Ser Leu Glu Asn Gly Val Pro Ser Arg Phe Ser Gly
      50      55      60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Ile Ile Ser Ser Leu Gln Pro
      65      70      75      80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ile Ser Tyr Ser Arg
      85      90      95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
      100      105

```

<210> 429

<211> 360

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 429

```

gagggtgcagc tgggtggagtc tgggggaggc ctgggtcaagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt acttataaca tgaactgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcatcc attaggagta gtagtaatta catatactac 180
gcagactcag tgaaggggcg attcaccatc tccagagaca acgccaagaa ctactgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatggc 300
agcagttggc acgactactc tgactactgg ggccaaggaa cctgggtcac cgtctcctca 360

```

<210> 430

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 430

Glu 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 Thr Tyr
      20             25             30
Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
      35             40             45
Ser Ser Ile Arg Ser Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp 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 Val Tyr Tyr Cys
      85             90             95
Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln
      100            105            110
Gly Thr Leu Val Thr Val Ser Ser
      115            120

```

<210> 431

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 431

```

gacatccaga tgacccagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtc gagtattagt agctggttgg cctgggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctataag gcgtctagtt tagaaagtgg ggtcccatca 180
agggtcagcg gcagtggatc tgggacagaa ttcactctca ccacagcag cctgcagcct 240
gatgatattg caacttatta ctgccaacag tatattagtt attctcggac gttcggccaa 300
gggaccaagg tggaaatcaa a                                     321

```

<210> 432

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 432

```

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 Gln Ser Ile Ser Ser 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 Glu 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 Ile Ser Tyr Ser Arg
      85             90             95

```

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 433

<211> 360

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 433

gagggtgcagc tgggtggagtc tggggggagggc ctgggtcaagc cggggggggtc cctgagactc 60
 tcctgtacag cctctggatt cacccttcagt acttataaca tgaattgggt cggccaggct 120
 ccagggaagg gactggagtg ggtctccatcc attaggagta gtagtaatta catatactac 180
 gcagactcag tgaaggggccg attcaccatc tccagagaca acgccaagag ttcactgtat 240
 ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatggc 300
 agcagttggc acgactactc tgactactgg ggccagggaa ccctgggtcac cgtctcctca 360

<210> 434

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 434

Glu 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 Thr Ala Ser Gly Phe Thr Phe Ser Thr Tyr
 20 25 30
 Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ser Ile Arg Ser Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser 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 Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 435

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 435

ggattcacct tcagtactta taac 24

<210> 436

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 436

Gly Phe Thr Phe Ser Thr Tyr Asn
1 5

<210> 437

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 437

attaggagta gtagtaatta cata 24

<210> 438

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 438

Ile Arg Ser Ser Ser Asn Tyr Ile
1 5

<210> 439

<211> 39

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 439

gcgagagatg gcagcagttg gtacgactac tctgactac 39

<210> 440

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 440

Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr
 1 5 10

<210> 441

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 441

gacatccaga tgaccacgtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc 60
 atcacttgcc gggccagtc gagtattagt agctgggtgg cctgggtatca acaggtagca 120
 gggaaagccc ctaaactcct gatctataag gcgtctagtt tagaaaatgg ggtcccatca 180
 aggttcagcg gcagtggtgc tgggacagaa ttcactctca tcacagcag cctgcagcct 240
 gatgattttg caacttatta ctgccaacag tatattagtt attctcggac gttcggccaa 300
 gggaccaagg tggaaatcaa a 321

<210> 442

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 442

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 Gln Ser Ile Ser Ser Trp
 20 25 30
 Leu Ala Trp Tyr Gln Gln Val Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Lys Ala Ser Ser Leu Glu Asn Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Glu Phe Thr Leu Ile Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ile Ser Tyr Ser Arg
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 443

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 443

cagagtatta gtagctgg 18

<210> 444

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 444

Gln Ser Ile Ser Ser Trp
1 5

<210> 445

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 445

aaggcgtct 9

<210> 446

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 446

Lys Ala Ser
1

<210> 447

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 447

caacagtata ttagttattc tcggacg 27

<210> 448

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 448

Gln Gln Tyr Ile Ser Tyr Ser Arg Thr
 1 5

<210> 449

<211> 360

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 449

gagggtgcagc tgggtggagtc tggggggaggc ctgggtcaagc cggggggggtc cctgagactc 60
 tcctgtacag cctctggatt caccttcagt acttataaca tgaattgggt ccgccaggct 120
 ccagggaagg gactggagtg ggtctcatcc attaggagta gtagtaatta catatactac 180
 gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagag ttcactgtat 240
 ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatggc 300
 agcagttggt acgactactc tgactactgg ggccaggga cctgggtcac cgtctcctca 360

<210> 450

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 450

Glu 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 Thr Ala Ser Gly Phe Thr Phe Ser Thr Tyr
 20 25 30
 Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ser Ile Arg Ser Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Ser 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 Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 451

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 451

```
gacatccaga tgaccagtc tccttcacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcaactggcc gggccagtc gagtattagt agctgggttg cctgggtatca acaggtacca 120
gggaaagccc ctaaaactcc gatctataag gcgtctagtt tagaaaatgg ggtcccatca 180
aggttcagcg gcagtggtgc tgggacagaa ttcactctca tcatcagcag cctgcagcct 240
gatgatittg caacttatta ctgccaacag tatattagtt attctcggac gttcggccaa 300
gggaccaagg tggaaatcaa a 321
```

<210> 452

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 452

```
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 Gln Ser Ile Ser Ser Trp
          20          25          30
Leu Ala Trp Tyr Gln Gln Val Pro Gly Lys Ala Pro Lys Leu Leu Ile
      35      40      45
Tyr Lys Ala Ser Ser Leu Glu Asn Gly Val Pro Ser Arg Phe Ser Gly
      50      55      60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Ile Ile Ser Ser Leu Gln Pro
65          70          75          80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ile Ser Tyr Ser Arg
          85          90          95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
      100      105
```

<210> 453

<211> 360

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 453

```
gagggtgcagc tgggtggagtc tggggggaggc ctgggtcaagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt acttataaca tgaactgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcatcc attaggagta gtagtaatta catatactac 180
gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagaa ctactgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatggc 300
agcagttggt acgactactc tgactactgg ggccagggaa ccctggtcac cgtctcctca 360
```

<210> 454

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 454

```

Glu 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 Thr Tyr
          20          25          30
Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
          35          40          45
Ser Ser Ile Arg Ser Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp 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 Val Tyr Tyr Cys
          85          90          95
Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln
          100          105          110
Gly Thr Leu Val Thr Val Ser Ser
          115          120

```

<210> 455

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 455

```

gacatccaga tgacccagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtc gagtattagt agctgggttg cctggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctataag gcgtctagtt tagaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatacagcag cctgcagcct 240
gatgattttg caacttatta ctgccaacag tatattagtt attctcggac gttcggccaa 300
gggaccaagg tggaaatcaa a                                     321

```

<210> 456

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 456

```

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 Gln Ser Ile Ser Ser 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 Glu 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 Ile Ser Tyr Ser Arg
          85          90          95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
          100          105

```

<210> 457

<211> 360

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 457

```

gaggtgcagc tgggtggagtc tgggggaggc ctggtcaagc cggggggggtc cctgagactc 60
tccgtgtacag cctctgggatt caccttcagt acttataaca tgaattgggt ccgccaggct 120
ccagggaagg gactggagtg ggtctcatcc attaggagta gtagtaatta catatactac 180
gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagaa ttcactgtat 240
ctgcaaatga acagcctgag agccgatgac acggctgtgt attactgtgc gagagatggc 300
agcagttggt acgactactc tgactactgg ggccagggaa ccttggtcac cgtctctca 360

```

<210> 458

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 458

```

Glu 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 Thr Ala Ser Gly Phe Thr Phe Ser Thr Tyr
 20           25           30
Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35           40           45
Ser Ser Ile Arg Ser Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp 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 Asp Asp Thr Ala Val Tyr Tyr Cys
 85           90           95
Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln
100           105           110
Gly Thr Leu Val Thr Val Ser Ser
115           120

```

<210> 459

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 459

```

ggattcacct tcagtactta taac          24

```

<210> 460

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 460

Gly Phe Thr Phe Ser Thr Tyr Asn
1 5

<210> 461

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 461

attaggagta gtagtaatta cata 24

<210> 462

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 462

Ile Arg Ser Ser Ser Asn Tyr Ile
1 5

<210> 463

<211> 39

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 463

gcgagagatg gcagcagttg gtacgactac tctgactac 39

<210> 464

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 464

Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr
 1 5 10

<210> 465

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 465

gacatccaga tgaccacagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc 60
 atcacttgcc gggccagtca gagtattagt agctgggtgg cctgggtatca acagatacca 120
 gggaaagccc ctaaaactcct gatctataag gcgtctagtt tagaaaatgg ggtcccatca 180
 aggttcagcg gcagtggatc tgggacagaa ttcactctca tcatcagcag cctgcagcct 240
 gatgattttg caacttatta ctgccaacag tatattagtt attctcggac gttcggccaa 300
 gggaccaagg tggaaatcaa a 321

<210> 466

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 466

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 Gln Ser Ile Ser Ser Trp
 20 25 30
 Leu Ala Trp Tyr Gln Gln Ile Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Lys Ala Ser Ser Leu Glu Asn Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Glu Phe Thr Leu Ile Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ile Ser Tyr Ser Arg
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 467

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 467

cagagtatta gtagctgg 18

<210> 468

<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 468
Gln Ser Ile Ser Ser Trp
1 5

<210> 469
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 469
aaggcgtct 9

<210> 470
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 470
Lys Ala Ser
1

<210> 471
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 471
caacagtata ttagttattc tcggacg 27

<210> 472
<211> 9
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 472

Gln Gln Tyr Ile Ser Tyr Ser Arg Thr
 1 5

<210> 473

<211> 360

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 473

gaggtgcagc tgggtggagtc tggggggaggc ctggtcaagc cggggggggtc cctgagactc 60
 tcctgtacag cctctggatt caccttcagt acttataaca tgaattgggt ccgccaggct 120
 ccaggaagg gactggagtg ggtctcatcc attaggagta gtagtaatta catatactac 180
 gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagaa ttcactgtat 240
 ctgcaaatga acagcctgag agccgatgac acggctgtgt attactgtgc gagagatggc 300
 agcagttggt acgactactc tgactactgg ggccagggaa ccctggtcac cgtctctca 360

<210> 474

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 474

Glu 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 Thr Ala Ser Gly Phe Thr Phe Ser Thr Tyr
 20 25 30
 Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ser Ile Arg Ser Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp 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 Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln
 100 105 110
 Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> 475

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 475

```

gacatccaga tgacccagtc tccctccacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtc gagtattagt agctgggttg cctgggtatca acagatacca 120
gggaaagccc ctaaactcct gatctataag gcgtctagtt tagaaaatgg ggtcccatca 180
agggttcagcg gcagtggtatc tgggacagaa ttcactctca tcatcagcag cctgcagcct 240
gatgattttg caacttatta ctgccaacag tatattagtt attctcggac gttcggccaa 300
gggaccaagg tggaaatcaa a                                     321

```

<210> 476

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 476

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 Gln Ser Ile Ser Ser Trp
20           25           30
Leu Ala Trp Tyr Gln Gln Ile Pro Gly Lys Ala Pro Lys Leu Leu Ile
35           40           45
Tyr Lys Ala Ser Ser Leu Glu Asn Gly Val Pro Ser Arg Phe Ser Gly
50           55           60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Ile Ile Ser Ser Leu Gln Pro
65           70           75           80
Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ile Ser Tyr Ser Arg
85           90           95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100          105

```

<210> 477

<211> 360

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 477

```

gagggtgcagc tgggtggagtc tgggggaggc ctgggtcaagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctgggatt caccttcagt acttataaca tgaactgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcatcc attaggagta gtagtaatta catatactac 180
gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagaa ctactgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatggc 300
agcagttggt acgactactc tgactactgg ggccaaggaa ccttggtcac cgtctcctca 360

```

<210> 478

<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 478

```

Glu 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 Thr Tyr
 20          25          30
Asn Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35          40          45
Ser Ser Ile Arg Ser Ser Ser Asn Tyr Ile Tyr Tyr Ala Asp 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 Val Tyr Tyr Cys
 85          90          95
Ala Arg Asp Gly Ser Ser Trp Tyr Asp Tyr Ser Asp Tyr Trp Gly Gln
100          105          110
Gly Thr Leu Val Thr Val Ser Ser
115          120

```

<210> 479

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 479

```

gacatccaga tgaccagtc tccctccacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtc gagtattagt agctggttg cctgggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctataag gcgtctagtt tagaaagtgg ggtcccatca 180
aggttcagcg gcagtggtatc tgggacagaa ttactctca ccatcagcag cctgcagcct 240
gatgatattg caacttatta ctgccaacag tatattagtt attctcggac gttcggccaa 300
gggaccaagg tggaaatcaa a 321

```

<210> 480

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 480

```

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 Gln Ser Ile Ser Ser 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 Glu 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 Ile Ser Tyr Ser Arg
 85          90          95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100          105

```

<210> 481

<211> 354

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 481

```
gaggtgcaac tagtggagtc tgggggaggc ttggtacagc ctgggggggc cctgagactc 60
tcctgtgtag tctctggatt caccctcggg gactacgaca tgcactgggt ccgtcaagct 120
acaggaagag gtctggagtg ggtctcaggt attgctcctg ctggtgacac atcctataca 180
ggctccgtga agggccgatt caccatctcc agagagaatg ccaagaactc cttgcatctt 240
caaatgaaca gcctgacaac cggggacacg gctatatatt attgtgctag agaggatata 300
gcagtgcctg gttttgatta ctggggccag ggaaccctgg tcaccgtctc ctca      354
```

<210> 482

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 482

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
      . . .

  1           5           10           15
Ser Leu Arg Leu Ser Cys Val Val Ser Gly Phe Thr Phe Gly Asp Tyr
      20           25           30
Asp Met His Trp Val Arg Gln Ala Thr Gly Arg Gly Leu Glu Trp Val
      35           40           45
Ser Gly Ile Ala Pro Ala Gly Asp Thr Ser Tyr Thr Gly Ser Val Lys
      50           55           60
Gly Arg Phe Thr Ile Ser Arg Glu Asn Ala Lys Asn Ser Leu His Leu
      65           70           75           80
Gln Met Asn Ser Leu Thr Thr Gly Asp Thr Ala Ile Tyr Tyr Cys Ala
      85           90           95
Arg Glu Asp Ile Ala Val Pro Gly Phe Asp Tyr Trp Gly Gln Gly Thr
      100          105          110
Leu Val Thr Val Ser Ser
      115
```

<210> 483

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 483

```
ggattcacct tcggtgacta cgac      24
```

<210> 484

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 484

Gly	Phe	Thr	Phe	Gly	Asp	Tyr	Asp
1				5			

<210> 485

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 485

attgctcctg ctggtgacac a 21

<210> 486

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 486

Ile	Ala	Pro	Ala	Gly	Asp	Thr
1				5		

<210> 487

<211> 36

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 487

gctagagagg atatagcagt gcctggtttt gattac 36

<210> 488

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 488

Ile	Ala	Pro	Ala	Gly	Asp	Thr
-----	-----	-----	-----	-----	-----	-----

Ala Arg Glu Asp Ile Ala Val Pro Gly Phe Asp Tyr
 1 5 10

<210> 489

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 489

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga acgaggcacc 60
 ctctcctgca gggccagtca gagtggttagc agcaacttag cctggtacca gcagaaacct 120
 ggccaggctc ccagactcct catctatggt gcatccacga gggeccactgg ctcccagcc 180
 aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240
 gaagattttg cagtttatta ctgtcagcag tataataagt ggccctccgtt cactttcggc 300
 cctgggacca aagtggattt caaa 324

<210> 490

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 490

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1 5 10 15
 Glu Arg Gly Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
 20 25 30
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45
 Tyr Gly Ala Ser Thr Arg Ala Thr Gly Phe Pro Ala Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
 65 70 75 80
 Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Lys Trp Pro Pro
 85 90 95

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

<210> 491

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 491

cagagtgtta gcagcaac 18

<210> 492

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 492

Gln Ser Val Ser Ser Asn
1 5

<210> 493

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 493

ggtgcatcc 9

<210> 494

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 494

Gly Ala Ser
1

<210> 495

<211> 30

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 495

cagcagtata ataagtggcc tccgttcact 30

<210> 496

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 496

Gln	Gln	Tyr	Asn	Lys	Trp	Pro	Pro	Phe	Thr
1				5					10

<210> 497

<211> 354

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 497

gaggtgcaac	tagtggagtc	tgggggaggg	ttggtacagc	ctgggggggtc	cctgagactc	60
tcctgtgtag	tctctggatt	caccttcggg	gactacgaca	tgcactgggt	ccgtcaagct	120
acaggaagag	gtctggagtg	ggtctcaggt	attgctcctg	ctggtgacac	atcctataca	180
ggctccgtga	agggccgatt	caccatctcc	agagagaatg	ccaagaactc	cttgcattct	240
caaatgaaca	gcctgacaac	cggggacacg	gctatatatt	attgtgctag	agaggatata	300
gcagtgcctg	gttttgatta	ctggggccag	ggaaccctgg	tcaccgtctc	ctca	354

<210> 498

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 498

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1				5						10				15	
Ser	Leu	Arg	Leu	Ser	Cys	Val	Val	Ser	Gly	Phe	Thr	Phe	Gly	Asp	Tyr
		20						25					30		
Asp	Met	His	Trp	Val	Arg	Gln	Ala	Thr	Gly	Arg	Gly	Leu	Glu	Trp	Val
		35					40					45			
Ser	Gly	Ile	Ala	Pro	Ala	Gly	Asp	Thr	Ser	Tyr	Thr	Gly	Ser	Val	Lys
	50					55					60				
Gly	Arg	Phe	Thr	Ile	Ser	Arg	Glu	Asn	Ala	Lys	Asn	Ser	Leu	His	Leu
65					70				75					80	
Gln	Met	Asn	Ser	Leu	Thr	Thr	Gly	Asp	Thr	Ala	Ile	Tyr	Tyr	Cys	Ala
			85					90						95	
Arg	Glu	Asp	Ile	Ala	Val	Pro	Gly	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
			100					105					110		
Leu	Val	Thr	Val	Ser	Ser										
			115												

<210> 499

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 499

```

gaaatagtga tgaacgcagtc tccagccacc ctgtctgtgt ctccagggga acgagggcacc 60
ctctctctgca gggccagtcga gagggttagc agcaacttag cctggtacca gcagaaacct 120
ggccaggctc ccagactcct catctatggt gcatccacga gggccactgg cttcccagcc 180
agggtcagtg gcagtggggc tgggacagag ttcactctca ccatcagcag cctgcagtct 240
gaagattttg cagtttatta ctgtcagcag tataataagt ggctccggt cactttcggc 300
cctgggacca aagtggatat caaa                                     324

```

<210> 500

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 500

```

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1           5           10           15
Glu Arg Gly Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
          20           25           30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
          35           40           45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Phe Pro Ala Arg Phe Ser Gly
          50           55           60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65           70           75           80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Lys Trp Pro Pro
          85           90           95
Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
          100          105

```

<210> 501

<211> 354

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 501

```

gagggtgcagc tgggtggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt caccctcggt gactacgaca tgcactgggt ccgccaagct 120
acaggaaaag gtctggagtg ggtctcagct attgctcctg ctggtgacac atactatcca 180
ggctccgtga agggccgatt caccatctcc agagaaaatg ccaagaactc cttgtatctt 240
caaatgaaca gcctgagagc cggggacacg gctgtgtatt actgtgctag agaggatata 300
gcagtgccctg gttttgatta ctggggccaa ggaaccctgg tcaccgtctc ctca      354

```

<210> 502

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 502

```

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

```

```

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

Asp Met His Trp Val Arg Gln Ala Thr Gly Lys Gly Leu Glu Trp Val
    35                      40                      45
Ser Ala Ile Ala Pro Ala Gly Asp Thr Tyr Tyr Pro Gly Ser Val Lys
    50                      55                      60
Gly Arg Phe Thr Ile Ser Arg Glu Asn Ala Lys Asn Ser Leu Tyr Leu
    65                      70                      75                      80
Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys Ala
    85                      90                      95
Arg Glu Asp Ile Ala Val Pro Gly Phe Asp Tyr Trp Gly Gln Gly Thr
    100                      105                      110
Leu Val Thr Val Ser Ser
    115

```

<210> 503

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 503

```

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
ctctcctgca gggccagtcg gactgttagc agcaacttag cctggtagca gcagaaacct 120
ggccaggtgc ccaggctcct catctatggt gcatccacca gggccactgg tatccagacc 180
aggttcagtg gcagtggtgc tgggacagag ttcactctca ccatcagcag cctgcagtct 240
gaagattttg cagtttatta ctgtcagcag tataataagt ggctccgtt cactttcggc 300
cctgggacca aagtgatat caaa                               324

```

<210> 504

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 504

```

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
  1           5           10           15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
    20           25           30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
    35           40           45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50           55           60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
    65           70           75           80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Lys Trp Pro Pro
    85           90           95
Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
    100          105

```

<210> 505

<211> 378

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 505

```

caaattctgc tgggtgcaatc tggacctgag gtgaaggagc ctggggcctc agtgaaggtc 60
tcctgcaagg ctcttggtta cacctttacc aactacgcta tcagctgggt gcgacaggtc 120
cctggacaag ggcttgagtg gatgggatgg gtcagcgctt acaatgggtc cacaactat 180
gcacatgaag tccagggcag agtcaccatg accacagaca catccacgac cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccatgt attactgtgc gagagggggt 300
gtagtcgtgc cagttgctcc ccacttctac aacggtatgg acgtctgggg ccaagggacc 360
acggtcaccc tctctca                                     378

```

<210> 506

<211> 126

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 506

```

Gln Ile Leu Leu Val Gln Ser Gly Pro Glu Val Lys Glu 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
Ala Ile Ser Trp Val Arg Gln Val Pro Gly Gln Gly Leu Glu Trp Met
 35             40             45
Gly Trp Val Ser Ala Tyr Asn Gly His Thr Asn Tyr Ala His Glu Val
 50             55             60
Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Thr Thr Ala Tyr
 65             70             75             80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Met Tyr Tyr Cys
 85             90             95
Ala Arg Gly Gly Val Val Val Pro Val Ala Pro His Phe Tyr Asn Gly
100            105            110
Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115            120            125

```

<210> 507

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 507

```

ggttacacct ttaccaacta cgct          24

```

<210> 508

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 508

Gly Tyr Thr Phe Thr Asn Tyr Ala
1 5

<210> 509

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 509

gtcagcgctt acaatggtca caca 24

<210> 510

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 510

Val Ser Ala Tyr Asn Gly His Thr
1 5

<210> 511

<211> 57

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 511

gcgagagggg gtgtagtcgt gccagttgct cccacttct acaacggtat ggacgtc 57

<210> 512

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 512

Ala Arg Gly Gly Val Val Val Pro Val Ala Pro His Phe Tyr Asn Gly

1 5 10 15
Met Asp Val

<210> 513

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 513

```
gatatgtga tgactcagtt tccactctcc ctgcccgta cccctggaga gccggcctcc 60
atctcctgca ggtctagtca gagcctcctg catattaatg aatacaacta tttggattgg 120
tacctaaaga agccagggca gtctccacag ctctgatct atttgggttt taatcgggcc 180
tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggctgagga tgttggggtc tattactgca tgcaagctct tcaaactccg 300
tggacgttag gcccaaggac caaggtggaa atcaaaa 336
```

<210> 514

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 514

```
Asp Ile Val Met Thr Gln Phe Pro Leu Ser Leu Pro Val Thr Pro Gly
1                      5                      10                      15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ile
20                      25                      30
Asn Glu Tyr Asn Tyr Leu Asp Trp Tyr Leu Lys Lys Pro Gly Gln Ser
35                      40                      45
Pro Gln Leu Leu Ile Tyr Leu Gly Phe Asn Arg Ala Ser Gly Val Pro
50                      55                      60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                      70                      75                      80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85                      90                      95
Leu Gln Thr Pro Trp Thr Leu Gly Gln Gly Thr Lys Val Glu Ile Lys
100                      105                      110
```

<210> 515

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 515

```
cagagcctcc tgcattataa tgaatacaac tat 33
```

<210> 516

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 516

Gln	Ser	Leu	Leu	His	Ile	Asn	Glu	Tyr	Asn	Tyr
1				5					10	

<210> 517

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 517

ttgggtttt	9
-----------	---

<210> 518

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 518

Leu	Gly	Phe
1		

<210> 519

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 519

atgcaagctc	ttcaaactcc	gtggacg	27
------------	------------	---------	----

<210> 520

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 520

Met Gln Ala Leu Gln Thr Pro Trp Thr
 1 5

<210> 521

<211> 378

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 521

cagggttcagc tgggtgcagtc tggacctgag gtgaaggagc ctggggcctc agtgaaggtc 60
 tcctgcaagg cttctgggta caccctttacc aactacgcta tcagctgggt gcgacaggtc 120
 cctggacaag ggcttgagtg gatgggatgg gtcagcgctt acaatgggtc cacaaactat 180
 gcacatgaag tccagggcag agtcaccatg accacagaca catccacgac cacagcctac 240
 atggagctga ggagcctgag atctgacgac acggccatgt attactgtgc gagaggggggt 300
 gtagtcgtgc cagttgctcc ccacttctac aacggtatgg acgtctgggg ccaagggacc 360
 acggtcaccg tctcctca 378

<210> 522

<211> 126

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 522

Gln Val Gln Leu Val Gln Ser Gly Pro Glu Val Lys Glu 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
 Ala Ile Ser Trp Val Arg Gln Val Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Trp Val Ser Ala Tyr Asn Gly His Thr Asn Tyr Ala His Glu Val
 50 55 60
 Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Thr Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Met Tyr Tyr Cys
 85 90 95
 Ala Arg Gly Gly Val Val Val Pro Val Ala Pro His Phe Tyr Asn Gly
 100 105 110
 Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> 523

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 523

```

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
atctcctgca ggtctagtc gagcctcctg catattaatg aatacaacta ttgggattgg 120
tacctaaaga agccagggca gtctccacag ctctgatct atttgggttt taatcgggoc 180
tccggggctc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaaac 240
agcagagtgg aggctgagga tgttgggggc tattactgca tgcaagctct tcaaactccg 300
tggacgttag gccaaaggac caaggtgga atcaaa 336

```

<210> 524

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 524

```

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1           5           10           15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ile
20          25          30
Asn Glu Tyr Asn Tyr Leu Asp Trp Tyr Leu Lys Lys Pro Gly Gln Ser
35          40          45
Pro Gln Leu Leu Ile Tyr Leu Gly Phe Asn Arg Ala Ser Gly Val Pro
50          55          60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65          70          75          80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85          90          95
Leu Gln Thr Pro Trp Thr Leu Gly Gln Gly Thr Lys Val Glu Ile Lys
100         105         110

```

<210> 525

<211> 378

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 525

```

caggttcagc tgggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctggtta cacctttacc aactacgcta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg gtcagcgctt acaatgggtc cacaaactat 180
gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagaggggggt 300
gtagtcgtgc cagttgctcc ccacttctac aacggtatgg acgtctgggg gcaagggacc 360
acggtcaccg tctctctca
378

```

<210> 526

<211> 126

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 526

```

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
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35          40          45
Gly Trp Val Ser Ala Tyr Asn Gly His Thr Asn Tyr Ala Gln Lys Leu
 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 Gly Gly Val Val Val Pro Val Ala Pro His Phe Tyr Asn Gly
100          105          110
Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115          120          125

```

<210> 527

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 527

```

gatattgtga tgactcagtc tccactctcc ctgcccgctca cccctggaga gccggcctcc 60
atctcctgca ggctctagtc gagcctcctg catattaatg aatacaacta ttgggattgg 120
tacctgcaga agccagggca gtctccacag ctctgatct atttgggttc taatcggggc 180
tccgggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggctgagga tgttgggggt tattactgca tgcaagctct tcaaactccg 300
tggacgttcg gccaaaggac caaggtggaa atcaaaa 336

```

<210> 528

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 528

```

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1          5          10          15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ile
 20          25          30
Asn Glu Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
 35          40          45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
 50          55          60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65          70          75          80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
 85          90          95
Leu Gln Thr Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100          105          110

```

<210> 529

<211> 351

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 529

```

gagggtgcagc tgggtggagtc tggggggaggc ttggtacagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt caccctaagt agctacgaca tgcactgggt ccgccaagca 120
acaggaaaag gtctggagtg ggtctcagct attggcagta ctggtgacac atactataca 180
ggctccgtga tgggccgatt caccatctcc agagacgctg ccaaaaactc cttctatctt 240
gaaatgaaca gcctgagagt cggggacacg gctgtatatt actgtgcaag agaggggaata 300
agaacacctt atgattattg gggccaggga gcccggtca ccgtctcctc a 351

```

<210> 530

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 530

```

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1      5      10      15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Ser Tyr
20     25     30
Asp Met His Trp Val Arg Gln Ala Thr Gly Lys Gly Leu Glu Trp Val
35     40     45
Ser Ala Ile Gly Ser Thr Gly Asp Thr Tyr Tyr Thr Gly Ser Val Met
50     55     60
Gly Arg Phe Thr Ile Ser Arg Asp Ala Ala Lys Asn Ser Phe Tyr Leu
65     70     75     80
Glu Met Asn Ser Leu Arg Val Gly Asp Thr Ala Val Tyr Tyr Cys Ala
85     90     95
Arg Glu Gly Ile Arg Thr Pro Tyr Asp Tyr Trp Gly Gln Gly Ala Arg
100    105    110
Val Thr Val Ser Ser
115

```

<210> 531

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 531

```

ggattcaccc taagtagcta cgac      24

```

<210> 532

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 532

Gly	Phe	Thr	Leu	Ser	Ser	Tyr	Asp
1				5			

<210> 533

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 533

attggcagta ctggtgacac a 21

<210> 534

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 534

Ile	Gly	Ser	Thr	Gly	Asp	Thr
1				5		

<210> 535

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 535

gcaagagagg gaataagaac accctatgat tat 33

<210> 536

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 536

gla gaa gln gln ala ala thr thr thr thr thr thr

Ala Arg Glu Gly Ile Arg Thr Pro Tyr Asp Tyr
 1 5 10

<210> 537

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 537

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
 ctctcctgca gggccagtc gagtgtagc agcaatgtag cctggtagca gcagaaacct 120
 ggccaggttc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc 180
 aggttcagtg gcagtgggtc tgggacagaa ttcactctca ccatcagcag cctgcagtct 240
 gaagatcttg cagtttatta ctgtcagcag tataataatt ggctccatt cactttcggc 300
 cctgggacca aagtggatat caaa 324

<210> 538

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 538

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
 20 25 30
 Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45
 Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
 65 70 75 80
 Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Pro
 85 90 95
 Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
 100 105

<210> 539

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 539

cagagtgtta gcagcaat 18

<210> 540

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 540

Gln	Ser	Val	Ser	Ser	Asn
1				5	

<210> 541

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 541

ggtgcatcc	9
-----------	---

<210> 542

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 542

Gly	Ala	Ser
1		

<210> 543

<211> 30

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 543

cagcagtata	ataattggcc	tccattcact	30
------------	------------	------------	----

<210> 544

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 544

Gln Gln Tyr Asn Asn Trp Pro Pro Phe Thr
 1 5 10

<210> 545

<211> 351

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 545

gaggtgcagc tgggtggagtc tggggggaggc ttggtacagc ctgggggggtc cctgagactc 60
 tcctgtgcag cctctggatt caccctaagt agctacgaca tgcactgggt ccgccaagca 120
 acaggaaaag gtctggagtg ggtctcagct attggcagta ctgggtgacac atactataca 180
 ggctccgtga tgggcccagatt caccatctcc agagacgctg ccaaaaaactc cttctatctt 240
 gaaatgaaca gcctgagagt cggggacacg gctgtatatt actgtgcaag agagggaata 300
 agaacaccct atgattattg gggccaggga accctggtea ccgtctcttc a 351

<210> 546

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 546

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Ser Tyr
 20 25 30
 Asp Met His Trp Val Arg Gln Ala Thr Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Gly Ser Thr Gly Asp Thr Tyr Tyr Thr Gly Ser Val Met
 50 55 60
 Gly Arg Phe Thr Ile Ser Arg Asp Ala Ala Lys Asn Ser Phe Tyr Leu
 65 70 75 80
 Glu Met Asn Ser Leu Arg Val Gly Asp Thr Ala Val Tyr Tyr Cys Ala
 85 90 95
 Arg Glu Gly Ile Arg Thr Pro Tyr Asp Tyr Trp Gly Gln Gly Thr Leu
 100 105 110
 Val Thr Val Ser Ser
 115

<210> 547

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 547

aaaataagtaa taacqcaqtc tccaqccacc ctgtctgtgt ctccaqqqqa aaqaqccacc 60

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ctctcctgca gggccagtca gagtgttagc agcaatgtag cctggtacca gcagaaacct 120
ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc 180
agggttcagt gcaagtgggtc tgggacagaa ttcaactctca ccatcagcag cctgcagtct 240
gaagattttg cagtttatta ctgtcagcag tataataatt ggcctccatt cactttcggc 300
cctgggacca aagtggatat caaa 324

```

<210> 548

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 548

```

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1      5      10      15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
      20      25      30

```

```

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
      35      40      45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
      50      55      60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
      65      70      75      80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Pro
      85      90      95
Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
      100      105

```

<210> 549

<211> 351

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 549

```

gaggtgcagc tgggtggagtc tggggggaggc ttggtacagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt caccctaagt agctacgaca tgcactgggt ccgccaaagct 120
acaggaaaag gtctggagtg ggtctcagct attggcagta ctggtgacac atactatcca 180
ggctccgtga agggccgatt caccatctcc agagaaaatg ccaagaactc cttgtatctt 240
caaatgaaca gctgagagc cggggacacg gctgtgtatt actgtgcaag agaggggaata 300
agaacacct atgattatlg gggccaagga accctggtea ccgtctctc a 351

```

<210> 550

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 550

```

Glu Val Gln Leu Val Gly Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

```

```

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1          5          10          15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Ser Tyr
          20          25          30
Asp Met His Trp Val Arg Gln Ala Thr Gly Lys Gly Leu Glu Trp Val
          35          40          45
Ser Ala Ile Gly Ser Thr Gly Asp Thr Tyr Tyr Pro Gly Ser Val Lys
          50          55          60
Gly Arg Phe Thr Ile Ser Arg Glu Asn Ala Lys Asn Ser Leu Tyr Leu
65          70          75          80
Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys Ala
          85          90          95
Arg Glu Gly Ile Arg Thr Pro Tyr Asp Tyr Trp Gly Gln Gly Thr Leu
          100          105          110
Val Thr Val Ser Ser
          115

```

<210> 551

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 551

```

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
ctctcctgca gggccagtc gagtgtagc agcaatttag cctggtacca gcagaaacct 120
ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc 180
aggttcagtg gcagtgggtc tgggacagag ttactctca ccatcagcag cctgcagtct 240
gaagattttg cagtttatta ctgtcagcag tataataatt ggcctccatt cactttcggc 300
cctgggacca aagtgatat caaa                                     324

```

<210> 552

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 552

```

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1          5          10          15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
          20          25          30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
          35          40          45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
          50          55          60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65          70          75          80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Pro
          85          90          95
Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
          100          105

```

<210> 553

<211> 351

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 553

```

gaggtgcagc tgggtggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctgggatt caccctaagt agctacgaca tgcactgggt ccgccaagca 120
acagaaaaag gtctggagtg ggtctcagct attggcagta ctggtgacac atactataca 180
ggctccgtga tgggccgatt caccatctcc agagacgctg ccaaaaactc cttctatctt 240
gaaatgaaca gcctgagagt cggggacacg gctgtatatt actgtgcaag agaggggaata 300
agaacaccccl atgattattg gggccaggga gcccggtca cgtctcctc a 351

```

<210> 554

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 554

```

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1             5             10             15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Ser Tyr
      20             25             30
Asp Met His Trp Val Arg Gln Ala Thr Gly Lys Gly Leu Glu Trp Val

      35             40             45
Ser Ala Ile Gly Ser Thr Gly Asp Thr Tyr Tyr Thr Gly Ser Val Met
      50             55             60
Gly Arg Phe Thr Ile Ser Arg Asp Ala Ala Lys Asn Ser Phe Tyr Leu
65             70             75             80
Glu Met Asn Ser Leu Arg Val Gly Asp Thr Ala Val Tyr Tyr Cys Ala
      85             90             95
Arg Glu Gly Ile Arg Thr Pro Tyr Asp Tyr Trp Gly Gln Gly Ala Arg
      100            105            110
Val Thr Val Ser Ser
      115

```

<210> 555

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 555

```

ggattcacc c taagtagcta cgac 24

```

<210> 556

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 556

Gly Phe Thr Leu Ser Ser Tyr Asp
1 . 5

<210> 557

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 557

attggcagta ctggtgacac a 21

<210> 558

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 558

Ile Gly Ser Thr Gly Asp Thr
1 5

<210> 559

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 559

gcaagagagg gaataagaac accctatgat tat 33

<210> 560

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 560

Ala Arg Glu Gly Ile Arg Thr Pro Tyr Asp Tyr
1 . 5 10

<210> 561

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 561

```

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcaatgtag cctggtacca gcagaaacct 120
ggccaggctc ccaggctcct catctatggg gcatccacca gggccactgg tatcccagcc 180
aggttcagtg gcagtgggtc tgggacagaa ttcaactctca ccatcagcag cctgcagtct 240
gaagattttg cagtttatta ctgtcagcag tataataatt ggcctccatt cactttcggc 300
cctgggacca aagtggatat caaa                                     324

```

<210> 562

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 562

```

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1             5             10             15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
 20             25             30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35             40             45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50             55             60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
 65             70             75             80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Pro
 85             90             95
Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100             105

```

<210> 563

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 563

```

cagagtgtta gcagcaat          18

```

<210> 564

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 564

Gln Ser Val Ser Ser Asn
1 5

<210> 565

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 565

ggtgcatcc 9

<210> 566

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 566

Gly Ala Ser
1

<210> 567

<211> 30

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 567

cagcagtata ataattggcc tccattcact 30

<210> 568

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 568

Gln Gln Tyr Asn Asn Trp Pro Pro Phe Thr
 1 5 10

<210> 569

<211> 351

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 569

gagggtgcagc tgggtggagtc tgggggagggc ttggtacagc ctgggggggtc cctgagactc 60
 tcctgtgcag cctctggatt caccctaagt agctacgaca tgcactgggt cgcgccaagca 120
 acaggaaaag gtctggagtg ggtctcagct attggcagta ctggtgacac atactataca 180
 ggctccgtga tgggccgatt caccatctcc agagaogctg ccaaaaactc ctctatctt 240
 gaaatgaaca gcctgagagt cggggacacg gctgtatatt actgtgcaag agagggaata 300
 agaacaccct atgattattg gggccaggga accctggta cgtctcctc a 351

<210> 570

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 570

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Ser Tyr
 20 25 30
 Asp Met His Trp Val Arg Gln Ala Thr Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Gly Ser Thr Gly Asp Thr Tyr Tyr Thr Gly Ser Val Met
 50 55 60
 Gly Arg Phe Thr Ile Ser Arg Asp Ala Ala Lys Asn Ser Phe Tyr Leu
 65 70 75 80
 Glu Met Asn Ser Leu Arg Val Gly Asp Thr Ala Val Tyr Tyr Cys Ala
 85 90 95
 Arg Glu Gly Ile Arg Thr Pro Tyr Asp Tyr Trp Gly Gln Gly Thr Leu
 100 105 110
 Val Thr Val Ser Ser
 115

<210> 571

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 571

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
 ctctcctgca gggccagtc gagtgtagc agcaatgtag cctggtacca gcagaaacct 120

```

ggccagggtc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc 180
aggttcagtg gcagtgggtc tgggacagaa ttcaactctca ccatcagcag cctgcagtct 240
gaagattttg cagtttatta ctgtcagcag tataataatt ggccctccatt cactttcggc 300
cctgggacca aagtggatat caaa 324

```

<210> 572

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 572

```

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1           5           10           15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20          25          30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35          40          45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50          55          60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65          70          75          80
Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Pro
85          90          95
Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100         105

```

<210> 573

<211> 351

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 573

```

gaggtgcagc tgggtggagtc tggggggaggc ttggtacagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt caccctaagt agctacgaca tgcaactgggt ccgccaagct 120
acaggaaaag gtctggagtg ggtctcagct attggcagta ctggtgacac atactatcca 180
ggctccgtga agggccgatt caccatctcc agagaaaatg ccaagaactc cttgtatctt 240
caaatgaaca gctgagagc cggggacacg gctgtgtatt actgtgcaag agaggggaata 300
agaacacctt atgattattg gggccaagga accctgggtca cgtctcctc a 351

```

<210> 574

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 574

```

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1           5           10           15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu Ser Ser Tyr
20          25          30

```

Asp Met His Trp Val Arg Gln Ala Thr Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Gly Ser Thr Gly Asp Thr Tyr Tyr Pro Gly Ser Val Lys
 50 55 60

Gly Arg Phe Thr Ile Ser Arg Glu Asn Ala Lys Asn Ser Leu Tyr Leu
 65 70 75 80
 Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys Ala
 85 90 95
 Arg Glu Gly Ile Arg Thr Pro Tyr Asp Tyr Trp Gly Gln Gly Thr Leu
 100 105 110
 Val Thr Val Ser Ser
 115

<210> 575

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 575

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60
 ctctcctgca gggccagtc gagtggttagc agcaatttag cctggtacca gcagaaacct 120
 ggccaggtgc ccaggctcct catctatggt gcatccacca gggccactgg tatccagacc 180
 aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240
 gaagattttg cagtttatta ctgtcagcag tataataatt ggcctccatt cactttcggc 300
 cctgggacca aagtggatat caaa 324

<210> 576

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 576

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
 20 25 30
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45
 Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
 65 70 75 80
 Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Pro
 85 90 95
 Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
 100 105

<210> 577

<211> 363

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 577

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gaagtgcagc tgggtggagtc tgggggaggg ttggtacagc ctggcaggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat gattatgccg tgcactgggt ccggcaagct 120
ccaggaaggg gcctggagtg ggtctcaggt attaatgga acagtggtag cataggctat 180

```

```

ggcgactctg tgaaggggcg attcaccatc tccagagaca acgccaagca ctccctgtat 240
ctgcaaatga acagtctgag acctgaggac acggccttgt attactgtgt aaaagaggtg 300
actacgggat actactacgg tatggacgtc tggggccaag ggaccacggt caccgtctcc 360
tca 363

```

<210> 578

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 578

```

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1      5      10      15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20     25     30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35     40     45
Ser Gly Ile Asn Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
50     55     60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys His Ser Leu Tyr
65     70     75     80
Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Leu Tyr Tyr Cys
85     90     95
Val Lys Glu Val Thr Thr Gly Tyr Tyr Gly Met Asp Val Trp Gly
100    105    110
Gln Gly Thr Thr Val Thr Val Ser Ser
115    120

```

<210> 579

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 579

```

ggattcacct ttgatgatta tgcc      24

```

<210> 580

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 580

Gly Phe Thr Phe Asp Asp Tyr Ala
 1 5

<210> 581

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 581

attaattgga acagtggtag cata 24

<210> 582

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 582

Ile Asn Trp Asn Ser Gly Ser Ile
 1 5

<210> 583

<211> 42

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 583

gtaaaagagg tgactacggg atactactac ggtatggacg tc 42

<210> 584

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 584

Val Lys Glu Val Thr Thr Gly Tyr Tyr Tyr Gly Met Asp Val
 1 5 10

<210> 585

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 585

```

gacatccagt tgaccagtc tccatccttc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgct gggccagtc gggcattagc agttatttag cctgggtatca gaaaaaacca 120
gggaaagccc ctaacctcct gatctatgat gcatccactt tgcaaagtgg ggtcccatca 180
aggtttcagcg gcagtggatc tgggacagaa ttcactctca cactcagcag cctgcagcct 240
gaagattttg caacttatta ctgtcaacag cttaatattt acccattcac ttcgggcct 300
gggaccaaag tggatatcaa a 321

```

<210> 586

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 586

```

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1           5           10           15
Asp Arg Val Thr Ile Thr Cys Trp Ala Ser Gln Gly Ile Ser Ser Tyr
20          25          30
Leu Ala Trp Tyr Gln Lys Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
35          40          45
Tyr Asp Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50          55          60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Leu Ser Ser Leu Gln Pro
65          70          75          80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ile Tyr Pro Phe
85          90          95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100         105

```

<210> 587

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 587

cagggcatta gcagttat 18

<210> 588

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 588

Gln	Gly	Ile	Ser	Ser	Tyr
1				5	

<210> 589

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 589

gatgcatcc	9
-----------	---

<210> 590

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 590

Asp	Ala	Ser
1		

<210> 591

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 591

caacagctta	atatttacc	attcact	27
------------	-----------	---------	----

<210> 592

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 592

Gln	Gly	Ile	Ser	Ser	Tyr	Met	Pro	His	Met
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

Gln Gln Leu Asn Ile Tyr Pro Phe Thr
1 5

<210> 593

<211> 363

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 593

```
gaagtgcagc tgggtggagtc tggggggaggc ttggtacagc ctggcaggcc cctgagactc 60
tcctgtgcag cctctggatt caccctttgat gattatgccg tgcactgggt ccggcaagct 120
ccaggggaagg gcctggagtg ggtctcaggt attaattgga acagtggtag cataggctat 180
gggactctg tgaagggccg attcaccatc tccagagaca acgccaagca ctccctgtat 240
ctgcaaatga acagtctgag acctgaggac acggccttgt attactgtgt aaaagagggtg 300
actacgggat actactacgg tatggacgtc tggggccaag ggaccacggt caccgtctcc 360
tca
```

<210> 594

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 594

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Gly Ile Asn Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys His Ser Leu Tyr

65 70 75 80
Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95
Val Lys Glu Val Thr Thr Gly Tyr Tyr Tyr Gly Met Asp Val Trp Gly
100 105 110
Gln Gly Thr Thr Val Thr Val Ser Ser
115 120
```

<210> 595

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 595

```
gacatccagt tgaccacgac tccatccttc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgct gggccagtcg gggcattagc agttatttag cctggatatca gaaaaaacca 120
gggaagccc ctacccctct gctctatgat gcctccactt tgcaaatgga ggtcccatca 180
```

```

gggaaagccc ctacccccct gacccatgac gacccacccc tgcacagcgg ggcacaccca 100
aggttcagcg gcagtggtac tgggacagaa ttactctctca cactcagcag cctgcagcct 240
gaagattttg caacttatta ctgtcaacag cttaatatatt acccattcac ttccggccct 300
gggaccaaag tggatatcaa a                                     321

```

<210> 596

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 596

```

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
1      5      10      15
Asp Arg Val Thr Ile Thr Cys Trp Ala Ser Gln Gly Ile Ser Ser Tyr
20     25     30
Leu Ala Trp Tyr Gln Lys Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
35     40     45
Tyr Asp Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50     55     60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Leu Ser Ser Leu Gln Pro
65     70     75     80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ile Tyr Pro Phe
85     90     95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100    105

```

<210> 597

<211> 363

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 597

```

gaagtgcagc tgggtggagtc tggggggaggc ttggtacagc ctggcaggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120
ccagggaagg gctctggagt ggtctcaggt attaatgga acagtggtag cataggctat 180
gcggactctg tgaagggccg attcaccatc tcagagaca acgccaagaa ctccctgtat 240

ctgcaaatga acagtctgag agctgaggac acggccttgt attactgtgt aaaagaggtg 300
actacgggat actactacgg tatggacgtc tgggggcaag ggaccacggt caccgtctcc 360
tca                                     363

```

<210> 598

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 598

```

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1      5      10      15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Asn Tyr

```

```

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Thr Thr Thr Asp Asp Tyr
  20          25          30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
  35          40          45
Ser Gly Ile Asn Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp 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
Val Lys Glu Val Thr Thr Gly Tyr Tyr Tyr Gly Met Asp Val Trp Gly
  100          105          110
Gln Gly Thr Thr Val Thr Val Ser Ser
  115          120

```

<210> 599

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 599

```

gacatccagt tgaccacgtc tccatccttc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtca gggcattagc agttatttag cctgggtatca gcaaaaacca 120
gggaaagccc ctaagctcct gatctatgat gcatccactt tgcaaagtgg ggtcccatca 180
agggttcagcg gcagtggatc tgggacagaa ttactcttca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtcaacag cttaatatatt acccattdac ttccggccct 300
gggaccaaag tggatatcaa a                                     321

```

<210> 600

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 600

```

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
  1          5          10          15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
  20          25          30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
  35          40          45
Tyr Asp Ala Ser Thr Leu Gln 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
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Asn Ile Tyr Pro Phe
  85          90          95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
  100          105

```

<210> 601

<211> 366

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 601

```

gaggtgcagt tgttggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60
tctgtgcag cctctggatt cactttagt agctatgcc tgaactgggt ccgccaggct 120
ccagggaagg ggctggattg ggtctcaggt atcagtggta atggtggtag cactactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca ttccaagaa cacgtgtat 240
gtgcaaatgc acagcctgag agtcgaggac acggccggtt actactgtgc gaaagcccg 300
tattacgatt tttggggggg gaatttcgat ctctggggcc gtggcaccca ggtcactgtc 360
tcctca

```

<210> 602

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 602

```

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1      5      10      15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20     25     30
Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Asp Trp Val
35     40     45
Ser Gly Ile Ser Gly Asn Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50     55     60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Ile Ser Lys Asn Thr Leu Tyr
65     70     75     80
Val Gln Met His Ser Leu Arg Val Glu Asp Thr Ala Val Tyr Tyr Cys
85     90     95
Ala Lys Ala Arg Tyr Tyr Asp Phe Trp Gly Gly Asn Phe Asp Leu Trp
100    105    110
Gly Arg Gly Thr Gln Val Thr Val Ser Ser
115    120

```

<210> 603

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 603

```

ggattcacgt ttagtagcta tgcc      24

```

<210> 604

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 604

Gly Phe Thr Phe Ser Ser Tyr Ala
1 5

<210> 605

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 605

atcagtggta atggtggtag cacc 24

<210> 606

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 606

Ile Ser Gly Asn Gly Gly Ser Thr
1 5

<210> 607

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 607

gcgaaagccc gttattacga ttttggggg gggaatttcg atctc 45

<210> 608

<211> 15

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 608

Ala Lys Ala Arg Tyr Tyr Asp Phe Trp Gly Gly Asn Phe Asp Leu
1 5 10 15

<210> 609

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 609

```

gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc atcagggtact tagcctggta tcagcagaaa 120
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggcac tggcatccca 180
gacaggttca gtgtcagtgt gtctgggaca gacttcactc tcaccatcac tagactggag 240
cctgaagatt ttgcagtcta ttactgtcag caatatggta gttcaccgct cactttcggc 300
ggagggacca aggtggagat caaa                                     324

```

<210> 610

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 610

```

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1             5             10             15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ile Arg
 20             25             30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
 35             40             45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
 50             55             60
Val Ser Val Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Arg Leu Glu
 65             70             75             80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
 85             90             95
Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100             105

```

<210> 611

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 611

cagagtgtta gcatcaggta c 21

<210> 612

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 612

Gln	Ser	Val	Ser	Ile	Arg	Tyr
1				5		

<210> 613

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 613

ggtgcatcc	9
-----------	---

<210> 614

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 614

Gly	Ala	Ser
1		

<210> 615

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 615

cagcaatatg	gtagttcacc	gctcact	27
------------	------------	---------	----

<210> 616

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 616

Gln	Gly	Met	Gln	Glu	Glu	Pro	Tyr	Met
-----	-----	-----	-----	-----	-----	-----	-----	-----

Gln Gln Tyr Gly Ser Ser Pro Leu Inr
 1 5

<210> 617

<211> 366

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 617

```
gaggtgcagt tgttggagtc tgggggaggc ttggtacagc ctgggggggc cctgagactc 60
tcctgtgcag cctctggatt cacgtttagt agctatgcca tgaactgggt ccgccaggct 120
ccagggaagg ggtctgattg ggtctcaggt atcagtggtg atggtggtag cacctactac 180
gcagactccg tgaaggcccg gttcaccatc tccagagaca ttccaagaa cacgtgtat 240
gtgcaaatgc acagcctgag agtcgaggac acggccggtt actactgtgc gaaagcccg 300
```

```
tattacgatt tttggggggg gaatttcgat ctctggggcc gtggcaccct ggtcactgtc 360
tcctca 366
```

<210> 618

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 618

```
Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Asp Trp Val
35 40 45
Ser Gly Ile Ser Gly Asn Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Ile Ser Lys Asn Thr Leu Tyr
65 70 75 80
Val Gln Met His Ser Leu Arg Val Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Lys Ala Arg Tyr Tyr Asp Phe Trp Gly Gly Asn Phe Asp Leu Trp
100 105 110
Gly Arg Gly Thr Leu Val Thr Val Ser Ser
115 120
```

<210> 619

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 619

```
gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
ctctctgaca gggccactca gactgttagc atcaggtact taccctgata taccagagaa 120
```

```

ctctccagca gggccagcca gagtgcagc accaggtacc cagccctggca ccagcagaaa 120
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
gacaggttca gtgtcagtggt gtctgggaca gacttcactc tcaccatcac tagactggag 240
cctgaagatt ttgcagtcta ttactgtcag caatatggta gttcaccgct cactttcggc 300
ggagggacca aggtggagat caaa 324

```

<210> 620

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 620

```

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1             5             10             15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ile Arg
             20             25             30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
             35             40             45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
             50             55             60

```

<210> 621

<211> 366

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 621

```

gaggtgcagc tggttgagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt cacttttagt agctatgcca tgagctgggt ccgccaggct 120
ccaggggaagg ggcctggagt ggtctcagct atcagtgga atggtggtag cactactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagcccg 300
tattacgatt tttggggggg gaatttcgat ctctggggcc gtggcaccct ggtoactgtc 360
tcctca 366

```

<210> 622

<211> 122

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 622

```

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1             5             10             15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
             20             25             30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
             35             40             45
Ser Ala Ile Ser Gly Asn Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
             50             55             60
Lys Gly Arg Phe Thr Ile 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 Lys Ala Arg Tyr Tyr Asp Phe Trp Gly Gly Asn Phe Asp Leu Trp
      100      105      110
Gly Arg Gly Thr Leu Val Thr Val Ser Ser
      115      120

```

<210> 623

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 623

```

gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc atcaggtact tagcctggta ccagcagaaa 120

```

```

cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgta ttactgtcag caatatggta gttcaccgct cactttcggc 300
ggagggacca aggtggagat caaaa                                324

```

<210> 624

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 624

```

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1      5      10      15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ile Arg
      20      25      30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
      35      40      45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
      50      55      60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65      70      75      80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
      85      90      95
Leu Thr Phe Gly Gly Thr Lys Val Glu Ile Lys
      100      105

```

<210> 625

<211> 381

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 625

```

caggttcagc tgggtgcagtc tggacctgag gtgaagaacc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctgggta cacctttacc acctatggta tcagttgggt acgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcggtt acaatggtaa aacaaacgat 180
gcacagaagt tccaggacag agtcgccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccatit attactgttc gagagatcgt 300
ttagtagtac cacctgccct ttattattcc tactacgtta tggacgtctg gggccaaggg 360
accacgggta ccgtctcctc a 381

```

<210> 626

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 626

```

Gln Val Gln Leu Val Gln Ser Gly Pro Glu Val Lys Asn Pro Gly Ala
 1           5           10           15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr 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 Gly Tyr Asn Gly Lys Thr Asn Asp Ala Gln Lys Phe

      50           55           60
Gln Asp Arg Val Ala 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 Ile Tyr Tyr Cys
      85           90           95
Ser Arg Asp Arg Leu Val Val Pro Pro Ala Leu Tyr Tyr Ser Tyr Tyr
      100          105          110
Val Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
      115          120          125

```

<210> 627

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 627

ggttacacct ttaccaccta tggt 24

<210> 628

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 628

```

Gly Tyr Thr Phe Thr Thr Tyr Gly
 1           6

```

1

3

<210> 629

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 629

atcagcgggtt acaatggtaa aaca 24

<210> 630

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 630

Ile Ser Gly Tyr Asn Gly Lys Thr
1 5

<210> 631

<211> 60

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 631

tcgagagatc gtttagtagt accacctgcc cttattatt cctactacgt tatggacgtc 60

<210> 632

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 632

Ser Arg Asp Arg Leu Val Val Pro Pro Ala Leu Tyr Tyr Ser Tyr Tyr
1 5 10 15
Val Met Asp Val
20

<210> 633

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 633

```

gatgttgtga tgactcagtc tccactctcc ctgcccgta cccttgaca gccggcctcc 60
atctcctgca ggtctagta aagcctcgta tacagtgatg gaaacaccta cttgaattgg 120
tttcagcaga ggccaggta atctccaagg cgcctaattt ataaggtttc taaccgggac 180
tctggggctc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc 240
agcaggggtg aggctgagga tgttgggggt tattactgca tgcaaggta acactggccg 300
tacacttttg gccaggggac caagctggag atcaaa 336

```

<210> 634

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 634

```

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1      5      10      15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
20     25     30
Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
35     40     45
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp Ser Gly Val Pro
50     55     60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65     70     75     80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
85     90     95
Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100    105    110

```

<210> 635

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 635

```

caaagcctcg tatacagtga tggaacacc tac 33

```

<210> 636

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 636

Gln	Ser	Leu	Val	Tyr	Ser	Asp	Gly	Asn	Thr	Tyr
1				5					10	

<210> 637

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 637

aaggtttct	9
-----------	---

<210> 638

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 638

Lys	Val	Ser
1		

<210> 639

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 639

atgcaaggta	cacactggcc	gtacact	27
------------	------------	---------	----

<210> 640

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 640

Met Gln Gly Thr His Trp Pro Tyr Thr
1 5

<210> 641

<211> 381

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 641

```
cagggtcagc tgggtgcagtc tggacctgag gtgaagaacc ctgggggcctc agtgaaggtc 60
tcttgcaagg cttctgggta caccctttacc acctatggta tcagttgggt acgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcgggt acaatggtaa aacaaacgat 180
gcacagaagt tocaggacag agtcgccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccattt attactgttc gagagatcgt 300
ttagtagtac caccctgccct ttattattcc tactacgtta tggacgtctg gggccaaggg 360
accacgggtca ccgtctcctc a 381
```

<210> 642

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 642

```
Gln Val Gln Leu Val Gln Ser Gly Pro Glu Val Lys Asn Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr 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 Gly Tyr Asn Gly Lys Thr Asn Asp Ala Gln Lys Phe
50 55 60
Gln Asp Arg Val Ala 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 Ile Tyr Tyr Cys
85 90 95
Ser Arg Asp Arg Leu Val Val Pro Pro Ala Leu Tyr Tyr Ser Tyr Tyr
100 105 110
Val Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125
```

<210> 643

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 643

```
gatgttgtga tgactcagtc tocactctcc ctgcccgtca cccttggaca gccgggcctcc 60
atctctgtga ggtctagtc aagcctcgta tacagtgatg gaaacaccta cttgaattgg 120
tttcagcaga ggccagggtca atctccaagg gcgctaattt ataaggtttc taaccgggac 180
tctggagctc cagacagatt cagcagcaat aatcagaca ctaatttcac actcaaaatc 240
```

```

ccggggggcc ccggccgggg ccggggggggc gggccggggc -----
agcagggtgg aggctgagga tggtgggggtt tattactgca tgcaaggtag acactggccg 300
tacacttttg gccagggggac caagctggag atcaaaa                               336

```

<210> 644

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 644

```

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
 1              5              10              15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
              20              25              30
Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
              35              40              45
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp Ser Gly Val Pro
              50              55              60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65              70              75              80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
              85              90              95
Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
              100              105              110

```

<210> 645

<211> 381

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 645

```

cagggttcagc tgggtgcagtc tggagctgag gtgaagaagc ctgggggcctc agtgaaggtc 60
tcctgcaagg cttctgggta cacccttacc acctatggta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcgggt acaatggtaa aacaaactat 180
gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgttc gagagatcgt 300
ttagtagtac caccctgccct ttattattcc tactacgtta tggacgtctg ggggcaaggg 360
accacgggtca cgtctcctc a                               381

```

<210> 646

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 646

```

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 Thr 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	Gly	Tyr	Asn	Gly	Lys	Thr	Asn	Tyr	Ala	Gln	Lys	Leu
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			
Ser	Arg	Asp	Arg	Leu	Val	Val	Pro	Pro	Ala	Leu	Tyr	Tyr	Ser	Tyr	Tyr
				100				105				110			
Val	Met	Asp	Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	
115				120				125							

<210> 647

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 647

gatgtttgtga	tgactcagtc	tccactctcc	ctgcccgta	ccttggaca	gccggcctcc	60
atctcctgca	ggtctagta	aagcctcgta	tacagtgatg	gaaacacctt	cttgaattgg	120
tttcagcaga	ggccaggcca	atctccaagg	cgctaattt	ataaggtttc	taaccgggac	180
tctgggggtc	cagacagatt	cagcggcagt	gggtcaggca	ctgatttcac	actgaaaatc	240
agcagggttg	aggtctagga	tgttggggtt	tattactgca	tgcaagggtac	acactggccg	300
tacacttttg	gccaggggac	caagctggag	atcaaa			336

<210> 648

$\langle 211 \rangle$ 112

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

<223> Synthetic

<400> 648

Asp	Val	Val	Met	Thr	Gln	Ser	Pro	Leu	Ser	Leu	Pro	Val	Thr	Leu	Gly
1				5					10					15	
Gln	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Leu	Val	Tyr	Ser
			20					25					30		
Asp	Gly	Asn	Thr	Tyr	Leu	Asn	Trp	Phe	Gln	Gln	Arg	Pro	Gly	Gln	Ser
		35					40					45			
Pro	Arg	Arg	Leu	Ile	Tyr	Lys	Val	Ser	Asn	Arg	Asp	Ser	Gly	Val	Pro
	50					55					60				
Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile
65				70					75					80	
Ser	Arg	Val	Glu	Ala	Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Met	Gln	Gly
			85						90					95	
Thr	His	Trp	Pro	Tyr	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys
			100					105					110		

<210> 649

<211> 381

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 649

```

cagggttcagc tgggtgcagtc tggacctgag gtgaagaacc ctggggcctc agtgaaggtc 60
tcttgcaagg cttctgggta cacccttacc acctatggta tcagttgggt acgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcgggt acaatggtaa aacaaacgat 180
gcacagaagt tccaggacag agtcgccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccattt attactgttc gagagatcgt 300
ttagtagtac caccctgccct taattattac tactacgtta tggacgtctg gggccaaggg 360
accaacgtca ccgtctctc a 381

```

<210> 650

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 650

```

Gln Val Gln Leu Val Gln Ser Gly Pro Glu Val Lys Asn Pro Gly Ala
 1           5           10           15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr 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 Gly Tyr Asn Gly Lys Thr Asn Asp Ala Gln Lys Phe
      50           55           60
Gln Asp Arg Val Ala 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 Ile Tyr Tyr Cys
      85           90           95
Ser Arg Asp Arg Leu Val Val Pro Pro Ala Leu Asn Tyr Tyr Tyr Tyr
      100          105          110
Val Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
      115          120          125

```

<210> 651

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 651

```

ggttacacct ttaccaccta tgggt          24

```

<210> 652

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 652

```

Gly Tyr Thr Phe Thr Thr Tyr Gly
 1           8

```

1

5

<210> 653

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 653

atcagcgggtt acaatggtaa aaca 24

<210> 654

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 654

Ile Ser Gly Tyr Asn Gly Lys Thr
1 5

<210> 655

<211> 60

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 655

tcgagagatc gtttagtagt accacctgcc cttaattatt actactacgt tatggacgtc 60

<210> 656

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 656

Ser Arg Asp Arg Leu Val Val Pro Pro Ala Leu Asn Tyr Tyr Tyr Tyr
1 5 10 15
Val Met Asp Val
20

<210> 657

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 657

```

gatgttgtga tgactcagtc tccactctcc ctgcccgtca cccttgagca gccggcctcc 60
atctcctgca ggtctagtc aagcctcgta tacagtgatg gaaacaccta cttgaattgg 120
tttcagcaga ggccagggtca atctccaagg cgcctaattt ataagggttc taaccgggac 180
tctgggggcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc 240
agcagggtgg aggctgagga tggtgggggt tattactgca tgcaaggtag acactggccg 300
tacacttttg gccaggggac caagctggag atcaaaa 336

```

- - -

<210> 658

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 658

```

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1      5      10      15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
20      25      30
Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
35      40      45
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp Ser Gly Val Pro
50      55      60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65      70      75      80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
85      90      95
Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100     105     110

```

<210> 659

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 659

```

caaagcctcg tatacagtga tggaaacacc tac 33

```

<210> 660

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 660

Gln	Ser	Leu	Val	Tyr	Ser	Asp	Gly	Asn	Thr	Tyr
1				5					10	

<210> 661

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 661

aaggtttct 9

<210> 662

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 662

Lys	Val	Ser
1		

<210> 663

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 663

atgcaaggta cacactggcc gtacact 27

<210> 664

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 664

Met Gln Gly Thr His Trp Pro Tyr Thr
1 5

<210> 665

<211> 381

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 665

```
caggttcagc tgggtgcagtc tggacctgag gtgaagaacc ctggggcctc agtgaaggtc 60
tccctgcaagg cttctgggta cacctttacc acctatggta tcagttgggt acgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcggtt acaatggtaa aacaaacgat 180
gcacagaagt tccaggacag agtcgccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgaagac acggccatctt attactgttc gagagatcgt 300
ttagtagtac cacctgccct taattattac tactacgtta tggacgtctg gggccaaggg 360
accacggtca ccgtctcctc a 381
```

<210> 666

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 666

```
Gln Val Gln Leu Val Gln Ser Gly Pro Glu Val Lys Asn Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr 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 Gly Tyr Asn Gly Lys Thr Asn Asp Ala Gln Lys Phe
50 55 60
Gln Asp Arg Val Ala 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 Ile Tyr Tyr Cys
85 90 95
Ser Arg Asp Arg Leu Val Val Pro Pro Ala Leu Asn Tyr Tyr Tyr Tyr
100 105 110
Val Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125
```

<210> 667

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 667

```
gatgttgatga tgactcagtc tccactctcc ctgcccgtca ccttgggaca gccggcctcc 60
atctcctgca ggtctagtca aagcctcgta tacagtgatg gaaacaccta cttgaattgg 120
```

```

tttcagcaga ggccagggtca atctccaagg cgcctaattt ataaggtttc taaccgggac 180
tctgggggtcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc 240
agcagggtgg aggtcgagga tggtggggtt tattactgca tgcaaggta acactggccg 300
tacacttttg gccaggggac caagctggag atcaaa 336

```

<210> 668

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 668

```

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1      5      10      15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
20     25     30
Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
35     40     45
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp Ser Gly Val Pro
50     55     60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65     70     75     80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
85     90     95
Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100    105    110

```

<210> 669

<211> 381

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 669

```

cagggtcagc tgggtcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tctgtcaagg cttctggtta cacctttacc acctatggta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcggtt acaatggtaa aacaaactat 180
gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgttc gagagatcgt 300
ttagtagtac cacctgccct taattattac tactacgtta tggacgtctg ggggcaaggg 360
accacggtca ccgtctcctc a 381

```

<210> 670

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 670

```

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 Thr 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 Gly Tyr Asn Gly Lys Thr Asn Tyr Ala Gln Lys Leu
 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
 Ser Arg Asp Arg Leu Val Val Pro Pro Ala Leu Asn Tyr Tyr Tyr Tyr
 100 105 110
 Val Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

<210> 671

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 671

gatgttggtga tgaactcagtc tccactctccc ctgcccggtca cccttgggaca gccgggctccc 60
 atctcctgca ggtctagtc aagcctcgta tacagtgatg gaaacaccta cttgaattgg 120
 ttccagcaga ggccaggcca atctccaagg cgcctaattt ataagggttc taaccgggac 180
 tctgggggtcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc 240
 agcaggggtgg aggcagagga tggtgggggtt tattactgca tgcaaggtag acactggccg 300
 tacacttttg gccaggggac caagctggag atcaaaa 336

<210> 672

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 672

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly

1 5 10 15
 Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
 20 25 30
 Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
 35 40 45
 Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp Ser Gly Val Pro
 50 55 60
 Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
 85 90 95
 Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105 110

<210> 673

<211> 381

<212> DNA

<213> Artificial Sequence

$\langle 220 \rangle$

<223> Synthetic

<400> 673

caggttcagc	tggtgcagtc	tggacctgag	gtgaagaacc	ctggggccctc	agtgaaggtc	60
tcttgcaagg	cttcttggtta	cacctttacc	acctatgtta	tcagttgggt	acacagagcc	120
ctcgacaag	ggcttgagtg	gatgggatg	atacggcgtt	acaattgttaa	aacaaacgat	180
gcacagaagt	tccaggagtg	atgocggcat	accacagaca	catccacgag	cacagcctac	240
atggagctga	ggaagcctgag	atctgacgac	acggccattt	attactgttc	gagagatcgt	300
ttagtagtac	cacctgcctt	ttattattac	tactacgtta	tggaagctctg	gggccaaagg	360
accacggtca	cgtctcctc	a				381

<210> 674

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 674

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Pro	Glu	Val	Lys	Asn	Pro	Gly	Ala
1			5						10					15	
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Thr	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	Gly	Tyr	Asn	Gly	Lys	Thr	Asn	Asp	Ala	Gln	Lys	Phe
	50					55					60				
Gln	Asp	Arg	Val	Ala	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	Ile	Tyr	Tyr	Cys
				85					90					95	
Ser	Arg	Asp	Arg	Leu	Val	Val	Pro	Pro	Ala	Leu	Tyr	Tyr	Tyr	Tyr	Tyr
				100				105					110		
Val	Met	Asp	Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	
			115				120					125			

<210> 675

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 675

ggttacacct ttaccaccta tggt 24

<210> 676

$\langle 211 \rangle$ 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 676

Gly Tyr Thr Phe Thr Thr Tyr Gly
1 5

<210> 677

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 677

atcagcgggtt acaatggtaa aaca 24

<210> 678

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 678

Ile Ser Gly Tyr Asn Gly Lys Thr
1 5

<210> 679

<211> 60

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 679

tcgagagatc gtttagtagt accacctgcc ctttattatt actactacgt tatggacgtc 60

<210> 680

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 680

Ser Arg Asp Arg Leu Val Val Pro Pro Ala Leu Tyr Tyr Tyr Tyr Tyr
1 5 10 15

Val Met Asp Val
20

<210> 681

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 681

```
gatgttgtga tgaactcagtc tcaactctcc ctgcccgtca cccctggaca gccggcctcc 60
atctcctgca ggtctagtc aagcctcgta tacagtgatg gaaacaccta cttgaattgg 120
tttcagcaga gcccaggcca atctccaagg cgctaattt ataaggtttc taaccgggac 180
tctgggggtcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc 240
agcagggtgg aggtcagga tgttggggtt tattactgca tgcaagggtac acactggccg 300
tacacttttg gccaggggac caagctggag atcaaa 336
```

<210> 682

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 682

```
Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1      5      10      15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
20     25     30
Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
35     40     45
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp Ser Gly Val Pro
50     55     60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65     70     75     80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
85     90     95
Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100    105    110
```

<210> 683

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 683

caaagcctcg tatacagtga tggaacacc tac 33

<210> 684

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 684

Gln	Ser	Leu	Val	Tyr	Ser	Asp	Gly	Asn	Thr	Tyr
1				5					10	

<210> 685

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 685

aaggtttct 9

<210> 686

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 686

Lys	Val	Ser
1		

<210> 687

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 687

atgcaaggta cacactggcc gtacact 27

<210> 688

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 688

Met Gln Gly Thr His Trp Pro Tyr Thr
 1 5

<210> 689

<211> 381

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 689

```

caggttcagc tgggtgcagtc tggacctgag gtgaagaacc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctgggta caccctttacc acctatggta tcagttgggt acgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcgggt acaatggtaa aacaaacgat 180
gcacagaagt tccaggacag agtcgccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccattt attactgttc gagagatcgt 300
ttagtagtac caccctgccct ttattattac tactacgtta tggacgtctg gggccaaggg 360
accacgggtca ccgtctcttc a 381

```

<210> 690

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 690

```

Gln Val Gln Leu Val Gln Ser Gly Pro Glu Val Lys Asn Pro Gly Ala
 1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Thr 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 Gly Tyr Asn Gly Lys Thr Asn Asp Ala Gln Lys Phe
 50 55 60
Gln Asp Arg Val Ala 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 Ile Tyr Tyr Cys
 85 90 95
Ser Arg Asp Arg Leu Val Val Pro Pro Ala Leu Tyr Tyr Tyr Tyr Tyr
 100 105 110
Val Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115 120 125

```

<210> 691

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 691


```

gatgttgtga tgactcagtc tccactctcc ctgcccgta cccttggaca gccggcctcc 60
atctcctgca ggtctagtc aagcctcgta tacagtgatg gaaacaccta cttgaattgg 120
tttcagcaga ggccaggta atctccaagg cgcctaattt ataagggttc taaccgggac 180
tctggggctc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc 240
agcagggtgg aggcagagga tggtggggtt tattactgca tgcaaggtag acactggccg 300
tacacttttg gccaggggac caagctggag atcaaaa 336

```

<210> 692

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 692

```

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
 1          5          10          15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
 20          25          30
Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
 35          40          45
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp Ser Gly Val Pro
 50          55          60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
 65          70          75          80
Ser Arg Val Glu Ala Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
 85          90          95
Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100          105          110

```

<210> 693

<211> 381

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 693

```

caggttcagc tgggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctgggta cacccttacc acctatggta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcgggt acaatggtaa aacaaaactat 180
gcacagaagc tcagggcagc agtcacatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgttc gagagatcgt 300
ttagtagtac cactgcctt ttattattac tactacgtta tggacgtctg ggggcaaggg 360
accacggta cagtcctcctc a 381

```

<210> 694

<211> 127

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 694

```

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 Thr 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 Gly Tyr Asn Gly Lys Thr Asn Tyr Ala Gln Lys Leu
      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
Ser Arg Asp Arg Leu Val Val Pro Pro Ala Leu Tyr Tyr Tyr Tyr Tyr
      100      105      110
Val Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
      115      120      125

```

<210> 695

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 695

```

gatgttgatga tgactcagtc tccactctcc ctgcccgatca cccttggaca gccggcctcc 60
atctcctgca ggtctagtc aagcctcgta tacagtgatg gaaacaccta cttgaattgg 120
tttcagcaga ggccaggcca atctccaagg cgcctaattt ataagggttc taaccgggac 180
tctggggatcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc 240
agcaggggtgg aggtgagga tgttggggtt tattactgca tgcaaggtag acactggccg 300
tacacttttg gccaggggac caagctggag atcaaa 336

```

<210> 696

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 696

```

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
  1      5      10      15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
      20      25      30
Asp Gly Asn Thr Tyr Leu Asn Trp Phe Gln Gln Arg Pro Gly Gln Ser
      35      40      45
Pro Arg Arg Leu Ile Tyr Lys Val Ser Asn Arg Asp Ser Gly Val Pro
      50      55      60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
      65      70      75      80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
      85      90      95
Thr His Trp Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
      100      105      110

```

<210> 697

<211> 384

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 697

```

cagggtgcacc tgggtggagtc tggggggaggc ttggtcaagc ctggagggtc ccgagactc 60
tcctgtgcag cctctggatt caccctcagt gaccactaca tgagctggat ccgccaggct 120
ccaggaagg ggctggagtg gatttcatac attagtaatg atggtggtac caaatactat 180
gtggactctg tggaggggccg attcatcatt tccagggaca acgccaagaa ctcattgtat 240
ctacatatga acagcctcag agccgacgac acggccgtgt attactgtgc gagagatcag 300
ggatatattg gctacgactc gtattattac tattcctacg gtatggacgt ctggggccaa 360
gggaccacgg tcaccgtcgc ctca 384

```

<210> 698

<211> 128

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 698

```

Gln Val His 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 His
 20      25      30
Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35      40      45
Ser Tyr Ile Ser Asn Asp Gly Gly Thr Lys Tyr Tyr Val Asp Ser Val
 50      55      60
Glu Gly Arg Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65      70      75      80
Leu His Met Asn Ser Leu Arg Ala Asp Asp Thr Ala Val Tyr Tyr Cys
 85      90      95
Ala Arg Asp Gln Gly Tyr Ile Gly Tyr Asp Ser Tyr Tyr Tyr Tyr Ser
100      105      110
Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ala Ser
115      120      125

```

<210> 699

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 699

```

ggattcacct tcagtgacca ctac 24

```

<210> 700

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 700

Gly Phe Thr Phe Ser Asp His Tyr
 1 5

<210> 701

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 701

attagtaatg atggtggtac caaa 24

<210> 702

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 702

Ile Ser Asn Asp Gly Gly Thr Lys
 1 5

<210> 703

<211> 63

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 703

gccagagatc agggatatat tggctacgac tcgtattatt actattccta cggtatggac 60
 gtc 63

<210> 704

<211> 21

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 704

Ala Arg Asp Gln Gly Tyr Ile Gly Tyr Asp Ser Tyr Tyr Tyr Tyr Ser
 1 5 10 15
 Tyr Gly Met Asp Val
 20

<210> 705

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 705

```

aaaattgtgt tgacgcagtc tccaggcacc ctgcctttgt ttccaggga aagagccacc 60
ctctcctgta gggccagtc .gagtgttaac aacaaattct tagcctggtt ccagcagaaa 120
tctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
gacaggttca gtggcagtggt gtctgggacc gacttcactc tcaccatcag cggactggag 240
cctgaagatt ttgaagtgtt ttattgtcaa gtatatggta actcactcac ttccggcgga 300
gggaccaagg tggagatcaa g                                     321

```

<210> 706

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 706

```

Lys Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Pro Leu Phe Pro Gly
 1           5           10           15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Asn Asn Lys
 20           25           30
Phe Leu Ala Trp Tyr Gln Gln Lys Ser Gly Gln Ala Pro Arg Leu Leu
 35           40           45
- - -
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
 50           55           60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Gly Leu Glu
 65           70           75           80
Pro Glu Asp Phe Glu Val Tyr Tyr Cys Gln Val Tyr Gly Asn Ser Leu
 85           90           95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100           105

```

<210> 707

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 707

```

cagagtgtta acaacaaatt c          21

```

<210> 708

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 708

Gln Ser Val Asn Asn Lys Phe
1 5

<210> 709

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 709

ggtgcatcc 9

<210> 710

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 710

Gly Ala Ser
1

<210> 711

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 711

caagtatatg gtaactcact cact 24

<210> 712

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 712

Gln Val Tyr Gly Asn Ser Leu Thr
 1 5

<210> 713

<211> 384

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 713

```
cagggtgcagc tgggtggagtc tggggggaggc ttggtcaagc ctggagggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt gaccactaca tgagctggat ccgccaggct 120
ccagggaagg ggctggagtg gatttcatac attagtaatg atggtgggtac caaatactat 180
gtggactctg tggagggccg attcatcatt tccagggaca acgccaagaa ctcatgtgat 240
ctacatatga acagcctcag agccgacgac acggcccggtg attactgtgc gagagatcag 300
ggatatattg gctacgactc gtattattac tattcctacg gtatggacgt ctggggccaa 360
gggaccacgg tcaccgtctc ctca 384
```

<210> 714

<211> 128

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 714

```
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 His
  20 25 30
Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
  35 40 45
Ser Tyr Ile Ser Asn Asp Gly Gly Thr Lys Tyr Tyr Val Asp Ser Val
  50 55 60
Glu Gly Arg Phe Ile Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
  65 70 75 80
Leu His Met Asn Ser Leu Arg Ala Asp Asp Thr Ala Val Tyr Tyr Cys
  85 90 95
Ala Arg Asp Gln Gly Tyr Ile Gly Tyr Asp Ser Tyr Tyr Tyr Tyr Ser
  100 105 110
Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
  115 120 125
```

<210> 715

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 715

```

gaaattgtgt tgacgcagtc tccaggcacc ctgcctttgt ttccagggga aagagccacc 60
ctctcctgta gggccagtc gagtggttaac aacaaattct tagcctggta ccagcagaaa 120
tctggccagg ctcccaggt cctcatctat ggtgcaccca gcagggccac tggcatccca 180
gacaggttca gtggcagtg gtctgggacc gacttcacto tcaccatcag cggactggag 240
cctgaagatt ttgaagtgt ttattgtcaa gtatatggta actcactcac ttccggcgga 300
gggaccaagg tggagatcaa a                                     321

```

<210> 716

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 716

```

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Pro Leu Phe Pro Gly
 1           5           10           15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Asn Asn Lys
          20           25           30
Phe Leu Ala Trp Tyr Gln Gln Lys Ser Gly Gln Ala Pro Arg Leu Leu
          35           40           45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
          50           55           60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Gly Leu Glu
65           70           75           80
Pro Glu Asp Phe Glu Val Tyr Tyr Cys Gln Val Tyr Gly Asn Ser Leu
          85           90           95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
          100          105

```

<210> 717

<211> 384

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 717

```

caggtgcagc tgggtggagtc tggggggaggc ttggtcaagc ctggagggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt gaccactaca tgagctggat ccgccaggct 120
ccagggaagg ggctggagtg ggtttcatac attagtaatg atgggtgtac caaatactac 180
gcagactctg tgaagggccg attcaccatc tccagggaca acgccaagaa ctcactgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gagagatcag 300
ggatatattg gctacgactc gtattattac tattcctacg gtatggacgt ctgggggcaa 360
gggaccacgg tcaccgtctc ctca                                     384

```

<210> 718

<211> 128

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 718

```

Gln Val Gln Leu Val Glu Ser Glv Glv Glv Leu Val Lvs Pro Glv Glv

```



```

1      5      10      15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp His
20      25      30
Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35      40      45
Ser Tyr Ile Ser Asn Asp Gly Gly Thr Lys Tyr Tyr Ala Asp 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 Val Tyr Tyr Cys
85      90      95
Ala Arg Asp Gln Gly Tyr Ile Gly Tyr Asp Ser Tyr Tyr Tyr Ser
100      105      110
Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115      120      125

```

<210> 719

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 719

```

gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtcg gagtggttaac aacaaattct tagcctggta ccagcagaaa 120
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
gacagggttca gtggcagtggt gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgtg ttactgtcaa gtatatggta actcactcac ttccggcgga 300
gggaccaagg tggagatcaa a 321

```

<210> 720

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 720

```

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1      5      10      15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Asn Asn Lys
20      25      30
Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35      40      45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50      55      60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65      70      75      80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Val Tyr Gly Asn Ser Leu
85      90      95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100      105

```

<210> 721

<211> 378

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 721

```

caaattctgc tgggtgcaatc tggacctgag gtgaaggagc ctgggggctc agtgaaggtc 60
tcctgcaagg ctcttggtta cacccttacc aactacgcta tcagctgggt gcgacaggtc 120
cctggacaag ggcttgagtg gatgggatgg gtcagcgctt acaatgggtc cacaaactat 180
gcacatgaag tccagggcag agtcaccatg accacagaca catccacgac cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccatgt attactgtgc gagagggggg 300
gtagtcgtgc cagttgctcc ccacttctac aacggtatgg acgtctgggg ccaagggacc 360
acggtcaccg tctcctca

```

<210> 722

<211> 126

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 722

```

Gln Ile Leu Leu Val Gln Ser Gly Pro Glu Val Lys Glu 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
Ala Ile Ser Trp Val Arg Gln Val Pro Gly Gln Gly Leu Glu Trp Met
      35             40             45
Gly Trp Val Ser Ala Tyr Asn Gly His Thr Asn Tyr Ala His Glu Val
 50             55             60
Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Thr Thr Ala Tyr
 65             70             75             80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Met Tyr Tyr Cys
      85             90             95
Ala Arg Gly Gly Val Val Val Pro Val Ala Pro His Phe Tyr Asn Gly
      100            105            110
Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
      115            120            125

```

<210> 723

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 723

```

ggttacacct ttaccaacta cgct          24

```

<210> 724

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 724

Gly Tyr Thr Phe Thr Asn Tyr Ala
 1 5

<210> 725

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 725

gtcagcgctt acaatggta caca 24

<210> 726

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 726

Val Ser Ala Tyr Asn Gly His Thr
 1 5

<210> 727

<211> 57

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 727

gcgagagggg gtgtagtcgt gccagttgct cccacttct acaacggat ggacgtc 57

<210> 728

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 728

Ala Arg Gly Gly Val Val Val Pro Val Ala Pro His Phe Tyr Asn Gly
 1 5 10 15
 Met Asp Val

<210> 729

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 729

```

gatattgtga  tgactcagtt  tccactctcc  ctgcccgta  cccctggaga  gccggcctcc  60
atctcctgca  ggtctagtca  gagcctcctg  catattaatg  aatacaacta  ttgggattgg  120
tacctaaaga  agccagggca  gtctccacag  ctctgatct  atttgggttt  taatcgggcc  180
tccggggctc  ctgacaggtt  cagtggcagt  ggatcaggca  cagattttac  actgaaaatc  240
agcagagtgg  aggetgagga  tgttggggtc  tattaactga  tgcaagctct  tcaaactccg  300
tggacgttcg  gccaaaggac  caaggtggaa  atcaaa      336

```

<210> 730

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 730

```

Asp Ile Val Met Thr Gln Phe Pro Leu Ser Leu Pro Val Thr Pro Gly
1           5           10           15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ile
20          25          30
Asn Glu Tyr Asn Tyr Leu Asp Trp Tyr Leu Lys Lys Pro Gly Gln Ser
35          40          45
Pro Gln Leu Leu Ile Tyr Leu Gly Phe Asn Arg Ala Ser Gly Val Pro
50          55          60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65          70          75          80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85          90          95
Leu Gln Thr Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100         105         110

```

<210> 731

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 731

```

cagagcctcc  tgcatattaa  tgaatacaac  tat      33

```

<210> 732

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 732

Gln	Ser	Leu	Leu	His	Ile	Asn	Glu	Tyr	Asn	Tyr
1				5					10	

<210> 733

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 733

ttgggtttt	9
-----------	---

<210> 734

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 734

Leu	Gly	Phe
1		

<210> 735

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 735

atgcaagctc	ttcaaactcc	gtggacg	27
------------	------------	---------	----

<210> 736

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 736

Met Gln Ala Leu Gln Thr Pro Trp Thr
1 5

<210> 737

<211> 378

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 737

```

caggttcagc tgggtgcagtc tggacctgag gtgaaggagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctgggta cacccttacc aactacgcta tcagctgggt gcgacaggtc 120
cctggacaag ggccttgagtg gatgggatgg gtcagcgctt acaatgggtc cacaaactat 180
gcacatgaag tccagggcag agtcaccatg accacagaca catccacgac cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccatgt attactgtgc gagaggggggt 300
gtagtcgtgc cagttgctcc ccacttctac aacggtatgg acgtctgggg ccaagggacc 360
acggtcaccg tctcctca

```

<210> 738

<211> 126

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 738

```

Gln Val Gln Leu Val Gln Ser Gly Pro Glu Val Lys Glu 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
Ala Ile Ser Trp Val Arg Gln Val Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Val Ser Ala Tyr Asn Gly His Thr Asn Tyr Ala His Glu Val
50 55 60
Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Thr Thr Ala Tyr
65 70 75 80
Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Met Tyr Tyr Cys
85 90 95
Ala Arg Gly Gly Val Val Val Pro Val Ala Pro His Phe Tyr Asn Gly
100 105 110
Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

```

<210> 739

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 739

```

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
atctcctgca ggtctagtca gagcctcctg catattaatg aatacaacta tttaggattgg 120
tacctaaaga agccagggca ctctccacag ctctcgtatc atttggggtt taatcggggc 180

```

```

taccctaaaga agccagggga gctcccaag gctccgaacc acccgggccc taccggggcc 180
tccgggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgga aggctgagga tgttggggtc tattactgca tgcaagctct tcaaaactccg 300
tggacgttcg gccaaaggac caaggtggaa atcaaa 336

```

<210> 740

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 740

```

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1           5           10           15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ile
20          25          30
Asn Glu Tyr Asn Tyr Leu Asp Trp Tyr Leu Lys Lys Pro Gly Gln Ser
35          40          45
Pro Gln Leu Leu Ile Tyr Leu Gly Phe Asn Arg Ala Ser Gly Val Pro
50          55          60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65          70          75          80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85          90          95
Leu Gln Thr Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100         105         110

```

<210> 741

<211> 378

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 741

```

caggttcagc tgggtcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcttgcaagg cttctgggta cacctttacc aactacgcta tcagctgggt ggcacaggcc 120
cctggacaag ggcttgagtg gatgggatgg gtcagcgctt acaatggta cacaactat 180
gcacagaagc tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240
atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagggggt 300
gtagtcgtgc cagttgctcc ccacttctac aacggtatgg acgtctgggg gcaagggacc 360
acggtcaccg tctctca 378

```

<210> 742

<211> 126

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 742

```

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

```

```

      35          40          45
Gly Trp Val Ser Ala Tyr Asn Gly His Thr Asn Tyr Ala Gln Lys Leu
  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 Gly Gly Val Val Val Pro Val Ala Pro His Phe Tyr Asn Gly
      100          105          110
Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
      115          120          125

```

<210> 743

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 743

```

gatattgtga tgactcagtc tccactctcc ctgcccgta cccctggaga gccggcctcc 60
atctcctgca ggctcagtc gagcctcctg catattaatg aatacaacta ttgggattgg 120
taactgcaga agccagggca gtctccacag ctctgatct atttgggttc taatcgggcc 180
tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggtcgagga tgttggggtt tattactgca tgcaagctct tcaaactccg 300
tggacgttcg gccaaaggac caagtgga atcaaa 336

```

<210> 744

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 744

```

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
  1          5          10          15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ile
      20          25          30
Asn Glu Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
      35          40          45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
      50          55          60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
      65          70          75          80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
      85          90          95
Leu Gln Thr Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
      100          105          110

```

<210> 745

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<220>

<221> VARIANT

<222> (1)...(8)

<223> Xaa = Any amino acid

<400> 745

Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
1				5			

<210> 746

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<220>

<221> VARIANT

<222> (1)...(8)

<223> Xaa - Any amino acid

<400> 746

Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
1				5			

<210> 747

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<220>

<221> VARIANT

<222> (1)...(20)

<223> Xaa = Any amino acid

<400> 747

Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
1				5					10					15		
Xaa	Xaa	Xaa	Xaa													
				20												

<210> 748

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<220>

<221> VARIANT

<222> (1)...(12)

<223> Xaa = Any amino acid

<400> 748

Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
1				5						10		

<210> 749

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<220>

<221> VARIANT

<222> (1)...(3)

<223> Xaa = Any amino acid

<400> 749

Xaa	Xaa	Xaa
1		

<210> 750

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<220>

<221> VARIANT

<222> (1)...(9)

<223> Xaa = Any amino acid

<400> 750

Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
1				5				

<210> 751

<211> 330

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 751

```

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1          5          10          15
Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
          20          25          30
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
          35          40          45
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
          50          55          60
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65          70          75          80
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
          85          90          95
Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
          100          105          110
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
          115          120          125
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130          135          140
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145          150          155          160
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
          165          170          175
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
          180          185          190
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
          195          200          205
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210          215          220
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225          230          235          240
Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
          245          250          255
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260          265          270
Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275          280          285
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290          295          300
Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305          310          315          320
Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
          325          330

```

<210> 752

<211> 327

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 752

```

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
 1          5          10          15
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
          20          25          30
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
          35          40          45
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
          50          55          60
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65          70          75          80
Tyr Thr Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asn Lys

```

```

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro
100 105 110
Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
115 120 125
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
130 135 140
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145 150 155 160
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
165 170 175
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
180 185 190
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
195 200 205
Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
210 215 220
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225 230 235 240
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
245 250 255
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
260 265 270
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
275 280 285
Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
290 295 300
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305 310 315 320
Leu Ser Leu Ser Leu Gly Lys
325

```

<210> 753

<211> 327

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 753

```

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65 70 75 80
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95
Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
100 105 110
Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
115 120 125
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
130 135 140
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145 150 155 160
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
165 170 175
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
180 185 190
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
195 200 205

```

190	200	205
Pro Ser Ser Ile Glu Lys Thr	Ile Ser Lys Ala	Lys Gly Gln Pro Arg
210	215	220
Glu Pro Gln Val Tyr Thr	Leu Pro Pro Ser Gln	Glu Glu Met Thr Lys
225	230	235
Asn Gln Val Ser Leu Thr	Cys Leu Val Lys Gly	Phe Tyr Pro Ser Asp
245	250	255
Ile Ala Val Glu Trp Glu	Ser Asn Gly Gln Pro	Glu Asn Asn Tyr Lys
260	265	270
Thr Thr Pro Pro Val Leu	Asp Ser Asp Gly Ser	Phe Phe Leu Tyr Ser
275	280	285
Arg Leu Thr Val Asp Lys	Ser Arg Trp Gln Glu	Gly Asn Val Phe Ser
290	295	300
Cys Ser Val Met His Glu	Ala Leu His Asn His	Tyr Thr Gln Lys Ser
305	310	315
Leu Ser Leu Ser Leu Gly	Lys	
325		

<210> 754

<211> 2076

<212> DNA

<213> Homo sapiens

<400> 754

```

atgggcacccg tcagctccag gcggtcctgg tggccgctgc cactgctgct gctgctgctg 60
ctgctcctgg gtcccgcggg cgcgcgtgcg caggaggacg aggacggcga ctacgaggag 120
ctggtgctag ccttgcttcc cgaggaggac ggccctggccg aagcaccga gcacggaacc 180
acagccacct tcacccgctg cgccaaggat ccgtggagggt tgcctggcac ctacgtgggtg 240
gtgctgaagg aggagaccca cctctcgcag tcagagcgca ctgcccgcg cctgcaggcc 300
caggctgccc gcgggggata cctcaccaag atcctgcatg tcttccatgg ccttcttcc 360
ggcttctcgg tgaagatgag tggcgacctg ctggagctgg ccttgaagtt gcccatgtc 420
gactacatcg aggaggactc ctctgtcttt gccagagca tcccgaggaa cctggagcgg 480
attacccttc cagcgtaccg ggcggatgaa taccagcccc ccgacggagg cagcctgggtg 540
gaggtgtatc tcttagacac cagcatacag agtgaccacc gggaaatcga gggcagggtc 600
atggtcacccg acttcagaaa tgtgcccagg gaggacggga ccgcttcca cagacaggcc 660
agcaagtgtg acagtcattg caccacctg gcaggggtgg tcagggccg ggatgccggc 720
gtggccaagg gtgccagcat gcgcagcctg cgcgtgctca actgccaagg gaagggcacg 780
gttagcggca cctcatagg cctggagttt attcgaaaa gccagctggt ccagcctgtg 840
gggcactggt tgggtgctgt gccctggtg ggtgggtaca gccgcgtcct caacgcccgc 900
tgccagcgcc tggcgagggc tggggtcgtg ctggtcaccc ctgcccggca cttccgggac 960
gatgcctgcc tctactcccc agcctcagct ccgaggtca tcacagttgg gccaccaat 1020

```

```

gccagggacc agccgggtgac cctggggact ttggggacca actttggccg ctgtgtggac 1080
ctctttgccc cagggggagga catcattggt gcctccagcg actgcagcac ctgctttgtg 1140
tcacagagtg ggacatcaca ggctgctgcc cagctggctg gcattgcagc catgatgtg 1200
tctgcccagc cggagctcac cctggccgag ttgaggcaga gactgatcca cttctctgcc 1260
aaagatgtca tcaatgagga ctgggttccct gaggaccagc gggtaactgac ccccaacctg 1320
gtggccgcgc tgcgcccgag caccatggg gcagggtggc agctgttttg caggactgtg 1380
tggtcagcac actcggggcc tacacggatg gccacagcca tcgcccgtg cgcccagat 1440
gaggagctgc tgagctgctc cagtttctcc aggagtggga agcggcgggg cgagcgcag 1500
gaggcccaag ggggcaagct ggtctgcgg gccacaacg cttttggggg tgagggtgtc 1560
tacgccattg ccagggtgtg cctgctaccc caggccaact gcagcgtcca cacagctcca 1620
ccagctgagg ccagcatggg gacccgtgt cactgccacc aacagggccca cgtccctaca 1680
ggctgcagct cccactggga ggtggaggac cttggcacc acaagccgcc tgtgctgagg 1740
ccacgagggtc agcccacca gtgcgtggg cacagggagg ccagcatcca cgttctctgc 1800
tgccatgccc caggtctgga atgcaaagtc aaggagcatg gaatcccggc cctcaggag 1860
caggtgaccc tggcctgcca ggagggtgg accctgactg gctgcagtgc cctccctggg 1920
acctccacg tcttgggggc ctacgcccga gacaacagc gtgtagtcag gagccgggac 1980
gtcagacta caggcagcac cagcgaagag gcggtgacag ccgttgccat ctgctgccgg 2040
agccggcacc tggcgaggc ctcacaggag ctccag 2076

```

<210> 755

<211> 692

<212> PRT

<213> Homo sapiens

<400> 755

```

Met Gly Thr Val Ser Ser Arg Arg Ser Trp Trp Pro Leu Pro Leu Leu
 1      5      10      15
Leu Leu Leu Leu Leu Leu Gly Pro Ala Gly Ala Arg Ala Gln Glu
 20      25      30
Asp Glu Asp Gly Asp Tyr Glu Glu Leu Val Leu Ala Leu Arg Ser Glu
 35      40      45
Glu Asp Gly Leu Ala Glu Ala Pro Glu His Gly Thr Thr Ala Thr Phe
 50      55      60
His Arg Cys Ala Lys Asp Pro Trp Arg Leu Pro Gly Thr Tyr Val Val
 65      70      75      80
Val Leu Lys Glu Glu Thr His Leu Ser Gln Ser Glu Arg Thr Ala Arg
 85      90      95
Arg Leu Gln Ala Gln Ala Ala Arg Arg Gly Tyr Leu Thr Lys Ile Leu
 100     105     110
His Val Phe His Gly Leu Leu Pro Gly Phe Leu Val Lys Met Ser Gly
 115     120     125
Asp Leu Leu Glu Leu Ala Leu Lys Leu Pro His Val Asp Tyr Ile Glu
 130     135     140
Glu Asp Ser Ser Val Phe Ala Gln Ser Ile Pro Trp Asn Leu Glu Arg
 145     150     155     160
Ile Thr Pro Pro Arg Tyr Arg Ala Asp Glu Tyr Gln Pro Pro Asp Gly
 165     170     175
Gly Ser Leu Val Glu Val Tyr Leu Leu Asp Thr Ser Ile Gln Ser Asp
 180     185     190
His Arg Glu Ile Glu Gly Arg Val Met Val Thr Asp Phe Glu Asn Val
 195     200     205
Pro Glu Glu Asp Gly Thr Arg Phe His Arg Gln Ala Ser Lys Cys Asp
 210     215     220
Ser His Gly Thr His Leu Ala Gly Val Val Ser Gly Arg Asp Ala Gly
 225     230     235     240
Val Ala Lys Gly Ala Ser Met Arg Ser Leu Arg Val Leu Asn Cys Gln
 245     250     255
Gly Lys Gly Thr Val Ser Gly Thr Leu Ile Gly Leu Glu Phe Ile Arg
 260     265     270
Lys Ser Gln Leu Val Gln Pro Val Gly Pro Leu Val Val Leu Leu Pro
 275     280     285
Leu Ala Gly Gly Tyr Ser Arg Val Leu Asn Ala Ala Cys Gln Arg Leu

```

```

290      295      300
Ala Arg Ala Gly Val Val Leu Val Thr Ala Ala Gly Asn Phe Arg Asp
 305      310      315      320
Asp Ala Cys Leu Tyr Ser Pro Ala Ser Ala Pro Glu Val Ile Thr Val
 325      330      335
Gly Ala Thr Asn Ala Gln Asp Gln Pro Val Thr Leu Gly Thr Leu Gly
 340      345      350
Thr Asn Phe Gly Arg Cys Val Asp Leu Phe Ala Pro Gly Glu Asp Ile
 355      360      365
Ile Gly Ala Ser Ser Asp Cys Ser Thr Cys Phe Val Ser Gln Ser Gly
 370      375      380
Thr Ser Gln Ala Ala Ala His Val Ala Gly Ile Ala Ala Met Met Leu
 385      390      395     400
Ser Ala Glu Pro Glu Leu Thr Leu Ala Glu Leu Arg Gln Arg Leu Ile
 405      410      415
His Phe Ser Ala Lys Asp Val Ile Asn Glu Ala Trp Phe Pro Glu Asp
 420      425      430
Gln Arg Val Leu Thr Pro Asn Leu Val Ala Ala Leu Pro Pro Ser Thr
 435      440      445
His Gly Ala Gly Trp Gln Leu Phe Cys Arg Thr Val Trp Ser Ala His
 450      455      460
Ser Gly Pro Thr Arg Met Ala Thr Ala Ile Ala Arg Cys Ala Pro Asp
 465      470      475     480
Glu Glu Leu Leu Ser Cys Ser Ser Phe Ser Arg Ser Gly Lys Arg Arg
 485      490      495
Gly Glu Arg Met Glu Ala Gln Gly Gly Lys Leu Val Cys Arg Ala His
 500      505      510
Asn Ala Phe Gly Gly Glu Gly Val Tyr Ala Ile Ala Arg Cys Cys Leu
 515      520      525
Leu Pro Gln Ala Asn Cys Ser Val His Thr Ala Pro Pro Ala Glu Ala
 530      535      540
Ser Met Gly Thr Arg Val His Cys His Gln Gln Gly His Val Leu Thr
 545      550      555     560
Gly Cys Ser Ser His Trp Glu Val Glu Asp Leu Gly Thr His Lys Pro
 565      570      575
Pro Val Leu Arg Pro Arg Glu Gln Pro Asn Gln Cys Val Glu His Arg

```

```

Pro Val Leu Arg Pro Arg Gly Gln Pro Asn Gln Cys Val Gly His Arg
580 585 590
Glu Ala Ser Ile His Ala Ser Cys Cys His Ala Pro Gly Leu Glu Cys
595 600 605
Lys Val Lys Glu His Gly Ile Pro Ala Pro Gln Glu Gln Val Thr Val
610 615 620
Ala Cys Glu Glu Gly Trp Thr Leu Thr Gly Cys Ser Ala Leu Pro Gly
625 630 635 640
Thr Ser His Val Leu Gly Ala Tyr Ala Val Asp Asn Thr Cys Val Val
645 650 655
Arg Ser Arg Asp Val Ser Thr Thr Gly Ser Thr Ser Glu Glu Ala Val
660 665 670
Thr Ala Val Ala Ile Cys Cys Arg Ser Arg His Leu Ala Gln Ala Ser
675 680 685
Gln Glu Leu Gln
690

```

<210> 756

<211> 692

<212> PRT

<213> Macaca mulata

<400> 756

```

Met Gly Thr Val Ser Ser Arg Arg Ser Trp Trp Pro Leu Pro Leu Pro
1 5 10 15
Leu Leu Leu Leu Leu Leu Leu Gly Pro Ala Gly Ala Arg Ala Gln Glu

```

```

20 25 30
Asp Glu Asp Gly Asp Tyr Glu Glu Leu Val Leu Ala Leu Arg Ser Glu
35 40 45
Glu Asp Gly Leu Ala Asp Ala Pro Glu His Gly Ala Thr Ala Thr Phe
50 55 60
His Arg Cys Ala Lys Asp Pro Trp Arg Leu Pro Gly Thr Tyr Val Val
65 70 75 80
Val Leu Lys Glu Glu Thr His Arg Ser Gln Ser Glu Arg Thr Ala Arg
85 90 95
Arg Leu Gln Ala Gln Ala Ala Arg Arg Gly Tyr Leu Thr Lys Ile Leu
100 105 110
His Val Phe His His Leu Leu Pro Gly Phe Leu Val Lys Met Ser Gly
115 120 125
Asp Leu Leu Glu Leu Ala Leu Lys Leu Pro His Val Asp Tyr Ile Glu
130 135 140
Glu Asp Ser Ser Val Phe Ala Gln Ser Ile Pro Trp Asn Leu Glu Arg
145 150 155 160
Ile Thr Pro Ala Arg Tyr Arg Ala Asp Glu Tyr Gln Pro Pro Lys Gly
165 170 175
Gly Ser Leu Val Glu Val Tyr Leu Leu Asp Thr Ser Ile Gln Ser Asp
180 185 190
His Arg Glu Ile Glu Gly Arg Val Met Val Thr Asp Phe Glu Ser Val
195 200 205
Pro Glu Glu Asp Gly Thr Arg Phe His Arg Gln Ala Ser Lys Cys Asp
210 215 220
Ser His Gly Thr His Leu Ala Gly Val Val Ser Gly Arg Asp Ala Gly
225 230 235 240
Val Ala Lys Gly Ala Gly Leu Arg Ser Leu Arg Val Leu Asn Cys Gln
245 250 255
Gly Lys Gly Thr Val Ser Gly Thr Leu Ile Gly Leu Glu Phe Ile Arg
260 265 270
Lys Ser Gln Leu Val Gln Pro Val Gly Pro Leu Val Val Leu Leu Pro
275 280 285
Leu Ala Gly Gly Tyr Ser Arg Val Phe Asn Ala Ala Cys Gln Arg Leu
290 295 300
Ala Arg Ala Gly Val Val Leu Val Thr Ala Ala Gly Asn Phe Arg Asp
305 310 315 320
Asp Ala Cys Leu Tyr Ser Pro Ala Ser Ala Pro Glu Val Ile Thr Val
325 330 335
Gly Ala Thr Asn Ala Gln Asp Gln Pro Val Thr Leu Gly Thr Leu Gly
340 345 350
Thr Asn Phe Gly Arg Cys Val Asp Leu Phe Ala Pro Gly Glu Asp Ile
355 360 365
Ile Gly Ala Ser Ser Asp Cys Ser Thr Cys Phe Val Ser Arg Ser Gly
370 375 380
Thr Ser Gln Ala Ala Ala His Val Ala Gly Ile Ala Ala Met Met Leu
385 390 395 400

```

```

Ser Ala Glu Pro Glu Leu Thr Leu Ala Glu Leu Arg Gln Arg Leu Ile
      405      410      415
His Phe Ser Ala Lys Asp Val Ile Asn Glu Ala Trp Phe Pro Glu Asp
      420      425      430
Gln Arg Val Leu Thr Pro Asn Leu Val Ala Ala Leu Pro Pro Ser Thr
      435      440      445
His Arg Ala Gly Trp Gln Leu Phe Cys Arg Thr Val Trp Ser Ala His
      450      455      460
Ser Gly Pro Thr Arg Met Ala Thr Ala Val Ala Arg Cys Ala Gln Asp
465      470      475      480
Glu Glu Leu Leu Ser Cys Ser Ser Phe Ser Arg Ser Gly Lys Arg Arg
      485      490      495
Gly Glu Arg Ile Glu Ala Gln Gly Gly Lys Arg Val Cys Arg Ala His
      500      505      510
Asn Ala Phe Gly Gly Glu Gly Val Tyr Ala Ile Ala Arg Cys Cys Leu
      515      520      525

```

```

Leu Pro Gln Val Asn Cys Ser Val His Thr Ala Pro Pro Ala Gly Ala
      530      535      540
Ser Met Gly Thr Arg Val His Cys His Gln Gln Gly His Val Leu Thr
545      550      555      560
Gly Cys Ser Ser His Trp Glu Val Glu Asp Leu Gly Thr His Lys Pro
      565      570      575
Pro Val Leu Arg Pro Arg Gly Gln Pro Asn Gln Cys Val Gly His Arg
      580      585      590
Glu Ala Ser Ile His Ala Ser Cys Cys His Ala Pro Gly Leu Glu Cys
      595      600      605
Lys Val Lys Glu His Gly Ile Pro Ala Pro Gln Glu Gln Val Ile Val
      610      615      620
Ala Cys Glu Asp Gly Trp Thr Leu Thr Gly Cys Ser Pro Leu Pro Gly
625      630      635      640
Thr Ser His Val Leu Gly Ala Tyr Ala Val Asp Asn Thr Cys Val Val
      645      650      655
Arg Ser Arg Asp Val Ser Thr Thr Gly Ser Thr Ser Lys Glu Ala Val
      660      665      670
Ala Ala Val Ala Ile Cys Cys Arg Ser Arg His Leu Val Gln Ala Ser
      675      680      685
Gln Glu Leu Gln
      690

```

<210> 757

<211> 694

<212> PRT

<213> Mus muscular

<400> 757

```

Met Gly Thr His Cys Ser Ala Trp Leu Arg Trp Pro Leu Leu Pro Leu
  1      5      10      15
Leu Pro Pro Leu Leu Leu Leu Leu Leu Leu Cys Pro Thr Gly Ala
      20      25      30
Gly Ala Gln Asp Glu Asp Gly Asp Tyr Glu Glu Leu Met Leu Ala Leu
      35      40      45
Pro Ser Gln Glu Asp Gly Leu Ala Asp Glu Ala Ala His Val Ala Thr
      50      55      60
Ala Thr Phe Arg Arg Cys Ser Lys Glu Ala Trp Arg Leu Pro Gly Thr
65      70      75      80
Tyr Ile Val Val Leu Met Glu Glu Thr Gln Arg Leu Gln Ile Glu Gln
      85      90      95
Thr Ala His Arg Leu Gln Thr Arg Ala Ala Arg Arg Gly Tyr Val Ile
      100      105      110
Lys Val Leu His Ile Phe Tyr Asp Leu Phe Pro Gly Phe Leu Val Lys
      115      120      125
Met Ser Ser Asp Leu Leu Gly Leu Ala Leu Lys Leu Pro His Val Glu
      130      135      140
Tyr Ile Glu Glu Asp Ser Phe Val Phe Ala Gln Ser Ile Pro Trp Asn
145      150      155      160
Leu Glu Arg Ile Ile Pro Ala Trp His Gln Thr Glu Glu Asp Arg Ser
      165      170      175
Pro Asp Gly Ser Ser Gln Val Glu Val Tyr Leu Leu Asp Thr Ser Ile
      180      185      190
Gln Gly Ala His Arg Glu Ile Glu Gly Arg Val Thr Ile Thr Asp Phe

```



```

      195      200      205
Asn Ser Val Pro Glu Glu Asp Gly Thr Arg Phe His Arg Gln Ala Ser
210      215      220
Lys Cys Asp Ser His Gly Thr His Leu Ala Gly Val Val Ser Gly Arg
225      230      235      240
Asp Ala Gly Val Ala Lys Gly Thr Ser Leu His Ser Leu Arg Val Leu
      245      250      255
Asn Cys Gln Gly Lys Gly Thr Val Ser Gly Thr Leu Ile Gly Leu Glu

```

```

      260      265      270
Phe Ile Arg Lys Ser Gln Leu Ile Gln Pro Ser Gly Pro Leu Val Val
      275      280      285
Leu Leu Pro Leu Ala Gly Gly Tyr Ser Arg Ile Leu Asn Ala Ala Cys
      290      295      300
Arg His Leu Ala Arg Thr Gly Val Val Leu Val Ala Ala Ala Gly Asn
305      310      315      320
Phe Arg Asp Asp Ala Cys Leu Tyr Ser Pro Ala Ser Ala Pro Glu Val
      325      330      335
Ile Thr Val Gly Ala Thr Asn Ala Gln Asp Gln Pro Val Thr Leu Gly
      340      345      350
Thr Leu Gly Thr Asn Phe Gly Arg Cys Val Asp Leu Phe Ala Pro Gly
      355      360      365
Lys Asp Ile Ile Gly Ala Ser Ser Asp Cys Ser Thr Cys Phe Met Ser
      370      375      380
Gln Ser Gly Thr Ser Gln Ala Ala Ala His Val Ala Gly Ile Val Ala
385      390      395      400
Arg Met Leu Ser Arg Glu Pro Thr Leu Thr Leu Ala Glu Leu Arg Gln
      405      410      415
Arg Leu Ile His Phe Ser Thr Lys Asp Val Ile Asn Met Ala Trp Phe
      420      425      430
Pro Glu Asp Gln Gln Val Leu Thr Pro Asn Leu Val Ala Thr Leu Pro
      435      440      445
Pro Ser Thr His Glu Thr Gly Gly Gln Leu Leu Cys Arg Thr Val Trp
      450      455      460
Ser Ala His Ser Gly Pro Thr Arg Thr Ala Thr Ala Thr Ala Arg Cys
465      470      475      480
Ala Pro Glu Glu Glu Leu Leu Ser Cys Ser Ser Phe Ser Arg Ser Gly
      485      490      495
Arg Arg Arg Gly Asp Trp Ile Glu Ala Ile Gly Gly Gln Gln Val Cys
      500      505      510
Lys Ala Leu Asn Ala Phe Gly Gly Glu Gly Val Tyr Ala Val Ala Arg
      515      520      525
Cys Cys Leu Val Pro Arg Ala Asn Cys Ser Ile His Asn Thr Pro Ala
      530      535      540
Ala Arg Ala Gly Leu Glu Thr His Val His Cys His Gln Lys Asp His
545      550      555      560
Val Leu Thr Gly Cys Ser Phe His Trp Glu Val Glu Asp Leu Ser Val
      565      570      575
Arg Arg Gln Pro Ala Leu Arg Ser Arg Arg Gln Pro Gly Gln Cys Val
      580      585      590
Gly His Gln Ala Ala Ser Val Tyr Ala Ser Cys Cys His Ala Pro Gly
      595      600      605
Leu Glu Cys Lys Ile Lys Glu His Gly Ile Ser Gly Pro Ser Glu Gln
      610      615      620
Val Thr Val Ala Cys Glu Ala Gly Trp Thr Leu Thr Gly Cys Asn Val
625      630      635      640
Leu Pro Gly Ala Ser Leu Thr Leu Gly Ala Tyr Ser Val Asp Asn Leu
      645      650      655
Cys Val Ala Arg Val His Asp Thr Ala Arg Ala Asp Arg Thr Ser Gly
      660      665      670
Glu Ala Thr Val Ala Ala Ala Ile Cys Cys Arg Ser Arg Pro Ser Ala
      675      680      685
Lys Ala Ser Trp Val Gln
      690

```

<210> 758

<211> 653

<212> PRT

<213> Homo sapiens

<400> 758

```

Glu Phe Arg Cys His Asp Gly Lys Cys Ile Ser Arg Gln Phe Val Cys
1      5      10      15
Asp Ser Asp Arg Cys Leu Asp Gly Ser Asp Glu Ala Ser Cys Pro
20
Val Leu Thr Cys Gly Pro Ala Ser Phe Gln Cys Asn Ser Ser Thr Cys
35      40      45
Ile Pro Gln Leu Trp Ala Cys Asp Asn Asp Pro Asp Cys Glu Asp Gly
50      55      60
Ser Asp Glu Trp Pro Gln Arg Cys Arg Gly Leu Tyr Val Phe Gln Gly
65      70      75      80
Asp Ser Ser Pro Cys Ser Ala Phe Glu Phe His Cys Leu Ser Gly Glu
85      90      95
Cys Ile His Ser Ser Trp Arg Cys Asp Gly Gly Pro Asp Cys Lys Asp
100      105      110
Lys Ser Asp Glu Glu Asn Cys Ala Val Ala Thr Cys Arg Pro Asp Glu
115      120      125
Phe Gln Cys Ser Asp Gly Asn Cys Ile His Gly Ser Arg Gln Cys Asp
130      135      140
Arg Glu Tyr Asp Cys Lys Asp Met Ser Asp Glu Val Gly Cys Val Asn
145      150      155      160
Val Thr Leu Cys Glu Gly Pro Asn Lys Phe Lys Cys His Ser Gly Glu
165      170      175
Cys Ile Thr Leu Asp Lys Val Cys Asn Met Ala Arg Asp Cys Arg Asp
180      185      190
Trp Ser Asp Glu Pro Ile Lys Glu Cys Gly Thr Asn Glu Cys Leu Asp
195      200      205
Asn Asn Gly Gly Cys Ser His Val Cys Asn Asp Leu Lys Ile Gly Tyr
210      215      220
Glu Cys Leu Cys Pro Asp Gly Phe Gln Leu Val Ala Gln Arg Arg Cys
225      230      235      240
Glu Asp Ile Asp Glu Cys Gln Asp Pro Asp Thr Cys Ser Gln Leu Cys
245      250      255
Val Asn Leu Glu Gly Gly Tyr Lys Cys Gln Cys Glu Glu Gly Phe Gln
260      265      270
Leu Asp Pro His Thr Lys Ala Cys Lys Ala Val Gly Ser Ile Ala Tyr
275      280      285
Leu Phe Phe Thr Asn Arg His Glu Val Arg Lys Met Thr Leu Asp Arg
290      295      300
Ser Glu Tyr Thr Ser Leu Ile Pro Asn Leu Arg Asn Val Val Ala Leu
305      310      315      320
Asp Thr Glu Val Ala Ser Asn Arg Ile Tyr Trp Ser Asp Leu Ser Gln
325      330      335
Arg Met Ile Cys Ser Thr Gln Leu Asp Arg Ala His Gly Val Ser Ser
340      345      350
Tyr Asp Thr Val Ile Ser Arg Asp Ile Gln Ala Pro Asp Gly Leu Ala
355      360      365
Val Asp Trp Ile His Ser Asn Ile Tyr Trp Thr Asp Ser Val Leu Gly
370      375      380
Thr Val Ser Val Ala Asp Thr Lys Gly Val Lys Arg Lys Thr Leu Phe
385      390      395      400
Arg Glu Asn Gly Ser Lys Pro Arg Ala Ile Val Val Asp Pro Val His
405      410      415
Gly Phe Met Tyr Trp Thr Asp Trp Gly Thr Pro Ala Lys Ile Lys Lys
420      425      430
Gly Gly Leu Asn Gly Val Asp Ile Tyr Ser Leu Val Thr Glu Asn Ile
435      440      445
Gln Trp Pro Asn Gly Ile Thr Leu Asp Leu Leu Ser Gly Arg Leu Tyr
450      455      460
Trp Val Asp Ser Lys Leu His Ser Ile Ser Ser Ile Asp Val Asn Gly
465      470      475      480
Gly Asn Arg Lys Thr Ile Leu Glu Asp Glu Lys Arg Leu Ala His Pro
485      490      495
Phe Ser Leu Ala Val Phe Glu Asp Lys Val Phe Trp Thr Asp Ile Ile

500      505      510
Asn Glu Ala Ile Phe Ser Ala Asn Arg Leu Thr Gly Ser Asp Val Asn
515      520      525
Leu Leu Ala Glu Asn Leu Leu Ser Pro Glu Asp Met Val Leu Phe His
530      535      540
Asn Leu Thr Gln Pro Arg Gly Val Asn Trp Cys Glu Arg Thr Thr Leu
545      550      555      560
Ser Asn Gly Gly Cys Gln Tyr Leu Cys Leu Pro Ala Pro Gln Ile Asn
565      570      575
Pro His Ser Pro Lys Phe Thr Cys Ala Cys Pro Asp Gly Met Leu Leu
580      585      590
Ala Arg Asp Met Arg Ser Cys Leu Thr Glu Ala Glu Ala Val Ala
595

```

595					600					605					
Thr	Gln	Glu	Thr	Ser	Thr	Val	Arg	Leu	Lys	Val	Ser	Ser	Thr	Ala	Val
610					615					620					
Arg	Thr	Gln	His	Thr	Thr	Thr	Arg	Pro	Val	Pro	Asp	Thr	Ser	Arg	Leu
625					630					635					
Pro	Gly	Ala	Thr	Pro	Gly	Leu	Thr	Thr	Val	Glu	Ile	Val	640		
645					650										

<210> 759

<211> 753

<212> PRT

<213> Homo sapiens

<400> 759

Met	Glu	Arg	Arg	Ala	Trp	Ser	Leu	Gln	Cys	Thr	Ala	Phe	Val	Leu	Phe
1				5					10					15	
Cys	Ala	Trp	Cys	Ala	Leu	Asn	Ser	Ala	Lys	Ala	Lys	Arg	Gln	Phe	Val
			20					25					30		
Asn	Glu	Trp	Ala	Ala	Glu	Ile	Pro	Gly	Gly	Pro	Glu	Ala	Ala	Ser	Ala
		35					40					45			
Ile	Ala	Glu	Glu	Leu	Gly	Tyr	Asp	Leu	Leu	Gly	Gln	Ile	Gly	Ser	Leu
	50				55						60				
Glu	Asn	His	Tyr	Leu	Phe	Lys	His	Lys	Asn	His	Pro	Arg	Arg	Ser	Arg
65				70						75					80
Arg	Ser	Ala	Phe	His	Ile	Thr	Lys	Arg	Leu	Ser	Asp	Asp	Asp	Arg	Val
			85					90					95		
Ile	Trp	Ala	Glu	Gln	Gln	Tyr	Glu	Lys	Glu	Arg	Ser	Lys	Arg	Ser	Ala
		100						105					110		
Leu	Arg	Asp	Ser	Ala	Leu	Asn	Leu	Phe	Asn	Asp	Pro	Met	Trp	Asn	Gln
		115					120					125			
Gln	Trp	Tyr	Leu	Gln	Asp	Thr	Arg	Met	Thr	Ala	Ala	Leu	Pro	Lys	Leu
	130					135					140				
Asp	Leu	His	Val	Ile	Pro	Val	Trp	Gln	Lys	Gly	Ile	Thr	Gly	Lys	Gly
145				150						155					160
Val	Val	Ile	Thr	Val	Leu	Asp	Asp	Gly	Leu	Glu	Trp	Asn	His	Thr	Asp
			165						170					175	
Ile	Tyr	Ala	Asn	Tyr	Asp	Pro	Glu	Ala	Ser	Tyr	Asp	Phe	Asn	Asp	Asn
			180					185					190		
Asp	His	Asp	Pro	Phe	Pro	Arg	Tyr	Asp	Pro	Thr	Asn	Glu	Asn	Lys	His
	195						200					205			
Gly	Thr	Arg	Cys	Ala	Gly	Glu	Ile	Ala	Met	Gln	Ala	Asn	Asn	His	Lys
	210					215					220				
Cys	Gly	Val	Gly	Val	Ala	Tyr	Asn	Ser	Lys	Val	Gly	Gly	Ile	Arg	Met
225				230						235					240
Leu	Asp	Gly	Ile	Val	Thr	Asp	Ala	Ile	Glu	Ala	Ser	Ser	Ile	Gly	Phe
			245						250					255	
Asn	Pro	Gly	His	Val	Asp	Ile	Tyr	Ser	Ala	Ser	Trp	Gly	Pro	Asn	Asp
			260					265					270		
Asp	Gly	Lys	Thr	Val	Glu	Gly	Pro	Gly	Arg	Leu	Ala	Gln	Lys	Ala	Phe
		275					280					285			

Glu	Tyr	Gly	Val	Lys	Gln	Gly	Arg	Gln	Gly	Lys	Gly	Ser	Ile	Phe	Val
290						295					300				
Trp	Ala	Ser	Gly	Asn	Gly	Gly	Arg	Gln	Gly	Asp	Asn	Cys	Asp	Cys	Asp
305					310					315					320
Gly	Tyr	Thr	Asp	Ser	Ile	Tyr	Thr	Ile	Ser	Ile	Ser	Ser	Ala	Ser	Gln
				325					330						335
Gln	Gly	Leu	Ser	Pro	Trp	Tyr	Ala	Glu	Lys	Cys	Ser	Ser	Thr	Leu	Ala
				340				345					350		
Thr	Ser	Tyr	Ser	Ser	Gly	Asp	Tyr	Thr	Asp	Gln	Arg	Ile	Thr	Ser	Ala
				355			360					365			
Asp	Leu	His	Asn	Asp	Cys	Thr	Glu	Thr	His	Thr	Gly	Thr	Ser	Ala	Ser
	370					375					380				
Ala	Pro	Leu	Ala	Ala	Gly	Ile	Phe	Ala	Leu	Ala	Leu	Glu	Ala	Asn	Pro
385					390					395					400
Asn	Leu	Thr	Trp	Arg	Asp	Met	Gln	His	Leu	Val	Val	Trp	Thr	Ser	Glu
				405					410						415
Tyr	Asp	Pro	Leu	Ala	Asn	Asn	Pro	Gly	Trp	Lys	Lys	Asn	Gly	Ala	Gly
				420				425					430		
Leu	Met	Val	Asn	Ser	Arg	Phe	Gly	Phe	Gly	Leu	Leu	Asn	Ala	Lys	Ala
	435						440					445			

```

Leu Val Asp Leu Ala Asp Pro Arg Thr Trp Arg Ser Val Pro Glu Lys
450          455          460
Lys Glu Cys Val Val Lys Asp Asn Asp Phe Glu Pro Arg Ala Leu Lys
465          470          475          480
Ala Asn Gly Glu Val Ile Ile Glu Ile Pro Thr Arg Ala Cys Glu Gly
          485          490          495
Gln Glu Asn Ala Ile Lys Ser Leu Glu His Val Gln Phe Glu Ala Thr
          500          505          510
Ile Glu Tyr Ser Arg Arg Gly Asp Leu His Val Thr Leu Thr Ser Ala
          515          520          525
Ala Gly Thr Ser Thr Val Leu Leu Ala Glu Arg Glu Arg Asp Thr Ser
          530          535          540
Pro Asn Gly Phe Lys Asn Trp Asp Phe Met Ser Val His Thr Trp Gly
          545          550          555          560
Glu Asn Pro Ile Gly Thr Trp Thr Leu Arg Ile Thr Asp Met Ser Gly
          565          570          575
Arg Ile Gln Asn Glu Gly Arg Ile Val Asn Trp Lys Leu Ile Leu His
          580          585          590
Gly Thr Ser Ser Gln Pro Glu His Met Lys Gln Pro Arg Val Tyr Thr
          595          600          605
Ser Tyr Asn Thr Val Gln Asn Asp Arg Arg Gly Val Glu Lys Met Val
          610          615          620
Asp Pro Gly Glu Glu Gln Pro Thr Gln Glu Asn Pro Lys Glu Asn Thr
          625          630          635          640
Leu Val Ser Lys Ser Pro Ser Ser Ser Ser Val Gly Gly Arg Arg Asp
          645          650          655
Glu Leu Glu Glu Gly Ala Pro Ser Gln Ala Met Leu Arg Leu Leu Gln
          660          665          670
Ser Ala Phe Ser Lys Asn Ser Pro Pro Lys Gln Ser Pro Lys Lys Ser
          675          680          685
Pro Ser Ala Lys Leu Asn Ile Pro Tyr Glu Asn Phe Tyr Glu Ala Leu
          690          695          700
Glu Lys Leu Asn Lys Pro Ser Gln Leu Lys Asp Ser Glu Asp Ser Leu
          705          710          715          720
Tyr Asn Asp Tyr Val Asp Val Phe Tyr Asn Thr Lys Pro Tyr Lys His
          725          730          735
Arg Asp Asp Arg Leu Leu Gln Ala Leu Val Asp Ile Leu Asn Glu Glu
          740          745          750
Asn

```

<210> 760

<211> 785

<212> PRT

<213> Homo sapiens

<400> 760

```

Met Pro Lys Gly Arg Gln Lys Val Pro His Leu Asp Ala Pro Leu Gly
1          5          10          15
Leu Pro Thr Cys Leu Trp Leu Glu Leu Ala Gly Leu Phe Leu Leu Val
          20          25          30
Pro Trp Val Met Gly Leu Ala Gly Thr Gly Gly Pro Asp Gly Gln Gly
          35          40          45
Thr Gly Gly Pro Ser Trp Ala Val His Leu Glu Ser Leu Glu Gly Asp
          50          55          60
Gly Glu Glu Glu Thr Leu Glu Gln Gln Ala Asp Ala Leu Ala Gln Ala
          65          70          75          80
Ala Gly Leu Val Asn Ala Gly Arg Ile Gly Glu Leu Gln Gly His Tyr
          85          90          95
Leu Phe Val Gln Pro Ala Gly His Arg Pro Ala Leu Glu Val Glu Ala
          100          105          110
Ile Arg Gln Gln Val Glu Ala Val Leu Ala Gly His Glu Ala Val Arg
          115          120          125
Trp His Ser Glu Gln Arg Leu Leu Arg Arg Ala Lys Arg Ser Val His
          130          135          140
Phe Asn Asp Pro Lys Tyr Pro Gln Gln Trp His Leu Asn Asn Arg Arg
          145          150          155          160
Ser Pro Gly Arg Asp Ile Asn Val Thr Gly Val Trp Glu Arg Asn Val
          165          170          175
Thr Gly Arg Gly Val Thr Val Val Val Val Asp Asp Gly Val Glu His
          180          185          190
Thr Ile Gln Asp Ile Ala Pro Asn Tyr Ser Pro Glu Gly Ser Tyr Asp
          195          200          205

```

```

Leu Asn Ser Asn Asp Pro Asp Pro Met Pro His Pro Asp Val Glu Asn
210 215 220
Gly Asn His His Gly Thr Arg Cys Ala Gly Glu Ile Ala Ala Val Pro
225 230 235 240
Asn Asn Ser Phe Cys Ala Val Gly Val Ala Tyr Gly Ser Arg Ile Ala
245 250 255
Gly Ile Arg Val Leu Asp Gly Pro Leu Thr Asp Ser Met Glu Ala Val
260 265 270
Ala Phe Asn Lys His Tyr Gln Ile Asn Asp Ile Tyr Ser Cys Ser Trp
275 280 285
Gly Pro Asp Asp Asp Gly Lys Thr Val Asp Gly Pro His Gln Leu Gly
290 295 300
Lys Ala Ala Leu Gln His Gly Val Ile Ala Gly Arg Gln Gly Phe Gly
305 310 315 320
Ser Ile Phe Val Val Ala Ser Gly Asn Gly Gly Gln His Asn Asp Asn
325 330 335
Cys Asn Tyr Asp Gly Tyr Ala Asn Ser Ile Tyr Thr Val Thr Ile Gly
340 345 350
Ala Val Asp Glu Glu Gly Arg Met Pro Phe Tyr Ala Glu Glu Cys Ala
355 360 365
Ser Met Leu Ala Val Thr Phe Ser Gly Gly Asp Lys Met Leu Arg Ser
370 375 380
Ile Val Thr Thr Asp Trp Asp Leu Gln Lys Gly Thr Gly Cys Thr Glu
385 390 395 400
Gly His Thr Gly Thr Ser Ala Ala Ala Pro Leu Ala Ala Gly Met Ile
405 410 415
Ala Leu Met Leu Gln Val Arg Pro Cys Leu Thr Trp Arg Asp Val Gln
420 425 430
His Ile Ile Val Phe Thr Ala Thr Arg Tyr Glu Asp Arg Arg Ala Glu
435 440 445
Trp Val Thr Asn Glu Ala Gly Phe Ser His Ser His Gln His Gly Phe
450 455 460

```

```

Gly Leu Leu Asn Ala Trp Arg Leu Val Asn Ala Ala Lys Ile Trp Thr
465 470 475 480
Ser Val Pro Tyr Leu Ala Ser Tyr Val Ser Pro Val Leu Lys Glu Asn
485 490 495
Lys Ala Ile Pro Gln Ser Pro Arg Ser Leu Glu Val Leu Trp Asn Val
500 505 510
Ser Arg Met Asp Leu Glu Met Ser Gly Leu Lys Thr Leu Glu His Val
515 520 525
Ala Val Thr Val Ser Ile Thr His Pro Arg Arg Gly Ser Leu Glu Leu
530 535 540
Lys Leu Phe Cys Pro Ser Gly Met Met Ser Leu Ile Gly Ala Pro Arg
545 550 555 560
Ser Met Asp Ser Asp Pro Asn Gly Phe Asn Asp Trp Thr Phe Ser Thr
565 570 575
Val Arg Cys Trp Gly Glu Arg Ala Arg Gly Thr Tyr Arg Leu Val Ile
580 585 590
Arg Asp Val Gly Asp Glu Ser Phe Gln Val Gly Ile Leu Arg Gln Trp
595 600 605
Gln Leu Thr Leu Tyr Gly Ser Val Trp Ser Ala Val Asp Ile Arg Asp
610 615 620
Arg Gln Arg Leu Leu Glu Ser Ala Met Ser Gly Lys Tyr Leu His Asp
625 630 635 640
Asp Phe Ala Leu Pro Cys Pro Pro Gly Leu Lys Ile Pro Glu Glu Asp
645 650 655
Gly Tyr Thr Ile Thr Pro Asn Thr Leu Lys Thr Leu Val Leu Val Gly
660 665 670
Cys Phe Thr Val Phe Trp Thr Val Tyr Tyr Met Leu Glu Val Tyr Leu
675 680 685
Ser Gln Arg Asn Val Ala Ser Asn Gln Val Cys Arg Ser Gly Pro Cys
690 695 700
His Trp Pro His Arg Ser Arg Lys Ala Lys Glu Glu Gly Thr Glu Leu
705 710 715 720
Glu Ser Val Pro Leu Cys Ser Ser Lys Asp Pro Asp Glu Val Glu Thr
725 730 735
Glu Ser Arg Gly Pro Pro Thr Thr Ser Asp Leu Leu Ala Pro Asp Leu
740 745 750
Leu Glu Gln Gly Asp Trp Ser Leu Ser Gln Asn Lys Ser Ala Leu Asp
755 760 765
Cys Pro His Gln His Leu Asp Val Pro His Gly Lys Glu Glu Gln Ile
770 775 780

```

Cys
785

<210> 761

<211> 692

<212> PRT

<213> *Macaca fascicularis*

<400> 761

```

Met Gly Thr Val Ser Ser Arg Arg Ser Trp Trp Pro Leu Pro Leu Pro
 1          5          10          15
Leu Leu Leu Leu Leu Leu Leu Gly Pro Ala Gly Ala Arg Ala Gln Glu
 20          25          30
Asp Glu Asp Gly Asp Tyr Glu Glu Leu Val Leu Ala Leu Arg Ser Glu
 35          40          45
Glu Asp Gly Leu Ala Asp Ala Pro Glu His Gly Ala Thr Ala Thr Phe
 50          55          60
His Arg Cys Ala Lys Asp Pro Trp Arg Leu Pro Gly Thr Tyr Val Val
 65          70          75          80
Val Leu Lys Glu Glu Thr His Arg Ser Gln Ser Glu Arg Thr Ala Arg
 85          90          95
Arg Leu Gln Ala Gln Ala Ala Arg Arg Gly Tyr Leu Thr Lys Ile Leu

```

```

His Val Phe 100 His Leu Leu 105 Pro Gly Phe Leu Val Lys Met Ser Gly
 115          120          125
Asp Leu Leu Glu Leu Ala Leu Lys Leu Pro His Val Asp Tyr Ile Glu
 130          135          140
Glu Asp Ser Ser Val Phe Ala Gln Ser Ile Pro Trp Asn Leu Glu Arg
 145          150          155          160
Ile Thr Pro Ala Arg Tyr Arg Ala Asp Glu Tyr Gln Pro Pro Lys Gly
 165          170          175
Gly Ser Leu Val Glu Val Tyr Leu Leu Asp Thr Ser Ile Gln Ser Asp
 180          185          190
His Arg Glu Ile Glu Gly Arg Val Met Val Thr Asp Phe Glu Ser Val
 195          200          205
Pro Glu Glu Asp Gly Thr Arg Phe His Arg Gln Ala Ser Lys Cys Asp
 210          215          220
Ser His Gly Thr His Leu Ala Gly Val Val Ser Gly Arg Asp Ala Gly
 225          230          235          240
Val Ala Lys Gly Ala Gly Leu Arg Ser Leu Arg Val Leu Asn Cys Gln
 245          250          255
Gly Lys Gly Thr Val Ser Gly Thr Leu Ile Gly Leu Glu Phe Ile Arg
 260          265          270
Lys Ser Gln Leu Val Gln Pro Val Gly Pro Leu Val Val Leu Leu Pro
 275          280          285
Leu Ala Gly Gly Tyr Ser Arg Val Phe Asn Ala Ala Cys Gln Arg Leu
 290          295          300
Ala Arg Ala Gly Val Val Leu Val Thr Ala Ala Gly Asn Phe Arg Asp
 305          310          315          320
Asp Ala Cys Leu Tyr Ser Pro Ala Ser Ala Pro Glu Val Ile Thr Val
 325          330          335
Gly Ala Thr Asn Ala Gln Asp Gln Pro Val Thr Leu Gly Thr Leu Gly
 340          345          350
Thr Asn Phe Gly Arg Cys Val Asp Leu Phe Ala Pro Gly Glu Asp Ile
 355          360          365
Ile Gly Ala Ser Ser Asp Cys Ser Thr Cys Phe Val Ser Arg Ser Gly
 370          375          380
Thr Ser Gln Ala Ala Ala His Val Ala Gly Ile Ala Ala Met Met Leu
 385          390          395          400
Ser Ala Glu Pro Glu Leu Thr Leu Ala Glu Leu Arg Gln Arg Leu Ile
 405          410          415
His Phe Ser Ala Lys Asp Val Ile Asn Glu Ala Trp Phe Pro Glu Asp
 420          425          430
Gln Arg Val Leu Thr Pro Asn Leu Val Ala Ala Leu Pro Pro Ser Thr
 435          440          445
His Arg Ala Gly Trp Gln Leu Phe Cys Arg Thr Val Trp Ser Ala His
 450          455          460
Ser Gly Pro Thr Arg Met Ala Thr Ala Val Ala Arg Cys Ala Gln Asp
 465          470          475          480
Glu Glu Leu Leu Ser Cys Ser Ser Phe Ser Arg Ser Gly Lys Arg Arg
 485          490          495
Gly Glu Arg Ile Glu Ala Gln Gly Gly Lys Arg Val Cys Arg Ala His
 500          505          510

```

```

      300      305      310
Asn Ala Phe Gly Gly Val Tyr Ala Ile Ala Arg Cys Cys Leu
   515      520      525
Leu Pro Gln Val Asn Cys Ser Val His Thr Ala Pro Pro Ala Gly Ala
   530      535      540
Ser Met Gly Thr Arg Val His Cys His Gln Gln Gly His Val Leu Thr
  545      550      555      560
Gly Cys Ser Ser His Trp Glu Val Glu Asp Leu Gly Thr His Lys Pro
   565      570      575
Pro Val Leu Arg Pro Arg Gly Gln Pro Asn Gln Cys Val Gly His Arg
   580      585      590
Glu Ala Ser Ile His Ala Ser Cys Cys His Ala Pro Gly Leu Glu Cys
   595      600      605

```

```

Lys Val Lys Glu His Gly Ile Pro Ala Pro Gln Glu Gln Val Ile Val
   610      615      620
Ala Cys Glu Asp Gly Trp Thr Leu Thr Gly Cys Ser Ala Leu Pro Gly
  625      630      635      640
Thr Ser His Val Leu Gly Ala Tyr Ala Val Asp Asn Thr Cys Val Val
   645      650      655
Arg Ser Arg Asp Val Ser Thr Thr Gly Ser Thr Ser Glu Glu Ala Val
   660      665      670
Ala Ala Val Ala Ile Cys Cys Arg Ser Arg His Leu Val Gln Ala Ser
   675      680      685
Gln Glu Leu Gln
   690

```

<210> 762

<211> 698

<212> PRT

<213> Mesocricetus auratus

<400> 762

```

Met Gly Thr Ser Cys Ser Ala Arg Pro Arg Trp Leu Leu Ser Pro Leu
   1       5       10       15
Leu Leu Leu Leu Leu Leu Arg Tyr Met Gly Ala Ser Ala Gln Asp
   20      25      30
Glu Asp Ala Glu Tyr Glu Glu Leu Met Leu Thr Leu Gln Ser Gln Asp
   35      40      45
Asp Gly Leu Ala Asp Glu Thr Asp Glu Ala Pro Gln Gly Ala Thr Ala
   50      55      60
Ala Phe His Arg Cys Pro Glu Glu Ala Trp Arg Val Pro Gly Thr Tyr
   65      70      75      80
Ile Val Met Leu Ala Glu Glu Ala Gln Trp Val His Ile Glu Gln Thr
   85      90      95
Met His Arg Leu Gln Thr Gln Ala Ala Arg Arg Gly Tyr Val Ile Lys
  100     105     110
Ile Gln His Ile Phe Tyr Asp Phe Leu Pro Ala Phe Val Val Lys Met
  115     120     125
Ser Ser Asp Leu Leu Asp Leu Ala Leu Lys Leu Pro His Val Lys Tyr
  130     135     140
Ile Glu Glu Asp Ser Leu Val Phe Ala Gln Ser Ile Pro Trp Asn Leu
  145     150     155     160
Asp Arg Ile Ile Pro Ala Gly Arg Gln Ala Gln Glu Tyr Ser Ser Ser
   165     170     175
Arg Lys Val Pro Ser Gly Ser Gly Gln Val Glu Val Tyr Leu Leu Asp
   180     185     190
Thr Ser Ile Gln Ser Asp His Arg Glu Ile Glu Gly Arg Val Thr Val
   195     200     205
Thr Asp Phe Asn Ser Val Pro Glu Glu Asp Gly Thr Arg Phe His Arg
   210     215     220
Gln Ala Ser Lys Cys Asp Ser His Gly Thr His Leu Ala Gly Val Val
  225     230     235     240
Ser Gly Arg Asp Ala Gly Val Ala Lys Gly Thr Ile Leu His Gly Leu
   245     250     255
Arg Val Leu Asn Cys Gln Gly Lys Gly Ile Val Ser Gly Ile Leu Thr
   260     265     270
Gly Leu Glu Phe Ile Trp Lys Ser Gln Leu Met Gln Pro Ser Gly Pro
   275     280     285
Gln Val Val Leu Leu Pro Leu Ala Gly Arg Tyr Ser Arg Val Leu Asn
   290     295     300
Thr Ala Cys Gln His Leu Ala Arg Thr Gly Val Val Leu Val Ala Ala

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Ala Gly Asn Phe Arg Asp Asp Ala Cys Leu Tyr Ser Pro Ala Ser Ala
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Pro Glu Val Ile Thr Val Gly Ala Thr Asp Val Gln Asp Gln Pro Val

          340          345          350
Thr Leu Gly Thr Leu Gly Thr Asn Phe Gly Arg Cys Val Asp Leu Phe
          355          360          365
Ala Pro Gly Lys Asp Ile Ile Gly Ala Ser Ser Asp Cys Ser Ala Cys
          370          375          380
Phe Met Ser Gln Ser Gly Thr Ser Gln Ala Ala Ala His Val Ala Gly
385          390          395          400
Ile Val Ala Met Met Leu Thr Leu Glu Pro Glu Leu Thr Leu Thr Glu
          405          410          415
Leu Arg Gln Arg Leu Ile His Phe Ser Thr Lys Asp Ala Ile Asn Met
          420          425          430
Ala Trp Phe Pro Glu Asp Gln Arg Val Leu Thr Pro Asn Leu Val Ala
          435          440          445
Thr Leu Pro Pro Ser Thr His Gly Thr Gly Gly Gln Leu Leu Cys Arg
          450          455          460
Thr Val Trp Ser Ala His Ser Gly Pro Thr Arg Ala Ala Thr Ala Thr
465          470          475          480
Ala Arg Cys Ala Pro Gly Glu Glu Leu Leu Ser Cys Ser Ser Phe Ser
          485          490          495
Arg Ser Gly Arg Arg Arg Gly Asp Arg Ile Glu Ala Ala Gly Thr Gln
          500          505          510
Gln Val Cys Lys Ala Leu Asn Ala Phe Gly Gly Glu Gly Val Tyr Ala
          515          520          525
Val Ala Arg Cys Cys Leu Leu Pro Arg Ala Asn Cys Ser Ile His Thr
          530          535          540
Thr Pro Ala Ala Arg Thr Ser Leu Glu Thr His Ala His Cys His Gln
545          550          555          560
Lys Asp His Val Leu Thr Gly Cys Ser Leu His Trp Glu Val Glu Gly
          565          570          575
Ile Gly Val Gln Pro Leu Ala Val Leu Arg Ser Arg His Gln Pro Gly
          580          585          590
Gln Cys Thr Gly His Arg Glu Ala Ser Val His Ala Ser Cys Cys His
          595          600          605
Ala Pro Gly Leu Glu Cys Lys Ile Lys Glu His Gly Ile Ser Gly Pro
          610          615          620
Ala Glu Gln Val Thr Val Ala Cys Glu Ala Gly Trp Thr Leu Thr Gly
625          630          635          640
Cys Asn Val Leu Pro Gly Ala Phe Ile Thr Leu Gly Ala Tyr Ala Val
          645          650          655
Asp Asn Thr Cys Val Ala Arg Ser Arg Val Thr Asp Thr Ala Gly Arg
          660          665          670
Thr Gly Glu Glu Ala Thr Val Ala Ala Ala Ile Cys Cys Arg Asn Arg
          675          680          685
Pro Ser Ala Lys Ala Ser Trp Val His Gln
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<211> 691

<212> PRT

<213> Rattus norvegicus

<400> 763

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Met Gly Ile Arg Cys Ser Thr Trp Leu Arg Trp Pro Leu Ser Pro Gln
 1          5          10          15
Leu Leu Leu Leu Leu Leu Cys Pro Thr Gly Ser Arg Ala Gln Asp
          20          25          30
Glu Asp Gly Asp Tyr Glu Glu Leu Met Leu Ala Leu Pro Ser Gln Glu
          35          40          45
Asp Ser Leu Val Asp Glu Ala Ser His Val Ala Thr Ala Thr Phe Arg
          50          55          60
Arg Cys Ser Lys Glu Ala Trp Arg Leu Pro Gly Thr Tyr Val Val Val
65          70          75          80
Leu Met Glu Glu Thr Gln Arg Leu Gln Val Glu Gln Thr Ala His Arg

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      85              90              95
Leu Gln Thr Trp Ala Ala Arg Arg Gly Tyr Val Ile Lys Val Leu His
      100              105              110
Val Phe Tyr Asp Leu Phe Pro Gly Phe Leu Val Lys Met Ser Ser Asp
      115              120              125
Leu Leu Gly Leu Ala Leu Lys Leu Pro His Val Glu Tyr Ile Glu Glu
      130              135              140
Asp Ser Leu Val Phe Ala Gln Ser Ile Pro Trp Asn Leu Glu Arg Ile
      145              150              155
Ile Pro Ala Trp Gln Gln Thr Glu Glu Asp Ser Ser Pro Asp Gly Ser
      160              165              170
Ser Gln Val Glu Val Tyr Leu Leu Asp Thr Ser Ile Gln Ser Gly His
      175              180              185
Arg Glu Ile Glu Gly Arg Val Thr Ile Thr Asp Phe Asn Ser Val Pro
      190              195              200
Glu Glu Asp Gly Thr Arg Phe His Arg Gln Ala Ser Lys Cys Asp Ser
      205              210              215
His Gly Thr His Leu Ala Gly Val Val Ser Gly Arg Asp Ala Gly Val
      220              225              230
Ala Lys Gly Thr Ser Leu His Ser Leu Arg Val Leu Asn Cys Gln Gly
      235              240              245
Lys Gly Thr Val Ser Gly Thr Leu Ile Gly Leu Glu Phe Ile Arg Lys
      250              255              260
Ser Gln Leu Ile Gln Pro Ser Gly Pro Leu Val Val Leu Leu Pro Leu
      265              270              275
Ala Gly Gly Tyr Ser Arg Ile Leu Asn Thr Ala Cys Gln Arg Leu Ala
      280              285              290
Arg Thr Gly Val Val Leu Val Ala Ala Ala Gly Asn Phe Arg Asp Asp
      295              300              305
Ala Cys Leu Tyr Ser Pro Ala Ser Ala Pro Glu Val Ile Thr Val Gly
      310              315              320
Ala Thr Asn Ala Gln Asp Gln Pro Val Thr Leu Gly Thr Leu Gly Thr
      325              330              335
Asn Phe Gly Arg Cys Val Asp Leu Phe Ala Pro Gly Lys Asp Ile Ile
      340              345              350
Gly Ala Ser Ser Asp Cys Ser Thr Cys Tyr Met Ser Gln Ser Gly Thr
      355              360              365
Ser Gln Ala Ala Ala His Val Ala Gly Ile Val Ala Met Met Leu Asn
      370              375              380
Arg Asp Pro Ala Leu Thr Leu Ala Glu Leu Arg Gln Arg Leu Ile Leu
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Phe Ser Thr Lys Asp Val Ile Asn Met Ala Trp Phe Pro Glu Asp Gln
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Glu Thr Gly Gly Gln Leu Leu Cys Arg Thr Val Trp Ser Ala His Ser
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      460              465              470
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Ala Phe Gly Gly Glu Gly Val Tyr Ala Val Ala Arg Cys Cys Leu Leu
      490              495              500
Pro Arg Val Asn Cys Ser Ile His Asn Thr Pro Ala Ala Arg Ala Gly
      505              510              515
Pro Gln Thr Pro Val His Cys His Gln Lys Asp His Val Leu Thr Gly
      520              525              530
Cys Ser Phe His Trp Glu Val Glu Asn Leu Arg Ala Gln Gln Gln Pro
      535              540              545
Leu Leu Arg Ser Arg His Gln Pro Gly Gln Cys Val Gly His Gln Glu
      550              555              560
      565              570              575
      580              585              590

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Ala Ser Val His Ala Ser Cys Cys His Ala Pro Gly Leu Glu Cys Lys
      595              600              605
Ile Lys Glu His Gly Ile Ala Gly Pro Ala Glu Gln Val Thr Val Ala
      610              615              620
Cys Glu Ala Gly Trp Thr Leu Thr Gly Cys Asn Val Leu Pro Gly Ala
      625              630              635
Ser Leu Pro Leu Gly Ala Tyr Ser Val Asp Asn Val Cys Val Ala Arg
      640              645              650
Ile Arg Asp Ala Gly Arg Ala Asp Arg Thr Ser Glu Glu Ala Thr Val
      655              660              665
Ala Ala Ala Ile Cys Cys Arg Ser Arg Pro Ser Ala Lys Ala Ser Trp
      670              675              680
      685
Val His Gln

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REFERENCES CITED IN THE DESCRIPTION

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Patentkrav

1. Humant antistof eller antigen-bindende fragment af et humant antistof, der specifikt binder human proprotein convertase subtilisin/kexin type 9 (hPCSK9) omfattende en HCVR af SEQ ID NO:90 og en LCVR af SEQ ID NO: 92.

5

2. Antistof eller antigen-bindende fragment ifølge krav 1, som er et IgG1 eller IgG4.

3. Isoleret nukleinsyremolekyle, der koder for antistoffet eller det antigen-bindende fragment ifølge krav 1 eller krav 2.

10

4. Ekspressionsvektor omfattende nukleinsyremolekylet ifølge krav 3.

5. Fremgangsmåde til fremstilling af et anti-humant PCSK9-antistof eller antigenbindende fragment af et antistof omfattende trinnene at indføre en

15 ekspressionsvektor ifølge krav 4 i en isoleret værtscelle, at dyrke cellen under betingelser, der gør det muligt at fremstille antistoffet eller fragmentet deraf, og at udvinde det således fremstillede antistof eller fragment.

6. Farmaceutisk sammensætning omfattende antistoffet eller det antigen-bindende
20 fragment ifølge krav 1 eller krav 2, og en farmaceutisk acceptabel bærer.

7. Antistof eller antigen-bindende fragment af et antistof ifølge krav 1 eller krav 2 til anvendelse til at svække eller inhibere en PCSK9-medieret sygdomme eller tilstand, hvor den PCSK9-medierede sygdom eller tilstand er hyperkolesterolæmi.

25

8. Anvendelse af et antistof eller antigen-bindende fragment af et antistof ifølge krav 1 eller krav 2 til fremstilling af et lægemiddel til anvendelse til at svække eller inhibere en PCSK9-medieret sygdom eller tilstand, hvor den PCSK9-medierede sygdom eller tilstand er hyperkolesterolæmi.

30

DRAWINGS

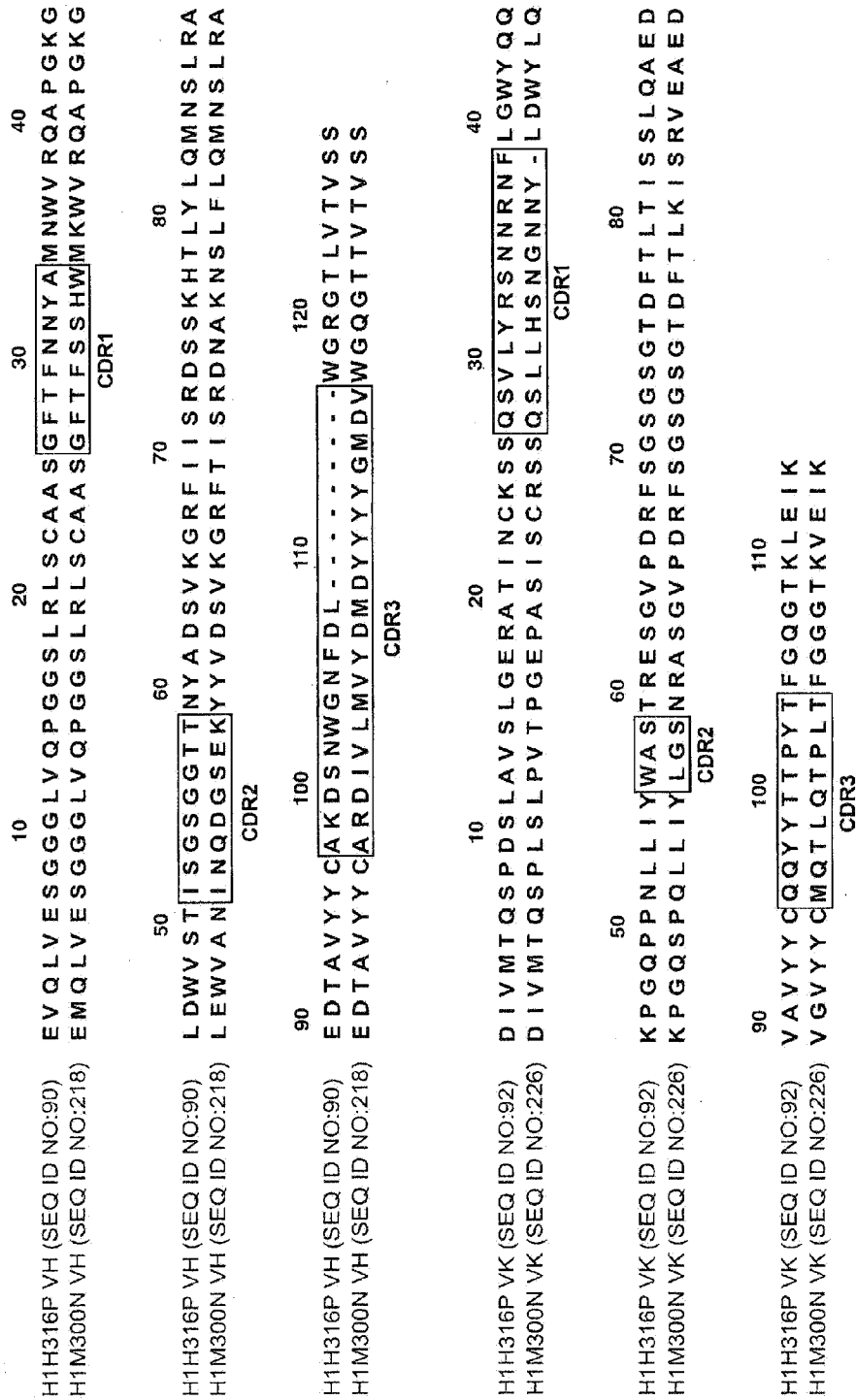


Fig. 1

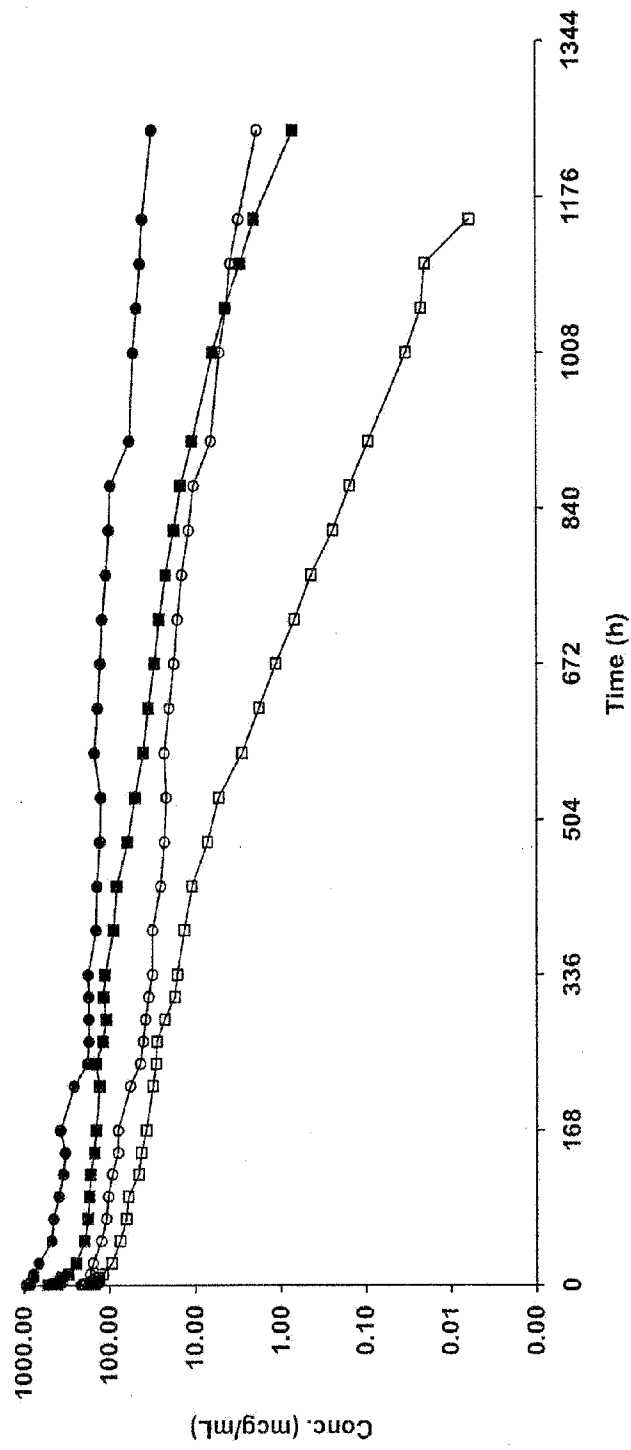


Fig. 2

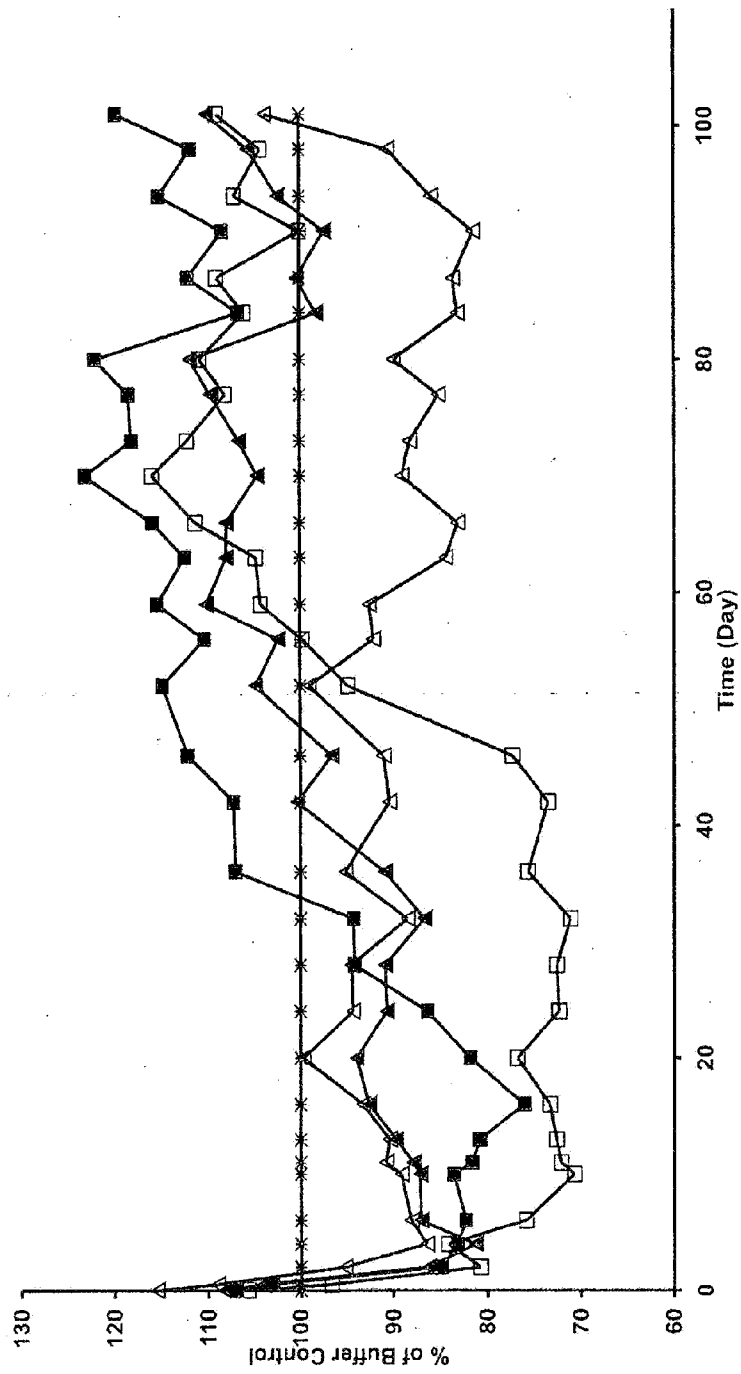


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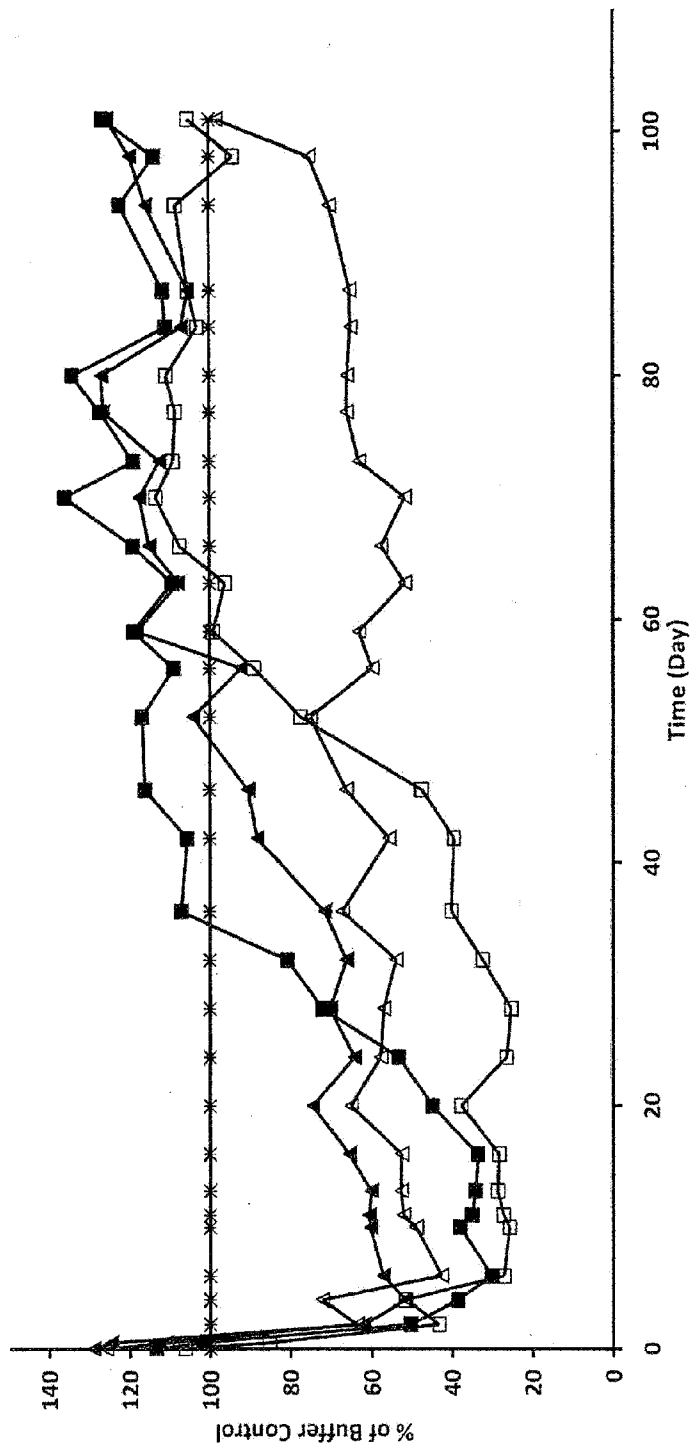


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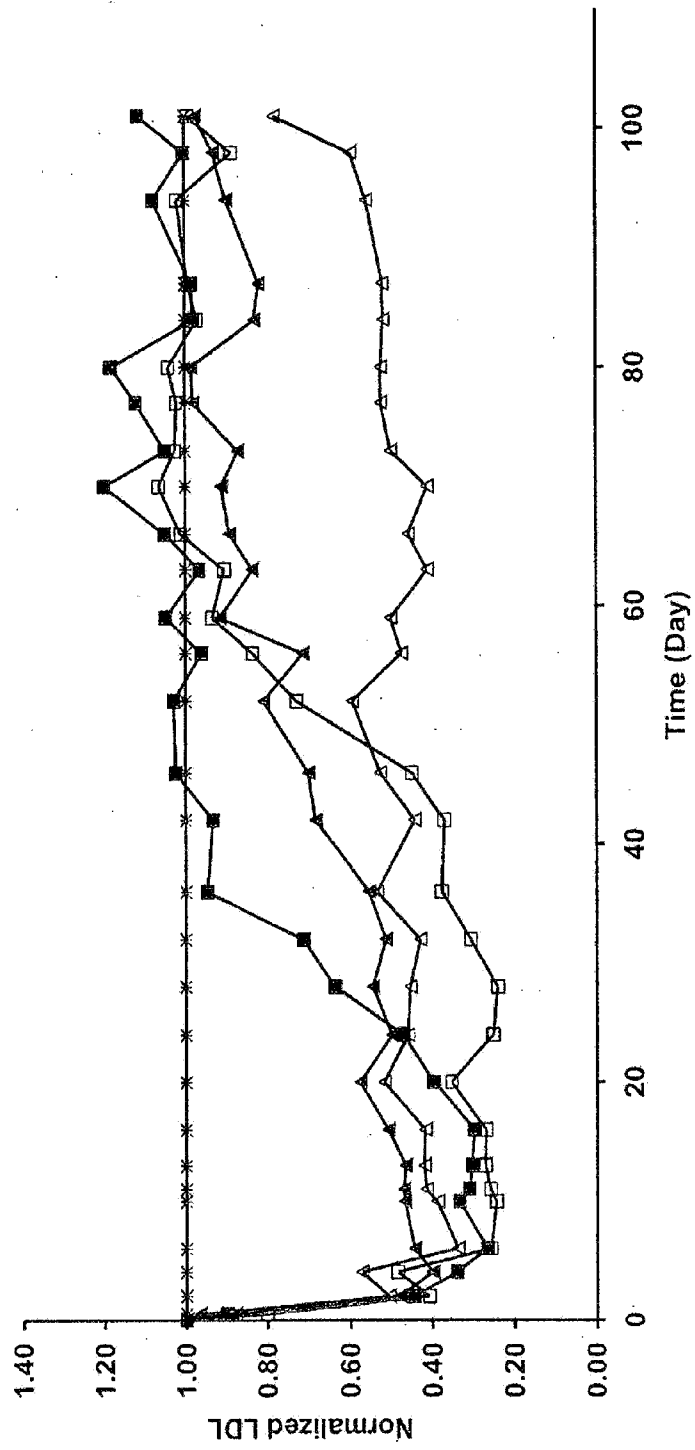


Fig. 5

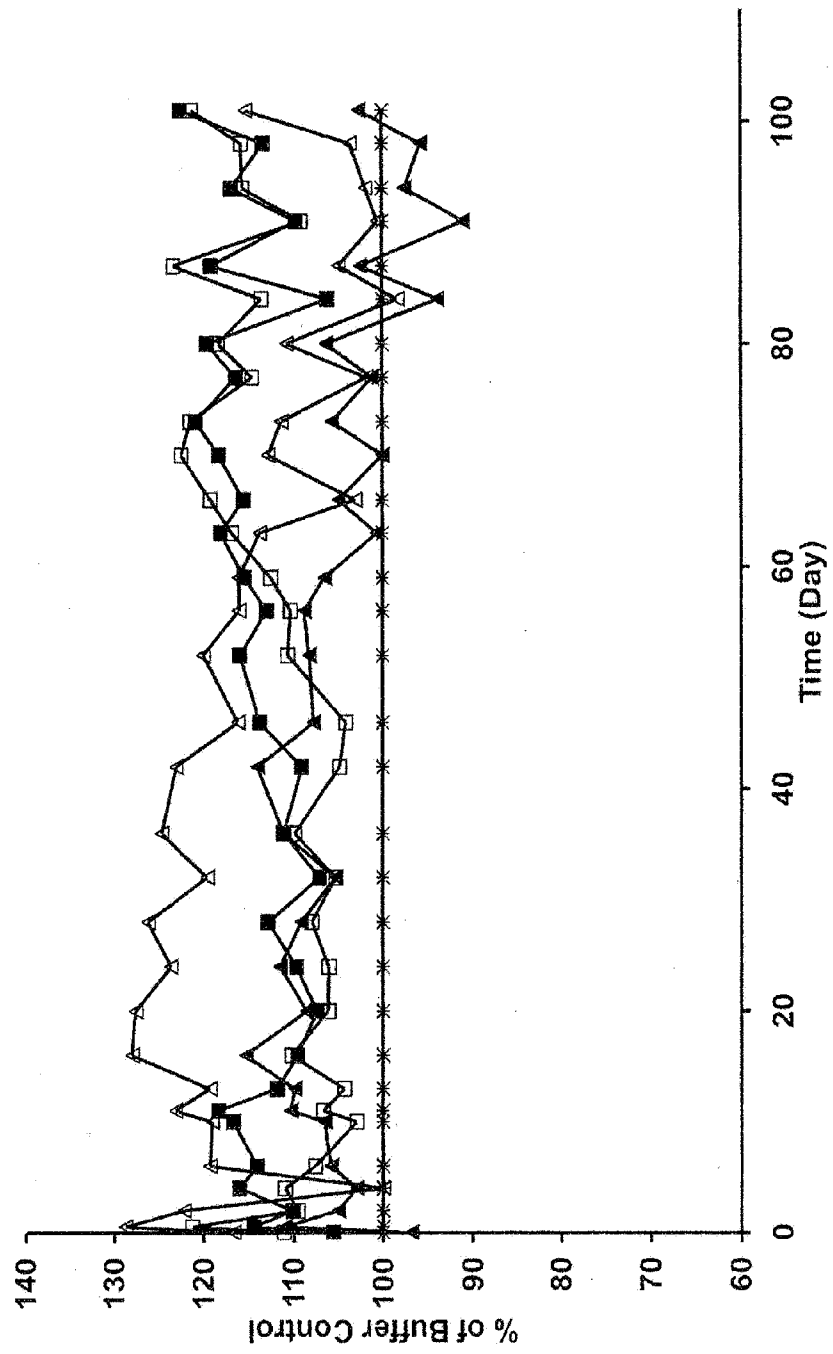


Fig. 6

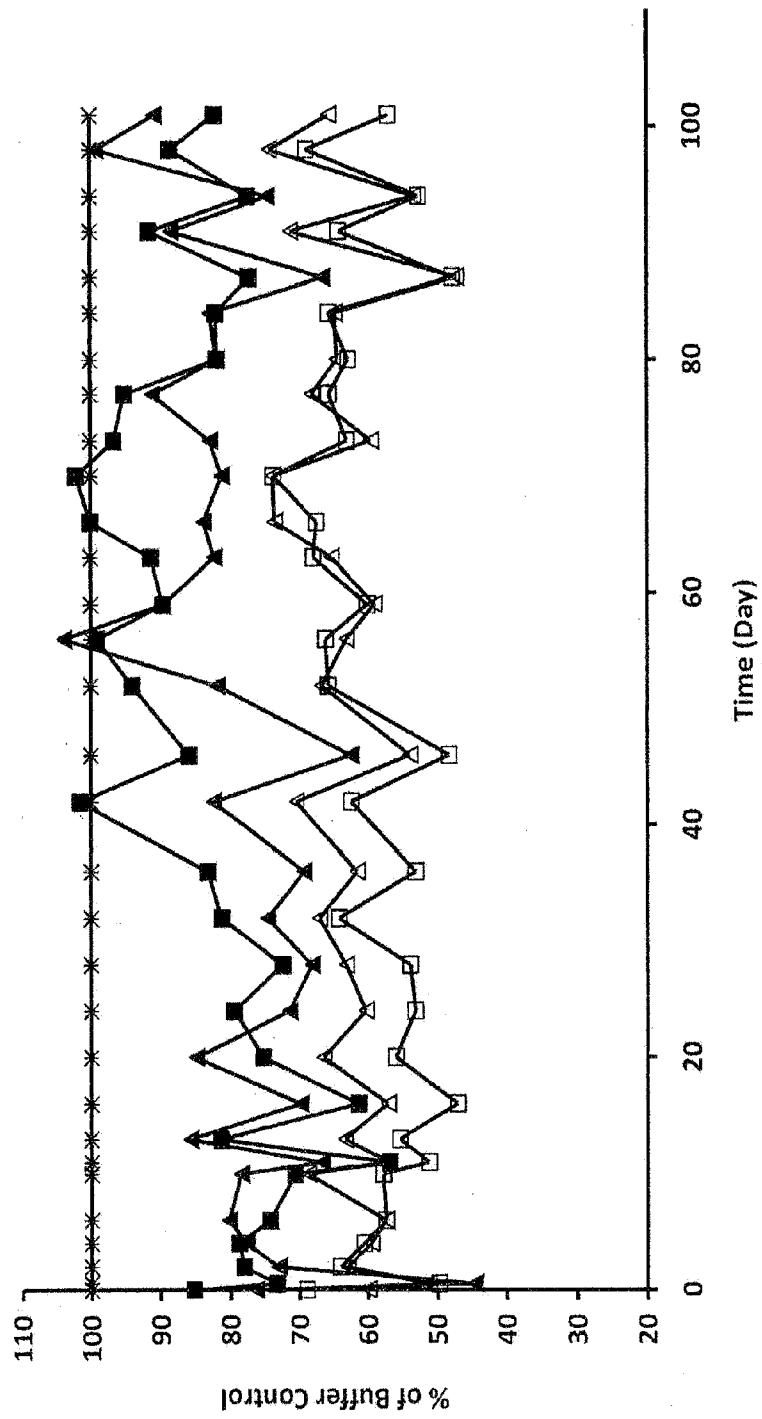


Fig. 7

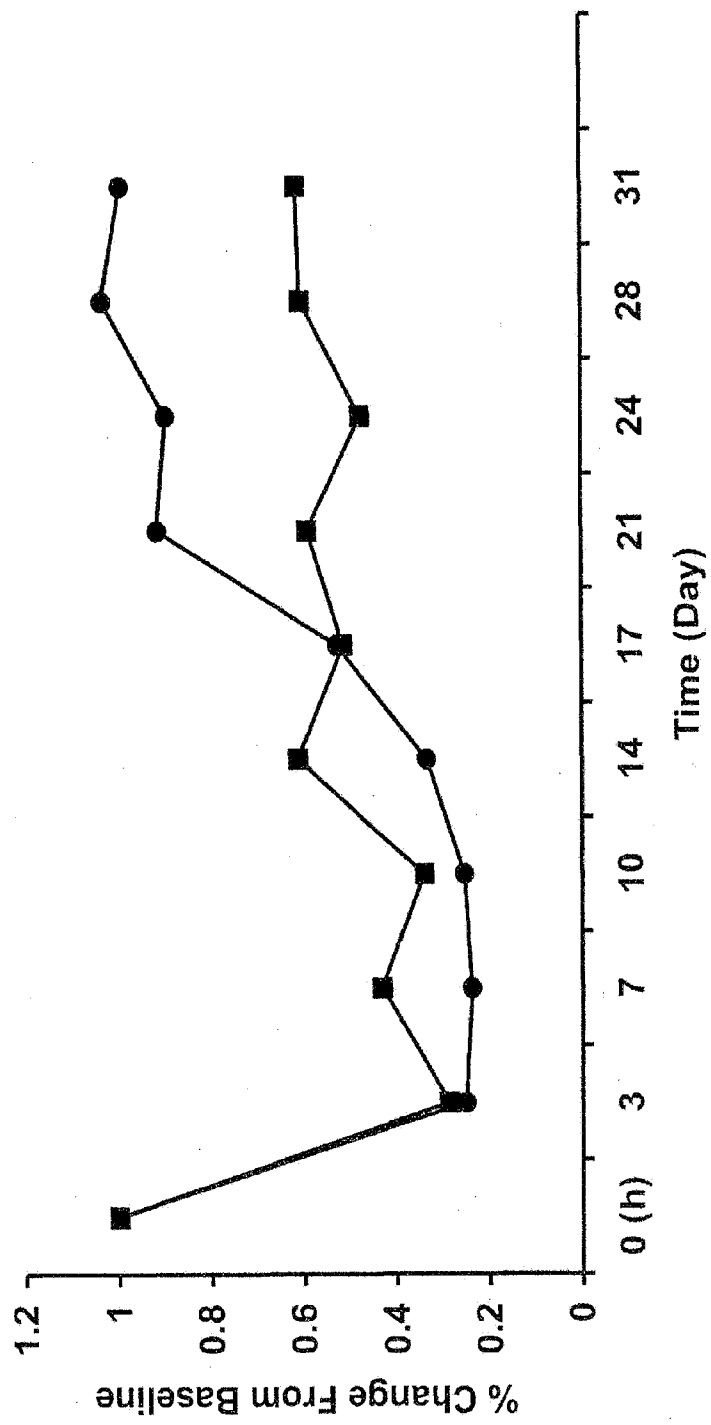


Fig. 8

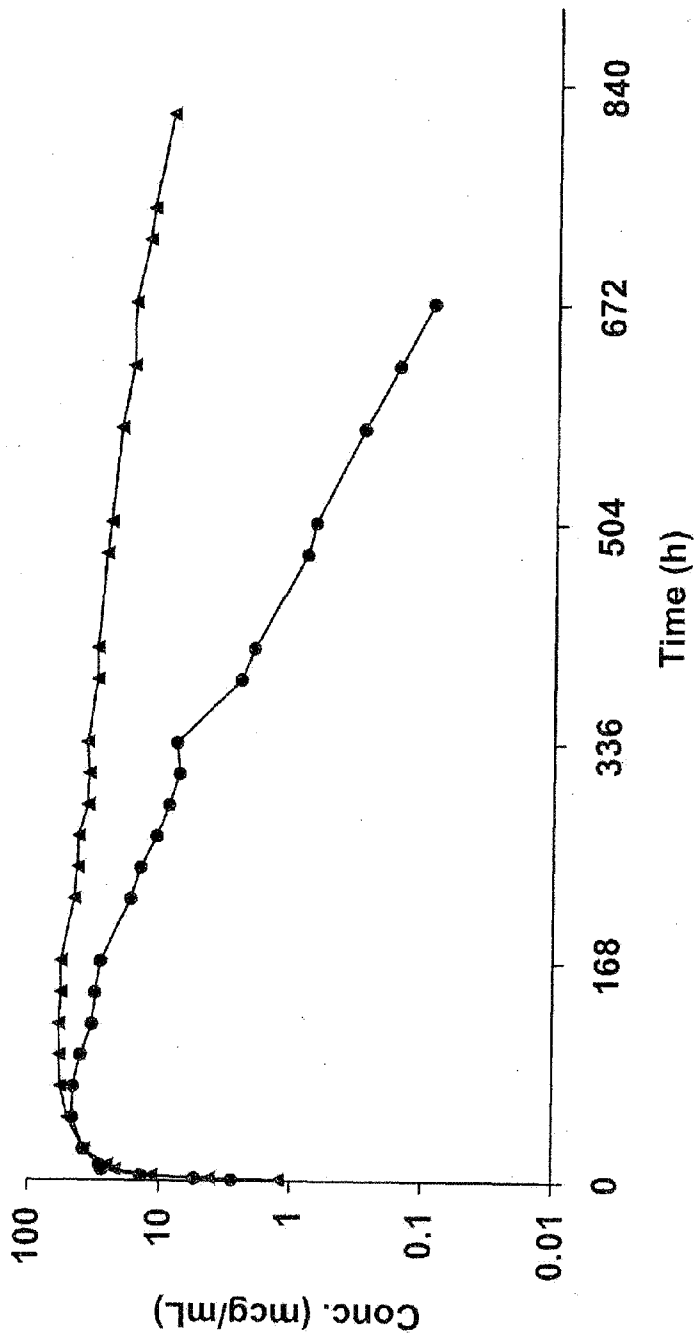


Fig. 9

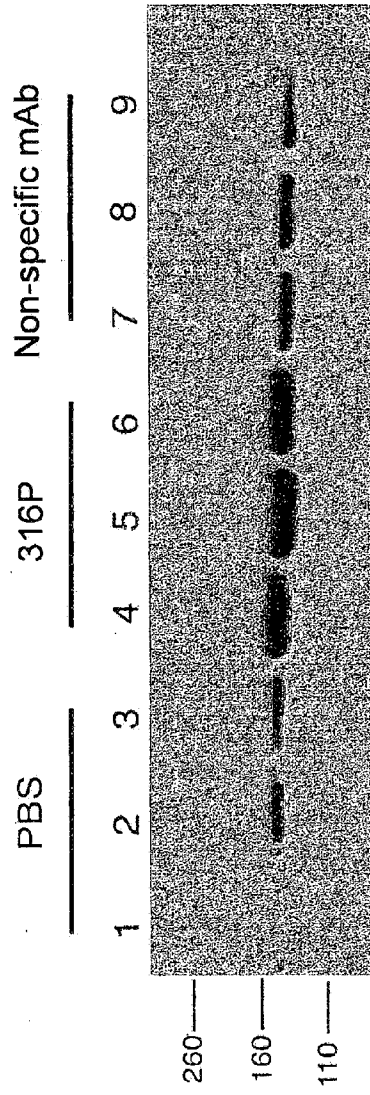


Fig. 10

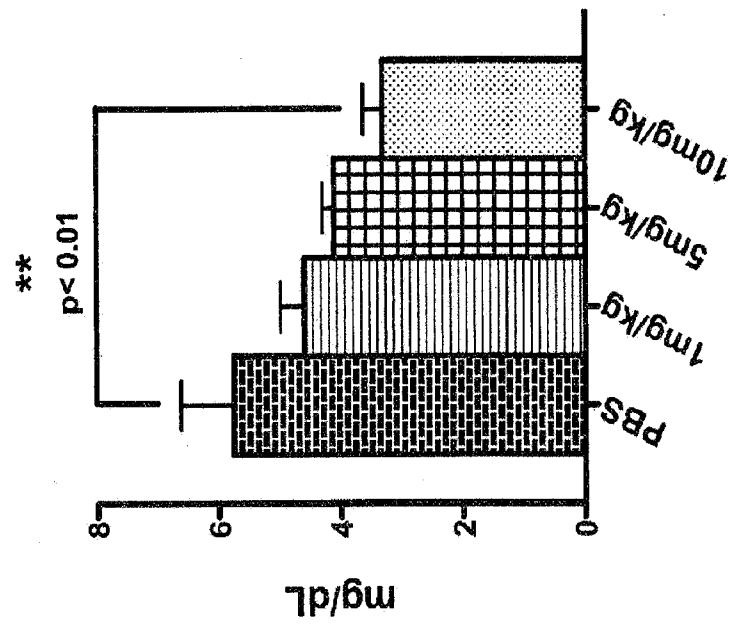


Fig. 11

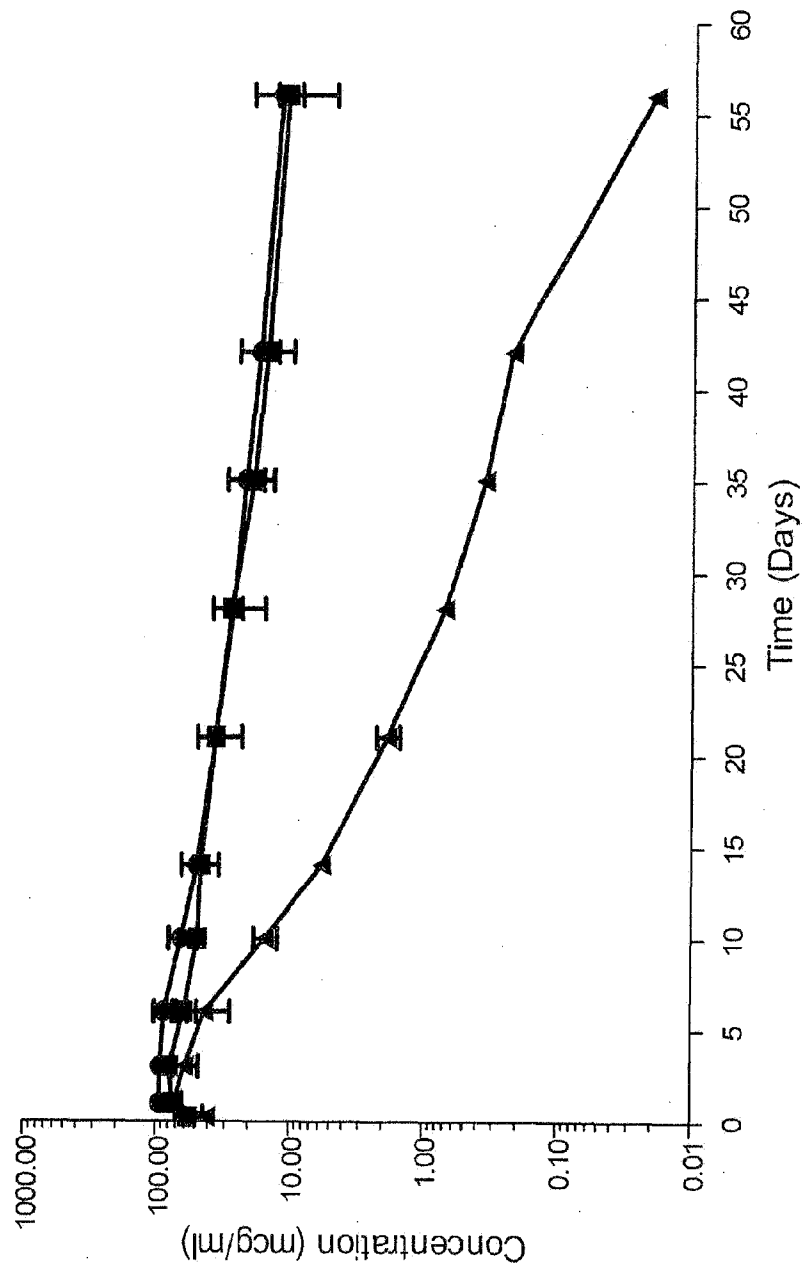


Fig. 12

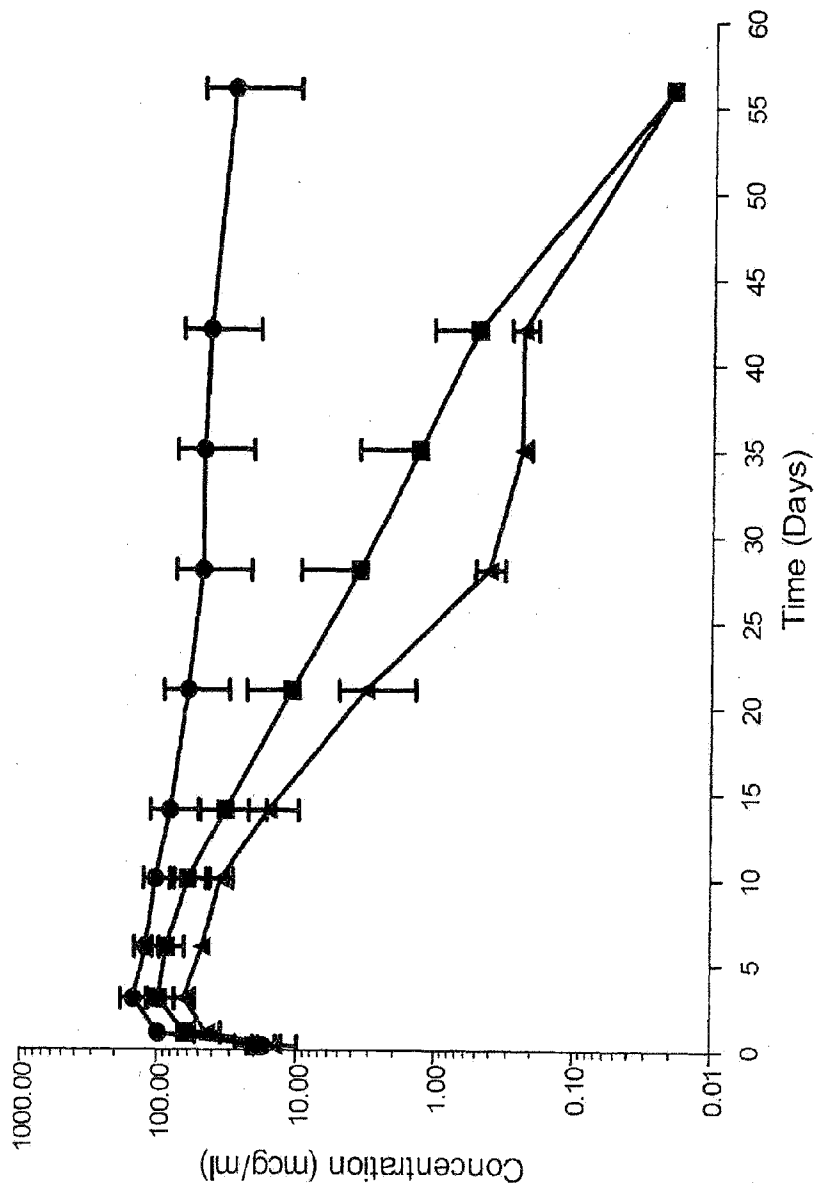


Fig. 13

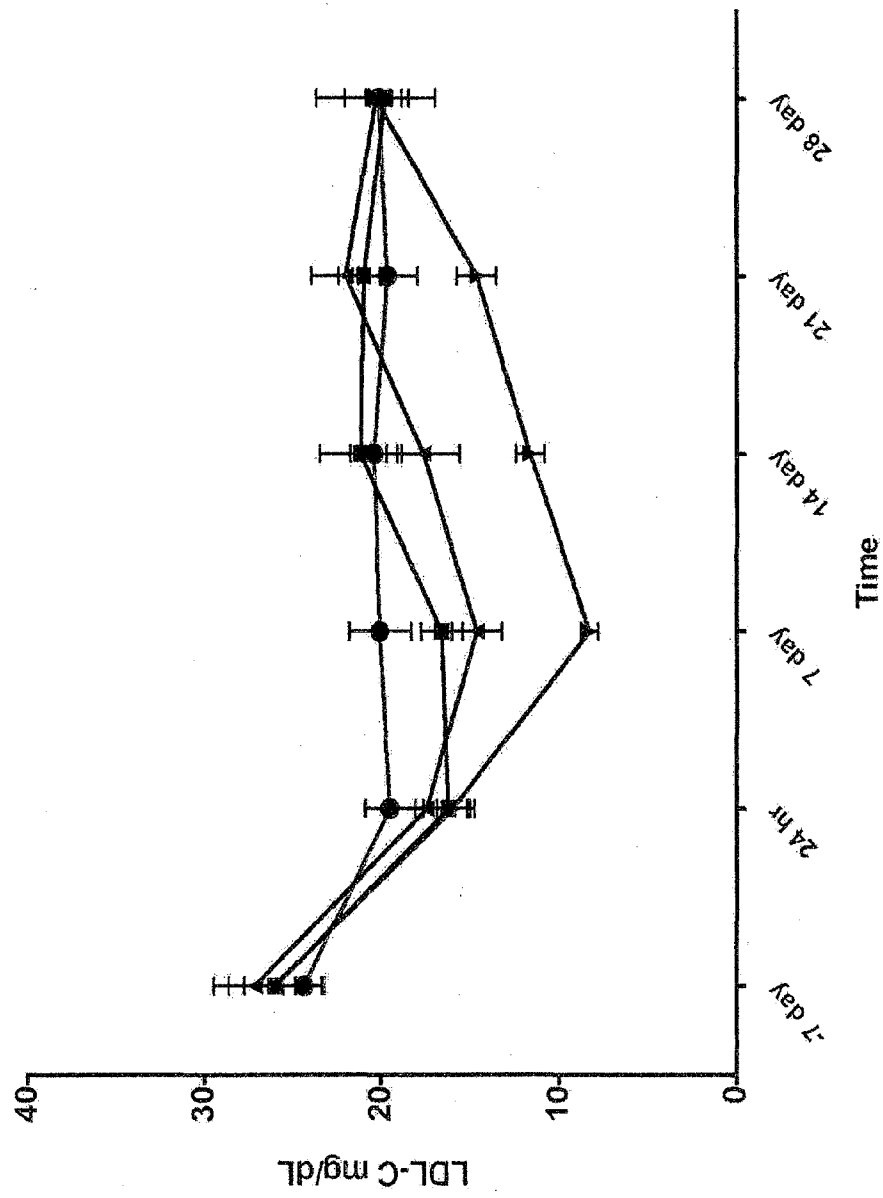


Fig. 14