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Magas emberi proteázaktivált receptor-2 affinitású emberi antitestek

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(54) **HIGH AFFINITY HUMAN ANTIBODIES TO HUMAN PROTEASE-ACTIVATED RECEPTOR-2**

HOCHAFFINE MENSCHLICHE ANTIKÖRPER DES MENSCHLICHEN PROTEASE-AKTIVIERTEN
REZEPTORS-2

ANTICORPS HUMAINS DE HAUTES AFFINITÉS DIRIGÉS CONTRE LE RÉCEPTEUR DE
PROTÉASE ACTIVÉ 2 HUMAIN

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Description**FIELD OF THE INVENTION**

5 **[0001]** The present invention relates to antibodies, and antigen-binding fragments thereof, which are specific for protease-activated receptor-2 (PAR-2).

BACKGROUND

10 **[0002]** Protease-activated receptors ("PARs") are a family of seven-transmembrane G-protein-coupled receptors. Among seven-transmembrane G-protein-coupled receptors PARs have a unique mode of activation; that is, PARs are activated by proteolytic cleavage at the amino terminus to generate a new N-terminal domain which serves as a "tethered ligand." The tethered ligand interacts with the extracellular loop-2 of the receptor thereby resulting in receptor activation. Currently, there are four known members of the PAR family, designated PAR-1, PAR-2, PAR-3 and PAR-4.

15 **[0003]** PAR-2 has also been referred to as "C140." (US 5,874,400). Both human and murine PAR-2 share the protease cleavage domain SKGRSLIG (residues 6-13 of SEQ ID NO:852, and residues 8-15 of SEQ ID NO:856). This sequence is cleaved between the R and S residues by a variety of proteases such as trypsin, as well as by mast cell tryptase, tissue factor/factor VIIa complex and factor Xa, neutrophil proteinase 3 (PR-3), human leukocyte elastase, and proteases originating from pathogenic organisms.

20 **[0004]** PAR-2 activity has been implicated in or associated with several diseases and conditions including inflammatory diseases, pain, gastrointestinal conditions, neurological diseases, and cardiovascular disorders (see, e.g., Linder et al., 2000, J. Immunol. 165:6504-6510; Vergnolle et al., 2001, Nature Medicine 7:821-826; Cenac et al., 2007, J. Clin. Investigation 117:636-647; Vergnolle, 2004, British J. Pharmacol. 141:1264-1274; Knight et al., 2001, J. Allergy Clin. Immunol. 108:797-803; Schmidlin et al., 2002, J. Immunol. 169:5315-5321). Antibodies that bind to PAR-2 have the
25 potential to antagonize the activity of PAR-2 *in vivo*. Anti-PAR-2 antibodies are therefore potentially useful for treating and/or ameliorating a variety of disease conditions.

[0005] Antibodies that bind to PAR-2, and certain therapeutic uses thereof, are mentioned in US 5,874,400, US 2007/0237759, WO 2009/005726, and US 2010/0119506. Nonetheless, there remains a need in the art for novel PAR-2 modulating agents, including anti-PAR-2 antibodies, that can be used to treat PAR-2-mediated diseases and conditions.

30

BRIEF SUMMARY OF THE INVENTION

[0006] The present invention provides human antibodies as defined in the claims that bind to human PAR-2. The antibodies of the invention are useful, *inter alia*, for inhibiting PAR-2-mediated signaling and for treating diseases and
35 disorders caused by or related to PAR-2 activation.

[0007] The present invention includes antibodies which interact with the N-terminal region of PAR-2 and block proteolytic cleavage at the activating PAR-2 protease cleavage site (as defined herein) but do not block proteolytic cleavage at one or more non-activating protease cleavage sites. According to certain embodiments, anti-PAR-2 antibodies which exhibit such proteolytic cleavage blocking properties interact with specific amino acids in the vicinity of the activating
40 PAR-2 protease cleavage site. For example, the present invention provides anti-PAR-2 antibodies with protease cleavage blocking activity and which interact with Val-42 and Asp-43 of human PAR-2 (SEQ ID NO:851), and may further interact with one or more human PAR-2 residues selected from the group consisting of Ser-37, Leu-38, Ile-39, Gly-40, and Gly-44.

[0008] According to some embodiments, the anti-PAR-2 antibodies of the present invention specifically bind to human PAR-2 and monkey PAR-2 but do not bind to at least one member selected from the group consisting of mouse, rat, rabbit, dog and pig PAR-2. The present invention also includes antibodies that are capable of inhibiting or attenuating
45 proteolytic activation of PAR-2 but do not block proteolytic cleavage of PAR-2. Exemplary methods for measuring/assessing an antibody's ability to block PAR-2 cleavage or proteolytic activation are described herein.

[0009] The antibodies of the invention can be full-length (for example, an IgG1 or IgG4 antibody) or may comprise only an antigen-binding portion (for example, a Fab, F(ab')₂ or scFv fragment), and may be modified to affect functionality,
50 e.g., to eliminate residual effector functions (Reddy et al., 2000, J. Immunol. 164:1925-1933).

[0010] Described herein is an antibody or antigen-binding fragment of an antibody comprising a heavy chain variable region (HCVR) having an amino acid sequence 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, 742, 746, 762, 766, 770, 786, 790, 794, 810, 814, 818, 834, and 838, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity. The antibody or antigen-binding portion of an antibody may comprise a HCVR having an amino acid

sequence selected from the group consisting of SEQ ID NO: 98, 146, 338, and 714.

[0011] Also described herein is an antibody or antigen-binding fragment of an antibody comprising a light chain variable region (LCVR) having an amino acid sequence 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, 744, 754, 764, 768, 778, 788, 792, 802, 812, 816, 826, 836, and 840, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity. The antibody or antigen-binding portion of an antibody may comprise a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 106, 154, 346, and 692.

[0012] Also described herein is an antibody or antigen-binding fragment thereof comprising 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, 714/692, 718/720, 722/730, 738/740, 742/744, 746/754, 762/764, 766/768, 770/778, 786/788, 790/792, 794/802, 810/812, 814/816, 818/826, 834/836, and 838/840. The antibody or fragment thereof may comprise a HCVR and LCVR selected from the amino acid sequence pairs of SEQ ID NO: 98/106, 146/154, 338/346, and 714/692.

[0013] Also described herein is an antibody or antigen-binding fragment of an antibody comprising a heavy chain CDR3 (HCDR3) domain having an amino acid sequence 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, 728, 752, 776, 800, and 824, 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 having an amino acid sequence 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, 736, 760, 784, 808, and 832, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0014] The antibody or antigen-binding portion of an antibody may comprise a HCDR3/LCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NO: 8/16, 32/40, 56/64, 80/88, 104/112, 128/136, 152/160, 176/184, 200/208, 224/232, 248/256, 272/280, 296/304, 320/328, 344/352, 368/376, 392/400, 416/424, 440/448, 464/472, 488/496, 512/520, 536/544, 560/568, 584/592, 608/616, 632/640, 656/664, 680/688, 704/712, 728/736, 752/760, 776/784, 800/808, and 824/832. The antibody or antigen-binding portion of an antibody may comprise a HCDR3/LCDR3 amino acid sequence pair selected from the group consisting of SEQ ID NO: 104/112, 152/160, 344/352 and 704/712. Non-limiting examples of anti-PAR-2 antibodies having these HCDR3/LCDR3 pairs are the antibodies designated H4H588N, H4H591 N, H4H618N, and H4H581 P, respectively.

[0015] Also described herein is an antibody or fragment thereof further comprising a heavy chain CDR1 (HCDR1) domain having an amino acid sequence 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, 724, 748, 772, 796, and 820, 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 having an amino acid sequence 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, 726, 750, 774, 798, and 822, 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 having an amino acid sequence 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, 732, 756, 780, 804, and 828, 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 having an amino acid sequence 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, 734, 758, 782, 806, and 830, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0016] Certain non-limiting, exemplary antibodies and antigen-binding fragments comprise HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 domains, respectively, selected from the group consisting of: (i) SEQ ID NO: 100, 102, 104, 108, 110 and 112 (e.g., H4H588N); (ii) SEQ ID NO: 148, 150, 152, 156, 158 and 160 (e.g., H4H591 N); (iii) SEQ ID NO: 340, 342, 344, 348, 350 and 352 (e.g., H4H618N); and (iv) SEQ ID NO: 700, 702, 704, 708, 710 and 712 (e.g.,

H4H581 P). The amino acid sequences of these exemplary CDRs are depicted in Figs. 2 and 3.

[0017] Also described herein is an antibody or antigen-binding fragment of an antibody which specifically binds PAR-2, wherein the antibody or fragment comprises the heavy and light chain CDR domains contained within heavy and light chain sequences 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, 714/692, 718/720, 722/730, 738/740, 742/744, 746/754, 762/764, 766/768, 770/778, 786/788, 790/792, 794/802, 810/812, 814/816, 818/826, 834/836, and 838/840. The antibody or fragment may comprise the CDR sequences contained within HCVRs and LCVRs selected from the amino acid sequence pairs of SEQ ID NO: 98/106, 146/154, 338/346, and 714/692. Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the boundaries of CDRs include, e.g., the Kabat definition, the Chothia definition, and the AbM definition. In general terms, the Kabat definition is based on sequence variability, the Chothia definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. See, e.g., Kabat, "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991); Al-Lazikani et al., J. Mol. Biol. 273:927-948 (1997); and Martin et al., Proc. Natl. Acad. Sci. USA 86:9268-9272 (1989). Public databases are also available for identifying CDR sequences within an antibody.

[0018] In another aspect, the invention provides nucleic acid molecules encoding the anti-PAR-2 antibodies or fragments thereof of the invention. 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, as are methods of producing the antibodies by culturing the host cells under conditions permitting production of the antibodies, and recovering the antibodies produced.

[0019] 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, 741, 745, 761, 765, 769, 785, 789, 793, 809, 813, 817, 833, and 837, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof. The antibody or fragment thereof may comprise a HCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 97, 145, 337, and 713.

[0020] Also described herein is an antibody or fragment thereof comprising 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, 743, 753, 763, 767, 777, 787, 791, 801, 811, 815, 825, 835, and 839, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof. The antibody or fragment thereof may comprise a LCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 105, 153, 345, and 715.

[0021] 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, 727, 751, 775, 799, and 823, 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, 735, 759, 783, 807, and 831, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof. The antibody or fragment thereof may comprise HCDR3 and LCDR3 sequences encoded by the nucleic acid sequence pairs selected from the group consisting of SEQ ID NO: 103/111, 151/159, 343/351, and 703/711.

[0022] Also described herein is an antibody or fragment thereof which further comprises 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, 723, 747, 771, 795,

and 819, 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, 725, 749, 773, 797, and 821, 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, 731, 755, 779, 803, and 827, 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, 733, 757, 781, 805, 829, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof.

[0023] The antibody or fragment thereof may comprise the heavy and light chain CDR sequences encoded by the nucleic acid sequences of SEQ ID NO: 97 and 105; SEQ ID NO: 145 and 153; SEQ ID NO: 337 and 345; or SEQ ID NO: 713 and 715.

[0024] Also described herein is an isolated antibody or antigen-binding fragment of an antibody that specifically binds PAR-2, comprising a HCDR3 and a LCDR3, wherein the HCDR3 comprises an amino acid sequence of the formula $X^1 - X^2 - X^3 - X^4 - X^5 - X^6 - X^7 - X^8 - X^9 - X^{10} - X^{11} - X^{12}$ (SEQ ID NO:843) wherein X^1 is Ala or Val, X^2 is Lys, X^3 is Gly or Glu, X^4 is Asp or Gly, X^5 is Phe or Asp, X^6 is Trp or Ser, X^7 is Ser or Gly, X^8 is Gly or Tyr, X^9 is Tyr or Asp, X^{10} is Phe or Leu, X^{11} is Asp or Ala, and X^{12} is Tyr; and the LCDR3 comprises an amino acid sequence of the formula $X^1 - X^2 - X^3 - X^4 - X^5 - X^6 - X^7 - X^8 - X^9$ (SEQ ID NO:846) wherein X^1 is Met or Gln, X^2 is Gln, X^3 is Ala or Tyr, X^4 is Thr or Lys, X^5 is Gln, Ser or Ile, X^6 is Phe or Ser, X^7 is Pro, X^8 is Thr or Leu, and X^9 is Thr or absent.

[0025] A more specific isolated antibody or fragment thereof that specifically binds PAR-2 may comprise a HCDR1 sequence of the formula $X^1 - X^2 - X^3 - X^4 - X^5 - X^6 - X^7 - X^8$ (SEQ ID NO:841), wherein X^1 is Gly, X^2 is Phe, X^3 is Thr, X^4 is Phe, X^5 is Ser or Arg, X^6 is Ser or Arg, X^7 is Tyr, and X^8 is Gly, Ala or Thr; a HCDR2 sequence of the formula $X^1 - X^2 - X^3 - X^4 - X^5 - X^6 - X^7 - X^8$ (SEQ ID NO:842), wherein X^1 is Ile, X^2 is Ser, Gly or Thr, X^3 is Tyr, Gly or Asp, X^4 is Asp, Gly or Ser, X^5 is Gly or Arg, X^6 is Ile, Gly or Ala, X^7 is Asn, Ser, Arg or Gly, and X^8 is Lys, Ala or Thr; a HCDR3 sequence of the formula $X^1 - X^2 - X^3 - X^4 - X^5 - X^6 - X^7 - X^8 - X^9 - X^{10} - X^{11} - X^{12}$ (SEQ ID NO:843) wherein X^1 is Ala or Val, X^2 is Lys, X^3 is Gly or Glu, X^4 is Asp or Gly, X^5 is Phe or Asp, X^6 is Trp or Ser, X^7 is Ser or Gly, X^8 is Gly or Tyr, X^9 is Tyr or Asp, X^{10} is Phe or Leu, X^{11} is Asp or Ala, and X^{12} is Tyr; a LCDR1 sequence of the formula $X^1 - X^2 - X^3 - X^4 - X^5 - X^6 - X^7 - X^8 - X^9 - X^{10} - X^{11}$ (SEQ ID NO:844) wherein X^1 is Gln, X^2 is Ser or Gly, X^3 is Leu or Ile, X^4 is Val or Ser, X^5 is His, Asn or Thr, X^6 is Ser, Asn or Tyr, X^7 is Asp or absent; X^8 is Gly or absent, X^9 is Asn or absent, X^{10} is Thr or absent, and X^{11} is Tyr or absent; a LCDR2 sequence of the formula $X^1 - X^2 - X^3$ (SEQ ID NO:845) wherein X^1 is Lys or Ala, X^2 is Ile, Ala or Thr, and X^3 is Ser; and a LCDR3 comprises an amino acid sequence of the formula $X^1 - X^2 - X^3 - X^4 - X^5 - X^6 - X^7 - X^8 - X^9$ (SEQ ID NO:846) wherein X^1 is Met or Gln, X^2 is Gln, X^3 is Ala or Tyr, X^4 is Thr or Lys, X^5 is Gln, Ser or Ile, X^6 is Phe or Ser, X^7 is Pro, X^8 is Thr or Leu, and X^9 is Thr or absent.

[0026] The invention encompasses anti-PAR-2 antibodies having a modified glycosylation pattern. In some applications, modification to remove undesirable glycosylation sites may be useful, or an antibody lacking a fucose moiety present on the oligosaccharide chain, for example, 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).

[0027] In another aspect, the invention provides a pharmaceutical composition as defined in the claims comprising a recombinant human antibody or fragment thereof which specifically binds PAR-2 and a pharmaceutically acceptable carrier. Also described herein is a composition which is a combination of a PAR-2 inhibitor and a second therapeutic agent. The PAR-2 inhibitor may be an antibody or fragment thereof. The second therapeutic agent may be any agent that is advantageously combined with a PAR-2 inhibitor. Exemplary agents that may be advantageously combined with a PAR-2 inhibitor include, without limitation, other agents that inhibit PAR-2 activity (including other antibodies or antigen-binding fragments thereof, peptide inhibitors, small molecule antagonists, etc) and/or agents which interfere with PAR-2 upstream or downstream signaling.

[0028] Also described herein are methods for inhibiting PAR-2 activity using the anti-PAR-2 antibody or antigen-binding portion of an 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 invention provides the isolated human antibody or antigen-binding fragment or the pharmaceutical composition of the invention for use in a method of treating a patient, wherein the patient exhibits one or more symptoms or indicia of a disease or disorder caused by PAR-2 activity, wherein the disease or disorder caused by PAR-2 activity is a disease or disorder selected from the group consisting of pain, pruritus, asthma, rheumatoid arthritis, fibrosis, atopic dermatitis, inflammatory bowel disease, ulcerative colitis, pancreatitis, ulcer, Crohn's disease, cancer, and Netherton's disease. The anti-PAR-2 antibody or antibody fragment of the invention may function to block the interaction between

PAR-2 and a protease (e.g., trypsin or trypsin-like serine proteases) or otherwise inhibit protease-mediated activation of PAR-2. Alternatively, or additionally, the anti-PAR-2 antibodies of the invention may interfere with the interaction between the PAR-2 tethered ligand and one or more of the PAR-2 extracellular loops (see, e.g., MacFarlane et al., 2001, Pharmacological Reviews 53:245-282 for a general discussion of PAR-2 proteolytic cleavage and activation). The antibody or antibody fragment may be used alone or in combination with one or more additional therapeutic agents.

[0029] The present invention also includes the use of an anti-PAR-2 antibody or antigen binding portion of an antibody of the invention in the manufacture of a medicament for the treatment of a disease or disorder related to or caused by PAR-2 activity in a patient, as defined in the claims.

[0030] Other embodiments will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[0031]

Fig. 1. Sequence comparison table of heavy chain variable regions and CDRs of antibodies H4H581P, H4H588N, H4H591N and H4H618N.

Fig. 2. Sequence comparison table of light chain variable regions and CDRs of antibodies H4H581P, H4H588N, H4H591N and H4H618N.

Fig. 3. The top panel (A) shows C- and N-terminal biotin labeled peptides corresponding to the sequence surrounding the activating PAR-2 protease cleavage site (GTNRSSKGRSLIGKVDGT; SEQ ID NO:852). The protease cleavage sites are designated by number 1 (an upstream, non-activating protease cleavage site) and number 2 (the activating PAR-2 protease cleavage site). The expected sizes of the uncleaved and cleaved fragments are indicated in the top table. The bottom panel (B) shows the fragment sizes that were observed following 0, 5, and 15 minutes of trypsin treatment in the presence of anti-PAR-2 antibodies or negative control.

Fig. 4. The top panel (A) shows the mouse, rat and human peptides corresponding to the sequence surrounding the activating PAR-2 protease cleavage sites (SEQ ID NOs:883, 858 and 852, respectively). The protease cleavage sites are designated by numbers 1 and 2 (upstream, non-activating protease cleavage sites) and number 3 (the activating PAR-2 protease cleavage site). The expected sizes of the uncleaved and cleaved fragments are indicated in the top table. The bottom panel (B) shows the fragment sizes that were observed following 0 and 5 minutes of trypsin treatment in the presence of anti-PAR-2 antibodies or negative control.

Fig. 5. Depiction of alanine scanning epitope mapping results for antibody binding to the sequence surrounding the PAR-2 activating protease cleavage site (SEQ ID NO:852). Open triangles represent protease cleavage sites located upstream from the activating PAR-2 protease cleavage site. The activating PAR-2 protease cleavage site is designated by a closed triangle. The numbers in parentheses indicate the amino acid numbering in the full-length human PAR-2 sequence (SEQ ID NO:851). Numbers in circles under the amino acid residues indicate the percent of $T_{1/2}$ of antibody binding to alanine-scan mutant peptide relative to the $T_{1/2}$ of antibody binding to wild-type peptide, as shown in Tables 24-26 and 28. If duplicate experiments were conducted, the average $T_{1/2}$ percentage is shown in the circle. Black circles with white numbers indicate amino acids that, when changed to alanine, reduce the $T_{1/2}$ of antibody binding to 30% or less of the $T_{1/2}$ of antibody binding to wild-type peptide. Such amino acids are defined herein as residues with which the antibody interacts.

DETAILED DESCRIPTION

[0032] Before the present invention is 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.

[0033] 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. As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1½. For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (e.g., 99.1, 99.2, 99.3, 99.4, etc.).

[0034] Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described.

Definitions

[0035] As used herein, the terms "proteinase-activated receptor-2," "protease-activated receptor-2," and "PAR-2",

refer to full-length PAR-2 protein. Human PAR-2 is encoded by the nucleic acid sequence shown in SEQ ID NO:850 and has the amino acid sequence of SEQ ID NO:851. Amino acid sequences of PAR-2 molecules from non-human species (e.g., mouse, monkey, rabbit, dog, pig, etc.) are available from public sources.

[0036] The term "PAR-2 fragment," as used herein, means a peptide or polypeptide comprising 4, 5, 6, 7, 8, 9, 10 or more contiguous amino acids located upstream from (*i.e.*, N-terminal to) the activating PAR-2 protease cleavage site (as defined herein below) and/or 4, 5, 6, 7, 8, 9, 10 or more contiguous amino acids located downstream from (*i.e.*, C-terminal to) the activating PAR-2 protease cleavage site. Exemplary PAR-2 fragments are illustrated in Example 2, Table 2 (designated Peptides "A" through "J"; *i.e.*, SEQ ID NOs:852 through 861, respectively).

[0037] The expressions "PAR-2" and "PAR-2 fragment," as used herein refer to the human PAR-2 protein or fragment unless specified as being from a non-human species (e.g., "mouse PAR-2," "mouse PAR-2 fragment," "monkey PAR-2," "monkey PAR-2 fragment," etc.).

[0038] As used in the context of the present disclosure, the expression "activating PAR-2 protease cleavage site" means the junction of residues Arg-36 and Ser-37 of human PAR-2 (SEQ ID NO:851). The activating PAR-2 protease cleavage site is the site which, when cleaved, results in the formation of the PAR-2 tethered ligand in the naturally occurring protein.

[0039] The term "PAR-2 protease," as used herein, means an enzyme which is capable of cleaving a PAR-2 or PAR-2 fragment at the activating PAR-2 protease cleavage site. Exemplary PAR-2 proteases include trypsin, cathepsin G, acrosin, tissue factor VIIa, tissue factor Xa, human airway trypsin-like protease, tryptase, membrane-type serine protease-1 (MT-SP1), TMPRSS2, protease-3, elastase, kallikrein-5, kallikrein-6, kallikrein-14, activated protein C, duodenase, gingipains-R, Der p1, Der p3, Der p9, thermolysin, serralsin, and *T. denticla* protease.

[0040] The term "antibody", as used herein, is intended to refer to immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains interconnected by disulfide bonds, as well as multimers thereof (e.g., IgM). Each heavy chain comprises a heavy chain variable region (abbreviated herein as HCVR or V_H) and a heavy chain constant region. The heavy chain constant region comprises three domains, C_{H1} , C_{H2} and C_{H3} . Each light chain comprises a light chain variable region (abbreviated herein as LCVR or V_L) and a light chain constant region. The light chain constant region comprises one domain (C_{L1}). The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L 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. In different embodiments of the invention, the FRs of the anti-Ang-2 antibody (or antigen-binding portion thereof) may be identical to the human germline sequences, or may be naturally or artificially modified. An amino acid consensus sequence may be defined based on a side-by-side analysis of two or more CDRs.

[0041] The term "antibody," as used herein, also includes antigen-binding fragments of full antibody molecules. The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. Antigen-binding fragments of an antibody may be derived, e.g., from full antibody molecules using any suitable standard techniques such as proteolytic digestion or recombinant genetic engineering techniques involving the manipulation and expression of DNA encoding antibody variable and optionally constant domains. Such DNA is known and/or is readily available from, e.g., commercial sources, DNA libraries (including, e.g., phage-antibody libraries), or can be synthesized. The DNA may be sequenced and manipulated chemically or by using molecular biology techniques, for example, to arrange one or more variable and/or constant domains into a suitable configuration, or to introduce codons, create cysteine residues, modify, add or delete amino acids, etc.

[0042] Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) $F(ab')_2$ fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (e.g., an isolated complementarity determining region (CDR)). Other engineered molecules, such as diabodies, triabodies, tetrabodies and minibodies, are also encompassed within the expression "antigen-binding fragment," as used herein.

[0043] An antigen-binding fragment of an antibody will typically comprise at least one variable domain. The variable domain may be of any size or amino acid composition and will generally comprise at least one CDR which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a V_H domain associated with a V_L domain, the V_H and V_L domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain V_H - V_H , V_H - V_L or V_L - V_L dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric V_H or V_L domain.

[0044] In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody of the present invention include: (i) V_H - C_{H1} ; (ii) V_H - C_{H2} ; (iii) V_H - C_{H3} ; (iv) V_H - C_{H1} - C_{H2} ; (v) V_H - C_{H1} - C_{H2} - C_{H3} ; (vi) V_H - C_{H2} - C_{H3} ; (vii) V_H - C_L ; (viii) V_L - C_{H1} ; (ix) V_L - C_{H2} ; (x) V_L - C_{H3} ; (xi) V_L - C_{H1} - C_{H2} ; (xii) V_L - C_{H1} - C_{H2} - C_{H3} ; (xiii) V_L - C_{H2} - C_{H3} ; and (xiv) V_L - C_L . In any configuration of variable

and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may consist of at least 2 (e.g., 5, 10, 15, 20, 40, 60 or more) amino acids which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody of the present invention may comprise a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric V_H or V_L domain (e.g., by disulfide bond(s)).

[0045] As with full antibody molecules, antigen-binding fragments may be monospecific or multispecific (e.g., bispecific). A multispecific antigen-binding fragment of an antibody will typically comprise at least two different variable domains, wherein each variable domain is capable of specifically binding to a separate antigen or to a different epitope on the same antigen. Any multispecific antibody format, including the exemplary bispecific antibody formats disclosed herein, may be adapted for use in the context of an antigen-binding fragment of an antibody of the present invention using routine techniques available in the art.

[0046] The constant region of an antibody is 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.

[0047] 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 antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs and in particular CDR3. However, the term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

[0048] The term "recombinant human antibody", as used herein, is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell (described further below), antibodies isolated from a recombinant, combinatorial human antibody library (described further below), antibodies isolated from an animal (e.g., a mouse) that is transgenic for human immunoglobulin genes (see e.g., Taylor et al. (1992) Nucl. Acids Res. 20:6287-6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies are subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[0049] Human antibodies can exist in two forms that are associated with hinge heterogeneity. In one form, an immunoglobulin 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.

[0050] 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.

[0051] An "isolated antibody," as used herein, means an antibody that has been identified and separated and/or recovered from at least one component of its natural environment. For example, an antibody that has been separated or removed from at least one component of an organism, tissue or cell in which the antibody naturally exists or is naturally produced is an "isolated antibody" for purposes of the present invention. An isolated antibody also includes an antibody *in situ* within a recombinant cell, as well as an antibody that has been subjected to at least one purification or isolation step. According to certain embodiments, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[0052] 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 a dissociation constant of 1×10^{-6} M or less. 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. For example, an antibody that "specifically binds" human PAR-2, as used in the context of the present invention, includes antibodies

that bind human PAR-2 or portion thereof (e.g., a PAR-2 fragment comprising the activating protease cleavage site) with a K_D of less than about 1000 nM, less than about 500 nM, less than about 300 nM, less than about 200 nM, less than about 100 nM, less than about 90 nM, less than about 80 nM, less than about 70 nM, less than about 60 nM, less than about 50 nM, less than about 40 nM, less than about 30 nM, less than about 20 nM, less than about 10 nM, less than about 5 nM, less than about 4 nM, less than about 3 nM, less than about 2 nM, less than about 1 nM or less than about 0.5 nM, as measured in a surface plasmon resonance assay. (See, e.g., Example 4, herein). An isolated antibody that specifically binds human PAR-2 may, however, have cross-reactivity to other antigens, such as PAR-2 molecules from other species.

[0053] A "neutralizing" or "blocking" antibody, as used herein, is intended to refer to an antibody whose binding to PAR-2: (i) interferes with the interaction between PAR-2 or a PAR-2 fragment and one or more proteases, (ii) prevents cleavage of PAR-2 or a PAR-2 fragment by a PAR-2 protease, (iii) inhibits the interaction between the PAR-2 tethered ligand and a PAR-2 extracellular loop, and/or (iv) results in inhibition of at least one biological function of PAR-2. The inhibition caused by a PAR-2 neutralizing or blocking antibody need not be complete so long as it is detectable using an appropriate assay. Exemplary assays for detecting PAR-2 inhibition are described herein.

[0054] The fully-human anti-PAR-2 antibodies disclosed herein may comprise one or more amino acid substitutions, insertions and/or deletions in the framework and/or CDR regions of the heavy and light chain variable domains as compared to the corresponding germline sequences. Such mutations can be readily ascertained by comparing the amino acid sequences disclosed herein to germline sequences available from, for example, public antibody sequence databases. The present invention includes antibodies, and antigen-binding fragments thereof, which are derived from any of the amino acid sequences disclosed herein, wherein one or more amino acids within one or more framework and/or CDR regions are back-mutated to the corresponding germline residue(s) or to a conservative amino acid substitution (natural or non-natural) of the corresponding germline residue(s) (such sequence changes are referred to herein as "germline back-mutations"). A person of ordinary skill in the art, starting with the heavy and light chain variable region sequences disclosed herein, can easily produce numerous antibodies and antigen-binding fragments which comprise one or more individual germline back-mutations or combinations thereof. In certain embodiments, all of the framework and/or CDR residues within the V_H and/or V_L domains are mutated back to the germline sequence. In other embodiments, only certain residues are mutated back to the germline sequence, e.g., only the mutated residues found within the first 8 amino acids of FR1 or within the last 8 amino acids of FR4, or only the mutated residues found within CDR1, CDR2 or CDR3. Furthermore, the antibodies of the present invention may contain any combination of two or more germline back-mutations within the framework and/or CDR regions, i.e., wherein certain individual residues are mutated back to the germline sequence while certain other residues that differ from the germline sequence are maintained. Once obtained, antibodies and antigen-binding fragments that contain one or more germline back-mutations can be easily tested for one or more desired property such as, improved binding specificity, increased binding affinity, improved or enhanced antagonistic or agonistic biological properties (as the case may be), reduced immunogenicity, etc. Antibodies and antigen-binding fragments obtained in this general manner are encompassed within the present invention.

[0055] Also described herein are anti-PAR-2 antibodies comprising variants of any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein having one or more conservative substitutions. For example, included are anti-PAR-2 antibodies having HCVR, LCVR, and/or CDR amino acid sequences with, e.g., 10 or fewer, 8 or fewer, 6 or fewer, 4 or fewer, etc. conservative amino acid substitutions relative to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein. The antibody may comprise an HCVR having the amino acid sequence of SEQ ID NO:698 with 8 or fewer conservative amino acid substitutions. The antibody may comprise an HCVR having the amino acid sequence of SEQ ID NO:698 with 6 or fewer conservative amino acid substitutions. The antibody may comprise an HCVR having the amino acid sequence of SEQ ID NO:698 with 4 or fewer conservative amino acid substitutions. The antibody may comprise an HCVR having the amino acid sequence of SEQ ID NO:698 with 2 or fewer conservative amino acid substitutions. The antibody may comprise an LCVR having the amino acid sequence of SEQ ID NO:706 with 8 or fewer conservative amino acid substitutions. The antibody may comprise an LCVR having the amino acid sequence of SEQ ID NO:706 with 6 or fewer conservative amino acid substitutions. The antibody may comprise an LCVR having the amino acid sequence of SEQ ID NO:706 with 4 or fewer conservative amino acid substitutions. The antibody may comprise an LCVR having the amino acid sequence of SEQ ID NO:706 with 2 or fewer conservative amino acid substitutions.

[0056] The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIAcore™ system (Biacore Life Sciences division of GE Healthcare, Piscataway, NJ).

[0057] The term " K_D ", as used herein, is intended to refer to the equilibrium dissociation constant of a particular antibody-antigen interaction.

[0058] The term "epitope" refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. Epitopes may

be either conformational or linear. A conformational epitope is produced by spatially juxtaposed amino acids from different segments of the linear polypeptide chain. A linear epitope is one produced by adjacent amino acid residues in a polypeptide chain. In certain circumstance, an epitope may include moieties of saccharides, phosphoryl groups, or sulfonyl groups on the antigen.

[0059] 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 95%, and more preferably at least about 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. A nucleic acid molecule having substantial identity to a reference nucleic acid molecule may, in certain instances, encode a polypeptide having the same or substantially similar amino acid sequence as the polypeptide encoded by the reference nucleic acid molecule.

[0060] 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 95% sequence identity, even more preferably at least 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 sequence identity 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 are 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: 1443-1445. A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

[0061] Sequence similarity for polypeptides, which is also referred to as sequence identity, 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 using 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 Altschul et al. (1997) *Nucleic Acids Res.* 25:3389-402.

Preparation of Human Antibodies

[0062] Methods for generating monoclonal antibodies, including fully human monoclonal antibodies are known in the art. Any such known methods can be used in the context of the present invention to make human antibodies that specifically bind to human PAR-2.

[0063] Using VELOCIMMUNE™ technology or any other known method for generating monoclonal antibodies, high affinity chimeric antibodies to PAR-2 are initially isolated having a human variable region and a mouse constant region. As in the experimental section 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. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

Bioequivalents

[0064] The anti-PAR-2 antibodies and antibody fragments of the present invention encompass proteins having amino

acid sequences that vary from those of the described antibodies, but that retain the ability to bind human PAR-2. Such variant antibodies 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 antibodies. Likewise, the anti-PAR-2 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-PAR-2 antibody or antibody fragment that is essentially bioequivalent to an anti-PAR-2 antibody or antibody fragment of the invention. Examples of such variant amino acid and DNA sequences are discussed above.

[0065] 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.

[0066] In one embodiment, two antigen-binding proteins are bioequivalent if there are no clinically meaningful differences in their safety, purity, and potency.

[0067] 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.

[0068] 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.

[0069] 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.

[0070] Bioequivalent variants of anti-PAR-2 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. In other contexts, bioequivalent antibodies may include anti-PAR-2 antibody variants comprising amino acid changes which modify the glycosylation characteristics of the antibodies, e.g., mutations which eliminate or remove glycosylation.

Biological Characteristics of the Antibodies

[0071] The antibodies of the present invention may function through complement-dependent cytotoxicity (CDC) or antibody-dependent cell-mediated cytotoxicity (ADCC). "Complement-dependent cytotoxicity" (CDC) refers to lysis of antigen-expressing cells by an antibody of the invention in the presence of complement. "Antibody-dependent cell-mediated cytotoxicity" (ADCC) refers to a cell-mediated reaction in which nonspecific cytotoxic cells that express Fc receptors (FcRs) (e.g., Natural Killer (NK) cells, neutrophils, and macrophages) recognize bound antibody on a target cell and thereby lead to lysis of the target cell. CDC and ADCC can be measured using assays that are well known and available in the art. (See, e.g., U.S. 5,500,362 and 5,821,337, and Clynes et al. (1998) Proc. Natl. Acad. Sci. (USA) 95:652-656).

[0072] Alternatively, or additionally, the antibodies of the invention may be therapeutically useful in blocking a PAR-2 interaction or inhibiting receptor component interaction. In the case of the PAR-2 antibodies of the present invention, the antibodies may function by, *inter alia*, blocking or obscuring the activating PAR-2 protease cleavage site. Alternatively, the antibodies of the invention may function by interfering with the interaction between the tethered ligand and one or more extracellular loops (e.g., loop-1, loop-2 and/or loop-3).

[0073] More specifically, the anti-PAR-2 antibodies of the invention may exhibit one or more of the following characteristics: (1) ability to bind to a human PAR-2 or human PAR-2 fragment and to a non-human (e.g., mouse, monkey, rat, rabbit, dog, pig, etc.) PAR-2 or PAR-2 fragment; (2) ability to bind to a human PAR-2 or human PAR-2 fragment but not to a non-human (e.g., mouse, monkey, rat, rabbit, dog, pig, etc.) PAR-2 or PAR-2 fragment; (3) ability to bind to a human PAR-2 or human PAR-2 fragment and to a monkey PAR-2 or monkey PAR-2 fragment, but not to a mouse, rat, rabbit, dog or pig PAR-2 or PAR-2 fragment; (4) ability to bind to a human PAR-2 or human PAR-2 fragment and to a human PAR-1, PAR-3 or PAR-4 or fragment thereof; (5) ability to bind to a human PAR-2 or human PAR-2 fragment but not to

a human PAR-1, PAR-3, or PAR-4 or fragment thereof; (6) ability to bind to a human PAR-2 or human PAR-2 fragment and to a non-human (e.g., mouse, monkey, rat, rabbit, dog, pig, etc.) PAR-1, PAR-3 or PAR-4 or fragment thereof; (7) ability to bind to a human PAR-2 or human PAR-2 fragment but not to a non-human (e.g., mouse, monkey, rat, rabbit, dog, pig, etc.) PAR-1, PAR-3 or PAR-4 or fragment thereof; (8) ability to block proteolytic cleavage of a PAR-2 or a PAR-2 fragment; (9) ability to block proteolytic cleavage of a human PAR-2 or human PAR-2 fragment and a non-human (e.g., mouse, monkey, rat, rabbit, dog, pig, etc.) PAR-2 or PAR-2 fragment; (10) ability to block proteolytic cleavage of a human PAR-2 or human PAR-2 fragment but not a non-human (e.g., mouse, monkey, rat, rabbit, dog, pig, etc.) PAR-2 or PAR-2 fragment; (11) ability to block proteolytic cleavage of a human PAR-2 or human PAR-2 fragment and a human PAR-1, PAR-3 or PAR-4 or fragment thereof; (12) ability to block proteolytic cleavage of a human PAR-2 or human PAR-2 fragment but not a human PAR-1, PAR-3 or PAR-4 or fragment thereof; (13) ability to block proteolytic cleavage of a human PAR-2 or human PAR-2 fragment and a non-human (e.g., mouse, monkey, rat, rabbit, dog, pig, etc.) PAR-1, PAR-3 or PAR-4 or fragment thereof; and/or (14) ability to block proteolytic cleavage of a human PAR-2 or human PAR-2 fragment but not a non-human (e.g., mouse, monkey, rat, rabbit, dog, pig, etc.) PAR-1, PAR-3 or PAR-4 or fragment thereof.

[0074] As used in items (8) - (14) above, the term "proteolytic cleavage" means cleavage of a PAR molecule (PAR-1, PAR-2, PAR-3 or PAR-4) or fragment thereof by a PAR-2 protease or other enzyme that is capable of cleaving PAR-2 at the activating PAR-2 protease cleavage site.

[0075] The N-terminal region of human PAR-2 has at least two "non-activating" protease cleavage sites, *i.e.*, sites that are capable of being cleaved by trypsin but do not result in activation of the receptor. The N-terminal non-activating protease cleavage sites are located: (a) at the junction of residues Arg-31 and Ser-32 of human PAR-2 (SEQ ID NO:851); and (b) at the junction of residues Lys-34 and Gly-35 of human PAR-2 (SEQ ID NO:851). The activating and non-activating cleavage sites at the N-terminus of PAR-2 are illustrated in Fig. 5 (white triangles indicate the non-activating protease cleavage sites and the black triangle indicates the activating PAR-2 protease cleavage site); see *also* Fig. 4. The present invention includes anti-PAR-2 antibodies that block the activating PAR-2 protease cleavage site but do not block one or both of the non-activating protease cleavage sites. Whether a candidate antibody blocks or does not block a particular protease cleavage site can be determined by a person of ordinary skill in the art using any suitable assay such as the exemplary *in vitro* blocking assays set forth in Example 8 herein. As illustrated in Example 8, the exemplary antibody H4H581 P was shown to block trypsin cleavage at the activating PAR-2 protease cleavage site and at the non-activating protease cleavage site located at the junction of residues Lys-34 and Gly-35 of human PAR-2 (SEQ ID NO:851), but did not block cleavage at the non-activating protease cleavage site located at the junction of residues Arg-31 and Ser-32 of human PAR-2 (SEQ ID NO:851). By contrast, the comparator antibody used in Example 8 blocked cleavage at the activating PAR-2 protease cleavage site and at both non-activating sites. The differential blocking capabilities of these exemplary anti-PAR-2 antibodies most likely reflects differences in the particular regions of the PAR-2 molecule with which these antibodies bind (see, *e.g.*, Example 9 herein).

[0076] As used herein, an antibody "does not bind" to a specified target molecule (e.g., mouse PAR-2, rat PAR-2, rabbit PAR-2, dog PAR-2, pig PAR-2, or fragment thereof) if the antibody, when tested for binding to the target molecule at 25°C in a surface plasmon resonance assay, exhibits a K_D of greater than 500 nM, or if tested for binding to the target molecule at 25°C in an enzyme-linked immunosorbent assay (ELISA) exhibits an EC_{50} of greater than 50 nM, or fails to exhibit any binding in either type of assay or equivalent thereof.

[0077] Certain anti-PAR-2 antibodies of the present invention are able to inhibit or attenuate PAR-2 activation in an *in vitro* cellular assay. A non-limiting, exemplary *in vitro* cellular assay for PAR-2 activation is illustrated in Example 6, herein. In this Example, cells are used which express PAR-2 and harbor a construct comprising NF- κ B fused to a reporter molecule (e.g., luciferase). Briefly, such cells are combined with an anti-PAR-2 antibody, followed by treatment with a PAR-2 protease. Cells that are treated with the protease in the presence of an inhibitory anti-PAR-2 antibody will exhibit significantly less or no reporter signal as compared to cells treated with the protease in the absence of an inhibitory anti-PAR-2 antibody. The concentration of antibody necessary to achieve half-maximal inhibition of reporter signal (IC_{50}) can be calculated using such an assay. The present invention includes inhibitory anti-PAR-2 antibodies that exhibit an IC_{50} of less than 300 nM when tested in an *in vitro* cellular assay for PAR-2 activation as described above. For example, the invention includes anti-PAR-2 antibodies with an IC_{50} of less than 300, 290, 280, 270, 260, 250, 240, 230, 220, 210, 200, 190, 180, 170, 160, 150, 140, 130, 120, 110, 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, 18, 16, 14, 12, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 nM when tested in an *in vitro* cellular assay for PAR-2 activation as described above in which the cells are incubated with the antibody for 1 h at 37°C followed by treatment with 20 nM trypsin (or other PAR-2 protease) for 5 h at 37°C.

[0078] The present invention includes anti-PAR-2 antibodies and antigen binding fragments thereof which bind to one or more of the following peptides: Peptide A (GTNRSSKGRSLIGKVDGT, SEQ ID NO:852); Peptide B (SLIGKVDGT-SHVTG, SEQ ID NO:853); Peptide C (SLIGKV, SEQ ID NO:854); Peptide D (N-terminal domain of human PAR-2 - mouse IgG, SEQ ID NO:855); Peptide E (LAPGRNNSKGRSLIGRLETQ, SEQ ID NO:856); Peptide F (GTNRSSKGRS-LIGRVDGT, SEQ ID NO:857); Peptide G (GPNSKGRSLIGRLDTP, SEQ ID NO:858); Peptide H (GTNKTSGKRS-LIGRN-

TGS, SEQ ID NO:859); Peptide I (GTNRTSKGRSLIGKTDSS, SEQ ID NO:860); Peptide J (GTSRPSKGRSLIGKADNT, SEQ ID NO:861); Peptide K (ATNATLDPRSFLLRNPND, SEQ ID NO:862); Peptide L (DTNNLAKPTLPIKTRGA, SEQ ID NO:863); or Peptide M (ESGSTGGGDDSTPSILPAP, SEQ ID NO:864). Additional information regarding these peptides can be found in Example 3 herein. These peptides may contain no additional labels or moieties, or they may contain an N-terminal or C-terminal label or moiety. In one embodiment, the label or moiety is biotin. In a binding assay, the location of a label (if any) may determine the orientation of the peptide relative to the surface upon which the peptide is bound. For example, if a surface is coated with avidin, a peptide containing an N-terminal biotin will be oriented such that the C-terminal portion of the peptide will be distal to the surface.

[0079] With regard to the aforementioned Peptides, the present invention includes anti-PAR-2 antibodies with one or more of the following binding profiles: (1) binding to Peptides A and B, but not binding to Peptide C; (2) binding to Peptides A, B and D, but not binding to Peptide C; (3) binding to Peptides A, B, D and F, but not binding to Peptide C; (4) binding to Peptides A, B, D and F, but not binding to either of Peptides C or E; (5) binding to Peptides A, B and D, but not binding to any of Peptides K, L or M; (6) binding to Peptides A, B and F, but not binding to any of Peptides K, L or M; (7) binding to Peptides A, B, D and F, but not binding to any of Peptides K, L or M; and/or (8) binding to at least three of Peptides A, B, C, D, E, F, G, I and J, but not binding to Peptide H. Other binding profiles of the antibodies of the invention will be evident from the examples herein.

Epitope Mapping and Related Technologies

[0080] 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 248:443-463), 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).

[0081] 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.

[0082] 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 antibodies, such that characterization can be focused on genetically distinct antibodies. 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-PAR-2 antibodies of the invention into groups of antibodies binding different epitopes.

[0083] The present invention includes anti-PAR-2 antibodies which bind to an epitope at or near (e.g., within 5, 10, 15 or 20 amino acids of) the activating PAR-2 protease cleavage site. In certain embodiments, the anti-PAR-2 antibodies bind to an epitope located upstream from (i.e., N-terminal to) the activating PAR-2 protease cleavage site. In certain other embodiments of the invention, the anti-PAR-2 antibodies bind to an epitope located downstream from (i.e., C-terminal to) the activating PAR-2 protease cleavage site. In yet other embodiments, the anti-PAR-2 antibodies of the invention may bind an epitope that includes both amino acid sequences located upstream from the activating PAR-2 protease cleavage site and amino acid sequences located downstream from the activating PAR-2 protease cleavage site.

[0084] Alternatively, the anti-PAR-2 antibodies of the invention may, in certain embodiments, bind to an epitope located on one or more extracellular loops of the PAR-2 protein (e.g., extracellular loop 1, extracellular loop 2 and/or extracellular loop 3).

[0085] The present invention includes isolated human antibodies or antigen-binding fragments thereof that interact with certain amino acid residues located downstream from the activating PAR-2 protease cleavage site. For example, the present invention includes isolated human antibodies or antigen-binding fragments thereof that interact with Val-42 and Asp-43 of human PAR-2 (SEQ ID NO:851). In addition to these two residues, the isolated human antibodies or antigen-binding fragments thereof may also interact with one or more of the following residues located downstream from the activating PAR-2 protease cleavage site: Ser-37, Leu-38, Ile-39, Gly-40 or Gly-44 of human PAR-2 (SEQ ID NO:851). In certain embodiments, the isolated human antibody or antigen binding fragment thereof does not interact with Lys-41 of human PAR-2 (SEQ ID NO:851). For example, the present invention includes isolated human antibodies or antigen-binding fragments thereof that interact with Ser-37, Leu-38, Ile-39, Gly-40, Val-42 and Asp-43 of human PAR-2 (SEQ ID NO:851), and do not interact with Lys-41 of human PAR-2 (SEQ ID NO:851). The experimental procedures illustrated

in Example 9 can be used to determine if a candidate anti-PAR-2 antibody "interacts with" or "does not interact with" a particular amino acid residue of PAR-2. For example, if a candidate antibody is tested for binding to a peptide having SEQ ID NO:879 (corresponding to the N-terminal region of PAR-2 wherein Val-42 of PAR-2 is mutated to alanine, see, e.g., Tables 24-28) using the procedure of Example 9, and the $T_{1/2}$ of the antibody is less than 30% the $T_{1/2}$ observed when the candidate antibody is tested for binding to the wild-type peptide (SEQ ID NO:871), then for purposes of the present disclosure, the candidate antibody is deemed to "interact with" the amino acid that was mutated to alanine (in this case, Val-42); that is, binding of the candidate antibody is substantially reduced when the amino acid corresponding to Val-42 is mutated to alanine (such residues are depicted by black circles in Figure 5). On the other hand, if a candidate antibody is tested for binding to a peptide having SEQ ID NO:878 (corresponding to the N-terminal region of PAR-2 wherein Lys-41 of PAR-2 is mutated to alanine, see, e.g., Tables 24-28) using the procedure of Example 9, and the $T_{1/2}$ of the antibody is greater than or equal to 30% the $T_{1/2}$ observed when the candidate antibody is tested for binding to the wild-type peptide (SEQ ID NO:871), then for purposes of the present disclosure, the candidate antibody is deemed to "not interact with" the amino acid that was mutated to alanine (in this case, Lys-41); that is, binding of the candidate antibody is not substantially reduced when the amino acid corresponding to Lys-41 is mutated to alanine (such residues are depicted by white circles in Figure 5).

[0086] Described herein are anti-PAR-2 antibodies that bind to the same epitope as the specific exemplary antibodies H4H581 P or H4H588N. Also described herein are anti-PAR-2 antibodies that cross-compete for binding to PAR-2 or a PAR-2 fragment with any of the specific exemplary antibodies described herein (e.g., H4H581 P, H4H588N, H4H591 N or H4H618N).

[0087] One can easily determine whether an antibody binds to the same epitope as, or competes for binding with, a reference anti-PAR-2 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-PAR-2 antibody described herein, the reference antibody is allowed to bind to a PAR-2 protein or peptide under saturating conditions. Next, the ability of a test antibody to bind to the PAR-2 molecule is assessed. If the test antibody is able to bind to PAR-2 following saturation binding with the reference anti-PAR-2 antibody, it can be concluded that the test antibody binds to a different epitope than the reference anti-PAR-2 antibody. On the other hand, if the test antibody is not able to bind to the PAR-2 molecule following saturation binding with the reference anti-PAR-2 antibody, then the test antibody may bind to the same epitope as the epitope bound by the reference anti-PAR-2 antibody described herein. 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, Biacore, flow cytometry or any other quantitative or qualitative antibody-binding assay available in the art. In accordance with certain aspects described herein, two antibodies bind to the same (or overlapping) epitope if, e.g., 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 are deemed to bind to 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 are deemed to have "overlapping epitopes" if only a subset of the amino acid mutations that reduce or eliminate binding of one antibody reduce or eliminate binding of the other.

[0088] To determine if an antibody competes for binding with a reference anti-PAR-2 antibody, the above-described binding methodology is performed in two orientations: In a first orientation, the reference antibody is allowed to bind to a PAR-2 molecule under saturating conditions followed by assessment of binding of the test antibody to the PAR-2 molecule. In a second orientation, the test antibody is allowed to bind to a PAR-2 molecule under saturating conditions followed by assessment of binding of the reference antibody to the PAR-2 molecule. If, in both orientations, only the first (saturating) antibody is capable of binding to the PAR-2 molecule, then it is concluded that the test antibody and the reference antibody compete for binding to PAR-2. 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 same epitope as the reference antibody, but may sterically block binding of the reference antibody by binding an overlapping or adjacent epitope.

Species Selectivity and Species Cross-Reactivity

[0089] According to certain embodiments of the invention, the anti-PAR-2 antibodies bind to human PAR-2 but not to PAR-2 from other species. Alternatively, the anti-PAR-2 antibodies of the invention, in certain embodiments, bind to human PAR-2 and to PAR-2 from one or more non-human species. For example, the anti-PAR-2 antibodies of the invention may bind to human PAR-2 and may bind or not bind, as the case may be, to one or more of mouse, rat, guinea pig, hamster, gerbil, pig, cat, dog, rabbit, goat, sheep, cow, horse, camel, cynomolgous, marmoset, rhesus or chimpanzee PAR-2.

Immunoconjugates

[0090] The invention encompasses anti-PAR-2 monoclonal antibodies conjugated to a therapeutic moiety ("immunoconjugate"), such as a cytotoxin, a chemotherapeutic drug, an immunosuppressant or a radioisotope. Cytotoxic agents include any agent that is detrimental to cells. Examples of suitable cytotoxic agents and chemotherapeutic agents for forming immunoconjugates are known in the art, see for example, WO 05/103081).

Multispecific Antibodies

[0091] The antibodies of the present invention may be monospecific, bi-specific, or multispecific. Multispecific antibodies 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; Kufer et al., 2004, Trends Biotechnol. 22:238-244. The anti-PAR-2 antibodies of the present invention 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 bi-specific or a multispecific antibody with a second binding specificity. For example, the present invention includes bi-specific antibodies wherein one arm of an immunoglobulin is specific for human PAR-2 or a fragment thereof, and the other arm of the immunoglobulin is specific for a second therapeutic target or is conjugated to a therapeutic moiety such as a trypsin inhibitor.

[0092] 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) C_H3 domain and a second Ig C_H3 domain, wherein the first and second Ig C_H3 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 C_H3 domain binds Protein A and the second Ig C_H3 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 C_H3 may further comprise a Y96F modification (by IMGT; Y436F by EU). Further modifications that may be found within the second C_H3 include: D16E, L18M, N44S, K52N, V57M, and V821 (by IMGT; D356E, L358M, N384S, K392N, V397M, and V422I by EU) in the case of IgG1 antibodies; N44S, K52N, and V821 (IMGT; N384S, K392N, and V422I by EU) in the case of IgG2 antibodies; and Q15R, N44S, K52N, V57M, R69K, E79Q, and V821 (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.

Therapeutic Formulation and Administration

[0093] The invention provides therapeutic compositions comprising the anti-PAR-2 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.

[0094] The dose of antibody may vary depending upon the age and the size of a subject to be administered, target disease, conditions, route of administration, and the like. The preferred dose is typically calculated according to body weight or body surface area. When an antibody of the present invention is used for treating a condition or disease associated with PAR-2 activity in an adult patient, it may be 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. Effective dosages and schedules for administering PAR-2 antibodies may be determined empirically; for example, patient progress can be monitored by periodic assessment, and the dose adjusted accordingly. Moreover, interspecies scaling of dosages can be performed using well-known methods in the art (e.g., Mordenti et al., 1991, Pharmaceut. Res. 8:1351).

[0095] 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, intra-

nasal, 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.

[0096] 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 pharmaceutical composition, the entire device is discarded.

[0097] Numerous reusable pen and autoinjector delivery devices have applications in the subcutaneous delivery of a pharmaceutical composition of the present invention. Examples include, but are not limited to AUTOPEN™ (Owen Mumford, Inc., Woodstock, UK), DISETRONIC™ pen (Disetronic Medical Systems, Bergdorf, 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 are not limited to the SOLOSTAR™ pen (sanofi-aventis), the FLEXPEN™ (Novo Nordisk), and the KWIKPEN™ (Eli Lilly), the SURECLICK™ Autoinjector (Amgen, Thousand Oaks, CA), the PENLET™ (Haselmeier, Stuttgart, Germany), the EPIPEN (Dey, L.P.), and the HUMIRA™ Pen (Abbott Labs, Abbott Park IL), to name only a few.

[0098] In certain situations, the pharmaceutical composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; 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.), 1974, CRC Pres., Boca Raton, Florida. 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, 1984, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138). Other controlled release systems are discussed in the review by Langer, 1990, Science 249:1527-1533.

[0099] 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.

[0100] 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.

Therapeutic Uses of the Antibodies

[0101] The antibodies of the invention are useful, *inter alia*, for the treatment, prevention and/or amelioration of any disease or disorder associated with PAR-2 activity, including diseases or disorders associated with the proteolytic activation of PAR-2. Exemplary diseases and disorders that can be treated with the anti-PAR-2 antibodies of the present invention include pain conditions such as nociceptive pain and visceral pain, as well as pain associated with conditions such as inflammation, post-operative incision, neuropathy, bone fracture, burn, osteoporotic fracture, bone cancer, gout, migraine headache, fibromyalgia, etc. The antibodies of the invention may also be used to treat, prevent and/or ameliorate inflammatory conditions such as joint inflammation, airway inflammation (e.g., asthma), skin inflammation, dermatitis

(e.g., atopic dermatitis, allergic contact dermatitis, etc.), inflammatory bowel disease (IBD), glomerulonephritis, interstitial cystitis, bladder inflammation, hyperalgesia, rheumatoid arthritis, osteoarthritis, inflammatory arthritis, multiple sclerosis, anti-phospholipid syndrome, alpha-1-antitrypsin deficiency, etc. The antibodies of the present invention may be used to treat fibrotic conditions, including, e.g., scleroderma, biliary cirrhosis, post-transplant fibrosis, renal fibrosis, lung fibrosis, liver fibrosis, pancreatic fibrosis, testicular fibrosis, hypertrophic scarring and cutaneous keloids. In certain embodiments, the antibodies of the invention are useful for the treatment of gastrointestinal conditions (e.g., celiac disease, Crohn's disease, ulcerative colitis, idiopathic gastroparesis, pancreatitis, irritable bowel syndrome (IBS) and ulcers (including gastric and duodenal ulcers)); acute lung injury; acute renal injury; and sepsis. The anti-PAR-2 antibodies of the present invention are also useful for the treatment of pruritus; e.g., dermal/pruritoceptive, neuropathic, neurogenic, and psychogenic itch, as well as pruritus associated with atopic dermatitis, psoriasis, burn scarring (burn-related itch), hypertrophic scarring, keloids, renal failure and hepatic failure. Other therapeutic uses of the anti-PAR-2 antibodies of the present invention include the treatment, prevention and/or amelioration of Alzheimer's disease, Netherton's disease, pathological angiogenesis, chronic urticaria, angioedema, mastocytosis, endometriosis, infertility (e.g., male infertility associated with testicular fibrosis), mast cell-mediated diseases, *Clostridium difficile* Toxin-A induced enteritis, and cancer (e.g., blood cell cancer, brain cancer, breast cancer, colon cancer, head and neck cancer, liver cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, skin cancer, stomach cancer, etc.).

Combination Therapies

[0102] The present invention relates to therapeutic administration regimens which comprise administering an anti-PAR-2 antibody of the present invention in combination with at least one additional therapeutically active component. Non-limiting examples of such additional therapeutically active components include other PAR-2 antagonists (e.g., anti-PAR-2 antibody or small molecule inhibitor of PAR-2 (e.g., N1-3-methylbutyryl-N4-6-aminohexanoyl-piperazine; ENMD-1068)), cytokine inhibitors (e.g., an interleukin-1 (IL-1) inhibitor (such as rilonacept or anakinra, a small molecule IL-1 antagonist, or an anti-IL-1 antibody); IL-18 inhibitor (such as a small molecule IL-18 antagonist or an anti-IL-18 antibody); IL-4 inhibitor (such as a small molecule IL-4 antagonist, an anti-IL-4 antibody or an anti-IL-4 receptor antibody); IL-6 inhibitor (such as a small molecule IL-6 antagonist, an anti-IL-6 antibody or an anti-IL-6 receptor antibody); antiepileptic drugs (e.g., gabapentin); nerve growth factor (NGF) inhibitors (e.g., a small molecule NGF antagonist or an anti-NGF antibody); low dose coxib; aspirin; NSAIDs; steroids (e.g., prednisone, methotrexate, etc.); low dose cyclosporine A; tumor necrosis factor (TNF) or TNF receptor inhibitors (e.g., a small molecule TNF or TNFR antagonist or an anti-TNF or TNFR antibody); uric acid synthesis inhibitors (e.g., allopurinol); uric acid excretion promoters (e.g., probenecid, sulfinpyrazone, benzbromarone, etc.); other inflammatory inhibitors (e.g., inhibitors of caspase-1, p38, IKK1/2, CTLA-4lg, etc.); and/or corticosteroids. The additional therapeutically active component(s) may be administered prior to, concurrent with, or after the administration of the anti-PAR-2 antibody of the present invention.

Diagnostic Uses of the Antibodies

[0103] The anti-PAR-2 antibodies of the present invention may also be used to detect and/or measure PAR-2 in a sample, e.g., for diagnostic purposes. For example, an anti-PAR-2 antibody, or fragment thereof, may be used to diagnose a condition or disease characterized by aberrant expression (e.g., over-expression, under-expression, lack of expression, etc.) of PAR-2. Exemplary diagnostic assays for PAR-2 may comprise, e.g., contacting a sample, obtained from a patient, with an anti-PAR-2 antibody of the invention, wherein the anti-PAR-2 antibody is labeled with a detectable label or reporter molecule. Alternatively, an unlabeled anti-PAR-2 antibody can be used in diagnostic applications in combination with a secondary antibody which is itself detectably labeled. The detectable label or reporter molecule can be a radioisotope, such as ^3H , ^{14}C , ^{32}P , ^{35}S , or ^{125}I a fluorescent or chemiluminescent moiety such as fluorescein isothiocyanate, or rhodamine; or an enzyme such as alkaline phosphatase, β -galactosidase, horseradish peroxidase, or luciferase. Specific exemplary assays that can be used to detect or measure PAR-2 in a sample include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence-activated cell sorting (FACS).

[0104] Samples that can be used in PAR-2 diagnostic assays include any tissue or fluid sample obtainable from a patient which contains detectable quantities of PAR-2 protein, or fragments thereof, under normal or pathological conditions. Generally, levels of PAR-2 in a particular sample obtained from a healthy patient (e.g., a patient not afflicted with a disease or condition associated with abnormal PAR-2 levels or activity) will be measured to initially establish a baseline, or standard, level of PAR-2. This baseline level of PAR-2 can then be compared against the levels of PAR-2 measured in samples obtained from individuals suspected of having a PAR-2 related disease or condition.

EXAMPLES

[0105] 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 (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, 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 PAR-2

[0106] An immunogen comprising human PAR-2 peptide having the amino acid sequence GTNRSSKGRSLIGKVDGT (SEQ ID NO:852) was administered directly, with an adjuvant to stimulate the immune response, to a VELOCIMMUNE® mouse comprising DNA encoding human Immunoglobulin heavy and kappa light chain variable regions. The antibody immune response was monitored by a PAR-2-specific immunoassay. When a desired immune response was achieved splenocytes were harvested and fused with mouse myeloma cells to preserve their viability and form hybridoma cell lines. The hybridoma cell lines were screened and selected to identify cell lines that produce PAR-2-specific antibodies. Using this technique several anti-PAR-2 chimeric antibodies (*i.e.*, antibodies possessing human variable domains and mouse constant domains) were obtained; exemplary antibodies generated in this manner were designated as follows: H2M588, H2M589, H1M590, H2M591, H1M592, H1M595, H2M609, H2M610, H2M611, H1M612, H1M613, H2M614, H1M615, H1M616, H3M617, H2M618, H1M619, and H3M620.

[0107] Anti-PAR-2 antibodies were also isolated directly from antigen-positive B cells without fusion to myeloma cells, as described in U.S. 2007/0280945A1. Using this method, several fully human anti-PAR-2 antibodies (*i.e.*, antibodies possessing human variable domains and human constant domains) were obtained; exemplary antibodies generated in this manner were designated as follows: H1 H571, H1 H572, H1 H573, H1 H574, H1 H575, H1 H576, H1 H577, H1H578, H1H579, H1H580, H1H581, H1H583, H1H584, H1H585, H1H586, and H1H587.

[0108] The biological properties of the exemplary anti-PAR-2 antibodies generated in accordance with the methods of this Example are described in detail in the Examples set forth below.

Example 2. Heavy and Light Chain Variable Region Amino Acid Sequences

[0109] Table 1 sets forth the heavy and light chain variable region amino acid sequence pairs of selected anti-PAR-2 antibodies and their corresponding antibody identifiers. The N, P and G designations refer to antibodies having heavy and light chains with identical CDR sequences but with sequence variations in regions that fall outside of the CDR sequences (*i.e.*, in the framework regions). Thus, N, P and G variants of a particular antibody have identical CDR sequences within their heavy and light chain variable regions but differ from one another within their framework regions.

Table 1

Name	HCVR/LCVR SEQ ID NOs	Name	HCVR/LCVR SEQ ID NOs	Name	HCVR/LCVR SEQ ID NOs
H1H571N	458/466	H1H571P	474/476	H1H571G	478/480
H1H572N	482/490	H1H572P	498/500	H1H572G	502/504
H1H573N	506/514	H1H573P	522/524	H1H573G	526/528
H1H574N	530/538	H1H574P	546/548	H1H574G	550/552
H1H575N	554/562	H1H575P	570/572	H1H575G	574/576
H1H576N	578/586	H1H576P	594/596	H1H576G	598/600
H1H577N	602/610	H1H577P	618/620	H1H577G	622/624
H1H578N	626/634	H1H578P	642/644	H1H578G	646/648
H1H579N	650/658	H1H579P	666/668	H1H579G	670/672
H1H580N	674/682	H1H580P	690/692	H1H580G	694/696
H1H581N	698/706	H1H581P	714/692	H1H581G	718/720
H1H583N	722/730	H1H583P	738/740	H1H583G	742/744
H1H584N	746/754	H1H584P	762/764	H1H584G	766/768
H1H585N	770/778	H1H585P	786/788	H1H585G	790/792

(continued)

Name	HCVR/LCVR SEQ ID NOs	Name	HCVR/LCVR SEQ ID NOs	Name	HCVR/LCVR SEQ ID NOs
H1H586N	794/802	H1H586P	810/812	H1H586G	814/816
H1H587N	818/826	H1H587P	834/836	H1H587G	838/840
H2M588N	98/106	H2M588P	114/116	H2M588G	118/120
H2M589N	122/130	H2M589P	138/140	H2M589G	142/144
H1M590N	218/226	H1M590P	234/236	H1M590G	238/240
H2M591N	146/154	H2M591P	162/164	H2M591G	166/168
H1M592N	242/250	H1M592P	258/260	H1M592G	262/264
H1M595N	266/274	H1M595P	282/284	H1M595G	286/288
H2M609N	170/178	H2M609P	186/188	H2M609G	190/192
H2M610N	194/202	H2M610P	210/212	H2M610G	214/216
H2M611N	290/298	H2M611P	306/308	H2M611G	310/312
H1M612N	2/10	H1M612P	18/20	H1M612G	22/24
H1M613N	410/418	H1M613P	426/428	H1M613G	430/432
H2M614N	314/322	H2M614P	330/332	H2M614G	334/336
H1M615N	26/34	H1M615P	42/44	H1M615G	46/48
H1M616N	50/58	H1M616P	66/68	H1M616G	70/72
H3M617N	362/370	H3M617P	378/380	H3M617G	382/384
H2M618N	338/346	H2M618P	354/356	H2M618G	358/360
H1M619N	74/82	H1M619P	90/92	H1M619G	94/96
H3M620N	386/394	H3M620P	402/404	H3M620G	406/408
FP3B12F6N	434/442	FP3B12F6P	450/452	FP3B12F6G	454/456

Example 3. Antibody Binding to PAR-2 Peptides

[0110] Synthetic peptides (Celtek Bioscience, Nashville, TN) of PAR-2 and PAR-2 related sequences were generated to characterize the binding profiles of anti-PAR-2 antibodies. Both biotinylated and unbiotinylated forms for the various peptides were generated for the examples set forth below. For biotinylated forms, biotin moieties were covalently attached to the peptide at either the C-terminus or the N-terminus via a G₄S linker. Table 2 sets forth the sequence and derivation of these peptides.

Table 2

Designation	Species	Gene	Sequence	SEQ ID NO:
Peptide A	Human	PAR-2	GTNRSSKGRSLIGKVDGT	852
Peptide B	Human	PAR-2	SLIGKVDGTSHVTG	853
Peptide C	Human	PAR-2	SLIGKV	854
Peptide D	Human	PAR-2	SLIGKVDGTSHVTGKGVTVE TVFSVDEFSASVLTGKLTTVF LP - mouse IgG2a	855
Peptide E	Mouse (<i>Mus musculus</i>)	PAR-2	LAPGRNNSKGRSLIGRLETQ	856

(continued)

Designation	Species	Gene	Sequence	SEQ ID NO:
Peptide F	Monkey (<i>Macaca mulatta</i>)	PAR-2	GTNRSSKGRSLIGRVDGT	857
Peptide G	Rat (<i>Rattus norvegicus</i>)	PAR-2	GPNSKGRSLIGRLDTP	858
Peptide H	Rabbit (<i>Oryctolagus cuniculus</i>)	PAR-2	GTNKTSGRSLIGRNTGS	859
Peptide I	Dog (<i>Canis familiaris</i>)	PAR-2	GTNRTSKGRSLIGKTDSS	860
Peptide J	Pig (<i>Sus scrofa</i>)	PAR-2	GTSRPSKGRSLIGKADNT	861
Peptide K	Human	PAR-1	ATNATLDPRSFLLRNPND	862
Peptide L	Human	PAR-3	DTNNLAKPTLPIKTFRGA	863
Peptide M	Human	PAR-4	ESGSTGGDDSTPSILPAP	864

[0111] Anti-PAR-2 antibodies were tested for their ability to bind to the PAR-2 peptides. Various PAR-2 Peptides (Table 3) were coated onto 96-well plates at a concentration of 2 µg/ml and incubated overnight followed by blocking in a suitable blocking agent for one hour. In a similar fashion, for biotinylated peptides (N-Term: N-terminal biotinylated; C-Term: C-terminal biotinylated), avidin was coated on plates at 2 µg/ml followed by incubation with biotinylated PAR-2 peptides at a concentration of 0.2 µg/ml and incubated for one hour. Purified anti-PAR-2 antibodies were added to the plate coated with PAR-2 peptides to a final concentration ranging from 0.2 to 2.0 µg/ml and incubated for one hour at room temperature. Detection of bound antibodies was determined with Horse-Radish Peroxidase (HRP) conjugated anti-mouse or human IgG (Jackson Immuno Research Lab, West Grove, PA) and developed by standard colorimetric response using tetramethylbenzidine (TMB) substrate. Absorbance was read at OD₄₅₀ for 0.1 second.

[0112] Relative binding (+++, ++, +) to unbiotinylated (No Biotin) or biotinylated Peptides A, B and C as compared to no binding (-) for each anti-PAR-2 antibody tested according to the observed OD₄₅₀ value (1.0 - 4.0, 0.50 - 0.99, 0.1 - 0.49, 0.0 - 0.09, respectively) is shown in Table 3. Control: "Sam11," a commercially available mouse monoclonal antibody that binds human PAR-2 (Santa Cruz Biotechnology, Santa Cruz, CA).

Table 3

Antibody	Peptide A			Peptide B			Peptide C	
	No Biotin	N-Term	C-Term	No Biotin	N-Term	C-Term	N-Term	C-Term
H2M588N	+++	+++	+++	+++	+++	+++	-	-
H2M589N	+++	+++	+++	+++	+++	+++	-	-
H1M590N	+++	+++	+++	-	-	-	-	-
H2M591N	+++	+++	+++	+++	+++	+++	-	-
H1M592N	+++	+++	+++	-	++	+++	+++	+++
H1M595N	+++	+++	+++	-	-	-	++	-
H2M609N	+++	+++	+++	-	-	-	-	-
H2M610N	+++	+++	+++	-	-	-	-	-
H2M611N	+++	+++	+++	+++	+++	+++	-	-
H1M612N	+++	+++	+++	-	-	-	-	-
H1M613N	+++	+++	+++	-	++	+++	+++	+++
H2M614N	++	+++	+++	-	-	-	-	-

(continued)

Antibody	Peptide A			Peptide B			Peptide C	
	No Biotin	N-Term	C-Term	No Biotin	N-Term	C-Term	N-Term	C-Term
H1M615N	+++	+++	+++	-	-	-	-	-
H1M616N	+++	+++	+++	-	-	-	-	-
H2M618N	+++	+++	+++	+++	+++	+++	-	-
H1M619N	+++	+++	+++	-	-	-	-	-
H3M620N	+++	++	+++	-	-	-	-	-
Control	-	-	-	+++	+++	+++	-	-

[0113] In a similar experiment, selected anti-PAR-2 antibodies cloned onto a mutant human IgG4 (SEQ ID NO:849) were tested for their ability to bind unbiotinylated and biotinylated forms of human PAR-2 peptides (as described above). Results are shown in Table 4.

Table 4

Antibody	Peptide A			Peptide B			Peptide C	
	No Biotin	N-Term	C-Term	No Biotin	N-Term	C-Term	N-Term	C-Term
H4H572P	-	-	-	-	-	-	--	-
H4H573P	+++	+++	+++	-	-	-	-	-
H4H576P	+	-	-	-	-	-	-	-
H4H578P	+++	+++	+++	-	-	-	-	-
H4H579P	+++	+++	+++	+++	+++	+++	-	-
H4H580P	+++	+++	+++	+++	+++	+++	-	-
H4H581P	+++	+++	+++	+++	+++	+++	++	+
H4H583P	+++	+++	+++	-	-	-	-	-
H4H584P	+++	+++	+++	+++	+++	+++	-	-
H4H585P	+++	+++	+++	+++	+++	+++	+	+
H4H587P	-	-	-	-	-	-	-	+
H4H588N	+++	+++	+++	+++	+++	+++	-	-
H4H591N	+++	+++	+++	+++	+++	+++	-	-
H4H618N	+++	+++	+++	+++	+++	+++	-	-
Control	-	-	-	+++	+++	+++	-	-

[0114] In another experiment, selected anti-PAR-2 antibodies were tested for binding to unbiotinylated Peptides D, K, L and M (as described above). Results for chimeric antibodies (e.g. H2M588N) and fully human antibodies (e.g. H4H572P) are shown in Tables 5 and 6, respectively. For Peptide D, detection of bound antibodies was determined with Horse-Radish Peroxidase (HRP) conjugated anti-mouse κ (Southern Biotech, Birmingham, AL).

Table 5

Antibody	Peptide D	Peptide K	Peptide L	Peptide M
H2M588N	+++	-	-	-
H2M589N	+++	-	-	-
H1M590N	-	-	-	-

(continued)

Antibody	Peptide D	Peptide K	Peptide L	Peptide M
H2M591 N	+++	-	-	-
H1M592N	+	-	-	-
H1M595N	-	-	-	-
H2M609N	+	-	-	-
H2M610N	-	-	-	-
H2M611 N	+	-	-	-
H1M612N	-	-	-	-
H1M613N	+	-	-	-
H2M614N	-	-	-	-
H1M615N	-	-	-	-
H1M616N	-	-	-	-
H2M618N	+++	-	-	-
H1M619N	-	-	-	-
H3M620N	-	-	-	-
Control	+++	-	-	-

Table 6

Antibody	Peptide D	Peptide K	Peptide L	Peptide M
H4H572P	+	-	-	-
H4H573P	+	-	-	-
H4H576P	+	-	-	-
H4H578P	+	-	-	-
H4H579P	+++	-	-	-
H4H580P	+++	-	-	-
H4H581P	+++	+	+	+
H4H583P	++	-	-	-
H4H584P	+++	-	-	-
H4H585P	+++	+	+	+
H4H587P	+	-	-	-
H4H588N	+++	-	-	-
H4H591N	+++	+	+	+
H4H618N	+++	-	-	-
Control	+++	-	-	-

[0115] In another experiment, selected anti-PAR-2 antibodies were tested for binding to N-terminal biotinylated mouse (Peptide E N-Term) and monkey (Peptide F N-Term) PAR-2 peptides (as described above).

Table 7

Antibody	Peptide E N-Term	Peptide F N-Term
H2M588N	-	+++
H2M589N	-	+++
H1M590N	+++	+++
H2M591N	-	+++
H1M592N	-	-
H1M595N	+++	+++
H2M609N	+++	+++
H2M610N	+++	+++
H2M611N	-	+++
H1M612N	+++	+++
H1M613N	-	-
H2M614N	+++	+++
H1M615N	+++	+++
H1M616N	+++	+++
H2M618N	-	+++
H1M619N	+++	+++
H3M620N	+++	++
Control	-	-

[0116] In another experiment, selected anti-PAR-2 antibodies cloned onto human IgG4 were tested for binding to unbiotinylated and biotinylated forms of Peptides E through J (as described above). Results are shown in Table 8.

Table 8

Antibody	Peptide E		Peptide F N-Term	Peptide G			Peptide H	Peptide I	Peptide J
	No Biotin	N-Term		No Biotin	N-Term	C-Term			
H4H572P	+	-	-	-	-	+	-	-	-
H4H573P	+++	+++	+++	+++	+++	++	+++	+++	+++
H4H576P	+	-	-	-	-	+	-	-	-
H4H578P	+++	+++	+++	+++	+++	+	+++	+++	+++
H4H579P	+++	+++	+++	+++	+++	+++	+	+++	+
H4H580P	+++	+++	+++	+++	+++	+++	-	+++	+
H4H581P	+++	+++	+++	+++	+++	+++	-	+++	+++
H4H583P	+++	+++	+++	+++	+++	+++	+++	+++	+++
H4H584P	+++	+++	+++	+++	+++	+++	-	+++	++
H4H585P	+++	+++	+++	+++	+++	+++	+	+++	+++
H4H587P	-	-	-	-	+	-	-	-	+
H4H588N	-	-	+++	-	+	-	-	-	-
H4H591N	+	+	+++	+	+	+	+	-	+
H4H618N	-	-	+++	-	-	-	-	-	-

(continued)

Antibody	Peptide E		Peptide F N-Term	Peptide G			Peptide H	Peptide I	Peptide J
	No Biotin	N-Term		No Biotin	N-Term	C-Term			
Control	-	-	-	-	-	-	-	-	-

[0117] In another experiment, selected anti-PAR-2 antibodies cloned onto human IgG4 were tested for binding to unbiotinylated and biotinylated forms of PAR-2 peptides (Peptides A, E, F and G; as described above). In this experiment, anti-PAR-2 antibodies, serially diluted threefold from 13.3 nM to 0.22 pM, were incubated on the peptide-coated plates for one hour at room temperature. Absorbance values at 450 nm were analyzed using a sigmoidal dose-response model in GraphPad Prism (GraphPad Software, Inc., La Jolla, CA) and EC₅₀ values were reported (Table 9). EC₅₀ values are defined as the antibody concentration required to achieve 50% maximal binding to PAR-2 peptide.

Table 9

Antibody	EC ₅₀ (nM)								
	Peptide A			Peptide E		Peptide F N-Term	Peptide G		
	No Biotin	C-Term	N-Term	No Biotin	N-Term		No Biotin	C-Term	N-Term
H4H572P	>50	>50	>50	>50	>50	>50	>50	>50	>50
H4H573P	0.093	0.022	0.093	0.355	0.016	0.018	0.014	10.130	0.017
H4H576P	>50	>50	>50	>50	>50	>50	>50	>50	>50
H4H578P	0.034	0.040	0.062	2.778	0.090	0.036	0.046	>50	0.081
H4H579P	0.038	0.076	0.077	0.713	0.540	0.061	0.055	0.044	0.059
H4H580P	0.090	0.202	0.160	2.533	0.932	0.148	0.139	0.100	0.142
H4H581P	0.012	0.028	0.020	0.029	0.032	0.020	0.020	0.013	0.019
H4H583P	0.008	0.018	0.015	0.019	0.014	0.013	0.012	0.630	0.015
H4H584P	0.012	0.015	0.019	2.152	0.511	0.012	0.013	0.015	0.012
H4H585P	0.017	0.021	0.026	0.308	0.189	0.017	0.018	0.021	0.017
H4H587P	>50	>50	>50	>50	>50	>50	>50	>50	>50
H4H588N	0.010	0.016	0.019	>50	>50	0.012	>50	>50	>50
H4H591N	0.010	0.016	0.022	>50	>50	0.011	>50	>50	>50
H4H618N	0.009	0.016	0.021	>50	>50	0.011	>50	>50	>50
Control	>50	>50	>50	>50	>50	>50	>50	>50	>50

[0118] As indicated by the foregoing experiments, antibodies H4H581 P, H4H588N, H4H591 N or H4H618N all show substantial binding to human Peptides A, B and D, which comprise the sequence SLIGKVDGT (amino acids 10-18 of SEQ ID NO:852), as well as to monkey Peptide F, which comprises the sequence SLIGRVDGT (amino acids 10-18 of SEQ ID NO:857). For antibodies H4H588N, H4H591 N and H4H618N, the sequence VDGT, located downstream from the activating PAR-2 protease cleavage site, appears to be particularly important for binding since changes to this sequence resulted in substantially reduced or no binding by these antibodies (see, e.g., binding data for Peptides E (mouse), G (rat), H (rabbit), I (dog) and J (pig)).

Example 4. Antigen Binding Affinity Determination

[0119] Equilibrium dissociation constants (K_D values) for antigen binding to selected purified PAR-2 antibodies were determined by surface kinetics using a real-time surface plasmon resonance biosensor assay. Antibody was captured on either a rabbit anti-mouse IgG polyclonal antibody (GE Healthcare, Piscataway, NJ) surface or a goat anti-human

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IgG polyclonal antibody (Jackson Immuno Research Lab, West Grove, PA) surface created through direct amine chemical coupling to a BIACORE™ CM5 sensor chip to form a captured antibody surface. Various concentrations (ranging from 15.6 to 250 nM) of monomeric human PAR-2 peptides (Peptides A and B) were injected at a rate of 100 μ l/min over the captured antibody surface for 90 seconds. Antigen-antibody binding and dissociation were monitored in real time at room temperature. Kinetic analysis was performed to calculate K_D and half-life of antigen/antibody complex dissociation (Table 10). For those antibodies where no $T_{1/2}$ value is shown, steady state analysis was used to calculate the K_D value. NB: no binding observed under current experimental conditions. ND: not determined.

Table 10

Antibody	Peptide A		Peptide B	
	K_D (nM)	$T_{1/2}$ (min)	K_D (nM)	$T_{1/2}$ (min)
H4H572P	NB	-	ND	-
H4H573P	749	-	ND	-
H4H576P	NB	-	ND	-
H4H578P	245	0.17	ND	-
H4H579P	15	4	>500	-
H4H580P	103	0.88	ND	-
H4H581P	9.44	1.4	>500	-
H4H583P	37.1	0.37	NB	-
H4H584P	22	0.73	>500	-
H4H585P	8.78	3.7	>500	-
H4H587P	NB	-	ND	-
H1M590N	173	-	ND	-
H1M592N	2100	-	ND	-
H1M595N	510	-	ND	-
H1M612N	180	-	ND	-
H1M613N	2100	-	ND	-
H1M615N	162	-	ND	-
H1M616N	144	-	ND	-
H1M619N	164	-	ND	-
H2M588N	4.47	60.8	61.7	7.7
H2M589N	3.75	51.3	128	7.3
H2M591N	4.22	42.7	151	8.1
H2M610N	71.3	-	360	0.8
H2M611N	72.8	4.1	1090	1.2
H2M614N	470	-	ND	-
H2M618N	9.62	6.7	126	3.5
Control	NB	-	149	0.1

[0120] In a similar experiment, K_D values for binding to unbiotinylated monomeric mouse (Peptide E) and N-terminal biotinylated monkey (Peptide F N-Term) PAR-2 peptides of selected antibodies cloned onto human IgG4 were determined (as described above) (Table 11). Antibodies H4H588N, H4H591 N, and H4H618N did not bind Peptide E, while the Control antibody did not bind to either Peptide E or F.

Table 11

Antibody	Peptide F N-Term	
	K _D (nM)	T _{1/2} (min)
H4H588N	7.10	24
H4H591N	8.54	21
H4H618N	13.8	5

[0121] In another series of experiments, equilibrium dissociation constants (K_D values) for purified antibody binding to selected biotinylated and unbiotinylated forms of PAR-2 peptides were determined by surface kinetics using a real-time surface plasmon resonance biosensor assay. Neutravidin (Pierce, Rockford, IL) was covalently coupled to the surface of a Biacore™ C1 chip or CM5 chip using amine coupling chemistry. Biotinylated (N-Term or C-Term) PAR-2 peptides (Peptides A and B) were immobilized on the surface via the high affinity binding interaction between biotin and the amine coupled Neutravidin.

[0122] In a first experiment using this format, varying concentrations (ranging from 5 to 100 µg/ml) of purified antibody were injected at a rate of 50 µl/min over a surface coated with immobilized peptide at low-density (<1 RU) for 300 seconds. Antibody-peptide binding and dissociation was monitored in real time 25°C (Table 12).

Table 12

Antibody	Peptide A C-Term		Peptide B C-Term	
	K _D (nM)	T _{1/2} (min)	K _D (nM)	T _{1/2} (min)
H2M588N	0.826	169	1.49	140
H1M590N	1.27	13	NB	-
H2M591N	0.545	209	1.82	94
H2M618N	1.8	79	2.32	60
Control	NB	-	0.99	19

[0123] In another similar experiment, K_D values for binding to a low-density surface (<1 RU) of biotinylated forms of Peptides A, B, C, E, F and G of selected antibodies cloned onto human IgG4 were determined (as described above). Results for binding to C-terminal and N-terminal biotinylated PAR-2 peptides are shown in Tables 13-14, respectively. In this experiment, only antibody H4H581 P demonstrated affinity for N-terminal biotinylated Peptide C (K_D of >100 nM), while all other antibodies tested, including the control, showed no binding to this peptide.

Table 13

Antibody	Peptide A C-Term		Peptide B C-Term	
	K _D (nM)	T _{1/2} (min)	K _D (nM)	T _{1/2} (min)
H4H579P	0.143	479	0.453	96
H4H581P	0.237	134	0.346	49
H4H583P	0.898	34	NB	-
H4H584P	0.688	55	1.66	15
H4H585P	0.151	493	0.376	123
H4H588N	0.517	141	1.03	70
H4H590N	3.56	3	NB	-
Control	NB	-	0.935	14

Table 14

Antibody	Peptide A N-Term		Peptide B N-Term		Peptide E N-Term		Peptide F N-Term		Peptide G N-Term	
	K _D (nM)	T _{1/2} (min)	K _D (nM)	T _{1/2} (min)	K _D (nM)	T _{1/2} (min)	K _D (nM)	T _{1/2} (min)	K _D (nM)	T _{1/2} (min)
H4H579P	1.61	46	5.44	55	3.40	20	0.796	70	1.16	38
H4H581P	0.498	41	2.72	38	1.13	21	0.272	78	0.354	62
H4H583P	0.412	46	NB	-	1.68	11	0.291	73	1.49	13
H4H584P	0.525	43	3.20	30	>100	-	0.565	40	1.39	15
H4H585P	1.69	48	5.41	63	>100	-	0.899	66	1.36	35
H4H588N	1.05	189	0.0272	>1155	NB	-	1.81	94	NB	-
H4H590N	1.52	3	NB	-	1.28	7	1.84	2	2.94	2
Control	NB	-	0.279	32	NB	-	NB	-	NB	-

[0124] In a similar experiment, K_D values for binding to monomeric biotinylated and unbiotinylated forms of PAR-2 peptides (Peptides A, B, E - M) for selected antibodies cloned onto human IgG4 were determined (as described above for the captured antibody surface). Results are shown in Tables 15-16. None of the antibodies tested showed binding to Peptides K, L or M.

Table 15

Antibody	Peptide A		Peptide B		Peptide E	
	K _D (nM)	T _{1/2} (min)	K _D (nM)	T _{1/2} (min)	K _D (nM)	T _{1/2} (min)
H4H579P	15	4.1	>500	-	>500	-
H4H581P	9.44	1.4	>500	-	>500	-
H4H583P	37.1	0.37	NB	-	>500	-
H4H584P	22	0.73	NB	-	NB	-
H4H585P	8.78	3.7	>500	-	>500	-
H4H588N	4.95	25.1	84	9	NB	-
H4H590N	>500	-	NB	-	>500	-
Control	ND	-	149	0.1	ND	-

Table 16

Antibody	Peptide F N-Term		Peptide G		Peptide H		Peptide I		Peptide J	
	K _D (nM)	T _{1/2} (min)	K _D (nM)	T _{1/2} (min)	K _D (nM)	T _{1/2} (min)	K _D (nM)	T _{1/2} (min)	K _D (nM)	T _{1/2} (min)
H4H579P	49.4	2	134	0.45	NB	-	311	0.26	NB	-
H4H581P	36.6	0.53	40.2	0.63	NB	-	143	0.07	NB	-
H4H583P	112	0.47	530	0.07	189	0.17	320	0.16	190	0.16
H4H584P	93.3	0.23	246	0.13	NB	-	>500	-	NB	-
H4H585P	46.2	2	162	0.33	NB	-	372	0.19	NB	-
H4H588N	10.8	20	NB	-	NB	-	NB	-	NB	-
H4H590N	>500	-	>500	-	>500	-	>500	-	>500	-

Example 5. Antibody Binding to Cells Engineered to Express PAR-2

[0125] To further characterize anti-PAR-2 antibodies, cells of the human embryonic kidney 293 cell line (HEK293) were genetically engineered to overexpress either full length human (SEQ ID NO:851) or mouse (SEQ ID NO:866) PAR-2.

[0126] HEK293 cells were transfected with an NF- κ B-luciferase-IRES-eGFP reporter plasmid. Stability of transfected cells was demonstrated by response to IL-1 β as detected by eGFP expression through flow cytometry and luciferase activity. A clonal cell line, named D9, having low background levels of luciferase activity and high levels of eGFP when induced with IL-1 β was made by a series of successive sorts of cell populations using flow cytometry. The 293/D9 cell line was then separately transfected with human PAR-2 or mouse PAR-2 to create the stable cell lines 293/D9/hPAR-2rec and 293/D9/mPAR-2rec, respectively.

[0127] Binding of anti-PAR-2 antibodies to 293/D9/hPAR-2rec cells was determined by ELISA. 293/D9 and 293/D9/hPAR-2rec cells were plated at a density of 5×10^4 cells/well in media and incubated overnight at 37°C and 5% CO₂. Purified antibody was added to the cells to a final concentration of 10 μ g/ml and incubated at room temperature for one hour. Cells were then fixed and washed before detection of bound antibodies with HRP conjugated anti-mouse IgG and developed by standard colorimetric response using TMB substrate. Absorbance was read at OD₄₅₀ for 0.1 second. The A₄₅₀ ratio of antibody binding to 293/D9/hPAR-2rec cells compared to 293/D9 cells is shown in Table 17.

Table 17

Antibody	A ₄₅₀ ratio
H2M588N	2.50
H2M589N	2.03
H1M590N	1.81
H2M591N	2.25
H1M592N	1.25
H1M595N	1.80
H2M609N	1.54
H2M610N	1.66
H2M611N	1.76
H1M612N	1.90
H1M613N	1.27
H2M614N	1.17
H1M615N	2.18
H1M616N	2.78
H2M618N	2.44
H1M619N	1.51
H3M620N	1.24
Control	1.49

[0128] In a similar experiment, anti-PAR-2 antibodies were tested for binding to 293/D9, 293/D9/hPAR-2rec and 293/D9/mPAR-2rec cells using electro-chemiluminescence technology (Meso Scale Discovery, MSD, Gaithersburg, MD). Cells were plated on MSD high-bind 96 well plates at a density of 4×10^4 cells/well in PBS and incubated for one hour at room temperature. Cells were then blocked in PBS with 2% BSA and incubated at room temperature for one hour. Anti-PAR-2 antibodies (ranging from 100 nM to 0.098 nM) were serially diluted two-fold in PBS with 0.5% BSA and incubated with the cells for one hour at room temperature followed by washing in PBS with 0.5% BSA. Sulfo-tagged anti-human IgG antibody (MSD) at a concentration of 0.1 μ g/ml was then added to the cell/antibody mixture and incubated at room temperature for an additional hour. After another wash, a 1 X non-surfactant containing read buffer was added and electro-chemiluminescent signal was read on the MSD Sector Imager. Signal of antibody binding to 293/D9 cells was subtracted from signal to 293/D9/hPAR-2rec or 293/D9/mPAR-2rec cells. Subtracted data were analyzed using a sigmoidal dose-response model in GraphPad Prism and EC₅₀ and B_{max} values were reported (Table 18). EC₅₀ values

are defined as the antibody concentration required to achieve 50% maximal binding ($B_{\max}$) to cells.

Table 18

Antibody	293/D9/hPAR-2rec		293/D9/mPAR-2rec	
	EC ₅₀ (nM)	B _{max} (MSD Unit)	EC ₅₀ (nM)	B _{max} (MSD Unit)
H4H579P	1.86	25049	NB	-
H4H580P	8.69	30177	NB	-
H4H581P	0.652	28224	NB	-
H4H583P	2.12	13252	9.28	7219
H4H584P	1.45	26044	NB	-
H4H585P	1.95	22540	NB	-
H4H588N	5.95	27549	NB	-
H4H590N	9.72	6554	5.76	13255

Example 6. *In vitro* Blocking of Human PAR-2 Activation By Anti-PAR-2 Antibodies

[0129] Blocking of PAR-2 activation (signaling) was determined by binding of selected purified anti-PAR-2 antibodies to 293/D9/hPAR-2rec cells (see Example 5) by a luciferase assay. 293/D9/hPAR-2rec cells were plated at a concentration ranging from 5×10^4 to 10^5 cells/well in a 96 well plate in low serum media and incubated overnight at 37°C with 5% CO₂. The media was removed and purified anti-PAR-2 antibodies were added to the cells at various concentrations (ranging from 51 pM to 1 μ M) and incubated for one hour at 37°C with 5% CO₂. Various concentrations of different serine proteases (Trypsin, Human Trypsin 1, Factor Xa and Lung Tryptase) were then added separately to the cell/antibody mixture and incubated for five hours at 37°C with 5% CO₂. Proteolytic cleavage of PAR-2 in this assay leads to expression of the NF- κ B-luciferase reporter construct, whereas a reduced or attenuated level of luciferase signal indicates inhibition of PAR-2 cleavage. IC₅₀ values are shown in Table 19. ND: not determined.

Table 19

Antibody	IC ₅₀ (nM)							
	Trypsin					10 nM Human Trypsin 1	200 nM Factor Xa	750 nM Lung Tryptase
	250 nM	75 nM	30 nM	20 nM	10 nM			
H2M588N	2.3	5.7	33.0	26.8	10.4	164.9	45.3	1.0
H2M589N	6.3	3.7	ND	ND	ND	ND	ND	ND
H1M591N	4.5	ND	ND	121.8	24.2	149.6	51.5	88.1
H2M618N	6.6	7.8	ND	70	12.4	153.5	54.2	7.0

[0130] As shown in Table 20, antibodies H4H581 P, H4H588N, H4H591 N and H4H618N were able to significantly block protease activation of PAR-2 in reporter cells. By contrast, anti-PAR-2 antibodies H4H592N, H4H595N, H4H611 N, H4H613N, H4H614N, H4H615N, H4H616N, H4H617N and H4H619N did not demonstrate any measurable blocking of PAR-2 cleavage/activation in this assay (data not shown).

Table 20

Antibody	20 nM Trypsin IC ₅₀ (nM)
H4H579P	4.1
H4H580P	3.5
H4H581P	1.1
H4H583P	14

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(continued)

Antibody	20 nM Trypsin IC ₅₀ (nM)
H4H584P	5.6
H4H585P	8.9
H4H588N	16.9
H4H591N	204.1
H4H618N	50.2

[0131] Under the experimental conditions used in this Example, no blocking of PAR-2 signaling was observed for antibodies H4H572P, H4H573P, H4H576P, H4H578P or H4H587P, whereas significant blockage (to varying degrees) was observed with antibodies H4H579P, H4H580P, H4H581 P, H4H583P, H4H584P, H4H585P, H4H588N, H4H591 N and H4H618N.

[0132] In another similar experiment, antibody blocking of PAR-2 signaling mediated by human Trypsin 1, Factor Xa and Lung Tryptase was determined for selected purified anti-PAR-2 antibodies cloned onto human IgG4 (as described above). Results are shown in Table 21.

Table 21. IC₅₀ (nM)

Antibody	10 nM Human Trypsin 1	200 nM Factor Xa	750 nM Lung Tryptase
H4H581P	7.4	5.3	1.1
H4H588N	42.7	17.1	1.6
H4H591N	104.7	74.6	62.9
H4H618N	92.2	47.2	8.5

[0133] HEK293/NFκB-luciferase cells expressing human, monkey, mouse or rat PAR-2 were treated with various proteases after preincubation with increasing amounts of anti-PAR-2 antibody H4H581 P, and the IC₅₀ was determined. Results are summarized in Table 22.

Table 22

Activator (6h)	PAR-2 Species	EC ₅₀ (nM)	H4H581P IC ₅₀ (nm)
Human Pancreatic Trypsin	Human	0.8	1.9
	mouse	1.4	491.0
	monkey	2.4	5.4
	rat	6.0	700.0
Human Kallikrein 5	Human	28.0	0.9
	mouse	ND	ND
	monkey	16.8	11
Human Kallikrein 14	Human	5.0	1.2
	mouse	8.0	256.0
	monkey	6.3	11.6
Bovine Factor Xa	Human	27.2	2.5
	mouse	46.3	340.4
	monkey	58.2	0.9

(continued)

Activator (6h)	PAR-2 Species	EC ₅₀ (nM)	H4H581P IC ₅₀ (nm)
Human Factor Xa	Human	46.3	1.1
	mouse	78.7	109
	monkey	ND	ND
Trypsin	Human	61.1	3.5
	mouse	ND	ND
	monkey	ND	ND

[0134] Under the particular experimental conditions used, the H4H581 P antibody effectively inhibited protease-activation of human and monkey PAR-2, but not mouse or rat PAR-2.

Example 7. *In vitro* Antibody Blocking of Human PAR-2 Dependent Calcium Mobilization

[0135] Blocking of trypsin-stimulated PAR-2 activation (signaling) was determined by treating HEK293 cells with selected purified anti-PAR-2 antibodies cloned onto human IgG4 in a calcium mobilization FLIPR assay (Molecular Devices, Sunnyvale, CA). Also tested in this assay was a non-PAR-2 specific control antibody.

[0136] Briefly, 8X10⁴ HEK293 cells were plated on Poly-D-Lysine plates (BD Biosciences, San Jose, CA) in low serum media (DME with 0.5% FBS) and incubated overnight at 37°C with 5% CO₂. The following day cells were incubated with various concentrations (ranging from 0 to 1 μM) of selected anti-PAR-2 antibodies, or a control antibody, followed by the addition of trypsin. Trypsin-mediated activation of PAR-2 is indicated by calcium mobilization. In-cell measurement of calcium signaling was measured using a Fluo-4 NW Calcium Assay Kit (Invitrogen, Carlsbad, CA) on a FlexStation 3 (Molecular Devices, Sunnyvale, CA). The antibody concentration necessary to cause half-maximal inhibition of trypsin-mediated calcium signaling (IC₅₀) was measured for each experimental and control antibody. Results are shown in Table 23 as IC₅₀ (nM).

Table 23

Antibody	100 nM Trypsin
H4H581P	54.96
H4H588N	29.47
Non-Specific Control	> 1000

[0137] As shown in this Example, antibodies H4H581P and H4H588N each inhibited trypsin-stimulated calcium signaling to a significant extent as compared to the control antibody.

Example 8. *In vitro* Blocking of Trypsin-mediated Cleavage of PAR-2 Peptides

[0138] A Matrix Assisted Laser Desorption Ionization - Time of Flight (MALDI-TOF) assay was developed to determine the ability of selected purified anti-PAR-2 antibodies to block Trypsin-mediated cleavage of human PAR-2 peptide (Peptide A, SEQ ID NO:852). Biotinylated versions of Peptide A (containing C-terminal or N-terminal biotin) were mixed with anti-PAR-2 antibody to achieve a 3:1 molar ratio of antibody to peptide, and then trypsin was added to the peptide-antibody mixture. Biotinylated peptides were recovered by immuno-precipitation (IP) via mono-avidin and analyzed by MALDI-TOF.

[0139] In a typical experiment, selected purified anti-PAR-2 antibodies cloned onto human IgG4 (H4H581 P and H4H588N) were tested for their ability to block Trypsin-mediated cleavage of the biotinylated PAR-2 peptides. A non-PAR-2-specific antibody of the same isotype was used as a negative control ("Neg Ctrl" in Fig. 3). For H4H581 P and the negative control antibody, biotinylated peptides were used at a final concentration of 4.75 μM and antibodies were used at 14.25 μM. For H4H588N, biotinylated peptides were used at a final concentration of 2.45 μM and the antibody at 7.35 μM. Peptide and antibody were mixed in PBS and allowed to come to equilibrium for 1 hr at room temperature. Trypsin (96 ng) was then added and the mixture incubated at 37°C for 0, 5, 10 and 15 minutes. At each time point an aliquot equaling 100 ng of biotinylated peptide was removed and mixed with 10 μl of monomeric avidin resin (Pierce)

for 1 minute. The bound peptides were rinsed 3x with 200 μ l of PBS and then eluted with 20 μ l of 100 mM glycine pH 2.5. Salt was removed from the eluted peptide mixture using ZipTips (Millipore). The molecular weights of the major biotinylated PAR-2 peptides produced after trypsin cleavage, as revealed by MALDI-TOF analysis, are summarized in Fig. 3.

[0140] The PAR-2 peptides used in these experiments contain two R/S protease cleavage sites. The first site (designated site "(1)" in Fig. 3) is an "upstream" cleavage site located N-terminal to the activating PAR-2 protease cleavage site. The activating PAR-2 protease cleavage site (designated site "(2)" in Fig. 3) is the site which, when cleaved, results in the formation of the PAR-2 tethered ligand in the naturally occurring protein. The sizes of the peptides detected following cleavage at the different sites are shown in the top portion of Fig. 3 (panel A).

[0141] As indicated in Fig. 3 (panel B), the C-terminal biotin PAR-2 peptide, when treated with the isotype-matched control antibody, followed by trypsin incubation, produced a cleavage fragment of 1558 Da (containing residues 10-18 of SEQ ID NO:852). The 1558 Da fragment is the result of cleavage at the activating PAR-2 protease cleavage site (2). This cleavage pattern was also observed in the experiment using the H4H588N anti-PAR-2 antibody. Thus, according to this assay, neither the control antibody nor the H4H588N antibody inhibit trypsin cleavage at the activating PAR-2 protease cleavage site (2).

[0142] By contrast, the C-terminal biotin PAR-2 peptide, when treated with the H4H581 P antibody, followed by trypsin incubation, produced a cleavage fragment of 2073 Da (containing residues 5-18 of SEQ ID NO:852). The 2073 Da fragment is the fragment produced by cleavage at the upstream cleavage site (1) only. Thus, cleavage at the activating PAR-2 protease cleavage site (2) was apparently blocked by the H4H581 P antibody.

[0143] Experiments with the N-terminal biotin PAR-2 peptide showed trypsin cleavage at the upstream cleavage site (1) and thus produced a 988 Da N-biotinylated fragment (containing residues 1-4 of SEQ ID NO:852) in the presence of all antibodies tested. Therefore, none of the antibodies tested blocked cleavage at the upstream cleavage site (1) under these experimental conditions.

[0144] As shown in Examples 6 and 7 above, both H4H581 P and H4H588N blocked PAR-2 activation by trypsin in cell-based assays. In the present Example, however, only H4H581 P blocked trypsin cleavage at the activating PAR-2 protease cleavage site. Without being bound by any mechanistic theory, it therefore appears that H4H588N may exert its inhibitory effect(s) by interfering with the interaction between the tethered ligand and one or more extracellular loops (e.g., loop 1, loop 2 and/or loop 3) of PAR-2. On the other hand, H4H581 P may inhibit PAR-2 activity primarily by blocking protease cleavage but may also interfere with tethered ligand interactions as well.

[0145] To further investigate the protease cleavage-blocking properties of anti-PAR-2 antibodies, additional MALDI-TOF experiments were conducted using C-terminal biotinylated mouse, rat and human PAR-2 peptides. (See Fig. 4). The antibodies tested in these experiments were H4H581 P, H4H588N, a comparator antibody having the heavy and light chain variable regions of the antibody referred to as "1A1" in WO 2009/005726 (referred to in Fig. 5 as "Comp. Ab"), and a negative control antibody (referred to in Fig. 4 as "Neg Ctrl"). The same experimental procedures that were used in the previous MALD-TOF experiment (described above) were used in this experiment as well.

[0146] The peptides used in these experiments each possess multiple sites capable of being cleaved by trypsin (designated "(1)," "(2)," and "(3)" in Fig. 5.) Site (3) for each peptide is the activating protease cleavage site. The sizes of the peptides produced following cleavage at the different sites are shown in the top portion (panel A) of Fig. 4.

[0147] As summarized in Fig. 4, the biotinylated human PAR-2 peptide, after being treated with H4H581 P, and following trypsin incubation, produced a 2074 kDa peptide which corresponds to cleavage at site (1) only. Thus, H4H581 P blocks cleavage at both site (2) and at site (3). By contrast, the human PAR-2 peptide, after being treated with the comparator antibody, and following trypsin incubation, remained at 2502 kDa which signifies no cleavage. Thus, the comparator antibody blocks all three protease cleavage sites in this assay, including the N-terminal-most site (1). When pre-treated with antibody H4H588N, the human PAR-2 peptide produces both a 1772 kDa and a 1558 kDa fragment following trypsin cleavage. This cleavage pattern suggests that H4H588N partially blocks cleavage at the activating site (3) but completely blocks the middle site (2).

[0148] This experiment was also conducted using a comparator antibody having the heavy and light chain variable regions of the antibody referred to as Sam-11 (Molino et al., *Arterioscler. Thromb. Vasc. Biol.* 18:825-832 (1998)). As expected, this particular comparator antibody did not block cleavage at any of the protease cleavage sites (data not shown).

Example 9. Epitope Mapping by Alanine Scanning Mutagenesis of PAR-2 Peptide

[0149] In order to more particularly identify the amino acids of PAR-2 with which the PAR-2 antibodies interact, an alanine scanning study was carried out using peptides comprising the activating PAR-2 protease cleavage site. For these experiments, 11 separate C-terminal biotinylated peptides were synthesized in which each amino acid from position 35 through 45 of human PAR-2 (SEQ ID NO:851) was individually replaced with an alanine (SEQ ID NOs: 871-882). An additional set of C-terminal biotinylated peptides was also used which comprise the 14 amino acids located immediately

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C-terminal to the activating PAR-2 protease cleavage site, with Val-42 and/or Asp-43 changed to alanine (SEQ ID NOs: 884-887).

[0150] The ability of each peptide mutant to bind to PAR-2 antibodies was measured using biolayer interferometry (Octet Red; ForteBio). Each peptide (2.5 µg/ml) was captured on streptavidin coated biosensor tips (Octet SA sensor) for 10 seconds. To measure binding and dissociation between each peptide and PAR-2 antibody, the peptide-coated biosensors were contacted with 200nM solutions of PAR-2 antibodies for 5 minutes (binding) followed by transfer to buffer with no antibody for 10 min (dissociation). The binding of PAR-2 antibody to each peptide was expressed as percent native signal after dividing individual antibody binding signals by the original peptide loading signal observed for that peptide, to correct for slight variations in peptide loading on the individual biosensors. Dissociation half-lives ($T_{1/2}$) were calculated from the dissociation curves using the Scrubber version 2.0a curve-fitting software, and relative half-lives were calculated by dividing observed half-lives for an individual peptide by the half-life of the native peptide. The results are expressed as percent binding and percent $T_{1/2}$ relative to WT peptide (Tables 24-28). [Comparator 1 = an antibody having the heavy and light chain variable regions of the antibody referred to as "1A1" in WO 2009/005726; Comparator 2 = an antibody having the heavy and light chain variable regions of the antibody referred to as Sam-11 (Molino et al., Arterioscler. Thromb. Vasc. Biol. 18:825-832 (1998)); and Comparator 3 = an antibody having the heavy and light chain variable regions of the antibody referred to as "PAR-B" in US 2010/0119506]. In certain cases, the binding experiments were repeated (indicated under the column headings Exp1 and Exp2). NB = no binding observed.

Table 24: H4H581P

SEQ ID NO:	SEQUENCE	% Rel Binding		% Rel $T_{1/2}$	
		Exp1	Exp2	Exp1	Exp2
871	GTNRSSKGRSLIGKVDGT-----GGGGSK-B	100	100	100	100
872	GTNRSSK <u>A</u> RLIGKVDGT-----GGGGSK-B	78	97	118	117
873	GTNRSSK <u>G</u> SLIGKVDGT-----GGGGSK-B	87	105	122	90
874	GTNRSSKGR <u>A</u> LIGKVDGT-----GGGGSK-B	45	56	7	3
875	GTNRSSKGRS <u>A</u> IGKVDGT-----GGGGSK-B	9	19	0.4	0
876	GTNRSSKGRSL <u>A</u> GKVDGT-----GGGGSK-B	8	14	0.2	0
877	GTNRSSKGRSLI <u>A</u> KVDGT-----GGGGSK-B	101	92	33	15
878	GTNRSSKGRSLIG <u>A</u> VDGT-----GGGGSK-B	113	109	63	49
879	GTNRSSKGRSLIGK <u>A</u> DGT-----GGGGSK-B	36	46	1	1
880	GTNRSSKGRSLIGKV <u>A</u> GT-----GGGGSK-B	18	5	36	4
881	GTNRSSKGRSLIGKVD <u>A</u> T-----GGGGSK-B	67	102	117	124
882	GTNRSSKGRSLIGKVDG <u>A</u> -----GGGGSK-B	65	91	129	94
884	SLIGKVDGTSHVTG-GGGGSK-B	---	100	---	100

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(continued)

SEQ ID NO:	SEQUENCE	% Rel Binding		% Rel T _{1/2}	
		Exp1	Exp2	Exp1	Exp2
885	SLIGKADGTSHVTG-GGGGSK-B	---	19	---	0
886	SLIGKV <u>A</u> GTSHVTG-GGGGSK-B	---	NB	---	NB
887	SLIGK <u>AA</u> GTSHVTG-GGGGSK-B	---	NB	---	NB

Table 25: H4H588N

SEQ ID NO:	SEQUENCE	% Rel Binding		% Rel T _{1/2}	
		Exp1	Exp2	Exp1	Exp2
871	GTNRSSKGRSLIGKVDGT-----GGGGSK-B	100	100	100	100
872	GTNRSSK <u>A</u> RLIGKVDGT-----GGGGSK-B	122	99	100	253
873	GTNRSSK <u>G</u> SLIGKVDGT-----GGGGSK-B	208	115	100	180
874	GTNRSSKGR <u>A</u> LIGKVDGT-----GGGGSK-B	119	93	100	70
875	GTNRSSKGRS <u>A</u> IGKVDGT-----GGGGSK-B	127	105	100	42
876	GTNRSSKGRSL <u>A</u> GKVDGT-----GGGGSK-B	92	85	36	8
877	GTNRSSKGRSLI <u>A</u> KVDGT-----GGGGSK-B	30	30	1	0
878	GTNRSSKGRSLIG <u>A</u> VDGT-----GGGGSK-B	217	121	108	60
879	GTNRSSKGRSLIGK <u>A</u> DGT-----GGGGSK-B	74	52	1	0
880	GTNRSSKGRSLIGKV <u>A</u> GT-----GGGGSK-B	35	8	4	5
881	GTNRSSKGRSLIGKVD <u>A</u> T-----GGGGSK-B	81	67	1	1
882	GTNRSSKGRSLIGKVDG <u>A</u> -----GGGGSK-B	125	121	94	33
884	SLIGKVDGTSHVTG-GGGGSK-B	-	100	-	100
885	SLIGK <u>A</u> DGTSHVTG-GGGGSK-B	-	83	-	0
886	SLIGKV <u>A</u> GTSHVTG-GGGGSK-B	-	NB	-	NB
887	SLIGK <u>AA</u> GTSHVTG-GGGGSK-B	-	NB	-	NB

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Table 26: Comparator 1

SEQ ID NO:	SEQUENCE	% Rel Binding		% Rel T _{1/2}	
		Exp1	Exp2	Exp1	Exp2
871	GTNRSSKGRSLIGKVDGT-----GGGGSK-B	100	100	100	100
872	GTNRSSK <u>A</u> ARSLIGKVDGT-----GGGGSK-B	111	111	29	27
873	GTNRSSK <u>G</u> ASLIGKVDGT-----GGGGSK-B	135	87	0.2	0
874	GTNRSSKGR <u>A</u> LIGKVDGT-----GGGGSK-B	126	102	223	148
875	GTNRSSKGRS <u>A</u> IGKVDGT-----GGGGSK-B	147	105	2	1
	B				
876	GTNRSSKGRSL <u>A</u> GKVDGT-----GGGGSK-B	156	108	47	41
877	GTNRSSKGRSLI <u>A</u> KVDGT-----GGGGSK-B	139	108	31	24
878	GTNRSSKGRSLIG <u>A</u> VDGT-----GGGGSK-B	118	84	3	2
879	GTNRSSKGRSLIGK <u>A</u> DGT-----GGGGSK-B	148	104	173	100
880	GTNRSSKGRSLIGKV <u>A</u> GT-----GGGGSK-B	124	102	192	111
881	GTNRSSKGRSLIGKVD <u>A</u> T-----GGGGSK-B	119	97	130	121
882	GTNRSSKGRSLIGKVDG <u>A</u> -----GGGGSK-B	132	119	154	116
884	SLIGKVDGTSHVTG-GGGGSK-B	---	NB	---	NB
885	SLIGK <u>A</u> DGTSHVTG-GGGGSK-B	---	NB	---	NB
886	SLIGKV <u>A</u> GTSHVTG-GGGGSK-B	---	NB	---	NB
887	SLIGK <u>AA</u> GTSHVTG-GGGGSK-B	---	NB	---	NB

Table 27: Comparator 2

SEQ ID NO:	SEQUENCE	% Rel Binding		% Rel T _{1/2}	
		Exp1	Exp2	Exp1	Exp2
871	GTNRSSKGRSLIGKVDGT-----GGGGSK-B	---	NB	---	NB
872	GTNRSSK <u>A</u> ARSLIGKVDGT-----GGGGSK-B	---	NB	---	NB

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(continued)

SEQ ID NO:	SEQUENCE	% Rel Binding		% Rel T _{1/2}	
		Exp1	Exp2	Exp1	Exp2
873	GTNRSSKGR <u>A</u> SLIGKVDGT-----GGGGSK-B	---	NB	---	NB
874	GTNRSSKGR <u>A</u> LIGKVDGT-----GGGGSK-B	---	NB	---	NB
875	GTNRSSKGRS <u>A</u> IGKVDGT-----GGGGSK-B	---	NB	---	NB
876	GTNRSSKGRSL <u>A</u> GKVDGT-----GGGGSK-B	---	NB	---	NB
877	GTNRSSKGRSLI <u>A</u> KVDGT-----GGGGSK-B	---	NB	---	NB
878	GTNRSSKGRSLIG <u>A</u> VDGT-----GGGGSK-B	---	NB	---	NB
879	GTNRSSKGRSLIGK <u>A</u> DGT-----GGGGSK-B	---	NB	---	NB
880	GTNRSSKGRSLIGKV <u>A</u> GT-----GGGGSK-B	---	NB	---	NB
881	GTNRSSKGRSLIGKVD <u>A</u> T-----GGGGSK-B	---	NB	---	NB
882	GTNRSSKGRSLIGKVDG <u>A</u> -----GGGGSK-B	---	NB	---	NB
884	SLIGKVDGTSHVTG-GGGGSK-B	---	100	---	100
885	SLIGK <u>A</u> DGTSHVTG-GGGGSK-B	---	120	---	159
886	SLIGKV <u>A</u> GTSHVTG-GGGGSK-B	---	88	---	27
887	SLIGK <u>A</u> <u>A</u> GTSHVTG-GGGGSK-B	---	87	---	27

Table 28: Comparator 3

SEQ ID NO:	SEQUENCE	% Rel Binding		% Rel T _{1/2}	
		Exp1	Exp2	Exp1	Exp2
871	GTNRSSKGRSLIGKVDGT-----GGGGSK-B	---	100	---	100
872	GTNRSSK <u>A</u> RS�IGKVDGT-----GGGGSK-B	---	101	---	109
873	GTNRSSKGR <u>A</u> SLIGKVDGT-----GGGGSK-B	---	98	---	7
874	GTNRSSKGR <u>A</u> LIGKVDGT-----GGGGSK-B	---	106	---	21
875	GTNRSSKGRS <u>A</u> IGKVDGT-----GGGGSK-B	---	115	---	79

(continued)

SEQ ID NO:	SEQUENCE	% Rel Binding		% Rel T _{1/2}	
		Exp1	Exp2	Exp1	Exp2
876	GTNRSSKGRSL <u>A</u> GKVDGT-----GGGGSK-B	---	92	---	7
877	GTNRSSKGRSLI <u>A</u> KVDGT-----GGGGSK-B	---	101	---	8
878	GTNRSSKGRSLIG <u>A</u> VDGT-----GGGGSK-B	---	109	---	95
879	GTNRSSKGRSLIGK <u>A</u> DGT-----GGGGSK-B	---	96	---	98
880	GTNRSSKGRSLIGKV <u>A</u> GT-----GGGGSK-B	---	99	---	120
881	GTNRSSKGRSLIGKVD <u>A</u> T-----GGGGSK-B	---	93	---	128
882	GTNRSSKGRSLIGKVDG <u>A</u> -----GGGGSK-B	---	117	---	118
884	SLIGKVDGTSHVTG-GGGGSK-B	---	NB	---	NB
885	SLIGK <u>A</u> DGTSHVTG-GGGGSK-B	---	NB	---	NB
886	SLIGKV <u>A</u> GTSHVTG-GGGGSK-B	---	NB	---	NB
887	SLIGK <u>AA</u> GTSHVTG-GGGGSK-B	---	NB	---	NB

[0151] The results from the alanine scanning experiments are summarized in Fig. 5, where the black circles indicate amino acids of PAR-2 which, when changed to alanine, substantially reduce binding by the corresponding antibody (*i.e.*, the T_{1/2} of antibody binding to the mutated peptide is less than 30% of the T_{1/2} of antibody binding to the wild-type peptide). (Open triangles in Fig. 5 indicate non-activating upstream protease cleavage sites, and the black triangle indicates the activating protease cleavage site). As illustrated in Fig. 5, Comparators 1 and 3 were sensitive to mutations at residues on both sides of the activating protease cleavage site. By contrast, antibodies H4H581 P and H4H588N are only sensitive to mutations at residues which are found C-terminal to the activating protease cleavage site. Thus, the H4H581 P binding site on PAR-2 appears to be shifted by about 2-4 amino acids in the C-terminal direction relative to binding site of the Comparator 1 and 3 antibodies, and the H4H588N binding site is shifted by about 2-4 amino acids in the C-terminal direction from the H4H581 P binding site. The Comparator 2 antibody only bound to the peptides comprising the 14 amino acids downstream from the activating PAR-2 protease cleavage site, *i.e.*, SLIGKVDGTSHVTG (residues 1-14 of SEQ ID NO:884), and was sensitive to mutations at the aspartic acid residue (Asp-43 of SEQ ID NO:851), but not to mutations at the valine residue (Val-42 of SEQ ID NO:851).

[0152] Significantly, this experiment indicates that antibodies H4H581 P and H4H588N both interact with the first V and D residues located C-terminal to the activating PAR-2 protease cleavage site (*i.e.*, Val-42 and Asp-43 of SEQ ID NO:851), whereas the Comparator 1 and 3 antibodies do not interact with either of these residues, and the Comparator 2 antibody interacts with Asp-43 but not Val-42. The shifted binding of H4H581 P on PAR-2 as compared to the comparator antibodies may explain the functional superiority of H4H581 P over the comparator as demonstrated in the following *in vivo* examples.

Example 10. Dose Response of Anti-PAR-2 Antibody in Pruritus Models

[0153] In this Example, the ability of the anti-PAR-2 antibody H4H581 P to attenuate itch in two different protease-induced pruritus models was assessed. Transgenic mice expressing human PAR-2 (hPAR2^{+/+}) were used for all cohorts in these experiments. Separate cohorts of mice received 150 mg/kg (s.c.) of an isotype control mAb or 10, 25, 50, 75, 100, and 150 mg/kg (s.c.) of H4H581 P. Twenty-four hours after antibody dosing all cohorts received 150 µg of porcine trypsin, or 10 µg recombinant human beta tryptase, (s.c., interscapular), which produced bouts of scratching behavior

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for 30 to 60 minutes. A dose-response relationship was observed in mice receiving H4H581 P prior to trypsin injection, with an estimated ED₅₀ of 25 mg/kg. The results of these experiments, expressed in terms of the percent change in the total number of scratching bouts recorded over a 30 minute period following trypsin administration, or over a 60 minute period following tryptase administration, are shown in Table 29 (all data are represented as mean $\pm$ SEM; ND = not determined; * = p<0.05 compared to the isotype control group).

Table 29

Dose of mAb H4H581P (mg/kg)	Percent Change in Scratching Bouts Relative to Control	
	Trypsin	Tryptase
10	9.9 $\pm$ 23.1	-40.7 $\pm$ 23.4
25	-26.6 $\pm$ 11.3	-38.5 $\pm$ 11.1
50	-31.3 $\pm$ 13.5	-47.7 $\pm$ 8.0*
75	-34.9 $\pm$ 4.7*	ND
100	-55.2 $\pm$ 8.0*	-39.6 $\pm$ 6.9*
150	-42.9 $\pm$ 9.7*	ND

[0154] As shown in this Example, mAb H4H581 P was able to block protease-induced pruritus behaviors in a dose dependent manner using two different protease-induced itch models.

Example 11. Reduction of Pruritus Behaviors by Administration of an Anti-PAR-2 Antibody in a Hapten-Induced Chronic Dermatitis Model

[0155] To further assess the ability of the anti-PAR-2 antibody H4H581P to reduce pruritus behaviors in a physiologically relevant disease state, a mouse model of chronic dermatitis was used. In this model, mice received repeated cutaneous applications of the haptenizing agent, oxazolone. This chronic oxazolone-induced dermatitis model has been shown to recapitulate many of the clinical, histological, and immunological hallmarks of atopic dermatitis in humans (Man et al., 2008, J. Invest. Dermatol. 128(1):79-86).

[0156] Mice were sensitized with a single cutaneous application of 1% oxazolone on the left ear or vehicle (100 mg/kg, s.c.). The mice then received nine total cutaneous applications (challenges) of 0.6% oxazolone between the scapulae beginning seven days after the sensitization application. Weekly dosing (3 total) of the H4H581 P anti-PAR2 antibody was initiated 24 hours prior to the first oxazolone challenge (100 mg/kg, s.c.). This dosing paradigm significantly reduced pruritus behaviors as measured by reduced numbers of scratching bouts elicited by the final oxazolone challenge. All data are represented as mean number of scratching bouts $\pm$ SEM for n=6 mice/group; * = p<0.05 by Tukey post-hoc test as compared to the Oxazolone + IgG control group; # = p<0.05 by Tukey post-hoc test compared to the Vehicle + IgG control group).

Table 30

Treatment	Time (minutes)						Total
	0-10	10-20	20-30	30-40	40-50	50-60	
Vehicle + IgG control	0.0 $\pm$ 0.0	0.8 $\pm$ 0.6	2.2 $\pm$ 1.4	3.4 $\pm$ 1.3	4.8 $\pm$ 2.0	2.4 $\pm$ 1.0	13.6 $\pm$ 4.2
Oxazolone + IgG control	0.5 $\pm$ 0.5	11.3 $\pm$ 3.9	24.8 $\pm$ 9.7	28.0 $\pm$ 7.3	21.0 $\pm$ 7.9	21.3 $\pm$ 7.3	#106.8 $\pm$ 33.2
Oxazolone + H4H581 P	0.2 $\pm$ 0.2	1.6 $\pm$ 1.2	*6.0 $\pm$ 2.4	16.6 $\pm$ 5.1	18.2 $\pm$ 4.8	18.0 $\pm$ 5.5	60.6 $\pm$ 11.6

[0157] Histological analysis showed a significant increase in epidermal hyperplasia and immune cell infiltrate in the oxazolone-challenged animals. (Data not shown). No significant differences were observed in any of these parameters between the H4H581 P anti-PAR2 antibody and the isotype control.

Example 12. Comparison of Pruritus Inhibiting Activities of mAb H4H581P

[0158] In this Example, the ability of mAb H4H581P to attenuate itching bouts in a mouse pruritus model was compared

to that of a comparator anti-PAR-2 mAb (Comparator "1A1" described in WO 2009/005726.

[0159] Transgenic mice expressing human PAR-2 (hPAR2^{+/+}) were divided into 3 cohorts. Cohort A received 50 mg/kg (s.c.) of an isotype control mAb, cohort B received 50 mg/kg (s.c.) of H4H581 P, and Cohort C received 50 mg/kg (s.c.) of the comparator anti-PAR-2 antibody. Twenty-four hours after antibody dosing all cohorts received 150 μ g of trypsin (s.c., interscapular), which produced bouts of scratching behavior for 30 minutes. The percent change in the number of scratching bouts observed for the treated mice as compared to control-treated mice is shown in Table 29 (all data are represented as mean $\pm$ SEM).

Table 31

Antibody Treatment (50 mg/kg)	(% change in scratching bouts from control)
mAb H4H581 P	- 41.1 $\pm$ 13.5
Comparator mAb	- 13.9 $\pm$ 9.9

[0160] As shown in this Example, mAb H4H581P was substantially more effective than the comparator mAb in reducing pruritus behaviors in the trypsin-induced itch model used herein.

[0161] The present invention is not to be limited in scope by the specific embodiments describe herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures.

SEQUENCE LISTING

[0162]

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<120> High Affinity Human Antibodies to Human Protease Activated Receptor-2

<130> 6110A-WO

<140> To be assigned

<141> Filed herewith

<150> 61/240,783

<151> 2009-09-09

<150> 61/242,821

<151> 2009-09-16

<150> 61/317,839

<151> 2010-03-26

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 30 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
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 45 Ala Lys Glu Asn Trp Ala Phe Asp Tyr
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 cttcagcaga ggccaggcca gcctccaaga ctctaatatt ataagatttc taaccgggttc 180
 tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
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 20 25 30
 Asp Gly Asn Thr Tyr Leu Ser Trp Leu Gln Gln Arg Pro Gly Gln Pro
 35 40 45
 25 Pro Arg Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60
 Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80
 Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Phe Cys Met Gln Ala
 85 90 95
 30 Thr Gln Phe Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
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35 <212> DNA

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 ccaggggaagg gcctagagtg ggtctcaggt attacttgga atagtggtaa catggcctat 180
 gcggaactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
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 20 25 30
 Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 25 Ser Gly Ile Thr Trp Asn Ser Gly Asn Met Ala 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
 30 Ala Lys Glu Asn Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110
 Thr Val Ser Ser
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 cttcagcaga ggccaggcca gcctccaaga ctctaatatt ataagatttc taaccgggtc 180
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 50 tacacttttg gccaggggac caagctggag atcaaa 336

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

<210> 21

<211> 348

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

25

<400> 21

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30	ccaggggaagg	gcctggagtg	ggtctcaggt	attacttgga	atagtggtaa	catgggctat	180
	gcggaactctg	tgaagggccg	attcaccatc	tccagagaca	acgccaagaa	ctccctgtat	240
	ctgcaaataga	acagtctgag	agctgaggac	acggccttgt	attactgtgc	aaaagaaaac	300
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<213> Artificial Sequence

40 <220>

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<400> 22

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	1				5					10					15	

50

55

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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 Thr Trp Asn Ser Gly Asn Met 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
 Ala Lys Glu Asn Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110
 Thr Val Ser Ser
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 cttcagcaga ggccaggcca gcctccaaga ctccctaattt ataagatttc taaccgggtc 180
 tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
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 tacacttttg gccaggggac caagctggag atcaaac 337

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<400> 24

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

<210> 25

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      ccagggaagg acctgaagtg ggtctcaggt attacttggg atggtggttag aaaagcctat 180
      gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctcttt 240
      ctgcaaatac acagtctgag agctgaggac acggccttct attactgtgc aaaagaagat 300
15      gaggcctttg actactgggg ccagggaacc ctggtcaccg tctcctca 348

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25 <400> 26

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

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55 <210> 28
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<212> DNA

<213> Artificial Sequence

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5 <223> Synthetic

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15 cttcagcaga ggccaggcca gctccaaga ctctaattt ataagatttc taaccggttt 180
tttgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
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25 <223> Synthetic

<400> 34

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

<210> 35

45 <211> 33

<212> DNA

<213> Artificial Sequence

<220>

50 <223> Synthetic

<400> 35

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55 <210> 36

<211> 11

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 1 5 10

 <210> 37
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 25 <220>
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 <400> 38
 Lys Ile Ser
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 40 <400> 39
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<213> Artificial Sequence

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ccaggaagg acctgaagtg ggtctcaggt attacttgga atgggtggtag aaaagcctat 180
gcggaactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctcttt 240
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20
Thr Met His Trp Val Arg Gln Val Pro Gly Lys Asp Leu Lys Trp Val
35
Ser Gly Ile Thr Trp Asn Gly Gly Arg Lys Ala Tyr Ala 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 Phe Tyr Tyr Cys
85      90      95
Ala Lys Glu Asp Glu Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100      105      110
Thr Val Ser Ser
115

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<210> 43

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<212> DNA

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<220>

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<400> 43

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cttcagcaga ggccaggcca gcctccaaga ctccataattt ataagatttc taaccgggtt 180
tttgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
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<400> 44

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20

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30

35

45

50

55

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1				5					10					15	
Gln	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Gln	Ser	Leu	Val	His	Ser
			20					25					30		
Asp	Gly	Asn	Thr	Tyr	Leu	Ser	Trp	Leu	Gln	Gln	Arg	Pro	Gly	Gln	Pro
		35					40					45			
Pro	Arg	Leu	Leu	Ile	Tyr	Lys	Ile	Ser	Asn	Arg	Phe	Phe	Gly	Val	Pro
	50					55					60				
Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ala	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	
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ccaggggaagg	gcctggagtg	ggtctcaggt	attacttggg	atggtggtag	aaaaggctat	180
gcggactctg	tgaagggccg	attcaccatc	tccagagaca	acgccaagaa	ctccctgtat	240
ctgcaaataa	acagtctgag	agctgaggac	acggccttgt	attactgtgc	aaaagaagat	300
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	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asp	Asp	Tyr
				20					25					30		
5	Thr	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
			35					40					45			
	Ser	Gly	Ile	Thr	Trp	Asn	Gly	Gly	Arg	Lys	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
10	65					70					75					80
	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Leu	Tyr	Tyr	Cys
				85						90					95	
	Ala	Lys	Glu	Asp	Glu	Ala	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val
				100					105					110		
15	Thr	Val	Ser	Ser												
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30	cttcagcaga	ggccaggcca	gcctccaaga	ctcctaattt	ataagatttc	taaccgggttc	180
	tctgggggtcc	cagacagatt	cagtggcagt	ggggcaggga	cagatttcac	actgaaaatc	240
	agcaggggtgg	aagctgagga	tgtcgggggt	tattactgca	tgcaagcaac	acaatttccg	300
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<400> 48

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

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 ccggggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag cagaggctat 180
 gcggactctg tgaagggccg cttcaccatc tccagagaca acgccaagaa ctccctgtat 240
 15 ctgcaaatac acagtctgag agctgaggac acggccttgt attactgtgt aaaagagaac 300
 tgggcctttg aatactgggg ccagggaacc ctggtcaccg tctcctca 348

<210> 50
 <211> 116
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 <213> Artificial Sequence

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 25
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 1 5 10 15
 Ser Leu Arg Val Ser Cys Ser Ala Ser Gly Phe Asn 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 Ser Trp Asn Ser Gly Ser Arg Gly Tyr Ala Asp Ser Val
 50 55 60
 35 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65 70 75 80
 40
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
 85 90 95
 Val Lys Glu Asn Trp Ala Phe Glu Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110
 Thr Val Ser Ser
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 <400> 52

 10 Gly Phe Asn Phe Asp Asp Tyr Ala
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 20 <400> 53
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 <210> 54
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 25 <212> PRT
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 35 Ile Ser Trp Asn Ser Gly Ser Arg
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 45 <400> 55
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 <210> 56
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 cttcagcaga ggccaggcca gcctccaaga ctctaattt ataaaatttc taaccgattc 180
 tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
 15 agcaggggtgg aagctgagga tgcggggctt tattactgca tgcaggctac acaatttccg 300
 tacacttttg gccaggggac caagctggag atcaaa 336

<210> 58
 <211> 112
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 25
 <400> 58
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 1 5 10 15
 Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser His Ser Leu Val His Ser
 20 25 30
 Asp Gly Ser Thr Tyr Leu Ser Trp Leu Gln Gln Arg Pro Gly Gln Pro
 35 40 45
 Pro Arg Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro
 50 55 60
 35 Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80
 Ser Arg Val Glu Ala Glu Asp Val Gly Leu Tyr Tyr Cys Met Gln Ala
 85 90 95
 40 Thr Gln Phe Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105 110

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 1 5 10

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 25 <220>
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 30 Lys Ile Ser
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 40
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 55 Met Gln Ala Thr Gln Phe Pro Tyr Thr
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 <210> 65
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<212> DNA

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<220>

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<400> 65

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      ccggggaagg gcctggagtg ggtctcaggt attagtTgga atagtggtag cagaggctat 180
      gcggactctg tgaagggccg cttcaccatc tccagagaca acgccaagaa ctccctgtat 240
      ctgcaaataa acagtctgag agctgaggac acggccttgt attactgtgt aaaagagaac 300
15      tgggcctttg aatactgggg ccaggggaacc ctggtcaccg tctcctca          348

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<210> 66

<211> 116

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 66

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      1          5          10          15
      Ser Leu Arg Val Ser Cys Ser Ala Ser Gly Phe Asn 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 Ser Trp Asn Ser Gly Ser Arg Gly Tyr Ala Asp Ser Val
      50          55          60
35      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
40      Val Lys Glu Asn Trp Ala Phe Glu Tyr Trp Gly Gln Gly Thr Leu Val
      100          105          110
      Thr Val Ser Ser
      115

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<210> 67

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 67

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 cttcagcaga ggccaggcca gcctccaaga ctctaattt ataaaatttc taaccgattc 180
 tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
 5 agcaggggtgg aagctgagga tgtcgggctt tattactgca tgcaggctac acaatttccg 300
 tacacttttg gccaggggac caagctggag atcaaa 336

<210> 68

<211> 112

10 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 68

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

<210> 69

<211> 348

35 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 69

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 45 ccaggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag cagaggctat 180
 gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
 ctgcaaata acagtctgag agctgaggac acggccttgt attactgtgt aaaagagaac 300
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<210> 70

<211> 116

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 70

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 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Asn Phe Asp Asp Tyr
 5
 20 25 30
 Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 10 Ser Gly Ile Ser Trp Asn Ser Gly Ser Arg 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
 15 Val Lys Glu Asn Trp Ala Phe Glu Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110
 Thr Val Ser Ser
 115
 20 <210> 71
 <211> 337
 <212> DNA
 <213> Artificial Sequence
 25 <220>
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 <400> 71
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 cttcagcaga ggccaggcca gcctccaaga ctctaatatt ataaaatttc taaccggttc 180
 tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
 agcaggggtgg aagctgagga tgtcgggggt tattactgca tgcaggctac acaatttccg 300
 35 tacacttttg gccaggggac caagctggag atcaaac 337
 <210> 72
 <211> 112
 <212> PRT
 40 <213> Artificial Sequence
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 45 <400> 72
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	Asp	Ile	Val	Met	Thr	Gln	Thr	Pro	Leu	Ser	Ser	Pro	Val	Thr	Leu	Gly
	1				5					10					15	
	Gln	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	His	Ser	Leu	Val	His	Ser
				20					25					30		
5	Asp	Gly	Ser	Thr	Tyr	Leu	Ser	Trp	Leu	Gln	Gln	Arg	Pro	Gly	Gln	Pro
			35					40					45			
	Pro	Arg	Leu	Leu	Ile	Tyr	Lys	Ile	Ser	Asn	Arg	Phe	Ser	Gly	Val	Pro
		50					55					60				
	Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ala	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile
10	65					70					75					80
	Ser	Arg	Val	Glu	Ala	Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Met	Gln	Ala
				85						90					95	
	Thr	Gln	Phe	Pro	Tyr	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys
				100					105					110		

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<210> 73
 <211> 348
 <212> DNA
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<220>
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<400> 73

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ccagggaagg	gcctggagtg	ggtctcaggt	attagttgga	atagtggtag	cagaggctat	180
gcggactctg	tgaagggccg	attcaccatc	tccagagaca	acgccaaaaa	ctccctgcat	240
ctgcaaattgt	acagtctgag	agctgaggac	acggccttgt	attactgtgc	aaaagagaac	300
tggtcctttg	actactgggg	ccagggaacc	ctggtcaccg	tctcctca		348

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<210> 74
 <211> 116
 <212> PRT
 <213> Artificial Sequence

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<220>
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<400> 74

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

<210> 75
 <211> 24
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 75
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<210> 76
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 76

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40				1				5			

<210> 77
 <211> 24
 <212> DNA
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<220>
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<400> 77
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<210> 78
 <211> 8
 <212> PRT
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<223> Synthetic

<400> 78

5 Ile Ser Trp Asn Ser Gly Ser Arg
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<210> 79

<211> 27

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 79

gcaaaagaga actggtcctt tgactac 27

<210> 80

20 <211> 9

<212> PRT

<213> Artificial Sequence

<220>

25 <223> Synthetic

<400> 80

30 Ala Lys Glu Asn Trp Ser Phe Asp Tyr
1 5

<210> 81

<211> 336

<212> DNA

35 <213> Artificial Sequence

<220>

<223> Synthetic

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<400> 81

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cttcagcaga ggccaggcca gcctccaaga ctctaattt ataagatttc ttaccgggtc 180

45

tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
agcagggtgg caactgagga tgtcgggggtt tattactgca tgcaagctac acaattgccg 300
tacacttttg gccaggggac caagctggag atcaaa 336

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<210> 82

<211> 112

<212> PRT

55 <213> Artificial Sequence

<220>

<223> Synthetic

EP 2 475 684 B1

<400> 82

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

<210> 83

<211> 33

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<400> 83

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<212> PRT

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35 <223> Synthetic

<400> 84

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50 <400> 85

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<210> 86

<211> 3

55 <212> PRT

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<223> Synthetic

<400> 86

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<210> 87

<211> 27

10 <212> DNA

<213> Artificial Sequence

<220>

15 <223> Synthetic

<400> 87

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<210> 88

20 <211> 9

<212> PRT

<213> Artificial Sequence

<220>

25 <223> Synthetic

<400> 88

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<210> 89

<211> 348

<212> DNA

35 <213> Artificial Sequence

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40 <400> 89

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ccaggggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag cagaggctat 180
gcggaactctg tgaagggccg attcaccatc tccagagaca acgcaaaaaa ctccctgcat 240
ctgcaaattgt acagtctgag agctgaggac acggccttgt attactgtgc aaaagagaac 300
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50 <210> 90

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<212> PRT

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55 <220>

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<400> 90

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	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Asp	Asp	Tyr
				20					25					30		
5	Ala	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
			35					40					45			
	Ser	Gly	Ile	Ser	Trp	Asn	Ser	Gly	Ser	Arg	Gly	Tyr	Ala	Asp	Ser	Val
		50				55					60					
	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Ser	Leu	His
10	65					70					75					80
	Leu	Gln	Met	Tyr	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Leu	Tyr	Tyr	Cys
					85					90					95	
	Ala	Lys	Glu	Asn	Trp	Ser	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val
				100					105					110		
15	Thr	Val	Ser	Ser												
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<210> 91

<211> 336

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 91

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30	cttcagcaga	ggccaggcca	gcctccaaga	ctcctaattt	ataagatttc	ttaccgggttc	180
	tctgggggtcc	cagacagatt	cagtggcagt	ggggcaggga	cagatttcac	actgaaaatc	240
	agcaggggtg	caactgagga	tgtcgggggt	tattactgca	tgcaagctac	acaattgccg	300
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<211> 112

<212> PRT

<213> Artificial Sequence

40 <220>

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<400> 92

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

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 <211> 348
 <212> DNA
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ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag cagaggctat 180
gcggaactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
15 ctgcaaataga acagtctgag agctgaggac acggccttgt attactgtgc aaaagagaac 300
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<210> 94
 <211> 116
 <212> PRT
 <213> Artificial Sequence

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25
 <400> 94

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    20      25      30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
    35      40      45
35 Ser Gly Ile Ser Trp Asn Ser Gly Ser Arg 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
40 Ala Lys Glu Asn Trp Ser Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
    100      105      110
Thr Val Ser Ser
    115
  
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 <210> 95
 <211> 337
 <212> DNA
 <213> Artificial Sequence

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 <220>
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55
 <400> 95

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 cttcagcaga ggccaggcca gcctccaaga ctctaattt ataagatttc taaccgggtc 180
 tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
 5 agcaggggtg aagctgagga tgtcgggggt tattactgca tgcaagctac acaattgccg 300
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<400> 96

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

<210> 97

<211> 357

35 <212> DNA

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<220>

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40

<400> 97

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 tcctgtgcag cctctggatt caccttttagc agctatgcca tgacctgggt ccgccaggct 120
 45 ccggggaagg ggctgtattg ggtctcagct attagtgggtg gtcgtggtag cgcatactac 180
 gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
 ctgcaaataa acagcctgcg agccgaggac acggccgtat attactgtgc gaaagagggg 300
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<210> 98

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<400> 98

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	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			
5	Ala	Met	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Tyr	Trp	Val
		35					40					45				
	Ser	Ala	Ile	Ser	Gly	Gly	Arg	Gly	Ser	Ala	Tyr	Tyr	Ala	Asp	Ser	Val
	50					55					60					
10	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		
15	Ala	Lys	Glu	Gly	Asp	Ser	Gly	Tyr	Asp	Leu	Ala	Tyr	Trp	Gly	Arg	Gly
			100						105					110		
	Thr	Leu	Val	Thr	Val	Ser	Ser									
			115													

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30 <210> 100
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35 <220>
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50 <220>
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<400> 101
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55 <210> 102
 <211> 8
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Ile Ser Gly Gly Arg Gly Ser Ala
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<210> 105

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45 gggaaagccc ctaagtcct gatctatgct gcatccagtt tgcaaagtgg gatcccatca 180
aagttcagcg gcagtggatc tgggacatat ttactctca ccacagcag cctgcagcct 240
gaagattttg cgacttatta ctgccaacaa tataaaagtt ccccgctcac ttcggcgga 300
gggaccaagg tggagatcaa a 321

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<210> 106

<211> 107

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 106

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

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<210> 108
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 30 <213> Artificial Sequence

<220>
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35 <400> 108

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					1				5	

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<400> 109
 50 gctgcatcc 9

<210> 110
 <211> 3
 <212> PRT
 55 <213> Artificial Sequence

<220>
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<400> 110

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1

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<210> 111
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<212> DNA
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<400> 111
caacaatata aaagttcccc gctcact 27

20

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<211> 9
<212> PRT
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<400> 112

Gln Gln Tyr Lys Ser Ser Pro Leu Thr
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30

<210> 113
<211> 357
<212> DNA
<213> Artificial Sequence

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<220>
<223> Synthetic

<400> 113

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ccggggaagg	ggctgtattg	ggtctcagct	attagtgggtg	gtcgtggtag	cgcatactac	180
gcagactccg	tgaagggccg	gttcaccatc	tccagagaca	attccaagaa	cacgctgtat	240
ctgcaaata	acagcctgcg	agccgaggac	acggccgtat	attactgtgc	gaaagagggg	300
gatagtggct	acgatttggc	ctactggggc	cggggaaccc	tggtcaccgt	ctcctca	357

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<210> 114
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<212> PRT
<213> Artificial Sequence

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<220>
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55

<400> 114

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

<210> 115

<211> 321

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

25

<400> 115

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	atcacttgtc	gggcgaggca	gggcattagt	aataatttag	cctggccttc	gcagaaacca	120
30	gggaaagccc	ctaagtcct	gatctatgct	gcatccagtt	tgcaaagtgg	gatcccatca	180
	aagttcagcg	gcagtggatc	tgggacatat	ttcactctca	ccatcagcag	cctgcagcct	240
	gaagattttg	cgacttatta	ctgccaacaa	tataaaagtt	ccccgctcac	tttcggcgga	300
	gggaccaagg	tggagatcaa	a				321

35 <210> 116

<211> 107

<212> PRT

<213> Artificial Sequence

40 <220>

<223> Synthetic

<400> 116

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

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<210> 117
 <211> 357
 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> Synthetic

10

<400> 117

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tcctgtgcag cctctggatt caccttttagc agctatgccca tgagctgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcagct attagtgggtg gtcgtggtag cgcatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatac acagcctgag agccgaggac acggccgtat attactgtgc gaaagagggg 300
gatagtggct acgatttggc ctactggggc cagggaaccc tggtcaccgt ctcctca 357
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20

<210> 118
 <211> 119
 <212> PRT
 <213> Artificial Sequence

25

<220>
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<400> 118

30

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  1           5           10           15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
      20           25           30
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35

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Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
      35           40           45
Ser Ala Ile Ser Gly Gly Arg Gly Ser Ala 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 Glu Gly Asp Ser Gly Tyr Asp Leu Ala Tyr Trp Gly Gln Gly
      100          105          110
Thr Leu Val Thr Val Ser Ser
      115
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<210> 119
 <211> 322
 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> Synthetic

<400> 119

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 atcacttgtc gggcgagtca gggcattagt aataatttag cctgggtttca gcagaaacca 120
 gggaaagccc ctaagtcctt gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
 5 aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
 gaagattttg caacttatta ctgccaacaa tataaaagtt ccccgctcac tttcggcgga 300
 gggaccaagg tggagatcaa ac 322

<210> 120

<211> 107

10 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

15

<400> 120

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

<210> 121

<211> 357

35 <212> DNA

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<220>

<223> Synthetic

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<400> 121

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 45 ccaggaaggg ggctgttttg ggtctcaggt attggtggta gtggtgggtcg cgcatactac 180
 gcagactccg tgaagggccg gttcacccctc tccagagaca attccaagaa cacgctgtat 240
 ctgcaaatac acagcctgag agccgaggac acggccgtat attactgtgc gaaagagggg 300
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<212> PRT

<213> Artificial Sequence

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

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<220>
 <223> Synthetic

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<210> 124
 <211> 8
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<220>
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<400> 124

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<400> 126

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<210> 127

<211> 36

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 127

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<210> 128

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25 <223> Synthetic

<400> 128

30 Ala Lys Glu Gly Asp Ser Gly Tyr Asp Leu Asp Tyr
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<210> 129

<211> 321

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atcacttgct gggcgaggca gggcataagt aattatcttag cctggcttca gcagaaacca 120
45 gggaaagccc ctaagtcctt gatctatgct gcatccagtt tgcaaagggg ggtcccatca 180
aagttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattctg caacttatta ctgccaacaa tataaaattt ccccgctcac tttcggcgga 300
50 gggaccaagg tggagatcaa g 321

<210> 130

<211> 107

<212> PRT

55 <213> Artificial Sequence

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EP 2 475 684 B1

<400> 130

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

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<211> 18

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<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 131

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30 <211> 6

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<213> Artificial Sequence

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35 <223> Synthetic

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<211> 9

<212> DNA

45 <213> Artificial Sequence

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50 <400> 133

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<210> 134

<211> 3

55 <212> PRT

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<223> Synthetic
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 Ala Ala Ser
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 <211> 27
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 caacaatata aaatttcccc gctcact 27
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 25 <223> Synthetic
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 Gln Gln Tyr Lys Ile Ser Pro Leu Thr
 30 1 5
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 45 ccaggggaagg ggctgttttg ggtctcaggc attgggtggta gtggtgggtcg cgcatactac 180
 gcagactccg tgaaggggccg gttcaccctc tccagagaca attccaagaa cacgctgtat 240
 ctgcaaataga acagcctgag agccgaggac acggccgtat attactgtgc gaaagagggg 300
 gatagtggct acgattttgga ctactggggc cggggaaccc tggtcaccgt ctctctca 357
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 50 <211> 119
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 55 <223> Synthetic
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	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Thr	Ser	Gly	Phe	Thr	Phe	Ser	Arg	Tyr
			20					25					30			
5	Thr	Met	Thr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Phe	Trp	Val
			35				40					45				
	Ser	Gly	Ile	Gly	Gly	Ser	Gly	Gly	Arg	Ala	Tyr	Tyr	Ala	Asp	Ser	Val
		50				55			60							
	Lys	Gly	Arg	Phe	Thr	Leu	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
10	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	Glu	Gly	Asp	Ser	Gly	Tyr	Asp	Leu	Asp	Tyr	Trp	Gly	Arg	Gly
			100					105					110			
15	Thr	Leu	Val	Thr	Val	Ser	Ser									
			115													

<210> 139

<211> 321

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

25

<400> 139

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30	atcacttgtc	gggcgaggca	gggcataagt	aattatcttag	cctggcttca	gcagaaacca	120
	gggaaagccc	ctaagtccct	gatctatgct	gcacccagtt	tgcaaagggg	gggtcccatca	180
	aagttcagcg	gcagtggatc	tgggacagat	ttcactctca	ccatcagcag	cctgcagcct	240
	gaagattctg	caacttatta	ctgccaacaa	tataaaattt	ccccgctcac	tttcggcgga	300
	gggaccaagg	tgagatcaa	a				321

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<210> 140

<211> 107

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 140

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

<210> 141

<211> 357

<212> DNA

20 <213> Artificial Sequence

<220>

<223> Synthetic

25 <400> 141

	gaggtgcagc	tgttggagtc	tgggggagggc	ttggtacagc	ctgggggggctc	cctgagactc	60
	tcctgtgcag	cctctggatt	cacctttagc	agatatacca	tgagctgggt	ccgccaggct	120
	ccaggggaagg	ggctggagtg	ggtctcagct	attggtggta	gtggtgggtcg	cgcatactac	180
30	gcagactccg	tgaagggccg	gttcaccatc	tcagagaca	attccaagaa	cacgctgtat	240
	ctgcaaata	acagcctgag	agccgaggac	acggccgtat	attactgtgc	gaaagagggg	300
	gatagtggct	acgatttga	ctactggggc	caggggaacc	tggtcacccg	ctcctca	357

<210> 142

35 <211> 119

<212> PRT

<213> Artificial Sequence

<220>

40 <223> Synthetic

<400> 142

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55

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	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	Arg	Tyr
			20					25					30			
5	Thr	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
			35				40					45				
	Ser	Ala	Ile	Gly	Gly	Ser	Gly	Gly	Arg	Ala	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
10	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	Glu	Gly	Asp	Ser	Gly	Tyr	Asp	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
			100					105					110			
15	Thr	Leu	Val	Thr	Val	Ser	Ser									
			115													

<210> 143

<211> 322

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

25

<400> 143

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30	atcacttgtc	gggcgagtc	gggcataagt	aattatttag	cctgggttca	gcagaaacca	120
	gggaaagccc	ctaagtccct	gatctatgct	gcatccagtt	tgcaaagtgg	gggtcccatca	180
	aggttcagcg	gcagtggatc	tgggacagat	ttcactctca	ccatcagcag	cctgcagcct	240
	gaagattttg	caacttatta	ctgccaacaa	tataaaattt	ccccgctcac	tttcggcgga	300
	gggaccaagg	tggagatcaa	ac				322

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<210> 144

<211> 107

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 144

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EP 2 475 684 B1

	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	Gly	Ile	Ser	Asn	Tyr
			20					25					30			
5	Leu	Ala	Trp	Phe	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Ser	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
10	65				70				75						80	
	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	Lys	Ile	Ser	Pro	Leu
				85					90					95		
	Thr	Phe	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys						
			100					105								

<210> 145

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 145

	gaggtgcagc	tggttgagtc	gggggggaggc	ttggtacagc	ctgggggggctc	cctgagactc	60
	tcctgtgcaa	cctctggatt	caccttttagc	agatatacca	tgacctgggt	ccgccaggct	120
	ccaggggaag	ggctgttttg	ggtctcaggt	attggtggta	gtggtgggtcg	cgcatactac	180
	gcagactccg	tgaagggccg	gttcaccctc	tccagagaca	attccaagaa	cacgctgtat	240
30	ctgcaaata	acagcctgag	agccgaggac	acggccgtat	attactgtgc	gaaagagggg	300
	gatagtggct	acgatttgga	ctactggggc	cggggaacct	tggtcacctg	ctcgctca	357

<210> 146

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 146

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

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	Ala Lys Glu Gly Asp Ser Gly Tyr Asp Leu Asp Tyr Trp Gly Arg Gly	
		100 105 110
	Thr Leu Val Thr Val Ser Ser	
		115
5	<210> 147 <211> 24 <212> DNA <213> Artificial Sequence	
10	<220> <223> Synthetic	
15	<400> 147 ggattcacct ttagcagata tacc 24	
20	<210> 148 <211> 8 <212> PRT <213> Artificial Sequence	
	<220> <223> Synthetic	
25	<400> 148	
	Gly Phe Thr Phe Ser Arg Tyr Thr 1 5	
30	<210> 149 <211> 24 <212> DNA <213> Artificial Sequence	
35	<220> <223> Synthetic	
40	<400> 149 attggtgga gtggtggtcg cgca 24	
45	<210> 150 <211> 8 <212> PRT <213> Artificial Sequence	
	<220> <223> Synthetic	
50	<400> 150	
	Ile Gly Gly Ser Gly Gly Arg Ala 1 5	
55	<210> 151 <211> 36 <212> DNA <213> Artificial Sequence	

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<220>
 <223> Synthetic

 <400> 151
 5 gcgaaagagg gggatagtgg ctacgatttg gactac 36

 <210> 152
 <211> 12
 <212> PRT
 10 <213> Artificial Sequence

 <220>
 <223> Synthetic

 15 <400> 152

 Ala Lys Glu Gly Asp Ser Gly Tyr Asp Leu Asp Tyr
 1 5 10

 20 <210> 153
 <211> 321
 <212> DNA
 <213> Artificial Sequence

 25 <220>
 <223> Synthetic

 <400> 153

 30 gacatccaga tgacccagta tccatcctca ctgtctgcat ctgtaggaga cagagtcacc 60
 atcacttgtc gggcgaggca gggcataagt aattatttag cctggcttca gcagaaacca 120
 gggaaagccc ctaagtccct gatctatgct gcatccagtt tgcaaagggg ggtcccatca 180
 aagttcagcg gcagtggatc tgggacagat ttactctca ccatcagcag cctgcagcct 240
 35 gaagattctg caacttatta ctgccaacaa tataaaattt ccccgctcac tttcggcgga 300
 gggaccaagg tggagatcaa g 321

 <210> 154
 <211> 107
 40 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Synthetic
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 <400> 154

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

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<210> 155
 <211> 18
 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> Synthetic

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<400> 155
 cagggcataa gtaattat 18

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<210> 156
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

35

<400> 156

Gln	Gly	Ile	Ser	Asn	Tyr
1				5	

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<210> 157
 <211> 9
 <212> DNA
 <213> Artificial Sequence

45

<220>
 <223> Synthetic

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<400> 157
 gctgcatcc 9

<210> 158
 <211> 3
 <212> PRT
 <213> Artificial Sequence

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<220>
 <223> Synthetic

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<400> 158

Ala Ala Ser
1

5

<210> 159
<211> 27
<212> DNA
<213> Artificial Sequence

10

<220>
<223> Synthetic

<400> 159

15 caacaatata aaatttcccc gctcact 27

<210> 160
<211> 9
<212> PRT
<213> Artificial Sequence

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<220>
<223> Synthetic

<400> 160

25

Gln Gln Tyr Lys Ile Ser Pro Leu Thr
1 5

<210> 161
<211> 357
<212> DNA
<213> Artificial Sequence

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<220>
<223> Synthetic

35

<400> 161

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tcctgtgcaa cctctggatt caccctttagc agatatacca tgacctgggt ccgccaggct 120
ccagggaagg ggctgttttg ggtctcaggt attggtggta gtggtgggtcg cgcatactac 180
gcagactccg tgaagggccg gttcacccctc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatac acagcctgag agccgaggac acggccgtat attactgtgc gaaagagggg 300
45 gatagtggct acgatttgga ctactggggc cggggaaccc tggtcaccgt ctccctca 357

<210> 162
<211> 119
<212> PRT
<213> Artificial Sequence

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<220>
<223> Synthetic

<400> 162

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

<210> 163

<211> 321

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

25

<400> 163

gacatccaga tgaccagtc tccatcctca ctgtctgcat ctgtaggaga cagagtcacc 60

30	atcacttgtc	gggcgaggca	gggcataagt	aattattttag	cctggcttca	gcagaaacca	120
	gggaaagccc	ctaagtcctt	gatctatgct	gcatccagtt	tgcaaagggg	ggtcccatca	180
	aagttcagcg	gcagtggatc	tgggacagat	ttcactctca	ccatcagcag	cctgcagcct	240
	gaagattctg	caacttatta	ctgccaacaa	tataaaattt	ccccgctcac	tttcggcgga	300
	gggaccaagg	tggagatcaa	a				321

35 <210> 164

<211> 107

<212> PRT

<213> Artificial Sequence

40 <220>

<223> Synthetic

<400> 164

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

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<210> 165
 <211> 357
 <212> DNA
 <213> Artificial Sequence

5

<220>
 <223> Synthetic

10

<400> 165

15

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gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttagc agatatacca tgagctgggt ccgccaggct 120
ccaggggaagg ggctggagtg ggtctcagct attggtggta gtggtggtcg cgcatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatac acagcctgag agccgaggac acggccgtat attactgtgc gaaagagggg 300
gatagtggct acgatttga ctactggggc caggggaacc tggtcacctg ctctca 357
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<210> 166
 <211> 119
 <212> PRT
 <213> Artificial Sequence

25

<220>
 <223> Synthetic

<400> 166

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

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          35          40          45
Ser Ala Ile Gly Gly Ser Gly Gly Arg Ala 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 Glu Gly Asp Ser Gly Tyr Asp Leu Asp Tyr Trp Gly Gln Gly
  100          105          110
Thr Leu Val Thr Val Ser Ser
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45

115

<210> 167
 <211> 322
 <212> DNA
 <213> Artificial Sequence

50

<220>
 <223> Synthetic

55

<400> 167

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 atcacttgtc gggcgagtca gggcataagt aattatttag cctgggtttca gcagaaacca 120
 gggaaagccc ctaagtccct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
 5 aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
 gaagattttg caacttatta ctgccaacaa tataaaattt ccccgctcac tttcggcgga 300
 gggaccaagg tggagatcaa ac 322

<210> 168

<211> 107

10 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

15

<400> 168

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

<210> 169

<211> 348

35 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

40

<400> 169

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 tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt cgggcaagct 120
 ccaggaagg gcctggaatg ggtctcaggt attagttgga atagcggtag caaaggcttt 180
 45 gcggactctg tgaagggccg gttcaccatc tccagagaca acgccaagaa ctccctctat 240
 ctgcaaataa acagtctgag agttgaagac acggccttgt attactgtgc aaaagagaac 300
 tggtcctttg actactgggg ccaggaacc ctggtcaccg tctcctca 348

<210> 170

<211> 116

50 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

55

<400> 170

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

<210> 171
 <211> 24
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 171
 ggattcacct ttgatgatta tgcc 24

<210> 172
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 172

				Gly	Phe	Thr	Phe	Asp	Asp	Tyr	Ala
				1				5			

<210> 173
 <211> 24
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 173
 attagttgga atagcggtag caaa 24

<210> 174
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>

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<223> Synthetic

<400> 174

5 Ile Ser Trp Asn Ser Gly Ser Lys
1 5

<210> 175

<211> 27

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

15

<400> 175

gcaaaagaga actggtcctt tgactac 27

<210> 176

20 <211> 9

<212> PRT

<213> Artificial Sequence

<220>

25 <223> Synthetic

<400> 176

30 Ala Lys Glu Asn Trp Ser Phe Asp Tyr
1 5

<210> 177

<211> 336

<212> DNA

35 <213> Artificial Sequence

<220>

<223> Synthetic

40

<400> 177

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atctcctgca ggtctagtca aagcctcgta cacagtgatg gaaatatcta cttgagttgg 120
cttcagcaga ggccaggcca gcctccaaga ctctaatatt ataagatttc taaccggttc 180
45 tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
agcagggttg aagctgaaga tgtcggaatt tattattgca tgcaagcttc gcattttccg 300

tacacttttg gccaggggac caagctggag atcaaa 336

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<210> 178

<211> 112

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 178

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

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<210> 179

<211> 33

<212> DNA

<213> Artificial Sequence

20

<220>

<223> Synthetic

<400> 179

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caaagcctcg tacacagtga tggaaatatc tac 33

<210> 180

<211> 11

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

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<400> 180

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	1				5					10	

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<210> 181

<211> 9

<212> DNA

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 181

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<210> 182

<211> 3

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

EP 2 475 684 B1

<400> 182

Lys Ile Ser
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5

<210> 183

<211> 27

<212> DNA

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 183

15

atgcaagctt cgcattttcc gtacact 27

<210> 184

<211> 9

<212> PRT

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<213> Artificial Sequence

<220>

<223> Synthetic

25

<400> 184

Met Gln Ala Ser His Phe Pro Tyr Thr
1 5

30

<210> 185

<211> 348

<212> DNA

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 185

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tcctgtgcag	cctctggatt	cacctttgat	gattatgcca	tgcactgggt	ccggcaagct	120
ccagggaagg	gcctggaatg	ggtctcaggt	attagttgga	atagcggtag	caaaggcttt	180
gcggactctg	tgaagggccg	gttcaccatc	tccagagaca	acgccaagaa	ctccctctat	240
ctgcaaataa	acagtctgag	agttgaagac	acggccttgt	attactgtgc	aaaagagaac	300
tggtcctttg	actactgggg	ccagggaacc	ctgggtcaccg	tctcctca		348

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<210> 186

<211> 116

<212> PRT

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<213> Artificial Sequence

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<223> Synthetic

55

<400> 186

EP 2 475 684 B1

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

<210> 187

<211> 336

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 187

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	atctcctgca	ggctctagta	aagcctcgta	cacagtgatg	gaaatatcta	cttgagttgg	120
30	cttcagcaga	ggccaggcca	gcctccaaga	ctcctaattt	ataagatttc	taaccgggttc	180
	tctgggggtcc	cagacagatt	cagtggcagt	ggggcagggga	cagatttcac	actgaaaatc	240
	agcaggggtgg	aagctgaaga	tgtcggaatt	tattattgca	tgcaagcttc	gcattttccg	300
	tacactttttg	gccaggggac	caagctggag	atcaaa			336

35 <210> 188

<211> 112

<212> PRT

<213> Artificial Sequence

40 <220>

<223> Synthetic

<400> 188

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

EP 2 475 684 B1

<210> 189
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 <212> DNA
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ccaggaagg  gcctggagtg  ggtctcaggt  attagttgga  atagcggtag  caaaggctat  180
gcggaactctg  tgaagggccg  attcaccatc  tccagagaca  acgccaagaa  ctccctgtat  240
ctgcaaata  acagtctgag  agctgaggac  acggccttgt  attactgtgc  aaaagagaac  300
tggtcctttg  actactgggg  ccaggaacc  ctggtcaccg  tctcctca  348
  
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<210> 190
 <211> 116
 <212> PRT
 <213> Artificial Sequence

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 <220>
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 <400> 190

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 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 Ser Trp Asn Ser Gly Ser Lys 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
 Ala Lys Glu Asn Trp Ser Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110
 Thr Val Ser Ser
 115

<210> 191
 <211> 337
 <212> DNA
 <213> Artificial Sequence

50
 <220>
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55
 <400> 191

EP 2 475 684 B1

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 atctcctgca ggtctagtca aagcctcgta cacagtgatg gaaatatcta cttgagttgg 120
 cttcagcaga ggccaggcca gcctccaaga ctctaattt ataagatttc taaccgggtc 180
 tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
 5 agcaggggtg aagctgagga tgtcggggtt tattactgca tgcaagcttc gcattttccg 300
 tacacttttg gccaggggac caagctggag atcaaac 337

<210> 192

<211> 112

10 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

15

<400> 192

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

<210> 193

<211> 348

35 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

40

<400> 193

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 tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120
 45 ccaggaagg gcctggagtg ggtctcaggt atcagttgga atagtggtag tagaggctat 180
 gcggactctg tgaagggccg attcaccatt tccagagaca acgcaaaaa ctccctgtat 240
 ctgcaaata acagtctgag aactgaggac acggcctttt attattgtac aaaagaagac 300
 gaggcttttg actactgggg ccaggaacc ctggtcaccg tctcctca 348

<210> 194

<211> 116

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

55

<400> 194

EP 2 475 684 B1

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

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25 <220>
 <223> Synthetic

<400> 195
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30 <210> 196
 <211> 8
 <212> PRT
 <213> Artificial Sequence

35 <220>
 <223> Synthetic

<400> 196

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					1				5			

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 <211> 24
 <212> DNA
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50 <220>
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<400> 197
 atcagttgga atagtggtag taga 24

55 <210> 198
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EP 2 475 684 B1

<220>

<223> Synthetic

<400> 198

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Ile Ser Trp Asn Ser Gly Ser Arg
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<210> 199

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<211> 27

<212> DNA

<213> Artificial Sequence

<220>

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<223> Synthetic

<400> 199

acaaaagaag acgaggcttt tgactac 27

20

<210> 200

<211> 9

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 200

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Thr Lys Glu Asp Glu Ala Phe Asp Tyr
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<210> 201

<211> 336

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<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 201

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cttcagcaga ggccaggcca gcctccaaga ctcttattt ataagatttc taaccggttc 180
tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
agcagggtgg aagctgagga tgcggggttt tattactgca tgcaggccac acaatttccg 300
tacacttttg gccaggggac caaactgcag atcaat 336

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<210> 202

<211> 112

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<213> Artificial Sequence

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<223> Synthetic

<400> 202

EP 2 475 684 B1

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

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<210> 203
 <211> 33
 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> Synthetic

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<400> 203
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<210> 204
 <211> 11
 <212> PRT
 <213> Artificial Sequence

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<220>
 <223> Synthetic

<400> 204

Gln	Ser	Leu	Val	His	Ser	Asp	Arg	Asn	Thr	Tyr
1				5					10	

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<210> 205
 <211> 9
 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> Synthetic

<400> 205
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<210> 206
 <211> 3
 <212> PRT
 <213> Artificial Sequence

55

<220>
 <223> Synthetic

EP 2 475 684 B1

<400> 206

Lys Ile Ser
1

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<210> 207
<211> 27
<212> DNA
<213> Artificial Sequence

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<220>
<223> Synthetic

15

<400> 207
atgcaggcca cacaatttc gtacact 27

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<210> 208
<211> 9
<212> PRT
<213> Artificial Sequence

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<400> 208

Met Gln Ala Thr Gln Phe Pro Tyr Thr
1 5

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<210> 209
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<212> DNA
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<220>
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<400> 209

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tcctgtgcag	cctctggatt	cacctttgat	gattatgcca	tgcactgggt	ccggcaagct	120
ccagggaagg	gcctggagtg	ggtctcaggt	atcagttgga	atagtggtag	tagaggctat	180
gcggactctg	tgaagggccg	attcaccatt	tccagagaca	acgccaaaaa	ctccctgtat	240
ctgcaaataa	acagtctgag	aactgaggac	acggcctttt	attattgtac	aaaagaagac	300
gaggcttttg	actactgggg	ccagggaacc	ctgggtcaccg	tctcctca		348

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<211> 116
<212> PRT
<213> Artificial Sequence

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<220>
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<400> 210

EP 2 475 684 B1

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

20 <210> 211

<211> 336

<212> DNA

<213> Artificial Sequence

25 <220>

<223> Synthetic

<400> 211

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atctcctgca ggtctagtca aagcctcgta cacagtgate gaaacaccta cttgagttgg 120

35 cttcagcaga ggccaggcca gcctccaaga ctcccttattt ataagatttc taaccgggttc 180
tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
agcaggggtgg aagctgagga tgcgggggtt tattactgca tgcaggccac acaatttccg 300
tacacttttg gccaggggac caagctggag atcaaa 336

40 <210> 212

<211> 112

<212> PRT

<213> Artificial Sequence

45 <220>

<223> Synthetic

<400> 212

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EP 2 475 684 B1

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

<210> 213

<211> 348

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 213

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 tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120
 ccagggaagg gcctggagtg ggtctcaggt atcagttgga atagtggtag tagaggctat 180
 gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
 ctgcaaatac acagtctgag agctgaggac acggccttgt attactgtac aaaagaagac 300
 gaggcctttt actactgggg ccagggaacc ctgggtcaccg tctcctca 348

<210> 214

<211> 116

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 214

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

EP 2 475 684 B1

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

<210> 215

<211> 337

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 215

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 atctcctgca ggtctagtca aagcctcgta cacagtgatc gaaacaccta cttgagttgg 120
 cttcagcaga ggccaggcca gcctccaaga ctccataattt ataagatttc taaccgggtc 180
 25 tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
 agcaggggtg aagctgagga tgtcgggggt tattactgca tgcaggccac acaatttccg 300
 tacacttttg gccaggggac caagctggag atcaaac 337

<210> 216

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 216

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

<210> 217

<211> 348

<212> DNA

<213> Artificial Sequence

EP 2 475 684 B1

<220>

<223> Synthetic

<400> 217

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tcctgtgcag cctctggctt cacctttgat gattatgcc a tgcactgggt ccggcaagct 120
ccggggaagg gcctagagtg ggtctcaggt attacttgga atagtgggtac catggcctat 180
gcggaactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
10 ctgcaaataga acagtctgag agctgaggac acggccttat attactgtgc aaaagaaaac 300
tgggcctttg actactgggg ccagggaacc ctggtcaccg tctcctca 348

<210> 218

<211> 116

15 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

20
<400> 218

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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 Thr Trp Asn Ser Gly Thr Met Ala Tyr Ala Asp Ser Val
30 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
35 Ala Lys Glu Asn Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110
Thr Val Ser Ser
115

40 <210> 219

<211> 24

<212> DNA

<213> Artificial Sequence

45 <220>

<223> Synthetic

<400> 219

50 ggcttcacct ttgatgatta tgcc 24

<210> 220

<211> 8

<212> PRT

<213> Artificial Sequence

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<400> 220
 Gly Phe Thr Phe Asp Asp Tyr Ala
 1 5
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 <400> 221
 15 attactgga atagtgtac catg 24
 <210> 222
 <211> 8
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 20 <213> Artificial Sequence
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 25 <400> 222
 Ile Thr Trp Asn Ser Gly Thr Met
 1 5
 30 <210> 223
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 35 <220>
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 <400> 223
 40 gcaaaagaaa actgggcctt tgactac 27
 <210> 224
 <211> 9
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 45 <220>
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 <400> 224
 50 Ala Lys Glu Asn Trp Ala Phe Asp Tyr
 1 5
 55 <210> 225
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 <212> DNA
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EP 2 475 684 B1

<220>

<223> Synthetic

<400> 225

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atctcctgca ggtctagtca cagcctcgta cacagtgatg gaaacaccta cttgagttgg 120
cttcagcaga ggccaggcca gcctccaaga ctccctaattt ataagatttc taaccgggttc 180
tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
10 agcaggggtgg aagctgagga tgtcgggggtt tatttctgca tgcaagctac acaatttccg 300
tacacttttg gccaggggac caagctggag atcaaa 336

<210> 226

<211> 112

15 <212> PRT

<213> Artificial Sequence

<220>

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20
<400> 226

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

<210> 227

<211> 33

40 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

45
<400> 227

cacagcctcg tacacagtga tggaacacc tac 33

<210> 228

50 <211> 11

<212> PRT

<213> Artificial Sequence

<220>

55 <223> Synthetic

<400> 228

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

5 <210> 229
<211> 9
<212> DNA
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10 <220>
<223> Synthetic

<400> 229
aagatttct 9

15 <210> 230
<211> 3
<212> PRT
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20 <220>
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<400> 230

25 Lys Ile Ser
1

30 <210> 231
<211> 27
<212> DNA
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35 <220>
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<400> 231
atgcaagcta cacaatttcc gtacact 27

40 <210> 232
<211> 9
<212> PRT
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45 <220>
<223> Synthetic

<400> 232

50 Met Gln Ala Thr Gln Phe Pro Tyr Thr
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55 <210> 233
<211> 348
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

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<400> 233

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5      gaagtgcagc  tgggtggagtc  tggggggaggc  ttggtacagc  ctggcagggtc  cctgagactc  60
      tcctgtgcag  cctctggctt  cacctttgat  gattatgcca  tgcactgggt  ccggcaagct  120
      ccggggaagg  gcctagagtg  ggtctcaggt  attacttgga  atagtgggtac  catggcctat  180
      gcggactctg  tgaagggcgc  attcaccatc  tccagagaca  acgccaagaa  ctccctgtat  240
      ctgcaaata  acagtctgag  agctgaggac  acggccttat  attactgtgc  aaaagaaaac  300
      tgggcctttg  actactgggg  ccaggaacc  ctggtcaccg  tctcctca  348

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10 <210> 234
 <211> 116
 <212> PRT
 <213> Artificial Sequence

15 <220>
 <223> Synthetic

<400> 234

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

```

<210> 235
 <211> 336
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 235

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      atctcctgca  ggtctagtca  cagcctcgta  cacagtgatg  gaaacaccta  cttgagttgg  120
      cttcagcaga  ggccaggcca  gcctccaaga  ctctaatatt  ataagatttc  taaccgggtc  180
      tctgggggtcc  cagacagatt  cagtggcagt  ggggcaggga  cagatttcac  actgaaaatc  240
      agcagggttg  aagctgagga  tgtcgggggt  tatttctgca  tgcaagctac  acaatttccg  300
      tacacttttg  gccaggggac  caagctggag  atcaaa  336

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55 <210> 236
 <211> 112
 <212> PRT
 <213> Artificial Sequence

EP 2 475 684 B1

<220>

<223> Synthetic

<400> 236

5

10

15

20

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

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<210> 237

<211> 348

<212> DNA

<213> Artificial Sequence

25

<220>

<223> Synthetic

<400> 237

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35

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tcctgtgcag cctctggcctt cacctttgat gattatgcca tgcactgggt ccggcaagct 120
ccaggaagg gcttgagtg ggtctcaggc attacttgga atagtggtag catgggctat 180
gcggactctg tgaagggcgc attcaccatc tccagagaca acgccaagaa ctccctgtat 240
ctgcaaataa acagtctgag agctgaggac acggccttgt attactgtgc aaaagaaaac 300
tgggcctttg actactgggg ccaggaacc ctggtcaccg tctcctca 348

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<210> 238

<211> 116

<212> PRT

<213> Artificial Sequence

40

<220>

<223> Synthetic

45

<400> 238

50

55

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

<210> 239

<211> 337

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

25

<400> 239

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	atctcctgca	ggctctagtc	cagcctcgta	cacagtgatg	gaaacaccta	cttgagttgg	120
30	cttcagcaga	ggccaggcca	gcctccaaga	ctcctaattt	ataagatttc	taaccgggttc	180
	tctgggggtcc	cagacagatt	cagtggcagt	ggggcaggga	cagatttcac	actgaaaatc	240
	agcaggggtg	aagctgagga	tgtcgggggt	tattactgca	tgcaagctac	acaatttccg	300
	tacacttttg	gccaggggac	caagctggag	atcaaac			337

35 <210> 240

<211> 112

<212> PRT

<213> Artificial Sequence

40 <220>

<223> Synthetic

<400> 240

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

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<210> 241
 <211> 384
 <212> DNA
 <213> Artificial Sequence

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<220>
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10

<400> 241

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tcctgtgcag  cctctggatt  cacctttgat  gattatgcca  tgcactgggt  ccggcaagct  120
ccaggaagg  gcctggagtg  ggtctcaggt  attagttgga  atagtggtag  cataggctat  180
gcggaactctg  tgaagggccg  attcaccatc  tccagagaca  acgccaagaa  ctccctgtat  240
ctgcaaataga  acagtctgag  agctgaggac  acggccttgt  attactgtgc  aaaagataga  300
ttccctccgt  ataagtataa  cagtgggtgt  ttttctgatg  cttttgaaat  ctggggccaa  360
gggacaatgg  tcaccgtctc  ttca                                     384
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20

<210> 242
 <211> 128
 <212> PRT
 <213> Artificial Sequence

25

<220>
 <223> Synthetic

<400> 242

30

35

40

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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 Ser 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
Ala Lys Asp Arg Phe Pro Pro Tyr Lys Tyr Asn Ser Gly Gly Phe Ser
```

45

```
100          105          110
Asp Ala Phe Glu Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
 115          120          125
```

<210> 243
 <211> 24
 <212> DNA
 <213> Artificial Sequence

50

<220>
 <223> Synthetic

55

<400> 243
 ggattcacct ttgatgatta tgcc 24

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5      <210> 244
      <211> 8
      <212> PRT
      <213> Artificial Sequence

      <220>
      <223> Synthetic

10     <400> 244

          Gly Phe Thr Phe Asp Asp Tyr Ala
           1             5

15     <210> 245
      <211> 24
      <212> DNA
      <213> Artificial Sequence

      <220>
20     <223> Synthetic

      <400> 245
      attagttgga atagtggttag cata      24

25     <210> 246
      <211> 8
      <212> PRT
      <213> Artificial Sequence

30     <220>
      <223> Synthetic

      <400> 246

35     Ile Ser Trp Asn Ser Gly Ser Ile
          1             5

40     <210> 247
      <211> 63
      <212> DNA
      <213> Artificial Sequence

      <220>
45     <223> Synthetic

      <400> 247

          gcaaaagata gattccctcc gtataagtat aacagtgggtg gtttttctga tgcttttgaa 60
          atc                                           63

50     <210> 248
      <211> 21
      <212> PRT
      <213> Artificial Sequence

55     <220>
      <223> Synthetic

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EP 2 475 684 B1

<400> 248

Ala Lys Asp Arg Phe Pro Pro Tyr Lys Tyr Asn Ser Gly Gly Phe Ser
1 5 10 15
5 Asp Ala Phe Glu Ile
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<210> 249

<211> 324

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

15

<400> 249

gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
20 ctctcctgca gggccagtca gagtttttagc agcagctact tagcctggta ccagcagaaa 120
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgtg ttactgtcag cagtatggta gttcaccgat caccttcggc 300
caagggacac gactggagat tgaa 324

25

<210> 250

<211> 108

<212> PRT

<213> Artificial Sequence

30

<220>

<223> Synthetic

<400> 250

35

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15
40 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Phe Ser Ser Ser
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
45 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
Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Glu
100 105

50

<210> 251

<211> 21

<212> DNA

<213> Artificial Sequence

55

<220>

<223> Synthetic

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<400> 251
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 <210> 252
 5 <211> 7
 <212> PRT
 <213> Artificial Sequence

 <220>
 10 <223> Synthetic

 <400> 252

 15 Gln Ser Phe Ser Ser Ser Tyr
 1 5

 <210> 253
 <211> 9
 20 <212> DNA
 <213> Artificial Sequence

 <220>
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 25
 <400> 253
 ggtgcatcc 9

 <210> 254
 30 <211> 3
 <212> PRT
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 35 <223> Synthetic

 <400> 254

 40 Gly Ala Ser
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 <210> 255
 <211> 27
 45 <212> DNA
 <213> Artificial Sequence

 <220>
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 50 <400> 255
 cagcagtatg gtagttcacc gatcacc 27

 <210> 256
 55 <211> 9
 <212> PRT
 <213> Artificial Sequence

 <220>

EP 2 475 684 B1

<223> Synthetic

<400> 256

5 Gln Gln Tyr Gly Ser Ser Pro Ile Thr
1 5

<210> 257

<211> 384

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

15

<400> 257

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tcctgtgcag cctctggatt caccctttgat gattatgcca tgcactgggt ccggcaagct 120
ccaggggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag cataggctat 180
gcggaactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
ctgcaaataa acagtctgag agctgaggac acggccttgt attactgtgc aaaagataga 300
ttccctccgt ataagtataa cagtgggtgg ttttctgatg cttttgaaat ctggggccaa 360
25 gggacaatgg tcaccgtctc ttca 384

<210> 258

<211> 128

<212> PRT

30 <213> Artificial Sequence

<220>

<223> Synthetic

35

<400> 258

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

<210> 259

55 <211> 324

<212> DNA

<213> Artificial Sequence

EP 2 475 684 B1

<220>

<223> Synthetic

<400> 259

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ctctcctgca gggccagtca gagtttttagc agcagctact tagcctggta ccagcagaaa 120
cctggccagg ctcccagget cctcatctat ggtgcatcca gcagggccac tggcatccca 180
gacaggttca gtggcagtggt gtctgggaca gacttcaactc tcaccatcag cagactggag 240
10 cctgaagatt ttgcagtgtgta ttactgtcag cagtatggta gttcaccgat caccttcggc 300
caagggacac gactggagat taaa 324

<210> 260

<211> 108

15 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

20
<400> 260

25 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 Phe Ser Ser Ser
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
30 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
35 Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> 261

<211> 384

40 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

45
<400> 261

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tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120
ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag cataggctat 180
gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
ctgcaaataa acagtctgag agctgaggac acggccttgt attactgtgc aaaagataga 300
ttccctccgt ataagtataa cagtgggtgggt ttttctgatg cttttgaaat ctggggccaa 360
55 gggacaatgg tcaccgtctc ttca 384

<210> 262

<211> 128

<212> PRT

EP 2 475 684 B1

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 262

10

15

20

25

30

35

40

45

50

55

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

<210> 263

<211> 325

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 263

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cctggccagg	ctcccaggct	cctcatctat	ggtgcatcca	gcagggccac	tggcatccca	180
gacaggttca	gtggcagtg	gtctgggaca	gacttcactc	tcaccatcag	cagactggag	240
cctgaagatt	ttgcagtgt	ttactgtcag	cagtatggta	gttcaccgat	caccttcggc	300
caagggacac	gactggagat	taaac				325

<210> 264

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

EP 2 475 684 B1

<400> 264
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 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Phe Ser Ser Ser
 5 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
 10 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
 15 Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
 100 105

<210> 265
 <211> 366
 <212> DNA
 20 <213> Artificial Sequence

<220>
 <223> Synthetic

25 <400> 265

gaggtgcagc tgggtggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60
 tcctgtgcag cctctggatt caccttcagt agctacgaca tgcactgggt ccgccaagtt 120
 30 acaggaagag gtctggaatg ggtctcagtc attggtactg ttggtgacac atactatcca 180
 ggctccctga agggccgatt caccatctcc agagaaaatg ccaagaactc cttgtatctt 240
 caaatgaaca cctgagagc cggggacacg gctgtttatt actgtgcaag aactggagca 300
 gcagccact cgtactacta cggtatggac gtctggggcc aaggggaccat ggtcaccgtc 360
 tcctca 366

35 <210> 266
 <211> 122
 <212> PRT
 <213> Artificial Sequence

40 <220>
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<400> 266

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50

55

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

<210> 267
 <211> 24
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 267
 ggattcacct tcagtagcta cgac 24

<210> 268
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 268

				Gly	Phe	Thr	Phe	Ser	Ser	Tyr	Asp
				1				5			

<210> 269
 <211> 21
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 269
 attggtactg ttggtgacac a 21

<210> 270
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>

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<223> Synthetic

<400> 270

5 Ile Gly Thr Val Gly Asp Thr
1 5

<210> 271

<211> 48

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

15

<400> 271

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20 <211> 16

<212> PRT

<213> Artificial Sequence

<220>

25 <223> Synthetic

<400> 272

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

<210> 273

<211> 336

<212> DNA

35 <213> Artificial Sequence

<220>

<223> Synthetic

40

<400> 273

45 gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
atctcctgca ggtctagtca gagcctcctg tatagtaatg gatacaacta tttggattgg 120
tacctacaga agccagggca gtctccacag ctctgatct atttgggttc taatcggggc 180
tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggctgagga tgttggaatt tattactgca tgcaagctct acaaactccg 300
tggacgttcg gccaaaggac caaggtggaa atcaaa 336

<210> 274

50 <211> 112

<212> PRT

<213> Artificial Sequence

<220>

55 <223> Synthetic

<400> 274

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	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	Tyr	Ser
				20					25					30		
5	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
10	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	Trp	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys
				100					105					110		

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<210> 275

<211> 33

<212> DNA

<213> Artificial Sequence

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<220>

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<400> 275

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<211> 11

<212> PRT

<213> Artificial Sequence

30

<220>

<223> Synthetic

35

<400> 276

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

40

<210> 277

<211> 9

<212> DNA

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 277

ttgggttct 9

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<210> 278

<211> 3

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

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<400> 278

Leu Gly Ser
1

5

<210> 279
<211> 27
<212> DNA
<213> Artificial Sequence

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<220>
<223> Synthetic

15

<400> 279
atgcaagctc tacaaactcc gtggacg 27

20

<210> 280
<211> 9
<212> PRT
<213> Artificial Sequence

25

<400> 280

Met Gln Ala Leu Gln Thr Pro Trp Thr
1 5

30

<210> 281
<211> 363
<212> DNA
<213> Artificial Sequence

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<220>
<223> Synthetic

<400> 281

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tcctgtgcag	cctctggatt	caccttcagt	agctacgaca	tgcaactgggt	ccgccaaagtt	120
acaggaaaag	gtctggaatg	ggtctcagtc	attggtactg	ttggtgacac	atactatcca	180
ggctccctga	agggccgatt	caccatctcc	agagaaaatg	ccaagaactc	cttgtatctt	240
caaatgaaca	ccctgagagc	cggggacacg	gctgtttatt	actgtgcaag	aactggagca	300
gcagcccact	cgtactacta	cggatatggac	gtctggggcc	aagggaccac	ggtcaccgtc	360
tcc						363

45

<210> 282
<211> 121
<212> PRT
<213> Artificial Sequence

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<220>
<223> Synthetic

55

<400> 282

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

<210> 283

<211> 336

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

25

<400> 283

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	atctcctgca	ggctctagtc	gagcctcctg	tatagtaatg	gatacaacta	tttgattgg	120
30	tacctacaga	agccagggca	gtctccacag	ctcctgatct	atttgggttc	taatcgggcc	180
	tccgggggtcc	ctgacagggt	cagtggcagt	ggatcaggca	cagattttac	actgaaaatc	240
	agcagagtgg	aggttgagga	tggttgaatt	tattactgca	tgcaagctct	acaaactccg	300
	tggacgttcg	gccaaaggac	caaggtggaa	atcaaa			336

35 <210> 284

<211> 112

<212> PRT

<213> Artificial Sequence

40 <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	Tyr	Ser
				20					25					30		
	Asn	Gly	Tyr	Asn	Tyr	Leu	Asp	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser
50			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
55	65					70				75						80

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Ser Arg Val Glu Ala Glu Asp Val Gly Ile 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

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<210> 285
<211> 364
<212> DNA
<213> Artificial Sequence

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<220>
<223> Synthetic

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<400> 285

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tcctgtgcag cctctggatt caccttcagt agctacgaca tgcactgggt ccgccaagct 120
acaggaaaag gtctggagtg ggtctcagct attggtactg ttggtgacac atactatcca 180
ggctccgtga agggccgatt caccatctcc agagaaaatg ccaagaactc cttgtatctt 240
caaatgaaca gcctgagagc cggggacacg gctgtgtatt actgtgcaag aactggagca 300
gcagcccact cgtactacta cggtatggac gtctgggggc aaggggaccac ggtcaccgtc 360
tcct 364

25

<210> 286
<211> 121
<212> PRT
<213> Artificial Sequence

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<220>
<223> Synthetic
<400> 286

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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 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 Thr Val 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 Thr Gly Ala Ala Ala His Ser Tyr Tyr Tyr Gly Met Asp Val Trp
100 105 110
Gly Gln Gly Thr Thr Val Thr Val Ser
115 120

50

<210> 287
<211> 337
<212> DNA
<213> Artificial Sequence

55

<220>
<223> Synthetic

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<400> 287

5 gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60
atctcctgca ggtctagtca gagcctcctg tataagtaatg gatacaacta tttggattgg 120

10 tacctgcaga agccagggca gtctccacag ctctgatct atttgggttc taatcggggcc 180
tccgggggtcc ctgacagggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggctgagga tgttgggggtt tattactgca tgcaagctct acaaaactccg 300
tggacgttcg gccaaaggac caaggtggaa atcaaac 337

<210> 288

<211> 112

15 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

20

<400> 288

25 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 Tyr 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
35 Leu Gln Thr Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 289

<211> 357

40 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

45

<400> 289

50 gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt caccttttagc agctatgcca tgacctgggt ccgccaggct 120
ccagggaagg ggctgtattg ggtctcagct attagtggta gtggtggttag cgcatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatac acagcctgag agccgaggac acggccgtat attactgtgc gaaagagggg 300
gatagtggct acgatttga ctactggggc cggggaaccc tggtcaccgt ctcgtca 357

55 <210> 290

<211> 119

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 290

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

10

Ser Ala Ile Ser Gly Ser Gly Gly Ser Ala 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 Glu Gly Asp Ser Gly Tyr Asp Leu Asp Tyr Trp Gly Arg Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

15

20

<210> 291

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<211> 24

<212> DNA

<213> Artificial Sequence

<220>

30

<223> Synthetic

<400> 291

ggattcacct ttagcagcta tgcc 24

35

<210> 292

<211> 8

<212> PRT

<213> Artificial Sequence

40

<220>

<223> Synthetic

<400> 292

45

Gly Phe Thr Phe Ser Ser Tyr Ala
1 5

<210> 293

<211> 24

50

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

55

<400> 293

attagtggtgta gtggtggtag cgca 24

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<210> 294
<211> 8
<212> PRT
<213> Artificial Sequence
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<220>
<223> Synthetic

<400> 294
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      Ile Ser Gly Ser Gly Gly Ser Ala
      1                      5

<210> 295
15 <211> 36
    <212> DNA
    <213> Artificial Sequence

    <220>
20 <223> Synthetic

    <400> 295
    gcgaaagagg gggatagtagg ctacgatttg gactac      36

25 <210> 296
    <211> 12
    <212> PRT
    <213> Artificial Sequence

30 <220>
    <223> Synthetic

    <400> 296

35      Ala Lys Glu Gly Asp Ser Gly Tyr Asp Leu Asp Tyr
      1                      5                      10

<210> 297
40 <211> 321
    <212> DNA
    <213> Artificial Sequence

    <220>
45 <223> Synthetic

    <400> 297

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      atcacttgtc gggcgaggca gggcattagt aattatttag cctggcttca gcagaaacca 120
50 gggaaagccc ctaagtccct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
      aagttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
      gaagattttg caacttatta ctgccaacaa tataaaagtt ccccgctcac tttcggcgga 300
      gggaccaagg tggagatcaa a                                     321

55 <210> 298
    <211> 107
    <212> PRT
    <213> Artificial Sequence

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<220>

<223> Synthetic

<400> 298

5

10

15

20

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

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100

105

<210> 299

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<211> 18

<212> DNA

<213> Artificial Sequence

<220>

30

<223> Synthetic

<400> 299

cagggcatta gtaattat 18

35

<210> 300

<211> 6

<212> PRT

<213> Artificial Sequence

40

<220>

<223> Synthetic

<400> 300

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Gln Gly Ile Ser Asn Tyr
 1           5

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<210> 301

<211> 9

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<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 301

gctgcatcc 9

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<210> 302
 <211> 3
 <212> PRT
 <213> Artificial Sequence
 5
 <220>
 <223> Synthetic
 <400> 302
 10
 Ala Ala Ser
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 <210> 303
 <211> 27
 <212> DNA
 <213> Artificial Sequence
 15
 <220>
 <223> Synthetic
 20
 <400> 303
 caacaatata aaagttcccc gctcact 27
 25
 <210> 304
 <211> 9
 <212> PRT
 <213> Artificial Sequence
 30
 <220>
 <223> Synthetic
 <400> 304
 35
 Gln Gln Tyr Lys Ser Ser Pro Leu Thr
 1 5
 <210> 305
 <211> 357
 <212> DNA
 <213> Artificial Sequence
 40
 <220>
 <223> Synthetic
 45
 <400> 305
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 tcctgtgcag cctctggatt caccttttagc agctatgcca tgacctgggt ccgccaggct 120
 50 ccagggaagg ggctgtattg ggtctcagct attagtggta gtggtggttag cgcatactac 180
 gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
 ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagagggg 300
 gatagtggct acgatttgga ctactggggc cggggaaccc tggtcaccgt ctcctca 357
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 <210> 306
 <211> 119
 <212> PRT
 <213> Artificial Sequence

EP 2 475 684 B1

<220>

<223> Synthetic

<400> 306

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10

15

20

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

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<210> 307

<211> 321

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<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

30

<400> 307

35

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atcacttgtc gggcgaggca gggcattagt aattatttag cctggcttca gcagaaacca 120
gggaaagccc ctaagtcctt gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aagttcagcg gcagtggatc tgggacagat ttactctca ccatcagcag cctgcagcct 240
gaagattttg caacttatta ctgccaacaa tataaaagtt ccccgctcac tttcggcgga 300
gggaccaagg tggagatcaa a                               321

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40

<210> 308

<211> 107

<212> PRT

<213> Artificial Sequence

45

<220>

<223> Synthetic

<400> 308

50

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

15

<210> 309

<211> 357

<212> DNA

<213> Artificial Sequence

20

<220>

<223> Synthetic

<400> 309

25

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	tcctgtgcag	cctctggatt	caccttttagc	agctatgcc	tgagctgggt	ccgccaggct	120
	ccaggggaagg	ggctggagtg	ggtctcagct	attagtggt	gtggtggtag	cgcatactac	180
	gcagactccg	tgaagggccg	gttcaccatc	tccagagaca	attccaagaa	cacgctgtat	240
30	ctgcaaata	acagcctgag	agccgaggac	acggccgtat	attactgtgc	gaaagagggg	300
	gatagtggct	acgatttgga	ctactggggc	cagggaaccc	tggtcaccgt	ctcctca	357

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<210> 310

<211> 119

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

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<400> 310

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	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	Ser	Gly	Gly	Ser	Ala	Tyr	Tyr	Ala	Asp	Ser	Val
50	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		
55	Ala	Lys	Glu	Gly	Asp	Ser	Gly	Tyr	Asp	Leu	Asp	Tyr	Trp	Gly	Gln	Gly
				100				105						110		
	Thr	Leu	Val	Thr	Val	Ser	Ser									
				115												

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<210> 311
 <211> 322
 <212> DNA
 <213> Artificial Sequence

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10
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atcacttgtc gggcgagtca gggcattagt aattatttag cctgggtttca gcagaaacca 120
gggaaagccc ctaagtcctt gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttatta ctgccaaaca tataaaagtt ccccgcctcac tttcggcgga 300
gggaccaagg tggagatcaa ac                                     322
  
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<210> 312
 <211> 107
 <212> PRT
 <213> Artificial Sequence

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 <223> Synthetic

25
 <400> 312

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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	Gly	Ile	Ser	Asn	Tyr
			20					25					30		
Leu	Ala	Trp	Phe	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Ser	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	Gln	Gln	Tyr	Lys	Ser	Ser	Pro	Leu
				85					90					95	
Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys					
			100					105							

<210> 313
 <211> 348
 <212> DNA
 <213> Artificial Sequence

45
 <220>
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 <400> 313

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 tcctgtgcag cctctggatt cacctttgat gattatgcc tgcactgggt ccggcaagtt 120
 ccaggaagg gcctggagtg ggtctcaggt attacttgga atagtggtag catagactat 180
 gcggaactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
 5 ctgcaaata acagtctgag agctgaggac acggccttct attattgtgt aaaagaagat 300
 gaggcctttt actactgggg ccaggaacc ctggtcaccg tctcctca 348

<210> 314

<211> 116

10 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

15

<400> 314

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

35

<210> 315

<211> 24

<212> DNA

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 315

45 ggattcacct ttgatgatta tgcc 24

<210> 316

<211> 8

<212> PRT

50 <213> Artificial Sequence

<220>

<223> Synthetic

55

<400> 316

Gly Phe Thr Phe Asp Asp Tyr Ala
 1 5

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<210> 317
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 <212> DNA
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 <220>
 <223> Synthetic
 <400> 317
 10 attacttgga atagtggtag cata 24
 <210> 318
 <211> 8
 <212> PRT
 15 <213> Artificial Sequence
 <220>
 <223> Synthetic
 20 <400> 318
 Ile Thr Trp Asn Ser Gly Ser Ile
 1 5
 25 <210> 319
 <211> 27
 <212> DNA
 <213> Artificial Sequence
 30 <220>
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 <400> 319
 35 gtaaaagaag atgaggcttt tgactac 27
 <210> 320
 <211> 9
 <212> PRT
 <213> Artificial Sequence
 40 <220>
 <223> Synthetic
 <400> 320
 45 Val Lys Glu Asp Glu Ala Phe Asp Tyr
 1 5
 50 <210> 321
 <211> 336
 <212> DNA
 <213> Artificial Sequence
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 55 <223> Synthetic
 <400> 321

EP 2 475 684 B1

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 atctcctgta ggtctagtca aagcctcgta cacagtgatg gaaacaccta tttgagttgg 120
 cttcagcaga ggccaggcca gcctccaaga ctctaatatt ataagatttc taaccgggttc 180
 tctgggggtcc cagacagaat cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
 5 agcaggggtg aggctgagga tgtcggcgtt tattattgca tgcaagctac acaatttccg 300
 tacacttttg gccaggggac caagctggag atcaaa 336

<210> 322

<211> 112

10 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

15

<400> 322

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

<210> 323

<211> 33

35 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

40

<400> 323

caaagcctcg tacacagtga tggaacacc tat 33

<210> 324

45 <211> 11

<212> PRT

<213> Artificial Sequence

<220>

50 <223> Synthetic

<400> 324

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

<210> 325

<211> 9

EP 2 475 684 B1

<212> DNA
 <213> Artificial Sequence

 <220>
 5 <223> Synthetic

 <400> 325
 aagatttct 9

 10 <210> 326
 <211> 3
 <212> PRT
 <213> Artificial Sequence

 15 <220>
 <223> Synthetic

 <400> 326

 20 Lys Ile Ser
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 <210> 327
 <211> 27
 25 <212> DNA
 <213> Artificial Sequence

 <220>
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 <400> 327
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 35 <210> 328
 <211> 9
 <212> PRT
 <213> Artificial Sequence

 40 <220>
 <223> Synthetic

 <400> 328

 45 Met Gln Ala Thr Gln Phe Pro Tyr Thr
 1 5

 <210> 329
 <211> 348
 50 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Synthetic

 55 <400> 329

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tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagtt 120
ccaggaaggg gcctggagtg ggtctcaggt attacttgga atagtggtag catagactat 180
gcggaactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
5 ctgcaaataga acagtctgag agctgaggac acggccttct attattgtgt aaaagaagat 300
gaggcttttg actactgggg ccaggaacc ctggtcaccg tctcctca 348

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<210> 330

<211> 116

10 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

15

<400> 330

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

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35 <210> 331

<211> 336

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

40

<400> 331

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atctcctgta ggtctagtca aagcctcgta cacagtgatg gaaacaccta tttgagttgg 120
cttcagcaga ggccaggcca gcctccaaga ctctaattt ataagatttc taaccgggtc 180
tctgggggtcc cagacagaat cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
agcagggtgg aggctgagga tgcggcggtt tattattgca tgcaagctac acaatttccg 300
50 tacacttttg gccaggggac caagctggag atcaaa 336

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<210> 332

<211> 112

<212> PRT

55 <213> Artificial Sequence

<220>

<223> Synthetic

EP 2 475 684 B1

<400> 332

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

<210> 333

<211> 348

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 333

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	ccaggggaagg	gcctggagtg	ggtctcaggt	attacttgga	atagtggtag	cataggctat	180
	gcggactctg	tgaagggccg	attcaccatc	tccagagaca	acgccaagaa	ctccctgtat	240
	ctgcaaataa	acagtctgag	agctgaggac	acggccttgt	attactgtgt	aaaagaagat	300
	gaggcttttg	actactgggg	ccaggggaacc	ctgggtcaccg	tctcctca		348

35

<210> 334

<211> 116

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 334

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50

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EP 2 475 684 B1

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

<210> 335

<211> 337

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

25

<400> 335

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30	atctcctgca	gggtctagtc	aagcctcgta	cacagtgatg	gaaacaccta	tttgagttgg	120
	cttcagcaga	ggccaggcca	gcctccaaga	ctcctaattt	ataagatttc	taaccgggttc	180

	tctgggggtcc	cagacagatt	cagtggcagt	ggggcaggga	cagatttcac	actgaaaatc	240
35	agcaggggtgg	aagctgagga	tgtcgggggt	tattactgca	tgcaagctac	acaatttccg	300
	tacactttttg	gccaggggac	caagctggag	atcaaac			337

<210> 336

<211> 112

40 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

45

<400> 336

50

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

<210> 337

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 337

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	tcctgtgcag	cctctggatt	cacctttaga	agttataacca	tgacctgggt	ccgccaggct	120
	ccaggaagg	gactggattg	ggtctcaggt	attactgata	gtggtgctgg	cacatactac	180
30	ggagactccg	tgaagggccg	gttcaccatc	tccagagaca	attccaagaa	cacgctgtat	240
	ctgcaaatga	acagcctgag	agccgaggac	acggccgtgt	attactgtgt	gaaagagggg	300
	gatagtggct	acgatttgga	ctactggggc	cagggaaccc	tggtcaccgt	ctcctca	357

<210> 338

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 338

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

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

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 <210> 339
 <211> 24
 <212> DNA
 <213> Artificial Sequence

15
 <220>
 <223> Synthetic

20
 <400> 339
 ggattcacct ttagaagta tacc 24

25
 <210> 340
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

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 <400> 340

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	1				5			

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 <210> 341
 <211> 24
 <212> DNA
 <213> Artificial Sequence

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 <220>
 <223> Synthetic

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 <400> 341
 attactgata gtggtgctgg caca 24

50
 <210> 342
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

55
 <400> 342

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	1				5			

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<210> 343
 <211> 36
 <212> DNA
 <213> Artificial Sequence
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 <220>
 <223> Synthetic
 <400> 343
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 <210> 344
 <211> 12
 <212> PRT
 15 <213> Artificial Sequence
 <220>
 <223> Synthetic
 20 <400> 344
 Val Lys Glu Gly Asp Ser Gly Tyr Asp Leu Asp Tyr
 1 5 10
 25 <210> 345
 <211> 321
 <212> DNA
 <213> Artificial Sequence
 30 <220>
 <223> Synthetic
 <400> 345
 35 gacatccaga tgacccagtc tccatcctca ctgtctgcat ctgtaggaga cagagtcacc 60
 atcacttgtc gggcgagtc gggcattagt acttatttag cctggcttca gcagaaacca 120
 gggaaagccc ctaagtccct gatctatgct acatccagtt tgcaaagtgg ggtcccatca 180
 aagttcagcg gcagtagatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
 gaagattttg caacttatta ctgccaacaa tataagagtt ccccgctcac ttctggcgga 300
 40 gggaccaagg tggagatcaa a 321
 <210> 346
 <211> 107
 <212> PRT
 45 <213> Artificial Sequence
 <220>
 <223> Synthetic
 50 <400> 346
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	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	Gly	Ile	Ser	Thr	Tyr
				20					25					30		
5	Leu	Ala	Trp	Leu	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Ser	Leu	Ile
			35				40						45			
	Tyr	Ala	Thr	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Lys	Phe	Ser	Gly
		50					55					60				
	Ser	Arg	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
10	65					70					75					80
	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Tyr	Lys	Ser	Ser	Pro	Leu
					85					90					95	
	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys					
				100					105							

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<210> 347
 <211> 18
 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> Synthetic

<400> 347
 25 cagggcatta gtacttat 18

<210> 348
 <211> 6
 <212> PRT
 30 <213> Artificial Sequence

<220>
 <223> Synthetic

35 <400> 348

	Gln	Gly	Ile	Ser	Thr	Tyr
	1				5	

40 <210> 349
 <211> 9
 <212> DNA
 <213> Artificial Sequence

45 <220>
 <223> Synthetic

<400> 349
 50 gctacatcc 9

<210> 350
 <211> 3
 <212> PRT
 55 <213> Artificial Sequence

<220>
 <223> Synthetic

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<400> 350

Ala Thr Ser
1

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<210> 351
<211> 27
<212> DNA
<213> Artificial Sequence

10

<220>
<223> Synthetic

15

<400> 351
caacaatata agagttcccc gctcact 27

20

<210> 352
<211> 9
<212> PRT
<213> Artificial Sequence

25

<400> 352

Gln Gln Tyr Lys Ser Ser Pro Leu Thr
1 5

30

<210> 353
<211> 357
<212> DNA
<213> Artificial Sequence

35

<220>
<223> Synthetic

<400> 353

40

gaggtgcagc	tgttggagtc	tgggggaggc	ttggtacagc	ctgggggggtc	cctgagactc	60
tcctgtgcag	cctctggatt	cacctttaga	agttatacca	tgacctgggt	ccgccaggct	120
ccagggaagg	gactggattg	ggtctcaggt	attactgata	gtggtgctgg	cacatactac	180
ggagactccg	tgaagggccg	gttcaccatc	tccagagaca	attccaagaa	cacgctgtat	240
ctgcaaata	acagcctgag	agccgaggac	acggccgtgt	attactgtgt	gaaagagggg	300
gatagtggct	acgatttga	ctactggggc	cagggaaccc	tggtcacctg	ctcctca	357

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<210> 354
<211> 119
<212> PRT
<213> Artificial Sequence

50

<220>
<223> Synthetic

55

<400> 354

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

<210> 355

<211> 321

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

25 <400> 355

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	atcacttgtc	gggcgagtc	gggcattagt	acttatttag	cctgggcttc	gcagaaacca	120
30	gggaaagccc	ctaagtccct	gatctatgct	acatccagtt	tgcaaagtgg	gggtcccatca	180
	aagttcagcg	gcagtagatc	tgggacagat	ttcactctca	ccatcagcag	cctgcagcct	240
	gaagattttg	caacttatta	ctgccaacaa	tataagagtt	ccccgctcac	tttcggcgga	300
	gggaccaagg	tggagatcaa	a				321

35 <210> 356

<211> 107

<212> PRT

<213> Artificial Sequence

40 <220>

<223> Synthetic

<400> 356

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

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<210> 357
 <211> 357
 <212> DNA
 <213> Artificial Sequence

5

<220>
 <223> Synthetic

10

<400> 357

15

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tcctgtgcag cctctggatt cacctttaga agttatacca tgagctgggt ccgccaggct 120
ccaggggaagg ggctggagtg ggtctcagct attactgata gtggtgctgg cacatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgt gaaagagggg 300
gatagtggct acgatttggg ctactggggc caggaaccc tggtcacctg ctctctca 357
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20

<210> 358
 <211> 119
 <212> PRT
 <213> Artificial Sequence

25

<220>
 <223> Synthetic

<400> 358

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

<210> 359
 <211> 322
 <212> DNA
 <213> Artificial Sequence

50

<220>
 <223> Synthetic

<400> 359

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 atcacttgtc gggcgagtc gggcattagt acttatttag cctgggtttca gcagaaacca 120
 gggaaagccc ctaagtccct gatctatgct acatccagtt tgcaaagtgg ggtcccatca 180
 aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
 gaagattttg caacttatta ctgccaacaa tataagagtt ccccgctcac tttcggcgga 300
 gggaccaagg tggagatcaa ac 322

10 <210> 360
 <211> 107
 <212> PRT
 <213> Artificial Sequence

15 <220>
 <223> Synthetic

<400> 360

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

35 <210> 361
 <211> 348
 <212> DNA
 <213> Artificial Sequence

40 <220>
 <223> Synthetic

<400> 361

45 gaagtgcaac tgggtggagtc tggggggagac ttggtacagc ctggcaggtc cctgagactc 60
 tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120
 ccagggaggg gcctagagtg ggtctcaggt attacttgga atagtgggtac catggcctat 180
 gcggactctg tggagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
 ctacaaatga acagtctgag agctgaggac acggccttat attactgtgc aagagaaaac 300
 tgggcctttg actactgggg ccaggaacc ctggtcaccg tctcctca 348

50 <210> 362
 <211> 116
 <212> PRT
 <213> Artificial Sequence

55 <220>
 <223> Synthetic

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<400> 362

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

20 <210> 363
 <211> 24
 <212> DNA
 <213> Artificial Sequence

25 <220>
 <223> Synthetic

<400> 363
 ggattcacct ttgatgatta tgcc 24

30 <210> 364
 <211> 8
 <212> PRT
 <213> Artificial Sequence

35 <220>
 <223> Synthetic

40 <400> 364

Gly	Phe	Thr	Phe	Asp	Asp	Tyr	Ala
1				5			

45 <210> 365
 <211> 24
 <212> DNA
 <213> Artificial Sequence

50 <220>
 <223> Synthetic

<400> 365
 attacttgga atagtgtac catg 24

55 <210> 366
 <211> 8
 <212> PRT
 <213> Artificial Sequence

EP 2 475 684 B1

<220>

<223> Synthetic

<400> 366

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Ile Thr Trp Asn Ser Gly Thr Met
1 5

<210> 367

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<211> 27

<212> DNA

<213> Artificial Sequence

<220>

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<223> Synthetic

<400> 367

gcaagagaaa actgggcctt tgactac 27

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<210> 368

<211> 9

<212> PRT

<213> Artificial Sequence

25

<220>

<223> Synthetic

<400> 368

30

Ala Arg Glu Asn Trp Ala Phe Asp Tyr
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<210> 369

<211> 336

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<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 369

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atctcctgca ggtctagtca cagcctcgta cacagtgatg gaaacaccta cttgagttgg 120
45 cttcagcaga ggccaggcca gcctccaaga ctctaatat ataagatttc taaccggttc 180
tctgggggtcc cagacagatt cagtggcagt gggccaggga cagatttcac actgaaaatc 240
agcagggtgg aagctgagga tgtcgggggt tatttctgca tgcaagctac acaatttccg 300
tacacttttg gccaggggac caagctggag atcaaa 336

50

<210> 370

<211> 112

<212> PRT

<213> Artificial Sequence

55

<220>

<223> Synthetic

<400> 370

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

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<210> 371
 <211> 33
 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> Synthetic

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<400> 371
 cacagcctcg tacacagtga tggaaacacc tac 33

30

<210> 372
 <211> 11
 <212> PRT
 <213> Artificial Sequence

35

<220>
 <223> Synthetic

<400> 372

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

40

<210> 373
 <211> 9
 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> Synthetic

50

<400> 373
 aagatttct 9

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<210> 374
 <211> 3
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

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<400> 374

Lys Ile Ser
1

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<210> 375
<211> 27
<212> DNA
<213> Artificial Sequence

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<220>
<223> Synthetic

15

<400> 375
atgcaagcta cacaatttcc gtacact 27

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<210> 376
<211> 9
<212> PRT
<213> Artificial Sequence

25

<400> 376

Met Gln Ala Thr Gln Phe Pro Tyr Thr
1 5

30

<210> 377
<211> 348
<212> DNA
<213> Artificial Sequence

35

<220>
<223> Synthetic

<400> 377

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gaagtgcagc	tgggtggagtc	tggggggagac	ttggtacagc	ctggcaggtc	cctgagactc	60
tctctgtgcag	cctctggatt	cacctttgat	gattatgcca	tgcactgggt	ccggcaagct	120
ccagggagggg	gcctagagtg	ggtctcaggt	attacttgga	atagtggtag	catggcctat	180
gcggactctg	tggagggccg	attcaccatc	tccagagaca	acgccaagaa	ctccctgtat	240
ctacaaatga	acagtctgag	agctgaggac	acggccttat	attactgtgc	aagagaaaac	300
tgggcctttg	actactgggg	ccagggaacc	ctgggcaccg	tctcctca		348

45

<210> 378
<211> 116
<212> PRT
<213> Artificial Sequence

50

<220>
<223> Synthetic

55

<400> 378

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

<210> 379

<211> 336

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

25

<400> 379

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	atctcctgca	gggtctagtc	cagcctcgta	cacagtgatg	gaaacaccta	cttgagttgg	120
30	cttcagcaga	ggccaggcca	gcctccaaga	ctcctaattt	ataagatttc	taaccgggttc	180
	tctgggggtcc	cagacagatt	cagtggcagt	gggccaggga	cagatttcac	actgaaaatc	240
	agcaggggtgg	aagctgagga	tgtcgggggtt	tatttctgca	tgcaagctac	acaatttccg	300
	tacactttttg	gccagggggac	caagctggag	atcaaa			336

35

<210> 380

<211> 112

<212> PRT

<213> Artificial Sequence

40

<220>

<223> Synthetic

<400> 380

45

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

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85 90 95
 Thr Gln Phe Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105 110

5 <210> 381
 <211> 348
 <212> DNA
 <213> Artificial Sequence

10 <220>
 <223> Synthetic

<400> 381

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 tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120
 ccaggggaagg gcctggagtg ggtctcaggt attacttggg atagtgggtac catgggctat 180
 gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
 ctgcaaatac acagtctgag agctgaggac acggccttgt attactgtgc aagagaaaac 300
 20 tgggcctttg actactgggg ccaggggaacc ctggtcaccg tctcctca 348

<210> 382
 <211> 116
 <212> PRT
 25 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 382

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

<210> 383
 50 <211> 337
 <212> DNA
 <213> Artificial Sequence

<220>
 55 <223> Synthetic

<400> 383

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atctcctgca ggtctagtca cagcctcgta cacagtgatg gaaacaccta cttgagttgg 120
cttcagcaga ggccaggcca gcctccaaga ctccctaattt ataagatttc taaccgggtc 180
tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240

10 agcaggggtg aagctgagga tgtcgggggt tattactgca tgcaagctac acaatttccg 300
tacacttttg gccaggggac caagctggag atcaaac 337

<210> 384

<211> 112

<212> PRT

15 <213> Artificial Sequence

<220>

<223> Synthetic

20 <400> 384

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

<210> 385

<211> 354

<212> DNA

40 <213> Artificial Sequence

<220>

<223> Synthetic

45 <400> 385

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tcctgtgcag cctctggatt cacctttgat gattatggca tgacctgggt ccgccaagtt 120
ccggggaagg ggctggagtg ggtctctgggt attaattgga atggtggttag tacagattat 180
gcagactctg tgaagggccg attcaccata tctagagaca acgccaagaa ctccctgtat 240
ctgcaaatga atagtctgag agccgaggac acggccttat attactgtgc gagagataag 300
gggttctacg gtatggacgt ctggggccaa gggaccacgg tcaccgtctc ctca 354

<210> 386

55 <211> 118

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 386

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 105
 110
 115

Glu Val Gln Leu Val Glu Ser Gly Gly Asn Val Val Arg Pro Gly Gly
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
 Gly Met Thr Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
 Ser Gly Ile Asn Trp Asn Gly Gly Ser Thr Asp Tyr Ala Asp Ser Val
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
 Ala Arg Asp Lys Gly Phe Tyr Gly Met Asp Val Trp Gly Gln Gly Thr
 Thr Val Thr Val Ser Ser

<210> 387

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 387

ggattcacct ttgatgatta tggc 24

<210> 388

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 388

Gly Phe Thr Phe Asp Asp Tyr Gly
 1 5

<210> 389

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 389

attaattgga atggtgtag taca 24

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<210> 390
<211> 8
<212> PRT
<213> Artificial Sequence
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<220>
<223> Synthetic

<400> 390
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      Ile Asn Trp Asn Gly Gly Ser Thr
      1              5

<210> 391
15 <211> 33
    <212> DNA
    <213> Artificial Sequence

    <220>
20 <223> Synthetic

    <400> 391
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25 <210> 392
    <211> 11
    <212> PRT
    <213> Artificial Sequence

30 <220>
    <223> Synthetic

    <400> 392

35      Ala Arg Asp Lys Gly Phe Tyr Gly Met Asp Val
      1              5              10

<210> 393
40 <211> 339
    <212> DNA
    <213> Artificial Sequence

    <220>
45 <223> Synthetic

    <400> 393

50      gacatcgtga tgaccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc 60
      atcaactgca agtccagcca gaatccttta tacaactcca acaaaaagaa gtacttagct 120
      tggtagcagg agaaaccagg acagccccct aaagctggta tttactgggc atctaccggg 180
      gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240
      atcaccagcc tacaggctga agatgtggca gtttattact gtcaacaata ttatagtact 300
      ccgtacactt ttggccaggg gaccaagctg gagatcaaa      339

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<210> 394
<211> 113

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<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 394

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

```

25 <210> 395
<211> 36
<212> DNA
<213> Artificial Sequence

30 <220>
<223> Synthetic

<400> 395
cagaatcctt tatacaactc caacaaaaag aagtac 36

35 <210> 396
<211> 12
<212> PRT
<213> Artificial Sequence

40 <220>
<223> Synthetic

<400> 396

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45      Gln Asn Pro Leu Tyr Asn Ser Asn Lys Lys Lys Tyr
      1           5           10

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50 <210> 397
<211> 9
<212> DNA
<213> Artificial Sequence

55 <220>
<223> Synthetic

<400> 397
tgggcatct 9

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<210> 398
 <211> 3
 <212> PRT
 <213> Artificial Sequence
 5
 <220>
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 10
 <400> 398
 Trp Ala Ser
 1
 15
 <210> 399
 <211> 27
 <212> DNA
 <213> Artificial Sequence
 20
 <220>
 <223> Synthetic
 <400> 399
 caacaatatt atagtactcc gtacact 27
 25
 <210> 400
 <211> 9
 <212> PRT
 <213> Artificial Sequence
 30
 <220>
 <223> Synthetic
 <400> 400
 35
 Gln Gln Tyr Tyr Ser Thr Pro Tyr Thr
 1 5
 40
 <210> 401
 <211> 351
 <212> DNA
 <213> Artificial Sequence
 45
 <220>
 <223> Synthetic
 <400> 401
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 tcctgtgcag cctctggatt cacctttgat gattatggca tgacctgggt ccgccaagtt 120
 ccggggaagg ggctggagtg ggtctctggt attaattgga atggtggtag tacagattat 180
 gcagactctg tgaagggccg attcaccata tctagagaca acgccaagaa ctccctgtat 240
 ctgcaaataa atagtctgag agccgaggac acggccttat attactgtgc gagagataag 300
 gggttctacg gtatggacgt ctggggccaa gggaccacgg tcaccgtctc c 351
 55
 <210> 402
 <211> 117
 <212> PRT
 <213> Artificial Sequence

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<220>

<223> Synthetic

<400> 402

5

10

15

20

```

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

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<210> 403

<211> 339

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<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

30

<400> 403

35

40

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gacatcgtga tgaccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc 60
atcaactgca agtccagcca gaatccttta tacaactcca acaaaaagaa gtacttagct 120
tggtaccagc agaaaccagg acagccccct aagctgggtca tttactgggc atctaccgg 180
gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240
atcaccagcc tacaggetga agatgtggca gtttattact gtcaacaata ttatagtact 300
ccgtacactt ttggccaggg gaccaagctg gagatcaaa 339

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<210> 404

<211> 113

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 404

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

<210> 405

<211> 352

<212> DNA

20 <213> Artificial Sequence

<220>

<223> Synthetic

25 <400> 405

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	tcctgtgcag	cctctggatt	cacctttgat	gattatggca	tgagctgggt	ccgccaagct	120
	ccaggggaagg	ggctggagtg	ggtctctggt	attaattgga	atggtggtag	tacaggttat	180
30	gcagactctg	tgaagggccg	attcaccatc	tcagagaca	acgccaagaa	ctccctgtat	240
	ctgcaaataa	acagtctgag	agccgaggac	acggccttgt	atcactgtgc	gagagataag	300
	gggttctacg	gtatggacgt	ctggggccaa	gggaccacgg	tcaccgtctc	ct	352

<210> 406

35 <211> 117

<212> PRT

<213> Artificial Sequence

<220>

40 <223> Synthetic

<400> 406

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55

EP 2 475 684 B1

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

<210> 407

<211> 340

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

25

<400> 407

	gacatcgtga	tgaccagtc	tccagactcc	ctggctgtgt	ctctgggcga	gagggccacc	60
30	atcaactgca	agtccagcca	gaatccttta	tacaactcca	acaaaaagaa	gtacttagct	120
	tggtaccagc	agaaaccagg	acagcctcct	aagctgctca	tttactgggc	atctaccggg	180
	gaatccgggg	tccctgaccg	attcagtggc	agcgggtctg	ggacagattt	cactctcacc	240
	atcagcagcc	tgcaggctga	agatgtggca	gtttattact	gtcaacaata	ttatagtact	300
	ccgtacactt	ttggccaggg	gaccaagctg	gagatcaaac			340

35

<210> 408

<211> 113

<212> PRT

<213> Artificial Sequence

40

<220>

<223> Synthetic

<400> 408

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50

55

EP 2 475 684 B1

	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	Asn	Pro	Leu	Tyr	Asn
				20					25					30		
5	Ser	Asn	Lys	Lys	Lys	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
10	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	Ser	Thr	Pro	Tyr	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile
				100					105					110		
15	Lys															

<210> 409

<211> 384

<212> DNA

20 <213> Artificial Sequence

<220>

<223> Synthetic

25 <400> 409

	gaagtgcagc	tggtggagtc	tgggggaggc	ttggtacagc	ctggcaggtc	cctgagactc	60
	tcctgtgcag	cctctggatt	cacctttgat	gattatgcca	tgcactgggt	ccggcaagct	120
	ccaggggaag	gcctggagtg	ggtctcaggt	attagttgga	atagtggtag	cataggctat	180
30	gcggaactct	tgaagggccg	attcaccatc	tccagagaca	acgccaagaa	ctccctgtat	240
	ctgcaaataa	acagtctgag	agctgaggac	acggccttgt	attactgtgc	aaaagataga	300
	ttccctccgt	ataagtataa	cagtgggtgt	ttttctgatg	cttttgaaat	ctggggccaa	360
	gggacaatgg	tcaccgtctc	ttca				384

35 <210> 410

<211> 128

<212> PRT

<213> Artificial Sequence

40 <220>

<223> Synthetic

<400> 410

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EP 2 475 684 B1

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

20 <210> 411
 <211> 24
 <212> DNA
 <213> Artificial Sequence

25 <220>
 <223> Synthetic

<400> 411
 ggattcacct ttgatgatta tgcc 24

30 <210> 412
 <211> 8
 <212> PRT
 <213> Artificial Sequence

35 <220>
 <223> Synthetic

40 <400> 412

Gly	Phe	Thr	Phe	Asp	Asp	Tyr	Ala
1				5			

45 <210> 413
 <211> 24
 <212> DNA
 <213> Artificial Sequence

50 <220>
 <223> Synthetic

<400> 413
 attagttgga atagtggtag cata 24

55 <210> 414
 <211> 8
 <212> PRT
 <213> Artificial Sequence

EP 2 475 684 B1

<220>

<223> Synthetic

<400> 414

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Ile Ser Trp Asn Ser Gly Ser Ile
1 5

<210> 415

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<211> 63

<212> DNA

<213> Artificial Sequence

<220>

15

<223> Synthetic

<400> 415

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gcaaaagata gattccctcc gtataagtat aacagtgggtg gtttttctga tgcttttgaa 60
atc 63

<210> 416

<211> 21

<212> PRT

25

<213> Artificial Sequence

<220>

<223> Synthetic

30

<400> 416

Ala Lys Asp Arg Phe Pro Pro Tyr Lys Tyr Asn Ser Gly Gly Phe Ser
1 5 10 15

35

Asp Ala Phe Glu Ile
20

<210> 417

<211> 324

<212> DNA

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<213> Artificial Sequence

<220>

<223> Synthetic

45

<400> 417

gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtttttagc agcagctact tagcctggta ccagcagaaa 120
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatcca 180
gacaggttca gtggcagtggt gtctgggaca gacttcaactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgtta ttactgtcag cagtatggta gttcaccgat cacccttcggc 300
caagggacac gactggagat tgaa 324

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<210> 418

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<211> 108

<212> PRT

<213> Artificial Sequence

EP 2 475 684 B1

<220>

<223> Synthetic

<400> 418

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10

15

20

25

30

35

40

45

50

55

```

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 Phe Ser Ser Ser
          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
Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Glu
          100          105

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<210> 419

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 419

cagagtttta gcagcagcta c 21

<210> 420

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 420

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Gln Ser Phe Ser Ser Ser Tyr
 1           5

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<210> 421

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 421

ggtgcatcc 9

<210> 422

<211> 3

<212> PRT

EP 2 475 684 B1

<213> Artificial Sequence

<220>

<223> Synthetic

5

<400> 422

Gly Ala Ser

1

10

<210> 423

<211> 27

<212> DNA

<213> Artificial Sequence

15

<220>

<223> Synthetic

<400> 423

20

cagcagtatg gtagttcacc gatcacc 27

<210> 424

<211> 9

<212> PRT

25

<213> Artificial Sequence

<220>

<223> Synthetic

30

<400> 424

Gln Gln Tyr Gly Ser Ser Pro Ile Thr

1

5

35

<210> 425

<211> 384

<212> DNA

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 425

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gaagtgcagc	tgggtggagtc	tggggggaggc	ttggtacagc	ctggcaggtc	cctgagactc	60
tcctgtgcag	cctctggatt	cacctttgat	gattatgcca	tgcactgggt	ccggcaagct	120
ccagggaagg	gcctggagtg	ggtctcaggt	attagttgga	atagtggtag	cataggctat	180
gcggaactctg	tgaagggccg	attcaccatc	tccagagaca	acgccaagaa	ctccctgtat	240
ctgcaaataga	acagtctgag	agctgaggac	acggccttgt	attactgtgc	aaaagataga	300
ttccctccgt	ataagtataa	cagtgggtgg	ttttctgatg	cttttgaaat	ctggggccaa	360
gggacaatgg	tcaccgtctc	ttca				384

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<210> 426

<211> 128

<212> PRT

<213> Artificial Sequence

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<220>

EP 2 475 684 B1

<223> Synthetic

<400> 426

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

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<210> 427

<211> 324

<212> DNA

25 <213> Artificial Sequence

<220>

<223> Synthetic

30 <400> 427

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      ctctcctgca gggccagtc gagtttttagc agcagctact tagcctggta ccagcagaaa 120
35     cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
      gacaggttca gtggcagtggt gtctgggaca gacttcactc tcaccatcag cagactggag 240
      cctgaagatt ttgcagtgtg ttactgtcag cagtatggta gttcaccgat caccttcggc 300
      caagggacac gactggagat taaa                                324

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40 <210> 428

<211> 108

<212> PRT

<213> Artificial Sequence

45 <220>

<223> Synthetic

<400> 428

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50     Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly

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55

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	1		5		10		15									
	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser	Gln	Ser	Phe	Ser	Ser	Ser
				20					25					30		
5	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	
10	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	Tyr	Gly	Ser	Ser	Pro	
				85						90				95		
	Ile	Thr	Phe	Gly	Gln	Gly	Thr	Arg	Leu	Glu	Ile	Lys				
				100					105							
15	<210> 429															
	<211> 384															
	<212> DNA															
	<213> Artificial Sequence															
20	<220>															
	<223> Synthetic															
	<400> 429															
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	tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120															
	ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag cataggctat 180															
	cggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240															
	ctgcaaatga acagtctgag agctgaggac acggccttgt attactgtgc aaaagataga 300															
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	gggacaatgg tcaccgtctc ttca 384															
	<210> 430															
	<211> 128															
35	<212> PRT															
	<213> Artificial Sequence															
	<220>															
	<223> Synthetic															
40	<400> 430															
	Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Arg
	1				5					10				15		
45	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	Ser	Trp	Asn	Ser	Gly	Ser	Ile	Gly	Tyr	Ala	Asp	Ser	Val
		50				55					60					
50	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Ser	Leu	Tyr
	65					70					75				80	
	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Leu	Tyr	Tyr	Cys
				85					90					95		
	Ala	Lys	Asp	Arg	Phe	Pro	Pro	Tyr	Lys	Tyr	Asn	Ser	Gly	Gly	Phe	Ser
				100					105					110		
55	Asp	Ala	Phe	Glu	Ile	Trp	Gly	Gln	Gly	Thr	Met	Val	Thr	Val	Ser	Ser
				115				120					125			

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<210> 431
 <211> 325
 <212> DNA
 <213> Artificial Sequence

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 <220>
 <223> Synthetic
 <400> 431
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 gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
 ctctcctgca gggccagtc gagtttttagc agcagctact tagcctggta ccagcagaaa 120
 cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
 gacaggttca gtggcagtggt gtctgggaca gacttcactc tcaccatcag cagactggag 240
 15 cctgaagatt ttgcagtgtt ttactgtcag cagtatggta gttcaccgat caccttcggc 300
 caagggacac gactggagat taaac 325

<210> 432
 <211> 108
 <212> PRT
 <213> Artificial Sequence

20
 <220>
 <223> Synthetic
 25
 <400> 432
 30
 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 Phe Ser Ser Ser
 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
 40 Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
 100 105

<210> 433
 <211> 366
 <212> DNA
 <213> Artificial Sequence

45
 <220>
 <223> Synthetic
 50
 <400> 433

55

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gaggtgcagc tgggtggagtc tggggggaggc ttggtacagc ctgggggggct cctgagactc 60
 tcctgtgcag cctctggatt caccttcagt agctacgaca tgcactgggt ccgccaagtt 120
 acaggaaaag gtctggaatg ggtctcagtc attggtactg ttggtgacac atactatcca 180
 5 ggctccctga agggccgatt caccatctcc agagaaaatg ccaagaactc cttgtatctt 240
 caaatgaaca ccctgagagc cggggacacg gctgtttatt actgtgcaag aactggagca 300
 gcagccact cgtactacta cggtatggac gtctggggcc aaggggaccat ggtcaccgctc 360
 tcctca 366

<210> 434
 10 <211> 122
 <212> PRT
 <213> Artificial Sequence

<220>
 15 <223> Synthetic

<400> 434

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

35 <210> 435
 <211> 24
 <212> DNA
 <213> Artificial Sequence

40 <220>
 <223> Synthetic

<400> 435
 45 ggattcacct tcagtagcta cgac 24

<210> 436
 <211> 8
 <212> PRT
 50 <213> Artificial Sequence

<220>
 <223> Synthetic

55 <400> 436

Gly Phe Thr Phe Ser Ser Tyr Asp
 1 5

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<210> 437
 <211> 21
 <212> DNA
 <213> Artificial Sequence
 5
 <220>
 <223> Synthetic
 <400> 437
 10 attgtactg ttggtgacac a 21
 <210> 438
 <211> 7
 <212> PRT
 15 <213> Artificial Sequence
 <220>
 <223> Synthetic
 20 <400> 438
 Ile Gly Thr Val Gly Asp Thr
 1 5
 25 <210> 439
 <211> 48
 <212> DNA
 <213> Artificial Sequence
 30 <220>
 <223> Synthetic
 <400> 439
 35 gcaagaactg gagcagcagc ccactgtac tactacggta tggacgtc 48
 <210> 440
 <211> 16
 <212> PRT
 <213> Artificial Sequence
 40 <220>
 <223> Synthetic
 <400> 440
 45 Ala Arg Thr Gly Ala Ala Ala His Ser Tyr Tyr Tyr Gly Met Asp Val
 1 5 10 15
 50 <210> 441
 <211> 321
 <212> DNA
 <213> Artificial Sequence
 <220>
 55 <223> Synthetic
 <400> 441

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5 gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
 ctctcctgca gggccagtc gagtggttagc agcagctact tagcctggta ccagcagaaa 120
 cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
 gacagggttca gtggcagtggt gtctgggaca gacttcactc tcaccatcag cagactggag 240
 cctgaagatt ttgcagtgtta ttactgtcag cagtatggta gctcaccac tttcggcgga 300
 gggaccaagg ttgagatcaa a 321

10 <210> 442
 <211> 107
 <212> PRT
 <213> Artificial Sequence

15 <220>
 <223> Synthetic

<400> 442

20 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 Ser Ser

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

<210> 443
 <211> 21
 <212> DNA
 40 <213> Artificial Sequence

<220>
 <223> Synthetic

45 <400> 443
 cagagtgtta gcagcagcta c 21

<210> 444
 <211> 7
 50 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

55 <400> 444

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Gln Ser Val Ser Ser Ser Tyr
1 5

5 <210> 445
<211> 9
<212> DNA
<213> Artificial Sequence

10 <220>
<223> Synthetic

<400> 445
ggtgcatcc 9

15 <210> 446
<211> 3
<212> PRT
<213> Artificial Sequence

20 <220>
<223> Synthetic

<400> 446

25 Gly Ala Ser
1

30 <210> 447
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

35 <400> 447
cagcagtatg gtagctcacc cact 24

40 <210> 448
<211> 8
<212> PRT
<213> Artificial Sequence

45 <220>
<223> Synthetic

<400> 448

50 Gln Gln Tyr Gly Ser Ser Pro Thr
1 5

<210> 449
<211> 363
<212> DNA
55 <213> Artificial Sequence

<220>
<223> Synthetic

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<400> 449

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5      gaggtgcagc  tgggtggagtc  tggggggaggc  ttggtacagc  ctggggggggtc  cctgagactc  60
      tcctgtgcag  cctctggatt  caccttcagt  agctacgaca  tgcactgggt  ccgccaagtt  120
      acaggaaaag  gtctggaatg  ggtctcagtc  attggtactg  ttggtgacac  atactatcca  180
      ggctccctga  agggccgatt  caccatctcc  agagaaaatg  ccaagaactc  cttgtatctt  240
      caaatgaaca  ccctgagagc  cggggacacg  gctgtttatt  actgtgcaag  aactgggagca  300
      gcagcccact  cgtactacta  cggtatggac  gtctggggcc  aaggggaccac  ggtcaccgtc  360
      tcc                                           363

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<210> 450

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 450

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

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<210> 451

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 451

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50      gaaatttgtt  tgacgcagtc  tccagggcacc  ctgtctttgt  ctccaggggga  aagagccacc  60
      ctctcctgca  gggccagtc  gagtgtagc  agcagctact  tagcctggta  ccagcagaaa  120
      cctggccagg  ctcccaggct  cctcatctat  ggtgcatcca  gcagggccac  tggcatccca  180
      gacagggttca  gtggcagtg  gtctgggaca  gacttcactc  tcaccatcag  cagactggag  240
55      cctgaagatt  ttgcagtgt  ttactgtcag  cagtatggta  gctcaccac  tttcggcgga  300
      gggaccaagg  tggagatcaa  a                                           321

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<210> 452

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<211> 107
<212> PRT
<213> Artificial Sequence

5 <220>
<223> Synthetic

<400> 452

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10      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 Ser Ser
        20         25         30
15      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
20      Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
        85         90         95
      Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        100        105

```

25 <210> 453
<211> 364
<212> DNA
<213> Artificial Sequence

30 <220>
<223> Synthetic

<400> 453

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35      gaggtgcagc tgggtggagtc tggggggaggc ttggtacagc ctgggggggct cctgagactc 60
      tcctgtgcag cctctggatt caccttcagt agctacgaca tgcactgggt ccgccaagct 120
      acaggaaaag gtctggagtg ggtctcagct attggtactg ttggtgacac atactatcca 180
      ggctccgtga agggccgatt caccatctcc agagaaaatg ccaagaactc cttgtatctt 240
40
      caaatgaaca gcttgagagc cggggacacg gctgtgtatt actgtgcaag aactggagca 300
      gcagcccact cgtactacta cggtatggac gtctgggggc aagggaccac ggtcaccgct 360
      tcct                                     364

```

45 <210> 454
<211> 121
<212> PRT
<213> Artificial Sequence

50 <220>
<223> Synthetic

<400> 454

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	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	Tyr
5				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	Thr	Val	Gly	Asp	Thr	Tyr	Tyr	Pro	Gly	Ser	Val	Lys
		50					55					60				
10	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	Thr	Gly	Ala	Ala	His	Ser	Tyr	Tyr	Gly	Met	Asp	Val	Trp		
				100				105				110				
15	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser							
			115				120									

<210> 455

<211> 322

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

25

<400> 455

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	ctctcctgca	gggccagtca	gagtgttagc	agcagctact	tagcctggta	ccagcagaaa	120
30	cctggccagg	ctcccaggct	cctcatctat	ggtgcatcca	gcagggccac	tggcatccca	180
	gacaggttca	gtggcagtg	gtctgggaca	gacttcactc	tcaccatcag	cagactggag	240
	cctgaagatt	ttgcagtgt	ttactgtcag	cagtatggta	gctcaccac	tttcggcgga	300
	gggaccaagg	tggagatcaa	ac				322

35 <210> 456

<211> 107

<212> PRT

<213> Artificial Sequence

40 <220>

<223> Synthetic

<400> 456

45	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	Ser	Ser
				20					25					30		
50	Tyr	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu

55

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35 40 45
 Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
 50 55 60
 5 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
 Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105
 10
 <210> 457
 <211> 345
 <212> DNA
 <213> Artificial Sequence
 15
 <220>
 <223> synthetic
 20
 <400> 457
 gaggtgcagc tgggtggagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggctc 60
 tcctgtaagg cttctggatt caccttcacc gactactata tgcactgggt gcgacaggcc 120
 cctggacaag ggcttgagtg gctgggatgg atcaacccta agagtgggtgc gacaaagtat 180
 gcacagaggt ttcagggcag ggtcaccatg accagggaca cgtccatcag cacagcctac 240
 25 atggaactga acggactaag atctgacgac acggccggtt tttactgtgc gcgaactgat 300
 gcttttgata tctggggcca agggacaatg gtcaccgtct cttca 345
 <210> 458
 <211> 115
 30 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Synthetic
 35 <400> 458
 Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15
 40 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Phe Thr Asp Tyr
 20 25 30
 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Leu
 35 40 45
 45 Gly Trp Ile Asn Pro Lys Ser Gly Ala Thr Lys Tyr Ala Gln Arg Phe
 50 55 60
 Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Asn Gly Leu Arg Ser Asp Asp Thr Ala Val Phe Tyr Cys
 85 90 95
 50 Ala Arg Thr Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr
 100 105 110
 Val Ser Ser
 115
 55 <210> 459
 <211> 24
 <212> DNA
 <213> Artificial Sequence

EP 2 475 684 B1

<220>
 <223> Synthetic

 <400> 459
 5 ggattcacct tcaccgacta ctat 24

 <210> 460
 <211> 8
 <212> PRT
 10 <213> Artificial Sequence

 <220>
 <223> Synthetic

 15 <400> 460

 Gly Phe Thr Phe Thr Asp Tyr Tyr
 1 5

 20 <210> 461
 <211> 24
 <212> DNA
 <213> Artificial Sequence

 25 <220>
 <223> Synthetic

 <400> 461
 30 atcaacccta agagtgggtgc gaca 24

 <210> 462
 <211> 8
 <212> PRT
 <213> Artificial Sequence
 35
 <220>
 <223> Synthetic

 <400> 462
 40
 Ile Asn Pro Lys Ser Gly Ala Thr
 1 5

 45 <210> 463
 <211> 24
 <212> DNA
 <213> Artificial Sequence

 <220>
 50 <223> Synthetic

 <400> 463
 gcgcgaactg atgcttttga tatc 24

 55 <210> 464
 <211> 8
 <212> PRT
 <213> Artificial Sequence

EP 2 475 684 B1

<220>

<223> Synthetic

<400> 464

5

Ala Arg Thr Asp Ala Phe Asp Ile
1 5

<210> 465

10

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

15

<223> Synthetic

<400> 465

20

gacatccagt tgacccagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtc gagtggttagt aactgggttg cctgggtatca gcagaaacca 120
gggaaagccc ctaaactcct gatctattcg gcgtctactt tagaaagtgg ggtcccatca 180
aggttcagcg gcagtgaatc tgggacagaa ttcactctca ccatacagcag cctgcagcct 240
gatgattttg caacttatta ctgccaacac tataatagtt attggacggt cggccaaggg 300
accaaggtgg aaatcaaacg a 321

25

<210> 466

<211> 107

<212> PRT

<213> Artificial Sequence

30

<220>

<223> Synthetic

<400> 466

35

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

50

<210> 467

<211> 18

<212> DNA

<213> Artificial Sequence

55

<220>

<223> Synthetic

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<400> 467
 cagagtgtta gtaactgg 18

 5 <210> 468
 <211> 6
 <212> PRT
 <213> Artificial Sequence

 10 <220>
 <223> Synthetic

 <400> 468

 15 Gln Ser Val Ser Asn Trp
 1 5

 20 <210> 469
 <211> 9
 <212> DNA
 <213> Artificial Sequence

 25 <220>
 <223> Synthetic

 <400> 469
 tcggcgtct 9

 30 <210> 470
 <211> 3
 <212> PRT
 <213> Artificial Sequence

 35 <220>
 <223> Synthetic

 <400> 470

 40 Ser Ala Ser
 1

 45 <210> 471
 <211> 24
 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Synthetic

 50 <400> 471
 caacactata atagttattg gacg 24

 55 <210> 472
 <211> 8
 <212> PRT
 <213> Artificial Sequence

 <220>

EP 2 475 684 B1

<223> Synthetic

<400> 472

5 Gln His Tyr Asn Ser Tyr Trp Thr
1 5

<210> 473

<211> 345

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

15

<400> 473

20 caggtgcagc tgggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggctc 60
tcctgtaagg cttctggatt caccttcacc gactactata tgcactgggt gcgacaggcc 120
cctggacaag ggcttgagtg gctgggatgg atcaacccta agagtgggtgc gacaaagtat 180
gcacagaggt ttcagggcag ggtcaccatg accagggaca cgtccatcag cacagcctac 240
atggaactga acggactaag atctgacgac acggccggtt tttactgtgc gcgaactgat 300
gcttttgata tctggggcca agggacaatg gtcaccgtct cttca 345

25

<210> 474

<211> 115

<212> PRT

<213> Artificial Sequence

30

<220>

<223> Synthetic

<400> 474

35

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

<210> 475

<211> 318

55 <212> DNA

<213> Artificial Sequence

<220>

EP 2 475 684 B1

<223> Synthetic

<400> 475

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      gggaaagccc ctaaacctct gatctattcg gcgtctactt tagaaagtgg ggtcccatca 180
      aggttcagcg gcagtgaatc tgggacagaa ttcactctca ccatcagcag cctgcagcct 240
10     gatgatTTTT caacttatta ctgccaacac tataatagtt attggacgtt cggccaaggg 300
      accaaggtgg aaatcaaa                                     318

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<210> 476

<211> 106

15 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

20

<400> 476

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

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<210> 477

<211> 345

40 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

45

<400> 477

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50     tcctgcaagg cttctggatt caccttcacc gactactata tgcactgggt gcgacaggcc 120
      cctggacaag ggcttgagtg gatgggatgg atcaacccta agagtgggtgc gacaaactat 180
      gcacagaagt ttcagggcag ggtcaccatg accagggaca cgtccatcag cacagcctac 240
      atggagctga gcaggctgag atctgacgac acggcctgtg attactgtgc gcgaactgat 300
      gcttttgata tctggggcca agggacaatg gtcaccgtct cttca                                     345

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55 <210> 478

<211> 115

<212> PRT

<213> Artificial Sequence

EP 2 475 684 B1

<220>

<223> Synthetic

<400> 478

5

10

15

20

```

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

```

<210> 479

<211> 319

25

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

30

<400> 479

35

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gacatccaga tgaccagtc tccttcacc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggccagtc gagtgtagt aactgggttg cctgggtatca gcagaaacca 120
gggaaagccc ctaagtcct gatctattcg gcgtctagtt tagaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttactctca ccatcagcag cctgcagcct 240
gatgattttg caacttatta ctgccaacac tataatagtt attggacggt cgccaagggt 300
accaaggtgg aaatcaaac
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<210> 480

<211> 106

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 480

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EP 2 475 684 B1

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

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<210> 481

<211> 354

<212> DNA

20 <213> Artificial Sequence

<220>

<223> Synthetic

25 <400> 481

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	tcctgtgcag	cgtctggatt	caccttcagt	agctatggca	tgcactgggt	ccgccaggct	120
	ccaggcaagg	ggctggagtg	ggtggcagtt	atatggtatg	atggaagtaa	taaatactat	180
30	gcagactccg	tgaagggccg	attcaccatc	tcagagaca	attccaagaa	cacgctgtat	240
	ctgcaaata	acagcctgag	agccgaggac	acggctgtgt	attactgtgc	gagagatgga	300
	tatagtggct	acgatgacta	ctggggccag	ggaaccctgg	tcaccgtctc	ctca	354

35 <210> 482

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

40 <223> Synthetic

<400> 482

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55

EP 2 475 684 B1

	Glu	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		
5	Gly	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
			35				40						45			
	Ala	Val	Ile	Trp	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
10	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	Tyr	Ser	Gly	Tyr	Asp	Asp	Tyr	Trp	Gly	Gln	Gly	Thr
			100						105					110		
15	Leu	Val	Thr	Val	Ser	Ser										
			115													

<210> 483
 <211> 24
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 483
 ggattcacct tcagtagcta tggc 24

<210> 484
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 484

				Gly	Phe	Thr	Phe	Ser	Ser	Tyr	Gly
				1				5			

<210> 485
 <211> 24
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 485
 atatggtatg atggaagtaa taaa 24

<210> 486
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>

EP 2 475 684 B1

<223> Synthetic

<400> 486

5 Ile Trp Tyr Asp Gly Ser Asn Lys
1 5

<210> 487

<211> 33

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

15

<400> 487

gcgagagatg gatatagtgg ctacgatgac tac 33

<210> 488

20 <211> 11

<212> PRT

<213> Artificial Sequence

<220>

25 <223> Synthetic

<400> 488

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

<210> 489

<211> 321

<212> DNA

35 <213> Artificial Sequence

<220>

<223> Synthetic

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<400> 489

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atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tacaaagtgg ggtcccatca 180
45 aggttcagcg gcagtggatc tggcacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacaa gattacaatt accctcggac gttcggccaa 300
gggaccaagg tggaaatcaa a 321

<210> 490

50 <211> 107

<212> PRT

<213> Artificial Sequence

<220>

55 <223> Synthetic

<400> 490

EP 2 475 684 B1

	Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
	1				5					10					15	
5	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Gly	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					
10	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	Arg
				85					90					95		
	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys					
15				100					105							

<210> 491

<211> 18

<212> DNA

20 <213> Artificial Sequence

<220>

<223> Synthetic

25 <400> 491

cagggcatta gaaatgat 18

<210> 492

<211> 6

30 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

35 <400> 492

Gln	Gly	Ile	Arg	Asn	Asp
1				5	

40 <210> 493

<211> 9

<212> DNA

45 <213> Artificial Sequence

<220>

<223> Synthetic

50 <400> 493

gctgcatcc 9

<210> 494

<211> 3

<212> PRT

55 <213> Artificial Sequence

<220>

<223> Synthetic

EP 2 475 684 B1

<400> 494

Ala Ala Ser
1

5

<210> 495
<211> 27
<212> DNA
<213> Artificial Sequence

10

<220>
<223> Synthetic

15

<400> 495
ctacaagatt acaattaccc tcggacg 27

20

<210> 496
<211> 9
<212> PRT
<213> Artificial Sequence

25

<400> 496

Leu Gln Asp Tyr Asn Tyr Pro Arg Thr
1 5

30

<210> 497
<211> 354
<212> DNA
<213> Artificial Sequence

35

<220>
<223> Synthetic

<400> 497

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tcctgtgcag	cgtctggatt	caccttcagt	agctatggca	tgcactgggt	ccgccaggct	120
ccaggcaagg	ggctggagtg	ggtggcagtt	atatggtatg	atggaagtaa	taaatactat	180
gcagactccg	tgaagggccg	attcaccatc	tccagagaca	attccaagaa	cacgctgtat	240
ctgcaaata	acagcctgag	agccgaggac	acggctgtgt	attactgtgc	gagagatgga	300
tatagtggct	acgatgacta	ctggggccag	ggaaccctgg	tcaccgtctc	ctca	354

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<210> 498
<211> 118
<212> PRT
<213> Artificial Sequence

50

<220>
<223> Synthetic

55

<400> 498

EP 2 475 684 B1

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 Trp 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 Arg Asp Gly Tyr Ser Gly Tyr Asp Asp Tyr Trp Gly Gln Gly Thr
 100 105 110
 Leu Val Thr Val Ser Ser
 115

<210> 499
 <211> 321
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 499

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 gggaaagccc ctaagctcct gatctatgct gcatccagtt tacaaagtgg ggtcccatca 180
 aggttcagcg gcagtggatc tggcacagat ttcaactctca ccatcagcag cctgcagcct 240
 gaagattttg caacttatta ctgtctacaa gattacaatt accctcggac gttcggccaa 300
 gggaccaagg tggaaatcaa a 321

<210> 500
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 500

EP 2 475 684 B1

	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	Gly	Ile	Arg	Asn	Asp
			20					25					30			
5	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
10	65					70					75				80	
	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Leu	Gln	Asp	Tyr	Asn	Tyr	Pro	Arg
				85						90				95		
	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys					
				100					105							

15

<210> 501
 <211> 354
 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> Synthetic

25

<400> 501

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tcctgtgcag  cgtctggatt  caccttcagt  agctatggca  tgcactgggt  ccgccaggct  120
ccaggcaagg  ggctagagtg  ggtggcagtt  atatggtatg  atggaagtaa  taaatactat  180
gcagactccg  tgaagggccg  attcaccatc  tccagagaca  attccaagaa  cgcgctgtat  240
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35

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ctgcaaataga  acagcctgag  agccgaggac  acggctgtgt  attactgtgc  gagagatgga  300
tatagtggct  acgatgacta  ctgggggccg  ggaaccctgg  tcaccgtctc  ctca  354
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<210> 502
 <211> 118
 <212> PRT
 <213> Artificial Sequence

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<220>
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<400> 502

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EP 2 475 684 B1

[illegible]

<210> 503

$\langle 211 \rangle$ 322

<212> DNA

<213> Artificial Sequence

 $\langle 220 \rangle$

<223> Synthetic

<400> 503

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	atcacttgcc	gggcaagtca	gggcattaga	aatgatttag	gctgggtatca	gcagaaacca	120
	gggaaagccc	ctaagctcct	gatctatgct	gcatccagtt	tacaaagtgg	ggtcccatca	180
	aggttcagcg	gcagtggatc	tggcacagat	ttcactctca	ccatcagcag	cctgcagcct	240
	gaagattttg	caacttatta	ctgtctacaa	gattacaatt	accctcggac	gttcggccaa	300
	gggaccaagg	tggaaatcaa	ac				322

<210> 504

<211> 107

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

<223> Synthetic

<400> 504

50 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 Gly 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

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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
 5 Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Asp Tyr Asn Tyr Pro Arg
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105
 10 <210> 505
 <211> 348
 <212> DNA
 <213> Artificial Sequence
 15 <220>
 <223> Synthetic
 <400> 505
 20 gaggtgcagc tgggtgcagtc tgggggagggc ttggtacagc ctggcaggtc cctgagactc 60
 tcctgtgcag cctctggatt cacctttgat gattatgcc a tgcactgggt ccgacaaggt 120
 ccagggaagg gcctggagtg ggtctcaggt attagttgga atggtggtag cgcaggctat 180
 gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
 ctgcaattga acagtctgag agctgaggac acggccttgt attactgtgc aaaagaagac 300
 25 tatgcttttg atatctgggg ccaagggaca atggtcaccg tctcctca 348
 <210> 506
 <211> 116
 <212> PRT
 30 <213> Artificial Sequence
 <220>
 <223> Synthetic
 35 <400> 506
 Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1 5 10 15
 40 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 Gly Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Gly Ile Ser Trp Asn Gly Gly Ser Ala Gly Tyr Ala Asp Ser Val
 50 55 60
 45 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65 70 75 80
 Leu Gln Leu Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
 85 90 95
 50 Ala Lys Glu Asp Tyr Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val
 100 105 110
 Thr Val Ser Ser
 115
 <210> 507
 55 <211> 24
 <212> DNA
 <213> Artificial Sequence

EP 2 475 684 B1

<220>
 <223> Synthetic

 <400> 507
 5 ggattcacct ttgatgatta tgcc 24

 <210> 508
 <211> 8
 <212> PRT
 10 <213> Artificial Sequence

 <220>
 <223> Synthetic

 15 <400> 508

 Gly Phe Thr Phe Asp Asp Tyr Ala
 1 5

 20 <210> 509
 <211> 24
 <212> DNA
 <213> Artificial Sequence

 25 <220>
 <223> Synthetic

 <400> 509
 30 attagttgga atggtggtag cgca 24

 <210> 510
 <211> 8
 <212> PRT
 35 <213> Artificial Sequence

 <220>
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 <400> 510
 40
 Ile Ser Trp Asn Gly Gly Ser Ala
 1 5

 45 <210> 511
 <211> 27
 <212> DNA
 <213> Artificial Sequence

 <220>
 50 <223> Synthetic

 <400> 511
 gcaaaagaag actatgctt tgatatc 27

 55 <210> 512
 <211> 9
 <212> PRT
 <213> Artificial Sequence

EP 2 475 684 B1

<220>

<223> Synthetic

<400> 512

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Ala Lys Glu Asp Tyr Ala Phe Asp Ile

10

1

5

<210> 513

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<212> DNA

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<213> Artificial Sequence

<220>

<223> Synthetic

20

<400> 513

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atctcctgca ggtctagtca aagcctcgta cacagtgatg gaaacaccta cttgagttgg 120
cttcagcaga ggccaggcca gctccaaga ctctaattt ataagatttc taaccggttc 180
25 tctggggtcc cagacagatt cagtggcagt ggggcagggg cagatttcac actgaaaatc 240
agcaggggtg aagctgagga tgcgggggtt tattactgca tgcaagctac acaatttccg 300
tacacttttg gccaggggac caaggtggag atcaaa 336

30

<210> 514

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

35

<223> Synthetic

<400> 514

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

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<210> 515

<211> 33

<212> DNA

<213> Artificial Sequence

EP 2 475 684 B1

<220>

<223> Synthetic

<400> 515

5 caaagcctcg tacacagtga tggaaacacc tac 33

<210> 516

 $\langle 211 \rangle$ 11

<212> PRT

10 <213> Artificial Sequence

<220>

<223> Synthetic

<400> 516

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

20 <210> 517

<211> 9

<212> DNA

<213> Artificial Sequence

25 <220>

<223> Synthetic

<400> 517

aagatttct 9

<210> 518

$\langle 211 \rangle$ 3

<212> PRT

<213> Artificial Sequence

35

<220>

<223> Synthetic

<400> 518

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Lys Ile Ser
1

<210> 519

45 <211> 27

<212> DNA

<213> Artificial Sequence

<220>

50 <223> Synthetic

<400> 519

atgcaagcta cacaatttcc gtacact 27

55 <210> 520

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<212> PRT

<213> Artificial Sequence

EP 2 475 684 B1

<220>

<223> Synthetic

<400> 520

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Met Gln Ala Thr Gln Phe Pro Tyr Thr
1 5

<210> 521

10

<211> 348

<212> DNA

<213> Artificial Sequence

<220>

15

<223> Synthetic

<400> 521

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ccagggaagg gcctggagtg ggtctcaggt attagttgga atggtggttag cgcaggctat 180
gctgactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
ctgcaattga acagtctgag agctgaggac acggccttgt attactgtgc aaaagaagac 300
tatgcttttg atatctgggg ccaagggaca atggtcaccg tctcttca 348

25

<210> 522

<211> 116

<212> PRT

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<213> Artificial Sequence

<220>

<223> Synthetic

35

<400> 522

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

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<210> 523

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<211> 336

<212> DNA

<213> Artificial Sequence

EP 2 475 684 B1

<220>

<223> Synthetic

<400> 523

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atctcctgca ggtctagtca aagcctcgta cacagtgatg gaaacaccta cttgagttgg 120
cttcagcaga ggccaggcca gcctccaaga ctccataattt ataagatttc taaccgggttc 180
tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
10 agcaggggtgg aagctgagga tgtcgggggtt tattactgca tgcaagctac acaatttccg 300
tacacttttg gccaggggac caagctggag atcaaa 336

<210> 524

<211> 112

15 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

20
<400> 524

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

<210> 525

<211> 348

40 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

45
<400> 525

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tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120
ccagggaagg gcctggagtg ggtctcaggt attagttgga atggtggtag cgcaggctat 180
gcggaactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
ctgcaaatga acagtctgag agctgaggac acggccttgt attactgtgc aaaagaagac 300
tatgcttttg atatctgggg ccaagggaca atggtcaccg tctcttca 348

55
<210> 526

<211> 116

<212> PRT

EP 2 475 684 B1

<213> Artificial Sequence

<220>

<223> Synthetic

5

<400> 526

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	1				5				10				15			
10	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	Ser	Trp	Asn	Gly	Gly	Ser	Ala	Gly	Tyr	Ala	Asp	Ser	Val
15		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			
20	Ala	Lys	Glu	Asp	Tyr	Ala	Phe	Asp	Ile	Trp	Gly	Gln	Gly	Thr	Met	Val
				100					105				110			
	Thr	Val	Ser	Ser												
				115												

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<211> 337

<212> DNA

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30 <220>

<223> Synthetic

<400> 527

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	atctcctgca	ggctctagtc	aagcctcgta	cacagtgatg	gaaacaccta	cttgagttgg	120
	cttcagcaga	ggccaggcca	gcctccaaga	ctcctaattt	ataagatttc	taaccggttc	180
	tctgggggtcc	cagacagatt	cagtggcagt	ggggcaggga	cagatttcac	actgaaaatc	240
	agcaggggtg	aagctgagga	tgtcgggggt	tattactgca	tgcaagctac	acaatttccg	300
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<210> 528

<211> 112

<212> PRT

45 <213> Artificial Sequence

<220>

<223> Synthetic

50 <400> 528

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

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<211> 348

<212> DNA

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 529

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	tcctgtgcag	cctctggatt	cacctttgaa	gattatgcc	tgcactgggt	ccggcaagct	120
	ccagggaagg	gcctggaatg	ggtctcaggt	attacttgga	atagtataa	taaaggctat	180
	gcggaactctg	tgaagggccg	attcaccatc	tccagagaca	acgccaagta	ctccctgtat	240
30	ctgcaaata	acagtctgag	agctgaggac	acggccttgt	attactgtgc	aaaagaggac	300
	tgggcgtttg	actactgggg	ccagggaacc	ctggtcaccg	tctcctca		348

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<210> 530

<211> 116

35

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

40

<400> 530

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

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<210> 531
 <211> 24
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 <213> Artificial Sequence
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 <211> 8
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 15 <213> Artificial Sequence
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 20 <400> 532
 Gly Phe Thr Phe Glu Asp Tyr Ala
 1 5
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 <211> 24
 <212> DNA
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 <400> 533
 35 attacttgga atagtgataa taaa 24
 <210> 534
 <211> 8
 <212> PRT
 40 <213> Artificial Sequence
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 <400> 534
 45 Ile Thr Trp Asn Ser Asp Asn Lys
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 50 <210> 535
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 55 <223> Synthetic
 <400> 535
 gcaaaagagg actgggcgtt tgactac 27

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<210> 536
 <211> 9
 <212> PRT
 <213> Artificial Sequence

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<220>
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<400> 536

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Ala Lys Glu Asp Trp Ala Phe Asp Tyr
 1 5

<210> 537
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 <213> Artificial Sequence

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<220>
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<400> 537

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 atcacttgct gtgcgagtc gggatattaac agttgggtag cctgggtatca gcagaaacca 120
 gggaaagccc ctaagctcct gatctacgct gcatccagtt tgcagagtgg ggtcccatca 180
 aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcgg cctccagcct 240
 gaagattttg caacttacta ttgtcaacag gctaacagtt tcccgtacac ttttggccag 300
 gggaccaagg tggaaatcaa a 321

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 <211> 107
 <212> PRT
 <213> Artificial Sequence

35

<220>
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<400> 538

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 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Asn Ser Trp

45

20 25 30
 Leu Ala 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 Gly Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Tyr
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 100 105

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<210> 539

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 <210> 540
 <211> 6
 <212> PRT
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 15
 <220>
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 <400> 540
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 1 5
 <210> 541
 25 <211> 9
 <212> DNA
 <213> Artificial Sequence
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 30 <223> Synthetic
 <400> 541
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 35 <210> 542
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 <213> Artificial Sequence
 40 <220>
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 <400> 542
 45
 Ala Ala Ser
 1
 <210> 543
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 50 <212> DNA
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 55
 <400> 543
 caacaggcta acagttccc gtacact 27

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 <212> PRT
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<400> 544

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Gln Gln Ala Asn Ser Phe Pro Tyr Thr
 1 5

<210> 545
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 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> Synthetic

20

<400> 545

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 tcctgtgcag cctctggatt cacctttgaa gattatgcca tgcactgggt ccggcaagct 120
 ccagggaagg gcctggaatg ggtctcagggt attacttgga atagtataa taaaggctat 180
 gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagta ctccctgtat 240
 ctgcaaatac acagtctgag agctgaggac acggccttgt attactgtgc aaaagaggac 300
 tgggcgcttg actactgggg ccagggaacc ctggtcaccg tctcctca 348

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<210> 546
 <211> 116
 <212> PRT
 <213> Artificial Sequence

35

<220>
 <223> Synthetic

<400> 546

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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 Glu 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 Thr Trp Asn Ser Asp Asn Lys Gly Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Tyr 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

50

Ala Lys Glu Asp Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110
 Thr Val Ser Ser
 115

55

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 atcacttgtc gtgcgagtc gggatattaac agttgggttag cctgggtatca gcagaaacca 120
 gggaaagccc ctaagctcct gatctacgct gcatccagtt tgcagagtgg ggtcccatca 180
 15 aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcgg cctccagcct 240
 gaagattttg caacttacta ttgtcaacag gctaacagtt tcccgtacac ttttggccag 300
 gggaccaagc tggagatcaa a 321

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 <212> PRT
 <213> Artificial Sequence

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 <220>
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 25
 <400> 548
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 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Asn 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 Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 35 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Gly Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Tyr
 85 90 95
 40 Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
 100 105

<210> 549
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 <212> DNA
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45
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 ccagggaagg gcctggagtg ggtctcaggt attacttggg atagtgataa taaaggctat 180
 gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctcccctgtat 240
 ctgcaaataa acagtctgag agctgaggac acggccttgt attactgtgc aaaagaggac 300

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348

<210> 550

<211> 116

<212> PRT

<213> Artificial Sequence

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<400> 550

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

<210> 551

<211> 322

<212> DNA

<213> Artificial Sequence

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<223> Synthetic

<400> 551

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	gggaaagccc	ctaagtcct	gatctatgct	gcattccagtt	tgcaaagtgg	ggtooccatca	180
45	aggttcagcg	gcagtggatc	tgggacagat	ttcactctca	ctatcagcag	cctgcagcct	240
	gaagattttg	caacttacta	ttgtcaacag	gctaacagtt	tcccgtagac	ttttggccag	300
	gggaccaagc	tgagatcaa	ac				322

<210> 552

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 552

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

<210> 553
 <211> 348
 <212> DNA
 20 <213> Artificial Sequence

<220>
 <223> Synthetic

25 <400> 553

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 tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120
 ccaggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag caaaggctat 180
 30 gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
 ctgcaaata acagtctgag acgtgaggac acggccttgt attactgtgt aaaagaggac 300
 tgggcgtttg actactgggg ccaggaacc ctggtcaccg tctctca 348

<210> 554
 35 <211> 116
 <212> PRT
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 40 <223> Synthetic

<400> 554

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

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 <212> DNA
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<400> 555
 ggattcacct ttgatgatta tgcc 24

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<400> 556

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 Gly Phe Thr Phe Asp Asp Tyr Ala
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 <212> DNA
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<400> 557
 attagttaga atagttagtag caaa 24

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 <210> 558
 <211> 8
 <212> PRT
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EP 2 475 684 B1

<220>

<223> Synthetic

<400> 558

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Ile Ser Trp Asn Ser Gly Ser Lys
1 5

<210> 559

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<211> 27

<212> DNA

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<220>

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<223> Synthetic

<400> 559

gtaaaagagg actgggcgtt tgactac 27

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<210> 560

<211> 9

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 560

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Val Lys Glu Asp Trp Ala Phe Asp Tyr
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<210> 561

<211> 315

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<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 561

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atcacttgcc aggcgagtc ggacattagc aactatTTaa attggtatca acaaaaacca 120
gggaaagccc ctaagttcct gatctacgat gcatccaatt tgggaacagg ggtcccatca 180
aggttcagtg gaagtggatc tgggacagat ttacttttca ccatcagcag cctgcagcct 240
gaagatattg cgacatatta ctgtcaacag tatgataatc tccctttcgg cggaggggacc 300
aaggtggaaa tcaaa 315

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<211> 105

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

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 5 Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Ser Asn Tyr
 20 25 30
 Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Phe Leu Ile
 35 40 45
 Tyr Asp Ala Ser Asn Leu Gly Thr Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 10 Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Asn Leu Pro Phe
 85 90 95
 Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105
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<210> 563
 <211> 18
 <212> DNA
 20 <213> Artificial Sequence

<220>
 <223> Synthetic

25 <400> 563
 caggacatta gcaactat 18

<210> 564
 <211> 6
 30 <212> PRT
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<220>
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35 <400> 564

Gln Asp Ile Ser Asn Tyr
 1 5
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<210> 565
 <211> 9
 <212> DNA
 45 <213> Artificial Sequence

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50 <400> 565
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<210> 566
 <211> 3
 <212> PRT
 55 <213> Artificial Sequence

<220>
 <223> Synthetic

EP 2 475 684 B1

<400> 566

Asp Ala Ser
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<212> DNA
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<220>
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<400> 567
caacagtatg ataatctccc t 21

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<210> 568
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<212> PRT
<213> Artificial Sequence

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<400> 568

Gln Gln Tyr Asp Asn Leu Pro
1 5

30

<210> 569
<211> 348
<212> DNA
<213> Artificial Sequence

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<220>
<223> Synthetic

<400> 569

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ccagggaagg	gcctggagtg	ggtctcaggt	attagttgga	atagtggtag	caaaggctat	180
gcggactctg	tgaagggccg	attcaccatc	tccagagaca	acgccaagaa	ctccctgtat	240
ctgcaaata	acagtctgag	acgtgaggac	acggccttgt	attactgtgt	aaaagaggac	300
tgggcgtttg	actactgggg	ccagggaacc	ctggtcaccg	tctcctca		348

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<210> 570
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<212> PRT
<213> Artificial Sequence

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<220>
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55

<400> 570

EP 2 475 684 B1

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

<210> 571

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20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 571

	gacatccaga	tgaccagtc	tccatcctcc	ctgtctgcat	ctgtaggaga	cagagtcacc	60
	atcacttgcc	aggcgagtca	ggacattagc	aactatttaa	attggtatca	acaaaaacca	120
30	gggaaagccc	ctaagttcct	gatctacgat	gcatccaatt	tgggaacagg	ggtcccatca	180
	aggttcagtg	gaagtggatc	tgggacagat	tttactttca	ccatcagcag	cctgcagcct	240
	gaagatattg	cgacatatta	ctgtcaacag	tatgataatc	tccctttcgg	cggaggggacc	300
	aaggtggaga	tcaaa					315

35 <210> 572

<211> 105

<212> PRT

<213> Artificial Sequence

40 <220>

<223> Synthetic

<400> 572

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

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<210> 573
 <211> 348
 <212> DNA
 <213> Artificial Sequence

5
 <220>
 <223> Synthetic

10
 <400> 573

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    tcctgtgcag  cctctggatt  cacctttgat  gattatgcc  tgcactgggt  ccggcaagct  120
    ccagggaagg  gcctggagtg  ggtctcaggt  attagttgga  atagtggtag  caaaggctat  180
    gcggaactctg  tgaagggccg  attcaccatc  tccagagaca  acgccaagaa  ctccctgtat  240
    ctgcaaataga  acagtctgag  agctgaggac  acggccttgt  attactgtgt  aaaagaggac  300
    tgggcgtttg  actactgggg  ccagggaacc  ctggtcaccg  tctcctca    348
  
```

<210> 574
 <211> 116
 <212> PRT
 <213> Artificial Sequence

20
 <220>
 <223> Synthetic

25
 <400> 574

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    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 Ser Trp Asn Ser Gly Ser Lys 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 Asp Trp Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
    100      105      110
    Thr Val Ser Ser
    115
  
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45
 <210> 575
 <211> 316
 <212> DNA
 <213> Artificial Sequence

50
 <220>
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55
 <400> 575

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 atcacttgcc aggcgagtc ggacattagc aactatttaa attggtatca gcagaaacca 120
 gggaaagccc ctaagtcct gatctacgat gcatccaatt tggaaacagg ggtcccatca 180
 5 aggttcagtg gaagtggatc tgggacagat tttactttca ccatcagcag cctgcagcct 240
 gaagatattg caacatatta ctgtcaacag tatgataatc tccctttcgg cggaggggacc 300
 aaggtggaga tcaaac 316

<210> 576

<211> 105

10 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

15

<400> 576

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

<210> 577

<211> 375

35 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

40

<400> 577

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 acctgtgcc tctccgggga cagtgtctct agcaacagtg ctgcttgga ctggatcagg 120
 45 cagtcccat cgagaggcct tgagtggctg ggaaggacat actacaggtc caagtggat 180
 aatgattatg cagtatctgt gaaaagtcga ataaccatca acccagacac atccaagaac 240
 cagttctccc tgcagctgaa ctctgtgact cccgaggaca cggctgtgta ttactgtgca 300
 agagggtata gcagcagctg gtacgggggt gcttttgata tctggggcca agggacaatg 360
 50 gtcaccgtct cttca 375

<210> 578

<211> 125

<212> PRT

<213> Artificial Sequence

55

<220>

<223> Synthetic

EP 2 475 684 B1

<400> 578

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

20 <210> 579
 <211> 30
 <212> DNA
 <213> Artificial Sequence

25 <220>
 <223> Synthetic

<400> 579
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30 <210> 580
 <211> 10
 <212> PRT
 <213> Artificial Sequence

35 <220>
 <223> Synthetic

40 <400> 580

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	1				5					10

45 <210> 581
 <211> 27
 <212> DNA
 <213> Artificial Sequence

50 <220>
 <223> Synthetic

<400> 581
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55 <210> 582
 <211> 9
 <212> PRT
 <213> Artificial Sequence

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<220>

<223> Synthetic

<400> 582

5

Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn
1 5

<210> 583

10

<211> 45

<212> DNA

<213> Artificial Sequence

<220>

15

<223> Synthetic

<400> 583

gcaagagggt atagcagcag ctggtacggg ggtgctttg atatc 45

20

<210> 584

<211> 15

<212> PRT

<213> Artificial Sequence

25

<220>

<223> Synthetic

<400> 584

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Ala Arg Gly Tyr Ser Ser Ser Trp Tyr Gly Gly Ala Phe Asp Ile
1 5 10 15

<210> 585

<211> 321

35

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

40

<400> 585

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atcacttgcc gggcaagtca gagcattagc agttatttaa gttggtatca gcagaaacca 120
45 gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccacagcag tctgcaacct 240
gaagattttg caacttacta ctgtcaacag agttacagta cccattcac ttcggccct 300
gggaccaagg tggaaatcaa a 321

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<210> 586

<211> 107

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 586

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

<210> 587
 <211> 18
 20 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

25 <400> 587
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30 <210> 588
 <211> 6
 <212> PRT
 <213> Artificial Sequence

35 <220>
 <223> Synthetic

<400> 588

					Gln	Ser	Ile	Ser	Ser	Tyr
40					1				5	

<210> 589
 <211> 9
 45 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

50 <400> 589
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55 <210> 590
 <211> 3
 <212> PRT
 <213> Artificial Sequence

<220>

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<223> Synthetic

<400> 590

5 Ala Ala Ser
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<210> 591

<211> 27

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

15

<400> 591

caacagagtt acagtacccc attcact 27

<210> 592

20 <211> 9

<212> PRT

<213> Artificial Sequence

<220>

25 <223> Synthetic

<400> 592

30 Gln Gln Ser Tyr Ser Thr Pro Phe Thr
1 5

<210> 593

<211> 375

<212> DNA

35 <213> Artificial Sequence

<220>

<223> Synthetic

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<400> 593

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acctgtgcc a tctccgggga cagtgtctct agcaacagtg ctgcttggaa ctggatcagg 120
cagtccccat cgagaggcct tgagtggctg ggaaggacat actacaggtc caagtggat 180
aatgattatg cagtatctgt gaaaagtcga ataaccatca acccagacac atccaagaac 240
cagttctccc tgcagctgaa ctctgtgact cccgaggaca cggctgtgta ttactgtgca 300
agagggtata gcagcagctg gtacgggggt gcttttgata tctggggcca agggacaatg 360
gtcaccgtct cttca 375

50 <210> 594

<211> 125

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 594

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

				85					90					95		
15	Tyr	Tyr	Cys	Ala	Arg	Gly	Tyr	Ser	Ser	Trp	Tyr	Gly	Gly	Ala	Phe	
			100					105					110			
	Asp	Ile	Trp	Gly	Gln	Gly	Thr	Met	Val	Thr	Val	Ser	Ser			
			115					120					125			

<210> 595
 <211> 321
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 595

30	gacatccaga	tgacccagtc	tccatcctcc	ctgtctgcat	ctgtaggaga	cagagtcacc	60
	atcacttgcc	gggcaagtca	gagcattagc	agttatttaa	gttggtatca	gcagaaacca	120
	gggaaagccc	ctaagctcct	gatctatgct	gcatccagtt	tgcaaagtgg	gggtcccatca	180
	aggttcagtg	gcagtggatc	tgggacagat	ttcactctca	ccatcagcag	tctgcaacct	240
	gaagattttg	caacttacta	ctgtcaacag	agttacagta	ccccattcac	tttcgggccct	300
35	gggacccaaag	tggatatcaa	a				321

<210> 596
 <211> 107
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 596

EP 2 475 684 B1

	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	Ser	Ile	Ser	Ser	Tyr
			20				25						30			
5	Leu	Ser	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
10	65					70					75					80
	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Tyr	Ser	Thr	Pro	Phe
					85					90					95	
	Thr	Phe	Gly	Pro	Gly	Thr	Lys	Val	Asp	Ile	Lys					
				100					105							

15

<210> 597

<211> 375

<212> DNA

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 597

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acctgtgcca tctccgggga cagtgtctct agcaacagtg ctgcttgga ctggatcagg 120
cagtcccat cgagaggcct tgagtggctg ggaaggacat actacaggtc caagtggat 180
aatgattatg cagtatctgt gaaaagtcga ataaccatca acccagacac atccaagaac 240

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30

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cagttctccc tgcagctgaa ctctgtgact cccgaggaca cggctgtgta ttactgtgca 300
agagggtata gcagcagctg gtacgggggt gcttttgata tctggggcca agggacaatg 360
gtcacctctc cttca

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<210> 598

<211> 125

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 598

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50

55

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

<210> 599

<211> 322

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 599

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	gggaaagccc	ctaagctcct	gatctatgct	gcattccagtt	tgcaaagtgg	gggtcccatca	180
	agggttcagt	gcagtggatc	tgggacagat	ttcactctca	ccatcagcag	tctgcaacct	240
	gaagattttg	caacttacta	ctgtcaacag	agttacagta	ccccattcac	tttcggccct	300
	gggaccaaaag	tgatatcaaa	ac				322

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<210> 600

<211> 107

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 600

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	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	Ser	Ile	Ser	Ser	Tyr
			20					25				30				
50	Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile

55

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35 40 45
 Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 5 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 Gln Gln Ser Tyr Ser Thr Pro Phe
 85 90 95
 Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
 100 105
 10
 <210> 601
 <211> 357
 <212> DNA
 <213> Artificial Sequence
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 <220>
 <223> Synthetic
 20
 <400> 601
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 ccaggcagtg ggctggagtg ggtctcatct attactggta gtggtgatta cgcatactac 180
 gcagactccg tgaagggccg gttcaccatc tccagagaca gttccaagaa cacgctctat 240
 ctacaaatga acagcctgag agccgacgac acggccgtat atttctgtac gagagaagac 300
 tatattaact cgtcctttga ctactggggc cagggaaacca cggtcaccgt ctccctca 357
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 <210> 602
 <211> 119
 <212> PRT
 <213> Artificial Sequence
 35
 <220>
 <223> Synthetic
 40
 <400> 602
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 Gln Val Gln Leu Gln Glu Ser Gly Gly Gly Ser Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly Phe Thr Phe Thr Asn Phe
 20 25 30
 Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Ser Gly Leu Glu Trp Val
 35 40 45
 50 Ser Ser Ile Thr Gly Ser Gly Asp Tyr Ala Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Asp Asp Thr Ala Val Tyr Phe Cys
 85 90 95
 55 Thr Arg Glu Asp Tyr Ile Asn Ser Ser Phe Asp Tyr Trp Gly Gln Gly
 100 105 110
 Thr Thr Val Thr Val Ser Ser
 115
 55
 <210> 603
 <211> 24
 <212> DNA
 <213> Artificial Sequence

EP 2 475 684 B1

<220>
 <223> Synthetic

 <400> 603
 5 ggattcacct ttaccaactt tgcc 24

 <210> 604
 <211> 8
 <212> PRT
 10 <213> Artificial Sequence

 <220>
 <223> Synthetic

 15 <400> 604

 Gly Phe Thr Phe Thr Asn Phe Ala
 1 5

 20 <210> 605
 <211> 24
 <212> DNA
 <213> Artificial Sequence

 25 <220>
 <223> Synthetic

 <400> 605
 30 attactggta gtggtgatta cgca 24

 <210> 606
 <211> 8
 <212> PRT
 35 <213> Artificial Sequence

 <220>
 <223> Synthetic

 <400> 606
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 Ile Thr Gly Ser Gly Asp Tyr Ala
 1 5

 45 <210> 607
 <211> 36
 <212> DNA
 <213> Artificial Sequence

 <220>
 50 <223> Synthetic

 <400> 607
 acgagagaag actatattaa ctcgtccttt gactac 36

 55 <210> 608
 <211> 12
 <212> PRT
 <213> Artificial Sequence

EP 2 475 684 B1

<220>

<223> Synthetic

<400> 608

5

Thr Arg Glu Asp Tyr Ile Asn Ser Ser Phe Asp Tyr
1 5 10

<210> 609

10

<211> 333

<212> DNA

<213> Artificial Sequence

<220>

15

<223> Synthetic

<400> 609

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atctcctgta ggtctagtca gagcctcgta cacagtgatg gaaataccta cttgagttgg 120
cttcagcgga ggccaggcca gcctccaaga ctcttaattt ataagatttc taaccgggttc 180
tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
agcaggggtgg aagctgagga tgtcgggggtt tattactgca tgcaagctac acaacttccg 300
acgttcggcc aagggaccaa ggtggaaatc aaa 333

25

<210> 610

<211> 111

<212> PRT

30

<213> Artificial Sequence

<220>

<223> Synthetic

35

<400> 610

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

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<210> 611

<211> 33

<212> DNA

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<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 611
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 5 <210> 612
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 <212> PRT
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 10 <220>
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 <400> 612

 15 Gln Ser Leu Val His Ser Asp Gly Asn Thr Tyr
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 <210> 613
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 20 <213> Artificial Sequence

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 25 <400> 613
 aagatttct 9

 <210> 614
 <211> 3
 30 <212> PRT
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 <220>
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 35
 <400> 614

 Lys Ile Ser
 40 1

 <210> 615
 <211> 24
 <212> DNA
 45 <213> Artificial Sequence

 <220>
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 <400> 615
 50 atgcaagcta cacaacttc gacg 24

 <210> 616
 <211> 8
 <212> PRT
 55 <213> Artificial Sequence

 <220>
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<400> 616

Met Gln Ala Thr Gln Leu Pro Thr
1 5

5

<210> 617

<211> 357

<212> DNA

<213> Artificial Sequence

10

<220>

<223> Synthetic

<400> 617

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tcctgtgcaa cctctggatt cacctttacc aactttgcca taagctgggt ccgccaggct 120
ccaggcagtg ggctggagtg ggtctcatct attactggta gtggtgatta cgcatactac 180
gcagactccg tgaagggccg gttcaccatc tccagagaca gttccaagaa cagctctat 240
20 ctacaaatga acagcctgag agccgacgac acggccgtat atttctgtac gagagaagac 300
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<210> 618

<211> 119

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<212> PRT

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<220>

<223> Synthetic

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<400> 618

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

50

<210> 619

<211> 333

<212> DNA

<213> Artificial Sequence

55

<220>

<223> Synthetic

<400> 619

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 cttcagcgga ggccaggcca gcctccaaga ctcctaattt ataagatttc taaccgggttc 180
 tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
 agcaggggtgg aagctgagga tgtcgggggtt tattactgca tgcaagctac acaacttccg 300
 acgttcggcc aagggaacca ggtggaaatc aaa 333

10 <210> 620
 <211> 111
 <212> PRT
 <213> Artificial Sequence

15 <220>
 <223> Synthetic

<400> 620

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

35 <210> 621
 <211> 357
 <212> DNA
 <213> Artificial Sequence

40 <220>
 <223> Synthetic

<400> 621

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 tcctgtgcag cctctggatt cacctttacc aactttgcca tgagctgggt ccgccaggct 120
 ccaggggaagg ggctggagtg ggtctcagct attactggta gtggtgatta cgcatactac 180
 gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240
 ctgcaaatac acagcctgag agccgaggac acggccgtat attactgtac gagagaagac 300
 50 tatattaact cgtcctttga ctactggggc cagggaaccc tggtcaccgt ctcctca 357

55 <210> 622
 <211> 119
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

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<400> 622

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

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20

<210> 623

<211> 334

<212> DNA

<213> Artificial Sequence

25

<220>

<223> Synthetic

<400> 623

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      atctcctgca ggtctagtca gagcctcgta cacagtgatg gaaataccta cttgagttgg 120
      cttcagcaga ggccaggcca gcctccaaga ctcctaattt ataagatttc taaccgggtc 180
35     tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
      agcaggggtgg aagctgagga tgtcgggggt tattactgca tgcaagctac acaacttccg 300
      acgttcggcc aagggaccaa ggtggaaatc aaac 334

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40

<210> 624

<211> 111

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 624

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55

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

<210> 625

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 625

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ccaggcaagg  ggctggagtg  ggtggcagtt  atatggtatg  atggaagtaa  taaatattat  180
gtagattccg  tgaagggccg  attcaccatc  tccagagaca  attccaagaa  cacgctgtat  240
ctgcaaata  acagcctgag  agccgaggac  acggctgtgt  attactgtgc  gagcgaaatt  300
acagttgggg  actggttcga  cccctggggc  cagggaaacc  tggtcaccgt  ctccctca  357

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<210> 626

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 626

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

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<210> 627
 <211> 24
 <212> DNA
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 5
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 <400> 627
 10 ggatttacct tcaggagata tggc 24
 <210> 628
 <211> 8
 <212> PRT
 15 <213> Artificial Sequence
 <220>
 <223> Synthetic
 20 <400> 628
 Gly Phe Thr Phe Arg Arg Tyr Gly
 1 5
 25 <210> 629
 <211> 24
 <212> DNA
 <213> Artificial Sequence
 30 <220>
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 <400> 629
 35 atatggtatg atggaagtaa taaa 24
 <210> 630
 <211> 8
 <212> PRT
 40 <213> Artificial Sequence
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 <400> 630
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 Ile Trp Tyr Asp Gly Ser Asn Lys
 1 5
 50 <210> 631
 <211> 36
 <212> DNA
 <213> Artificial Sequence
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 55 <223> Synthetic
 <400> 631
 gcgagcgaaa ttacagttgg ggactgggtc gacccc 36

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<210> 632
 <211> 12
 <212> PRT
 <213> Artificial Sequence

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<220>
 <223> Synthetic

<400> 632

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Ala	Ser	Glu	Ile	Thr	Val	Gly	Asp	Trp	Phe	Asp	Pro
1				5					10		

<210> 633
 <211> 321
 <212> DNA
 <213> Artificial Sequence

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<220>
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<400> 633

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atcacttgtc	gggcaagtca	gggcattaga	aatgatttag	gctggtatca	gcagaaacca	120
gggaaagccc	ctaaactcct	gatctatgct	gcatccagtt	tacacagtgg	gggtcccatca	180
aggttcagcg	gcagtggatc	tggcacagat	ttcactctca	ccatcagcag	cctgcagcct	240
gaagattttg	caacttatta	ctgtctacag	gattttcaatt	accctctcac	tttcggcgga	300
gggaccaagg	tggagatcaa	a				321

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<210> 634
 <211> 107
 <212> PRT
 <213> Artificial Sequence

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<220>
 <223> Synthetic

<400> 634

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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	Gly	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	His	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	Phe	Asn	Tyr	Pro	Leu
				85					90				95		
Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys					
			100					105							

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<210> 635
 <211> 18

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<212> DNA
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 <220>
 5 <223> Synthetic

 <400> 635
 cagggcatta gaaatgat 18

 10 <210> 636
 <211> 6
 <212> PRT
 <213> Artificial Sequence

 15 <220>
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 <400> 636

 20 Gln Gly Ile Arg Asn Asp
 1 5

 <210> 637
 <211> 9
 25 <212> DNA
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 <220>
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 30
 <400> 637
 gctgcatcc 9

 35 <210> 638
 <211> 3
 <212> PRT
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 40 <220>
 <223> Synthetic

 <400> 638

 45 Ala Ala Ser
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 <210> 639
 <211> 27
 50 <212> DNA
 <213> Artificial Sequence

 <220>
 <223> Synthetic

 55 <400> 639
 ctacaggatt tcaattaccc tctcact 27

 <210> 640

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

5 <220>
<223> Synthetic

<400> 640

10 Leu Gln Asp Phe Asn Tyr Pro Leu Thr
1 5

<210> 641
<211> 357
15 <212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

20 <400> 641

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tcctgtgcag cgctccggatt taccttcagg agatatggca tgcactgggt ccgccagggt 120
ccaggcaagg ggctggagtg ggtggcagtt atatgggatg atggaagtaa taaatattat 180
gtagattccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaatac acagcctgag agccgaggac acggctgtgt attactgtgc gagcgaaatt 300
acagttgggg actggttcga cccctggggc cagggaaccc tggtcaccgt ctctctca 357

30 <210> 642
<211> 119
<212> PRT
<213> Artificial Sequence

35 <220>
<223> Synthetic

<400> 642

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

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<210> 643
<211> 321
<212> DNA
<213> Artificial Sequence

5

<220>
<223> Synthetic

10

<400> 643

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gggaaagccc ctaaactcct gatctatgct gcatccagtt tacacagtgg ggtcccatca 180
aggttcagcg gcagtggatc tggcacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag gatttcaatt accctctcac tttcggcgga 300
gggaccaagg tggagatcaa a                                     321
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<210> 644
<211> 107
<212> PRT
<213> Artificial Sequence

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<220>
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<400> 644

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40

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 1           5           10           15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly 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 His 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 Phe Asn Tyr Pro Leu
      85           90           95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
      100           105
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<210> 645
<211> 357
<212> DNA
<213> Artificial Sequence

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<220>
<223> Synthetic

<400> 645

55

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tcctgtgcag cgtctggatt taccttcagg agatatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatgggtatg atggaagtaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca actccaagaa cacgctgtat 240
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ctgcaaata acagcctgag agccgaggac acggctgtgt attactgtgc gagcgaaatt 300
acagttgggg actggttcga cccctggggc caggggaaccc tggtcaccgt ctctca 357

5 <210> 646
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<212> PRT
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10 <220>
<223> Synthetic

<400> 646

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

<210> 647
<211> 322
<212> DNA
35 <213> Artificial Sequence

<220>
<223> Synthetic

40 <400> 647

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gggaaagccc ctaagctcct gatctatgct gcatccagtt tacaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tggcacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag gatttcaatt accctctcac tttcggcgga 300
gggaccaagg tggagatcaa ac 322

50 <210> 648
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<212> PRT
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<220>
55 <223> Synthetic

<400> 648

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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 Gly Ile Arg Asn Asp
20 25 30
5 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
10 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 Phe Asn Tyr Pro Leu
85 90 95
15 Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 649
<211> 357
20 <212> DNA
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<220>
<223> Synthetic
25 <400> 649

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tcctgtgtag cctctggatt caccttcagt agatatggca tgcactgggt ccgccaggct 120
30 ccaggcaagg ggctggagtg gctgatagtt atatcatatg atggaattaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacggtgtat 240
ctgcaaatac acagcctgag agctgaggac acgggagtggt attactgtgc gaaaggggac 300
tttttgagtg gttactttga ctactggggc caggggaaccc tggtcactgt ctctca 357

<210> 650
<211> 119
35 <212> PRT
<213> Artificial Sequence

<220>
40 <223> Synthetic
<400> 650

45

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55

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

<210> 651
 <211> 24
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 651
 ggattcacct tcagtagata tggc 24

<210> 652
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 652

				Gly	Phe	Thr	Phe	Ser	Arg	Tyr	Gly
40				1				5			

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

<220>
 <223> Synthetic

<400> 653
 atatcatatg atggaattaa taaa 24

<210> 654
 <211> 8
 <212> PRT
 <213> Artificial Sequence

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EP 2 475 684 B1

<223> Synthetic

<400> 654

5 Ile Ser Tyr Asp Gly Ile Asn Lys
1 5

<210> 655

<211> 36

10 <212> DNA

<213> Artificial Sequence

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15 <223> Synthetic

<400> 655

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<210> 656

20 <211> 12

<212> PRT

<213> Artificial Sequence

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25 <223> Synthetic

<400> 656

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35 <210> 657

<211> 336

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<213> Artificial Sequence

40 <220>

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<400> 657

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cttcaccaga ggccaggcca gcctccaaga ctctaatatt ataagatttc taaccgggtc 180
tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgcaaadc 240
agcagggtgg aagctgagga tgtcgggatt tattactgca tgcaaggtag acaatttccg 300
50 actttcggcg gagggaccaa ggtggagatc aaacga 336

<210> 658

<211> 112

<212> PRT

55 <213> Artificial Sequence

<220>

<223> Synthetic

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<400> 658

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

<210> 659

<211> 33

20 <212> DNA

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25

<400> 659

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<400> 660

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<211> 9

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50 <400> 661

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<210> 662

<211> 3

55 <212> PRT

<213> Artificial Sequence

<220>

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<223> Synthetic

<400> 662

5 Lys Ile Ser
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<210> 663

<211> 24

10 <212> DNA

<213> Artificial Sequence

<220>

15 <223> Synthetic

<400> 663

atgcaaggta cacaatttcc gact 24

<210> 664

20 <211> 8

<212> PRT

<213> Artificial Sequence

<220>

25 <223> Synthetic

<400> 664

30 Met Gln Gly Thr Gln Phe Pro Thr
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<210> 665

<211> 357

<212> DNA

35 <213> Artificial Sequence

<220>

<223> Synthetic

40 <400> 665

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ccaggcaagg ggctggagtg gctgatagtt atatcatatg atggaattaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacggtgtat 240
ctgcaaatac acagcctgag agctgaggac acgggagtggt attactgtgc gaaaggggac 300
ttttggagtg gttactttga ctactggggc caggggaacc tggtcaccgt ctccctca 357

<210> 666

50 <211> 119

<212> PRT

<213> Artificial Sequence

<220>

55 <223> Synthetic

<400> 666

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	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	Val	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Arg	Tyr
				20					25					30		
5	Gly	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Leu
			35					40					45			
	Ile	Val	Ile	Ser	Tyr	Asp	Gly	Ile	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	Val	Tyr
10	65					70					75				80	
	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Gly	Val	Tyr	Tyr	Cys
				85						90				95		
	Ala	Lys	Gly	Asp	Phe	Trp	Ser	Gly	Tyr	Phe	Asp	Tyr	Trp	Gly	Gln	Gly
				100					105					110		
15	Thr	Leu	Val	Thr	Val	Ser	Ser									
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<210> 667

<211> 333

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

25 <400> 667

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	atctcctgca	ggctctagtc	aagcctcgtc	cacagtgatg	gaaacaccta	cttgagttgg	120
30	cttcaccaga	ggccaggcca	gcctccaaga	ctcctaattt	ataagatttc	taaccgggttc	180
	tctgggggtcc	cagacagatt	cagtggcagt	ggggcaggga	cagatttcac	actgcaaata	240
	agcaggggtg	aagctgagga	tgtcgggatt	tattactgca	tgcaagggtac	acaattttccg	300
	actttcggcg	gagggaccaa	ggtggagatc	aaa			333

35 <210> 668

<211> 111

<212> PRT

<213> Artificial Sequence

40 <220>

<223> Synthetic

<400> 668

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

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<210> 669
 <211> 357
 <212> DNA
 <213> Artificial Sequence

5
 <220>
 <223> Synthetic

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 <400> 669

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tcctgtgcag cctctggatt caccttcagt agatatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatcatatg atggaattaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
15 ctgcaaataga acagcctgag agctgaggac acggctgtgt attactgtgc gaaaggggac 300
ttttggagtg gttactttga ctactggggc cagggaaccc tggtcaccgt ctccctca 357
  
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<210> 670
 <211> 119
 <212> PRT
 <213> Artificial Sequence

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 <220>
 <223> Synthetic

25
 <400> 670

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30 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Tyr
    20      25      30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
    35      40      45
35 Ala Val Ile Ser Tyr Asp Gly Ile 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
40 Ala Lys Gly Asp Phe Trp Ser Gly Tyr Phe Asp Tyr Trp Gly Gln Gly
    100      105      110
Thr Leu Val Thr Val Ser Ser
    115
  
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 <210> 671
 <211> 334
 <212> DNA
 <213> Artificial Sequence

50
 <220>
 <223> Synthetic

<400> 671

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cttcagcaga ggccaggcca gcctccaaga ctctaattt ataagatttc taaccgggtc 180
tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
5 agcagggtgg aagctgagga tgtcggggtt tattactgca tgcaagggtac acaatttccg 300
actttcggcg gagggacaa ggtggagatc aaac 334

<210> 672

<211> 111

10 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

15

<400> 672

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

<210> 673

<211> 357

35 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 673

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45 ccaggcaagg ggctggagtg ggtggtagtt atatcatatg atggaattaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacggtgtat 240
ctgcaaatac acagcctgag agctgaggac acggctgtgt atcactgtgc gaaaggggac 300
ttttggagtg gttactttga ctactggggc cagggaaccc tggtcaccgt ctctctca 357

50 <210> 674

<211> 119

<212> PRT

<213> Artificial Sequence

55

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<223> Synthetic

<400> 674

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

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

<220>
 <223> Synthetic

<400> 675
 ggattcacct tcagtagata tggc 24

<210> 676
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 676

				Gly	Phe	Thr	Phe	Ser	Arg	Tyr	Gly
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 <211> 24
 <212> DNA
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<400> 677
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<210> 678
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 <212> PRT
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<223> Synthetic

<400> 678

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<210> 679

<211> 36

10 <212> DNA

<213> Artificial Sequence

$\langle 220 \rangle$

<223> Synthetic

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<400> 679

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<210> 680

20 <211> 12

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<213> Artificial Sequence

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25 <223> Synthetic

<400> 680

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1 5 10

<210> 681

<211> 336

<212> DNA

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 $\langle 220 \rangle$

<223> Synthetic

40 <400> 681

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cttcaccaga	ggccaggcca	gcctccaaga	ctcctaattt	ataagatttc	taaccggttc	180
tctggggtcc	cagacagatt	cagtggcagt	ggggcaggga	cagatttcac	actgcaaadc	240
agcagggtgg	aagctgagga	tgtcgggatt	tattactgca	tgcaagcaac	acaattttccg	300
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<212> PRT

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55 <223> Synthetic

<400> 682

EP 2 475 684 B1

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

<210> 683
 <211> 33
 <212> DNA
 <213> Artificial Sequence

<220>
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<400> 683
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<210> 684
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<220>
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<400> 684

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 <212> DNA
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<220>
 <223> Synthetic

<400> 685
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<210> 686
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 <212> PRT
 <213> Artificial Sequence

<220>

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<223> Synthetic

<400> 686

5 Lys Ile Ser
1

<210> 687

<211> 24

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

15

<400> 687

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<210> 688

20 <211> 8

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<213> Artificial Sequence

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25 <223> Synthetic

<400> 688

30 Met Gln Ala Thr Gln Phe Pro Thr
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<210> 689

<211> 357

<212> DNA

35 <213> Artificial Sequence

<220>

<223> Synthetic

40

<400> 689

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ccaggcaagg ggctggagtg ggtggtagtt atatcatatg atggaattaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacggtgtat 240
ctgcaaataga acagcctgag agctgaggac acggctgtgt atcactgtgc gaaaggggac 300
ttttggagtg gttactttga ctactggggc cagggaaccc tggtcaccgt ctccctca 357

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<400> 690

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

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	<211> 333
	<212> DNA
	<213> Artificial Sequence
25	<220>
	<223> Synthetic
	<400> 691
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	atctcctgca ggtctagtca aagcctcgta cacagtgatg gaaacaccta cttgagttgg 120
	cttcaccaga ggccaggcca gcctccaaga ctccctaattt ataagatttc taaccgggttc 180
	tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgcaaatac 240
	agcaggggtgg aagctgagga tgtcgggatt tattactgca tgcaagcaac acaattttccg 300
35	actttcggcg gagggaccaa ggtggagatc aaa 333

	<210> 692
	<211> 111
	<212> PRT
40	<213> Artificial Sequence

	<220>
	<223> Synthetic

45	<400> 692
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EP 2 475 684 B1

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

<210> 693

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 693

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ccaggcaagg  ggctggagtg  ggtggcagtt  atatcatatg  atggaattaa  taaatactat  180
gcagactccg  tgaagggccg  attcaccatc  tocagagaca  attccaagaa  cacgctgtat  240
ctgcaaata  acagcctgag  agctgaggac  acggctgtgt  attactgtgc  gaaaggggac  300

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<210> 694

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 694

EP 2 475 684 B1

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	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Arg	Tyr
				20					25					30		
5	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	Ile	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
10	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	Gly	Asp	Phe	Trp	Ser	Gly	Tyr	Phe	Asp	Tyr	Trp	Gly	Gln	Gly
				100					105					110		
15	Thr	Leu	Val	Thr	Val	Ser	Ser									
				115												

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<211> 334

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<223> Synthetic

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<400> 695

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30	cttcagcaga	ggccaggcca	gcctccaaga	ctcctaattt	ataagatttc	taaccgggttc	180
	tctgggggtcc	cagacagatt	cagtggcagt	ggggcaggga	cagatttcac	actgaaaatc	240
	agcaggggtgg	aagctgagga	tgctgggggt	tattactgca	tgcaagcaac	acaatttccg	300
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35 <210> 696

<211> 111

<212> PRT

<213> Artificial Sequence

40 <220>

<223> Synthetic

<400> 696

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

55

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50 55 60
 Asp Arg Phe Ser Gly Ser Gly Ala 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 Gln Phe Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105 110

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 <213> Artificial Sequence

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 <400> 697

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 ccaggcaagg ggctggagtg ggtgatagtt atatcatatg atggaattaa taaatactat 180
 gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacggtatat 240
 ctgcaaatac acagcctgag agccgaggac acggctgtgt attactgtgc gaaaggggac 300
 ttttggagtg gttactttga ctattggggc cagggaaccc tggtcaccgt ctccctca 357

 <210> 698
 <211> 119
 <212> PRT
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 <220>
 <223> Synthetic

 <400> 698

 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 Val Ala Ser Gly Phe Thr Phe Ser Arg Tyr
 20 25 30
 Gly Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ile Val Ile Ser Tyr Asp Gly Ile 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 Val 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 Gly Asp Phe Trp Ser Gly Tyr Phe Asp Tyr Trp Gly Gln Gly
 100 105 110
 Thr Leu Val Thr Val Ser Ser
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 <210> 699
 <211> 24
 <212> DNA
 <213> Artificial Sequence

 <220>

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<223> Synthetic
 <400> 699
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 <210> 700
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 <212> PRT
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 <220>
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 <400> 700
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 Gly Phe Thr Phe Ser Arg Tyr Gly
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 <210> 701
 <211> 24
 <212> DNA
 <213> Artificial Sequence
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 <220>
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 atatcatatg atggaattaa taaa 24
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 <210> 702
 <211> 8
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 Ile Ser Tyr Asp Gly Ile Asn Lys
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 <400> 703
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 <210> 704
 <211> 12
 <212> PRT
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<220>

<223> Synthetic

<400> 704

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Ala Lys Gly Asp Phe Trp Ser Gly Tyr Phe Asp Tyr
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<210> 705

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<211> 336

<212> DNA

<213> Artificial Sequence

<220>

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<223> Synthetic

<400> 705

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cttcaccaga ggccaggcca gcctccaaga ctctaattt ataagatttc taaccgggtc 180
tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgcaaata 240
agcagggtgg aagctgagga tgcggtatt tattactgca tgcaagctac acaatttccg 300
actttcggcg gagggaccaa ggtggaaatc aaacga 336

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<210> 706

<211> 112

<212> PRT

<213> Artificial Sequence

30

<220>

<223> Synthetic

<400> 706

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

50

<210> 707

<211> 33

<212> DNA

<213> Artificial Sequence

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<220>

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<400> 707
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 5 <210> 708
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 10 <220>
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 <400> 708

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

 <210> 709
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 <212> DNA
 20 <213> Artificial Sequence

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 25 <400> 709
 aagatttct 9

 <210> 710
 <211> 3
 30 <212> PRT
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 35
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 Lys Ile Ser
 40 1

 <210> 711
 <211> 24
 <212> DNA
 45 <213> Artificial Sequence

 <220>
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 <400> 711
 50 atgcaagcta cacaatttcc gact 24

 <210> 712
 <211> 8
 <212> PRT
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 <220>
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<400> 712

Met Gln Ala Thr Gln Phe Pro Thr
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5

<210> 713

<211> 357

<212> DNA

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<220>

<223> Synthetic

<400> 713

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tcctgtgtag cctctggatt caccttcagt agatatggca tacactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtgatagtt atatcatatg atggaattaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacggtatat 240
20 ctgcaaataga acagcctgag agccgaggac acggctgtgt attactgtgc gaaaggggac 300
ttttggagtg gttactttga ctattggggc cagggaaccc tggtcaccgt ctcctca 357

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<210> 714

<211> 119

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<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

30

<400> 714

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

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<210> 715

<211> 333

<212> DNA

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 715

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 cttcaccaga ggccaggcca gcctccaaga ctctaattt ataagatttc taaccgggtc 180
 tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgcaaata 240
 5 agcagggtgg aagctgagga tgtcggtatt tattactgca tgcaagctac acaatttccg 300
 actttcggcg gagggacaa ggtggagatc aaa 333

<210> 716

<211> 111

10 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

15

<400> 716

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

<210> 717

<211> 357

35 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 717

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 45 ccaggcaagg ggctggagtg ggtggcagtt atatcatatg atggaattaa taaatactat 180
 gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
 ctgcaaataga acagcctgag agctgaggac acggctgtgt attactgtgc gaaaggggac 300
 ttttggagtg gttactttga ctattggggc cagggaaccc tggtcaccgt ctccctca 357

<210> 718

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 718

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	1				5					10					15	
	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Arg	Tyr
				20					25					30		
5	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	Ile	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
10	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	Gly	Asp	Phe	Trp	Ser	Gly	Tyr	Phe	Asp	Tyr	Trp	Gly	Gln	Gly
				100					105					110		
15	Thr	Leu	Val	Thr	Val	Ser	Ser									
				115												

<210> 719

<211> 334

20 <212> DNA

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<220>

<223> Synthetic

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<400> 719

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	atctcctgca	ggctctagtca	aagcctcgta	cacagtgatg	gaaacaccta	cttgagttgg	120
30	cttcagcaga	ggccaggcca	gcctccaaga	ctcctaattt	ataagatttc	taaccgggttc	180
	tctgggggtcc	cagacagatt	cagtggcagt	ggggcaggga	cagatttcac	actgaaaatc	240
	agcaggggtgg	aagctgagga	tgtcgggggt	tattactgca	tgcaagctac	acaatttccg	300
	actttcggcg	gagggaccaa	ggtggagatc	aaac			334

35 <210> 720

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<212> PRT

<213> Artificial Sequence

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EP 2 475 684 B1

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

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<210> 721

<211> 357

<212> DNA

20 <213> Artificial Sequence

<220>

<223> Synthetic

25 <400> 721

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	tcctgtacag	cgtccggatt	tacgttcagg	agatatggca	tgcactgggt	ccgccaggct	120
	ccaggcaagg	ggctggagtg	ggtggcagtt	atttggatatg	atggaagtaa	taaataattat	180
30	gcagactccg	tgaagggacg	attcaccata	accagagaca	attccaagaa	cacgttgttat	240
	ctgcaaata	acagcctgag	agccgaggac	acggctatat	atTTTTgtgc	gagcgaaata	300
	acaattgggg	actggttcga	cccccggggc	cagggaaacc	tggtcacccg	ctcctca	357

35 <210> 722

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

40 <223> Synthetic

<400> 722

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EP 2 475 684 B1

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

<210> 723
 <211> 24
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 723
 ggatttacgt tcaggagata tggc 24

<210> 724
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
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<400> 724

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<210> 725
 <211> 24
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 725
 atttggtatg atggaagtaa taaa 24

<210> 726
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>

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<223> Synthetic

<400> 726

⁵ Ile Trp Tyr Asp Gly Ser Asn Lys
 1 5

<210> 727

<211> 36

10 <212> DNA

<213> Artificial Sequence

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<223> Synthetic

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<400> 727

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<210> 728

20 <211> 12

<212> PRT

<213> Artificial Sequence

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25 <223> Synthetic

<400> 728

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<210> 729

<211> 324

<212> DNA

35 <213> Artificial Sequence

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<223> Synthetic

40 <400> 729

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atcacttgtc	gggcaagtca	gggcattaga	aatgatttag	gctgggtttca	acagaaacca	120
gggaaagtcc	ctaaactcct	gatctatgct	gcatccactt	tacacagtgg	ggtcccatca	180
aggttcagcg	gcagtggatt	tggcacagat	ttcactctca	ccatcagcag	cctgcagcct	240
gaagattttg	caacttatta	ctgtctacag	gattttcaatt	accctctcac	tttcggcgga	300
gggaccaagg	tggagatcaa	acga				324

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50 <211> 108

<212> PRT

<213> Artificial Sequence

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55 <223> Synthetic

<400> 730

EP 2 475 684 B1

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

<210> 731

<211> 18

<212> DNA

20 <213> Artificial Sequence

<220>

<223> Synthetic

25 <400> 731

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<210> 732

<211> 6

30 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

35 <400> 732

Gln	Gly	Ile	Arg	Asn	Asp
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40 <210> 733

<211> 9

<212> DNA

45 <213> Artificial Sequence

<220>

<223> Synthetic

50 <400> 733

gctgcatcc 9

<210> 734

<211> 3

<212> PRT

55 <213> Artificial Sequence

<220>

<223> Synthetic

EP 2 475 684 B1

<400> 734

Ala Ala Ser
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<210> 735
<211> 27
<212> DNA
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<220>
<223> Synthetic

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<400> 735
ctacaggatt tcaattaccc tctcact 27

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<210> 736
<211> 9
<212> PRT
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25

<400> 736

Leu Gln Asp Phe Asn Tyr Pro Leu Thr
1 5

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<210> 737
<211> 357
<212> DNA
<213> Artificial Sequence

35

<220>
<223> Synthetic

<400> 737

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ccaggcaagg	ggctggagtg	ggtggcagtt	atttggtatg	atggaagtaa	taaatattat	180
gcagactccg	tgaagggacg	attcaccata	accagagaca	attccaagaa	cacgttgtat	240
ctgcaaata	acagcctgag	agccgaggac	acggctatat	atttttgtgc	gagcgaaata	300
acaattgggg	actggttcga	cccccggggc	caggggaacc	tggtcaccgt	ctcctca	357

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<210> 738
<211> 119
<212> PRT
<213> Artificial Sequence

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<220>
<223> Synthetic

55

<400> 738

EP 2 475 684 B1

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

<210> 739
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 <212> DNA
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<220>
 <223> Synthetic

<400> 739

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	atcacttgtc	gggcaagtca	gggcattaga	aatgatttag	gctgggtttca	acagaaacca	120
	gggaaagtcc	ctaaactcct	gatctatgct	gcatccactt	tacacagtgg	gggtcccatca	180
	aggttcagcg	gcagtggatt	tggcacagat	ttcactctca	ccatcagcag	cctgcagcct	240
	gaagattttg	caacttatta	ctgtctacag	gattttcaatt	accctctcac	tttcggcgga	300
	gggaccaagg	tgagatcaa	a				321

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 <211> 107
 <212> PRT
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<220>
 <223> Synthetic

<400> 740

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

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 <210> 741
 <211> 357
 <212> DNA
 <213> Artificial Sequence

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 <220>
 <223> Synthetic

25
 <400> 741

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	tcctgtgcag	cgtctggatt	tacgttcagg	agatatggca	tgcactgggt	ccgccaggct	120
	ccaggcaagg	ggctggagtg	ggtggcagtt	atttggtatg	atggaagtaa	taaatactat	180
30	gcagactccg	tgaagggccg	attcaccatc	tccagagaca	actccaagaa	cacgctgtat	240
	ctgcaaatga	acagcctgag	agccgaggac	acggctgtgt	attactgtgc	gagcgaaata	300
	acaattgggg	actggttcga	cccccggggc	caggaaccc	tggtcaccgt	ctcctca	357

35
 <210> 742
 <211> 119
 <212> PRT
 <213> Artificial Sequence

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 <400> 742

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

<210> 743

<211> 322

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 743

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	atcacttgcc	gggcaagtca	gggcattaga	aatgatttag	gctgggtatca	gcagaaacca	120
30	gggaaagccc	ctaagctcct	gatctatgct	gcatccagtt	tacaaagtgg	gggtcccatca	180
	aggttcagcg	gcagtggatc	tggcacagat	ttcactctca	ccatcagcag	cctgcagcct	240
	gaagattttg	caacttatta	ctgtctacag	gatttcaatt	accctctcac	tttcggcgga	300
	gggaccaagg	tgagatcaa	ac				322

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<211> 107

<212> PRT

<213> Artificial Sequence

40 <220>

<223> Synthetic

<400> 744

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

55

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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 Phe Asn Tyr Pro Leu
 85 90 95
 5 Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 745

<211> 357

10 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 745

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 20 ccaggcaagg ggctggagtg ggtggtagtt atatcatatg atggaattaa taaatactat 180
 gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacggtgtat 240
 ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gaaaggggac 300
 ttttgagtg gttactttga ctactggggc caggggaacc tggtcacctg ctccctca 357

25 <210> 746

<211> 119

<212> PRT

<213> Artificial Sequence

30 <220>

<223> Synthetic

<400> 746

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

<210> 747

<211> 24

<212> DNA

55 <213> Artificial Sequence

<220>

<223> Synthetic

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<400> 747
 ggattcacct tcagtagata tggc 24

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

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 <220>
 <223> Synthetic

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 <400> 748
 Gly Phe Thr Phe Ser Arg Tyr Gly
 1 5

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 <210> 749
 <211> 24
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25
 <220>
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 <400> 749
 atatcatatg atggaattaa taaa 24

35
 <210> 750
 <211> 8
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40
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45
 <400> 750
 Ile Ser Tyr Asp Gly Ile Asn Lys
 1 5

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 <212> DNA
 <213> Artificial Sequence

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 <220>
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 <211> 12
 <212> PRT
 <213> Artificial Sequence

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<400> 752

Ala Lys Gly Asp Phe Trp Ser Gly Tyr Phe Asp Tyr
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5

<210> 753

<211> 336

<212> DNA

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 753

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cttcaccaga ggccaggcca gcctccaaga ctctaatatt ataagatttc taaccggttc 180
tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgcaaadc 240
agcaggggtgg aagctgagga tgcggggatt tattactgca tgcaagctac acaatttcgc 300
actttcggcg gagggaccaa ggtggagatc aaacga 336

<210> 754

<211> 112

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<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 754

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40

45

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

<210> 755

<211> 33

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<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

55

<400> 755

caaagcctcg tacacagtga tggaaacacc tac 33

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<210> 756
 <211> 11
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 <220>
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 <400> 756
 Gln Ser Leu Val His Ser Asp Gly Asn Thr Tyr
 1 5 10
 15
 <210> 757
 <211> 9
 <212> DNA
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 <223> Synthetic
 <400> 757
 aagatttct 9
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 <210> 758
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 <212> PRT
 <213> Artificial Sequence
 30
 <220>
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 <400> 758
 35
 Lys Ile Ser
 1
 40
 <210> 759
 <211> 24
 <212> DNA
 <213> Artificial Sequence
 <220>
 <223> Synthetic
 45
 <400> 759
 atgcaagcta cacaatttc gact 24
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 <210> 760
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 <212> PRT
 <213> Artificial Sequence
 55
 <220>
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 <400> 760

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Met Gln Ala Thr Gln Phe Pro Thr
1 5

5 <210> 761
<211> 357
<212> DNA
<213> Artificial Sequence

10 <220>
<223> Synthetic

<400> 761

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tcctgtgtag cctctggatt caccttcagt agatatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggtagtt atatcatatg atggaattaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacggtgtat 240
ctgcaaatac acagcctgag agctgaggac acggctgtgt attactgtgc gaaaggggac 300
20 ttttggagtg gttactttga ctactggggc cagggaaccc tggtcaccgt ctctca 357

25 <210> 762
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

30 <400> 762

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

50 <210> 763
<211> 333
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 763

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atctcctgca ggtctagtc aagcctcgta cacagtgatg gaaacaccta cttgagttgg 120
cttcaccaga ggccaggcca gcctccaaga ctctaattt ataagatttc taaccgggtc 180
tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgcaaata 240
5 agcaggggtg aagctgagga tgtcgggatt tattactgca tgcaagctac acaatttccg 300
actttcggcg gagggacaa ggtggagatc aaa 333

<210> 764

<211> 111

10 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 764

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

35 <210> 765

<211> 357

<212> DNA

<213> Artificial Sequence

40 <220>

<223> Synthetic

<400> 765

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tcctgtgcag cctctggatt caccttcagt agatatggca tgcactgggt ccgccaggct 120
ccaggcaagg ggctggagtg ggtggcagtt atatcatatg atggaattaa taaatactat 180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
ctgcaaataga acagcctgag agctgaggac acggctgtgt attactgtgc gaaaggggac 300
50 ttttggagtg gttactttga ctactggggc cagggaaccc tggtcaccgt ctccctca 357

<210> 766

<211> 119

55 <212> PRT

<213> Artificial Sequence

<220>

EP 2 475 684 B1

<223> Synthetic

<400> 766

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

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<210> 767

<211> 334

<212> DNA

25 <213> Artificial Sequence

<220>

<223> Synthetic

30 <400> 767

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      atctcctgca ggtctagtca aagcctcgta cacagtgatg gaaacaccta cttgagttgg 120
      cttcagcaga ggccaggcca gcctccaaga ctctaattt ataagatttc taaccggttc 180
35     tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
      agcaggggtgg aagctgagga tgtcgggggtt tattactgca tgcaagctac acaatttccg 300
      actttcggcg gagggaccaa ggtggagatc aaac 334

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<210> 768

40 <211> 111

<212> PRT

<213> Artificial Sequence

<220>

45 <223> Synthetic

<400> 768

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

<210> 769

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 769

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	ccaggcaagg	ggctggagtg	gctgatagtt	atatcatatg	atggaattaa	taaatactat	180
	gcagactccg	tgaagggccg	attcaccatc	tccagagaca	attccaagaa	cacggtgtat	240
30	ctgcaaata	acagcctgag	agctgaggac	acggctgtgt	attactgtgc	gaaaggggac	300
	ttttggagtg	gatactttga	ctactggggc	cagggaaccc	tggtcacctg	ctcctca	357

<210> 770

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 770

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

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<210> 771
 <211> 24
 <212> DNA
 <213> Artificial Sequence
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 <220>
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 <400> 771
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 <210> 772
 <211> 8
 <212> PRT
 15 <213> Artificial Sequence
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 20 <400> 772
 Gly Phe Thr Phe Ser Arg Tyr Gly
 1 5
 25 <210> 773
 <211> 24
 <212> DNA
 <213> Artificial Sequence
 30 <220>
 <223> Synthetic
 <400> 773
 35 atatcatatg atggaattaa taaa 24
 <210> 774
 <211> 8
 <212> PRT
 40 <213> Artificial Sequence
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 Ile Ser Tyr Asp Gly Ile Asn Lys
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 50 <210> 775
 <211> 36
 <212> DNA
 <213> Artificial Sequence
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 55 <223> Synthetic
 <400> 775
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<210> 776
 <211> 12
 <212> PRT
 <213> Artificial Sequence

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<220>
 <223> Synthetic

<400> 776

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Ala	Lys	Gly	Asp	Phe	Trp	Ser	Gly	Tyr	Phe	Asp	Tyr
1				5					10		

<210> 777
 <211> 336
 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> Synthetic

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<400> 777

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cttcaccaga	ggccaggcca	gcctccaaga	ctcctaattt	ataagatttc	taaccgggtc	180
tctggggtcc	cagacagatt	cagtggcagt	ggggcagggg	cagatttcac	actgcaaata	240
agcaggggtg	aagctgagga	tgtcgggatt	tattactgca	tgcaagggtac	acaatttccg	300
actttcggcg	gagggaccaa	ggtggagatc	aaacga			336

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<210> 778
 <211> 112
 <212> PRT
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<220>
 <223> Synthetic

<400> 778

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

45

50

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

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<210> 779

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<211> 33
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 Gln Ser Leu Val His Ser Asp Gly Asn Thr Tyr
 1 5 10
 <210> 781
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 30 <223> Synthetic
 <400> 781
 aagatttct 9
 35 <210> 782
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 <400> 782
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 Lys Ile Ser
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 <210> 783
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<210> 784
 <211> 8
 <212> PRT
 <213> Artificial Sequence

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<220>
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<400> 784

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Met Gln Gly Thr Gln Phe Pro Thr
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<210> 785
 <211> 357
 <212> DNA
 <213> Artificial Sequence

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<220>
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<400> 785

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 tcctgtgtag cctctggatt caccttcagt agatatggca tgcactgggt ccgccagggt 120
 ccaggcaagg ggctggagtg gctgatagtt atatcatatg atggaattaa taaatactat 180
 gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacggtgtat 240
 ctgcaaatac acagcctgag agctgaggac acggctgtgt attactgtgc gaaaggggac 300
 30 ttttggagtg gatactttga ctactggggc cagggaaccc tggtcaccgt ctctca 357

<210> 786
 <211> 119
 <212> PRT
 <213> Artificial Sequence

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<220>
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<400> 786

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

Thr Leu Val Thr Val Ser Ser
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<210> 787
 <211> 333
 <212> DNA
 <213> Artificial Sequence

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<220>
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<400> 787

15

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atctcctgca ggtctagtca aagcctcgta cacagtgatg gaaacaccta cttgagttgg 120
cttcaccaga ggccaggcca gcctccaaga ctccctaattt ataagatttc taaccgggtc 180
tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgcaaadc 240
agcaggggtgg aagctgagga tgtcgggatt tattactgca tgcaaggtag acaatttccg 300
actttcggcg gagggaccaa ggtggagatc aaa 333
  
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<210> 788
 <211> 111
 <212> PRT
 <213> Artificial Sequence

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<220>
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<400> 788

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Asp Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro Val Thr Leu Gly
1      5      10      15
Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20      25      30
Asp Gly Asn Thr Tyr Leu Ser Trp Leu His Gln Arg Pro Gly Gln Pro
35      40      45
Pro Arg Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro
50      55      60
Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Gln Ile
65      70      75      80
Ser Arg Val Glu Ala Glu Asp Val Gly Ile Tyr Tyr Cys Met Gln Gly
85      90      95
Thr Gln Phe Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100     105     110
  
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<210> 789
 <211> 357
 <212> DNA
 <213> Artificial Sequence

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<220>
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<400> 789

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 ccaggcaagg ggctggagtg ggtggcagtt atatcatatg atggaattaa taaatactat 180
 gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240
 ctgcaaatac acagcctgag agctgaggac acggctgtgt attactgtgc gaaaggggac 300
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10 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 790

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 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 Ile Asn Lys Tyr Tyr Ala Asp Ser Val
 25 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
 30 Ala Lys Gly Asp Phe Trp Ser Gly Tyr Phe Asp Tyr Trp Gly Gln Gly
 100 105 110
 Thr Leu Val Thr Val Ser Ser
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35 <210> 791

<211> 334

<212> DNA

<213> Artificial Sequence

40 <220>

<223> Synthetic

<400> 791

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 cttcagcaga ggccaggcca gcctccaaga ctctaatatt ataagatttc taaccgggtc 180
 tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
 agcagggtgg aagctgagga tgtcgggggt tattactgca tgcaagggtac acaatttccg 300
 50 actttcggcg gagggaccaa ggtggagatc aaac 334

<210> 792

<211> 111

<212> PRT

55 <213> Artificial Sequence

<220>

<223> Synthetic

EP 2 475 684 B1

<400> 792

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

<210> 793

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 793

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	ccaggcaagg	ggctggagtg	ggtggtagtt	atatcatatg	atggaattaa	taaatactat	180
	gcagactccg	tgaagggccg	attcaccatc	tccagagaca	attccaagaa	cacggtgtat	240
	ctgcaaata	acagcctgag	agctgaggac	acggctgtgt	attactgtgc	gaaaggggac	300
35	ttttggagtg	gttactttga	ctactggggc	cagggaaccc	tggtcaccgt	ctcctca	357

<210> 794

<211> 119

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 794

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

<210> 795
 <211> 24
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Synthetic

<400> 795
 ggattcacct tcagtagata tggc 24

<210> 796
 <211> 8
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<220>
 <223> Synthetic

<400> 796

				Gly	Phe	Thr	Phe	Ser	Arg	Tyr	Gly
				1				5			

<210> 797
 <211> 24
 <212> DNA
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<220>
 <223> Synthetic

<400> 797
 atatcatatg atggaattaa taaa 24

<210> 798
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>

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<223> Synthetic

<400> 798

Ile Ser Tyr Asp Gly Ile Asn Lys
1 5

<210> 799

<211> 36

10 <212> DNA

<213> Artificial Sequence

$\langle 220 \rangle$

<223> Synthetic

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<400> 799

gcgaaagggg acttttgag tggttacttt gactac 36

<210> 800

20 <211> 12

<212> PRT

<213> Artificial Sequence

 $\langle 220 \rangle$

25 <223> Synthetic

<400> 800

30 Ala Lys Gly Asp Phe Trp Ser Gly Tyr Phe Asp Tyr
1 5 10

<210> 801

$\langle 211 \rangle$ 321

<212> DNA

35 <213> Artificial Sequence

 $\langle 220 \rangle$

<223> Synthetic

40 <400> 801

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atcacttgcc	gggcaagtca	gggcattaga	aatgatttag	gctgggtatca	gcagaaacca	120
gggaaagccc	ctaagcgcct	gatctatgct	gcatccagtt	tgcaaagtgg	ggtcccatca	180
aggttcagcg	gcagtggatc	tgggacagaa	ttcactctca	caatcagcag	cctgcagcct	240
gaagattttg	caacttatta	ctgtctacag	cataatagtt	accctccgac	gttcggccaa	300
gggaccaagg	tggagatcaa	a				321

<210> 802

50 <211> 107

<212> PRT

<213> Artificial Sequence

<220>

55 <223> Synthetic

<400> 802

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	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	Gly	Ile	Arg	Asn	Asp
				20					25					30		
5	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
10		65				70					75					80
	Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Leu	Gln	His	Asn	Ser	Tyr	Pro	Pro
					85					90					95	
	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys					
				100					105							

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<210> 803
 <211> 18
 <212> DNA
 <213> Artificial Sequence

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<220>
 <223> Synthetic

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<400> 803
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<210> 804
 <211> 6
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic

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<400> 804

Gln	Gly	Ile	Arg	Asn	Asp
1				5	

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<210> 805
 <211> 9
 <212> DNA
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<220>
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<400> 805
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<210> 806
 <211> 3
 <212> PRT
 <213> Artificial Sequence

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<220>
 <223> Synthetic

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<400> 806

Ala Ala Ser
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<210> 807

<211> 27

<212> DNA

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 807

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ctacagcata atagttaccc tccgacg 27

<210> 808

<211> 9

<212> PRT

<213> Artificial Sequence

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<220>

<223> Synthetic

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<400> 808

Leu Gln His Asn Ser Tyr Pro Pro Thr
1 5

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<210> 809

<211> 357

<212> DNA

<213> Artificial Sequence

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<220>

<223> Synthetic

<400> 809

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ccaggcaagg	ggctggagtg	ggtggtagtt	atatcatatg	atggaattaa	ttaaatactat	180
gcagactccg	tgaagggccg	attcaccatc	tccagagaca	attccaagaa	cacggtgtat	240
ctgcaaata	acagcctgag	agctgaggac	acggctgtgt	attactgtgc	gaaaggggac	300
ttttggagtg	gttactttga	ctactggggc	caggggaacc	tggtcaccgt	ctcctca	357

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<210> 810

<211> 119

<212> PRT

<213> Artificial Sequence

50

<220>

<223> Synthetic

55

<400> 810

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

<210> 811

<211> 321

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 811

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30	gggaaagccc	ctaagcgcct	gatctatgct	gcatccagtt	tgcaaagtgg	ggccccatca	180
	aggttcagcg	gcagtggatc	tgggacagaa	ttcactctca	caatcagcag	cctgcagcct	240
	gaagattttg	caacttatta	ctgtctacag	cataatagtt	accctccgac	gttcgggcaa	300
	gggaccaagg	tggaaatcaa	a				321

35 <210> 812

<211> 107

<212> PRT

<213> Artificial Sequence

40 <220>

<223> Synthetic

<400> 812

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	1				5					10					15	

50

55

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

<210> 813

<211> 357

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 813

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	ccaggcaagg	ggctggagtg	ggtggcagtt	atatcatatg	atggaattaa	taaatactat	180
	gcagactccg	tgaagggccg	attcaccatc	tccagagaca	attccaagaa	cacgctgtat	240
	ctgcaaata	acagcctgag	agctgaggac	acggctgtgt	attactgtgc	gaaaggggac	300
30	ttttggagtg	gttactttga	ctactggggc	caggaaccc	tggtcaccgt	ctcctca	357

<210> 814

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

<400> 814

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	1				5					10					15	
45	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Arg	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	Ile	Asn	Lys	Tyr	Tyr	Ala	Asp	Ser	Val
		50					55					60				
50	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	Gly	Asp	Phe	Trp	Ser	Gly	Tyr	Phe	Asp	Tyr	Trp	Gly	Gln	Gly
55				100					105					110		
	Thr	Leu	Val	Thr	Val	Ser	Ser									
				115												

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<210> 815
 <211> 322
 <212> DNA
 <213> Artificial Sequence

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 <220>
 <223> Synthetic

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 <400> 815

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atcacttgcc gggcaagtca gggcattaga aatgatttag gctggatatca gcagaaacca 120
gggaaagccc ctaagcgctt gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
15 aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240
gaagattttg caacttatta ctgtctacag cataatagtt accctccgac gttcggccaa 300
gggaccaagg tggaaatcaa ac 322
  
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<210> 816
 <211> 107
 <212> PRT
 <213> Artificial Sequence

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 <220>
 <223> Synthetic

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 <400> 816

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

<210> 817
 <211> 357
 <212> DNA
 <213> Artificial Sequence

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 <220>
 <223> Synthetic

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 <400> 817

55

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 tcctgtgtag cctctggatt caccttcagt agatatggca tgcactgggt ccgccaggct 120
 ccaggcaagg ggctggagtg gctgatagtt atatcatatg atggaattaa taaatactat 180
 gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacggtgtat 240
 5 ctgcaaataga acagcctgag agttgaggac acgggagtggt attactgtgc gaaaggggac 300
 ttttgagagtg gttactttga ctactggggc caggggaaccc tggtcaccgt ctccctca 357

<210> 818

<211> 119

10 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 818

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1 5 10 15
 20 Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Ser Arg Tyr
 20 25 30
 Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu
 35 40 45
 25 Ile Val Ile Ser Tyr Asp Gly Ile 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 Val Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Gly Val Tyr Tyr Cys
 85 90 95
 30 Ala Lys Gly Asp Phe Trp Ser Gly Tyr Phe Asp Tyr Trp Gly Gln Gly
 100 105 110
 Thr Leu Val Thr Val Ser Ser
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35 <210> 819

<211> 24

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<213> Artificial Sequence

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<400> 819

ggattcacct tcagtagata tggc 24

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<210> 820

<211> 8

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<220>

<223> Synthetic

<400> 820

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Gly Phe Thr Phe Ser Arg Tyr Gly
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<210> 821
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 10 atatcatatg atggaattaa taaa 24
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 Ile Ser Tyr Asp Gly Ile Asn Lys
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 <210> 823
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 35 gcgaaagggg acctttggag tggttacttt gactac 36
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 Ala Lys Gly Asp Phe Trp Ser Gly Tyr Phe Asp Tyr
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 <211> 327
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 <213> Artificial Sequence
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 <220>
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 <400> 825

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gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
 ctctcctgca gggccagtc gagtgtagc agcagctact tagcctggta ccagcagaaa 120
 cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
 gacagggttca gtggcagtggt gtctgggaca gacttcactc tcaccatcag cagactggag 240
 cctgaagatt ttgcagtgtt ttactgtcag cagtatggta gctcacctg gacgttcggc 300
 caagggacca aggtggaaat caaacga 327

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 <211> 109
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<400> 826

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

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<220>
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<400> 827
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<210> 828
 <211> 7
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 <213> Artificial Sequence

<220>
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<400> 828

Gln Ser Val Ser Ser Ser Tyr
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<210> 829
 <211> 9
 <212> DNA
 <213> Artificial Sequence
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 <400> 829
 10 ggtgcatcc 9
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 20 <400> 830
 Gly Ala Ser
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 25 <210> 831
 <211> 27
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 35 cagcagtatg gtagctcacc gtggacg 27
 <210> 832
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 40 <220>
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 45 Gln Gln Tyr Gly Ser Ser Pro Trp Thr
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 50 <211> 357
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 55 <223> Synthetic
 <400> 833

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5 caggtgcagc tgggtggagtc tggggggaggc gtggtccagc ctgggaggtc cctgagactc 60
 tcctgtgtag cctctggatt caccttcagt agatatggca tgcactgggt ccgccaggct 120
 ccaggcaagg ggctggagtg gctgatagtt atatcatatg atggaattaa taaatactat 180
 gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacggtgtat 240
 ctgcaaatac acagcctgag agttgaggac acgggagtggt attactgtgc gaaaggggac 300
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<210> 834

<211> 119

10 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 834

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

35

115

<210> 835

40 <211> 324

<212> DNA

<213> Artificial Sequence

<220>

45 <223> Synthetic

<400> 835

50 gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
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 cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
 gacaggttca gtggcagtg gtctgggaca gacttctc tcaccatcag cagactggag 240
 cctgaagatt ttgcagtgt ttactgtcag cagtatggta gctcaccgtg gacgttcggc 300
 caagggacca aggtggaaat caaa 324

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<210> 836

<211> 108

<212> PRT

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<213> Artificial Sequence

<220>

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<400> 836

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	1				5					10					15	
10	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser	Gln	Ser	Val	Ser	Ser	Ser
				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
15		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	
20	Trp	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys				
				100					105							

<210> 837

<211> 357

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<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 837

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	tcctgtgcag	cctctggatt	caccttcagt	agatatggca	tgcactgggt	ccgccaggct	120
35	ccaggcaagg	ggctggagtg	ggtggcagtt	atatcatatg	atggaattaa	taaatactat	180
	gcagactccg	tgaagggccg	attcaccatc	tccagagaca	attccaagaa	cacgctgtat	240
	ctgcaaataa	acagcctgag	agctgaggac	acggctgtgt	attactgtgc	gaaaggggac	300
	ttttggagtg	gttactttga	ctactggggc	caggaaccc	tggtcaccgt	ctcctca	357

40 <210> 838

<211> 119

<212> PRT

<213> Artificial Sequence

45 <220>

<223> Synthetic

<400> 838

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	Gln	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Val	Val	Gln	Pro	Gly	Arg
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	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Arg	Tyr
				20					25					30		
5	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	Ile	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
10	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	Gly	Asp	Phe	Trp	Ser	Gly	Tyr	Phe	Asp	Tyr	Trp	Gly	Gln	Gly
				100					105					110		
15	Thr	Leu	Val	Thr	Val	Ser	Ser									
				115												

<210> 839

<211> 325

20 <212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 839

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	ctctcctgca	gggccagtc	gagtgttagc	agcagctact	tagcctggta	ccagcagaaa	120
30	cctggccagg	ctcccaggct	cctcatctat	ggtgcatcca	gcagggccac	tggcatccca	180
	gacaggttca	gtggcagtg	gtctgggaca	gacttcactc	tcaccatcag	cagactggag	240
	cctgaagatt	ttgcagtgt	ttactgtcag	cagtatggta	gctcacctgt	gacgttcggc	300
	caagggacca	aggtggaaat	caaac				325

35 <210> 840

<211> 108

<212> PRT

<213> Artificial Sequence

40 <220>

<223> Synthetic

<400> 840

	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	Ser	Ser
				20					25					30		
	Tyr	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu
50			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	

55

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Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
85 90
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

5
<210> 841
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<222> (3)...(3)
<223> Xaa = Thr
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<222> (4)...(4)
<223> Xaa = Phe
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<222> (5)...(5)
<223> Xaa = Ser or Arg
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<220>
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<222> (6)...(6)
<223> Xaa = Ser or Arg
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<220>
<221> VARIANT
<222> (7)...(7)
<223> Xaa = Tyr
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<220>
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<222> (8)...(8)
<223> Xaa = Gly, Ala, or Thr
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<400> 841

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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 <210> 842
 <211> 8
 <212> PRT
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<220>
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 <223> Xaa = Ile

15
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 <221> VARIANT
 <222> (2)...(2)
 <223> Xaa = Ser, Gly, or Thr

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 <222> (3)...(3)
 <223> Xaa = Tyr, Gly, or Asp

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 <222> (4)...(4)
 <223> Xaa = Asp, Gly, or Ser

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 <222> (5)...(5)
 <223> Xaa = Gly or Arg

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 <221> VARIANT
 <222> (6)...(6)
 <223> Xaa = Ile, Gly, or Ala

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 <222> (7)...(7)
 <223> Xaa = Asn, Ser, Arg, or Gly

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 <222> (8)...(8)
 <223> Xaa = Lys, Ala, or Thr

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 <400> 842

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1 5

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 <210> 843
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 <212> PRT
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<223> Synthetic

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5 <221> VARIANT

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

<223> Xaa = Ala or Val

<220>

10 <221> VARIANT

<222> (2)...(2)

<223> Xaa = Lys

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

<223> Xaa = Gly or Glu

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20 <221> VARIANT

<222> (4)...(4)

<223> Xaa = Asp or Gly

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<222> (5)...(5)

<223> Xaa = Phe or Asp

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30 <221> VARIANT

<222> (6)...(6)

<223> Xaa = Trp or Ser

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35 <221> VARIANT

<222> (7)...(7)

<223> Xaa = Ser or Gly

<220>

40 <221> VARIANT

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

<223> Xaa = Gly or Tyr

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

<223> Xaa = Tyr or Asp

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<222> (10)...(10)

<223> Xaa = Phe or Leu

<220>

55 <221> VARIANT

<222> (11)...(11)

<223> Xaa = Asp or Ala

<220>
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 <223> Xaa = Tyr
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 Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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 <223> Xaa = Ser or Gly

 <220>
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 <223> Xaa = Leu or Ile

 <220>
 35
 <221> VARIANT
 <222> (4)...(4)
 <223> Xaa = Val or Ser

 <220>
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 <221> VARIANT
 <222> (5)...(5)
 <223> Xaa = His, Asn, or Thr

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 <223> Xaa = Ser, Asn, or Tyr

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 <223> Xaa = Asn or absent

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 <222> (10)...(10)
 <223> Xaa = Thr or absent

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 <222> (11)...(11)
 <223> Xaa = Tyr or absent

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 <400> 844

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 1 5 10

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 <210> 845
 <211> 3
 <212> PRT
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 <222> (1)...(1)
 <223> Xaa = Lys or Ala

 35
 <220>
 <221> VARIANT
 <222> (2)...(2)
 <223> Xaa = Ile, Ala, or Thr

 40
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 <221> VARIANT
 <222> (3)...(3)
 <223> Xaa = Ser

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 <400> 845
 Xaa Xaa Xaa

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 <210> 846
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 <220>
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 $\langle 222 \rangle (1) \dots (1)$

<223> Xaa = Met or Gln

<220>

5 <221> VARIANT

 $\langle 222 \rangle (2) \dots (2)$

<223> Xaa = Gln

<220>

10 <221> VARIANT

 $\langle 222 \rangle \quad (3) \dots (3)$

<223> Xaa = Ala or Tyr

<220>

15 <221> VARIANT

 $\langle 222 \rangle \quad (4) \dots (4)$

<223> Xaa = Thr or Lys

<220>

20 <221> VARIANT

$\langle 222 \rangle$ (5)...(5)

<223> Xaa = Gln, Ser, or Ile

<220>

25 <221> VARIANT

 $\langle 222 \rangle$ (6)...(6)

<223> Xaa = Phe or Ser

 $\langle 220 \rangle$

30 <221> VARIANT

$\langle 222 \rangle$ (7)...(7)

<223> Xaa = Pro

<220>

35 <221> VARIANT

$\langle 222 \rangle$ (8)...(8)

<223> Xaa = Thr or Leu

<220>

40 <221> VARIANT

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

<223> Xaa = Thr or absent

<400> 846

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 847

50 <211> 330

<212> PRT

<213> Artificial Sequence

$\langle 220 \rangle$

55 <223> Synthetic

<400> 847

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	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		
5	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
10	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		
15	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
20	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		
25	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
30	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
35			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
40	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys						
					325					330						

<210> 848

<211> 327

45 <212> PRT

<213> Artificial Sequence

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<223> Synthetic

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<400> 848

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	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		
5	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
10	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	Ser	Cys	Pro	Ala	Pro
				100					105					110		
15	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
20	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		
25	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
30	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
35			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
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<211> 327

45 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic

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<400> 849

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	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr
				20					25					30		
5	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
10		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	
15	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
20		130					135					140				
	Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	Gln	Phe	Asn	Trp	Tyr	Val	Asp
	145					150					155				160	
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				165					170						175	
25	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				
30	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
35				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				
40	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser
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 <213> Artificial Sequence

50 <220>
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<400> 850

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 gtctacacaa ttgtgtttgt ggtgggtttg ccaagtaacg gcatggccct gtgggtcttt 300
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 <212> PRT
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<220>
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<400> 851

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5				20					25					30		
	Ser	Lys	Gly	Arg	Ser	Leu	Ile	Gly	Lys	Val	Asp	Gly	Thr	Ser	His	Val
			35					40					45			
	Thr	Gly	Lys	Gly	Val	Thr	Val	Glu	Thr	Val	Phe	Ser	Val	Asp	Glu	Phe
		50					55					60				
10	Ser	Ala	Ser	Val	Leu	Thr	Gly	Lys	Leu	Thr	Thr	Val	Phe	Leu	Pro	Ile
	65					70					75				80	
	Val	Tyr	Thr	Ile	Val	Phe	Val	Val	Gly	Leu	Pro	Ser	Asn	Gly	Met	Ala
				85					90					95		
	Leu	Trp	Val	Phe	Leu	Phe	Arg	Thr	Lys	Lys	Lys	His	Pro	Ala	Val	Ile
				100					105					110		
15	Tyr	Met	Ala	Asn	Leu	Ala	Leu	Ala	Asp	Leu	Leu	Ser	Val	Ile	Trp	Phe
			115					120					125			
	Pro	Leu	Lys	Ile	Ala	Tyr	His	Ile	His	Ala	Asn	Asn	Trp	Ile	Tyr	Gly
		130					135					140				
20	Glu	Ala	Leu	Cys	Asn	Val	Leu	Ile	Gly	Phe	Phe	Tyr	Gly	Asn	Met	Tyr
	145				150						155				160	
	Cys	Ser	Ile	Leu	Phe	Met	Thr	Cys	Leu	Ser	Val	Gln	Arg	Tyr	Trp	Val
				165					170					175		
	Ile	Val	Asn	Pro	Met	Gly	His	Ser	Arg	Lys	Lys	Ala	Asn	Ile	Ala	Ile
				180					185					190		
25	Gly	Ile	Ser	Leu	Ala	Ile	Trp	Leu	Leu	Ile	Leu	Leu	Val	Thr	Ile	Pro
			195					200					205			
	Leu	Tyr	Val	Val	Lys	Gln	Thr	Ile	Phe	Ile	Pro	Ala	Leu	Asn	Ile	Thr
		210					215					220				
	Thr	Cys	His	Asp	Val	Leu	Pro	Glu	Gln	Leu	Leu	Val	Gly	Asp	Met	Phe
	225				230						235				240	
30	Asn	Tyr	Phe	Leu	Ser	Leu	Ala	Ile	Gly	Val	Phe	Leu	Phe	Pro	Ala	Phe
				245					250					255		
	Leu	Thr	Ala	Ser	Ala	Tyr	Val	Leu	Met	Ile	Arg	Met	Leu	Arg	Ser	Ser
			260					265					270			
35	Ala	Met	Asp	Glu	Asn	Ser	Glu	Lys	Lys	Arg	Lys	Arg	Ala	Ile	Lys	Leu
			275					280					285			
	Ile	Val	Thr	Val	Leu	Ala	Met	Tyr	Leu	Ile	Cys	Phe	Thr	Pro	Ser	Asn
		290					295					300				
	Leu	Leu	Leu	Val	Val	His	Tyr	Phe	Leu	Ile	Lys	Ser	Gln	Gly	Gln	Ser
	305				310						315				320	
40	His	Val	Tyr	Ala	Leu	Tyr	Ile	Val	Ala	Leu	Cys	Leu	Ser	Thr	Leu	Asn
				325					330					335		
	Ser	Cys	Ile	Asp	Pro	Phe	Val	Tyr	Tyr	Phe	Val	Ser	His	Asp	Phe	Arg
				340					345					350		
	Asp	His	Ala	Lys	Asn	Ala	Leu	Leu	Cys	Arg	Ser	Val	Arg	Thr	Val	Lys
45																
			355					360					365			
	Gln	Met	Gln	Val	Ser	Leu	Thr	Ser	Lys	Lys	His	Ser	Arg	Lys	Ser	Ser
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<210> 852

<211> 18

<212> PRT

55 <213> Human

<400> 852

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 35 40 45
 Thr Ile Lys Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu
 50 55 60
 Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu
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 Met Ile Ser Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val Ser
 85 90 95
 Glu Asp Asp Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu

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			130				135					140				
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	145				150						155				160	
	Ile	Glu	Arg	Thr	Ile	Ser	Lys	Pro	Lys	Gly	Ser	Val	Arg	Ala	Pro	Gln
				165						170					175	
10	Val	Tyr	Val	Leu	Pro	Pro	Pro	Glu	Glu	Glu	Met	Thr	Lys	Lys	Gln	Val
			180					185					190			
	Thr	Leu	Thr	Cys	Met	Val	Thr	Asp	Phe	Met	Pro	Glu	Asp	Ile	Tyr	Val
		195					200					205				
	Glu	Trp	Thr	Asn	Asn	Gly	Lys	Thr	Glu	Leu	Asn	Tyr	Lys	Asn	Thr	Glu
15		210				215						220				
	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Tyr	Phe	Met	Tyr	Ser	Lys	Leu	Arg
	225				230					235					240	
	Val	Glu	Lys	Lys	Asn	Trp	Val	Glu	Arg	Asn	Ser	Tyr	Ser	Cys	Ser	Val
				245					250					255		
20	Val	His	Glu	Gly	Leu	His	Asn	His	His	Thr	Thr	Lys	Ser	Phe	Ser	Arg
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	Thr	Pro	Gly	Lys												
			275													
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30	<400> 856															
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 Gly Ser
 <210> 860
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 15
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 20 1 5 10 15
 Ser Ser
 <210> 861
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 40 1 5 10 15
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 <211> 18
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 Gly Ala

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<211> 19
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<400> 864

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15 <210> 865
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 <212> DNA
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20 <400> 865

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2772

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 <213> Mouse

55 <400> 866

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5				20					25					30		
	Asn	Asn	Ser	Lys	Gly	Arg	Ser	Leu	Ile	Gly	Arg	Leu	Glu	Thr	Gln	Pro
			35					40					45			
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Claims

- 55 1. An isolated human antibody or antigen-binding fragment thereof that specifically binds to human PAR-2 (SEQ ID NO:851) and interacts with Val-42 and Asp-43 of human PAR-2, wherein the antibody or antigen-binding fragment comprises the complementarity determining regions (CDRs) comprising HCDR1-HCDR2-HCDR3 / LCDR1-LCDR2-LCDR3 amino acid sequences selected from the group consisting of: (a) SEQ ID NOs:100-102-104 / 108-110-112;

and (b) SEQ ID NOs:700-702-704 / 708-710-712.

2. The isolated human antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment also interacts with one or more residues selected from the group consisting of Ser-37, Leu-38, Ile-39, Gly-40, and Gly-44 of human PAR-2.
3. The isolated human antibody or antigen-binding fragment of claim 1 or 2, wherein the antibody or antigen-binding fragment does not interact with Lys-41 of human PAR-2.
4. The isolated human antibody or antigen-binding fragment of any one of claims 1 to 3, wherein the antibody or antigen-binding fragment interacts with Ser-37, Leu-38, Ile-39, Gly-40, Val-42 and Asp-43 of human PAR-2, but does not interact with Lys-41 of human PAR-2.
5. The isolated human antibody or antigen binding fragment of any one of claims 1 to 4, wherein the antibody or antigen-binding fragment blocks trypsin cleavage of human PAR-2 at the activating cleavage site located at the junction of residues Arg-36 and Ser-37 of human PAR-2.
6. The isolated human antibody or antigen-binding fragment of claim 5, wherein the antibody or antigen-binding fragment does not block trypsin cleavage of human PAR-2 at one or more non-activating cleavage sites selected from the non-activating cleavage site located at the junction of residues Arg-31 and Ser-32 of human PAR-2 and the non-activating cleavage site located at the junction of residues Lys-34 and Gly-35 of human PAR-2.
7. The isolated human antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment is selected from the group consisting of: (a) an antibody comprising a heavy chain variable region (HCVR) having the amino acid sequence of SEQ ID NO:714, and a light chain variable region (LCVR) having the amino acid sequence of SEQ ID NO:692; and (b) an antibody comprising a HCVR having the amino acid sequence of SEQ ID NO:98, and a LCVR having the amino acid sequence of SEQ ID NO:106.
8. A pharmaceutical composition comprising the antibody or antigen-binding fragment of any one of claims 1 to 7, and a pharmaceutically acceptable carrier or diluent.
9. The isolated human antibody or antigen-binding fragment of any one of claims 1 to 7 or the pharmaceutical composition of claim 8 for use in a method of treating a patient, wherein the patient exhibits one or more symptoms or indicia of a disease or disorder caused by PAR-2 activity wherein the disease or disorder caused by PAR-2 activity is a disease or disorder selected from the group consisting of pain, pruritus, asthma, rheumatoid arthritis, fibrosis, atopic dermatitis, inflammatory bowel disease, ulcerative colitis, pancreatitis, ulcer, Crohn's disease, cancer, and Netherton's disease.
10. The isolated antibody, antigen-binding fragment or composition of claim 9, for use according to claim 9, where the method further comprises administering to the patient at least one additional therapeutically active component selected from the group consisting of an IL-1 inhibitor, an IL-18 inhibitor, an IL-4 inhibitor, an IL-4 receptor inhibitor, an IL-6 inhibitor, an IL-6 receptor inhibitor, a nerve growth factor (NGF) inhibitor, a tumor necrosis factor (TNF) inhibitor, a TNF receptor inhibitor, a uric acid synthesis inhibitor and a corticosteroid.
11. Use of the isolated antibody or antigen-binding fragment of any one of claims 1 to 7, or the pharmaceutical composition of claim 8, in the manufacture of a medicament for use in treating a patient who exhibits one or more symptoms or indicia of a disease or disorder caused by PAR-2 activity, wherein the disease or disorder caused by PAR-2 activity is a disease or disorder selected from the group consisting of pain, pruritus, asthma, rheumatoid arthritis, fibrosis, atopic dermatitis, inflammatory bowel disease, ulcerative colitis, pancreatitis, ulcer, Crohn's disease, cancer, and Netherton's disease.
12. A nucleic acid molecule encoding an antibody or antigen-binding fragment thereof according to any one of claims 1 to 7, a recombinant expression vector carrying the nucleic acid, or a host cell into which the vector has been introduced.
13. A method of producing an antibody or antigen-binding fragment thereof according to any one of claims 1 to 7, the method comprising culturing a host cell according to claim 12 under conditions permitting production of the antibodies, and recovering the antibodies produced.

Patentansprüche

- 5 **1.** Isolierter humaner Antikörper oder Antigenbindungsfragment davon, der bzw. das spezifisch an humanes PAR-2 (SEQ ID NO:851) bindet und mit Val-42 und ASP-43 von humanem PAR-2 interagiert, wobei der Antikörper oder das Antigenbindungsfragment die Komplementarität bestimmenden Bereiche (CDRs) umfasst, die HCDR1-HCDR2-HCDR3/LCDR1-LCDR2-LCDR3-Aminosäuresequenzen umfassen, die ausgewählt sind aus der Gruppe bestehend aus: (a) SEQ ID NOs:100-102-104/108-110-112; und (b) SEQ ID NOs:700-702-704/708-710-712.
- 10 **2.** Isolierter humaner Antikörper oder Antigenbindungsfragment nach Anspruch 1, wobei der Antikörper oder das Antigenbindungsfragment zudem mit einem oder mehreren Resten interagiert, die ausgewählt sind aus der Gruppe bestehend aus Ser-37, Leu-38, Ile-39, Gly-40 und Gly-44 von humanem PAR-2.
- 15 **3.** Isolierter humaner Antikörper oder Antigenbindungsfragment nach Anspruch 1 oder 2, wobei der Antikörper oder das Antigenbindungsfragment nicht mit Lys-41 von humanem PAR-2 interagiert.
- 20 **4.** Isolierter humaner Antikörper oder Antigenbindungsfragment nach einem der Ansprüche 1 bis 3, wobei der Antikörper oder das Antigenbindungsfragment mit Ser-37, Leu-38, Ile-39, Gly-40, Val-42 und Asp-43 von humanem PAR-2 interagiert, aber nicht mit Lys-41 von humanem PAR-2 interagiert.
- 25 **5.** Isolierter humaner Antikörper oder Antigenbindungsfragment nach einem der Ansprüche 1 bis 4, wobei der Antikörper oder das Antigenbindungsfragment Trypsinspaltung von humanem PAR-2 an der aktivierenden Spaltstelle blockiert, die sich an der Verbindungsstelle der Reste Arg-36 und Ser-37 von humanem PAR-2 befindet.
- 30 **6.** Isolierter humaner Antikörper oder Antigenbindungsfragment nach Anspruch 5, wobei der Antikörper oder das Antigenbindungsfragment Trypsinspaltung von humanem PAR-2 an einer oder mehreren nicht aktivierenden Spaltstellen nicht blockiert, die ausgewählt sind aus der nicht aktivierenden Spaltstelle, die sich an der Verbindungsstelle der Reste Arg-31 und Ser-32 von humanem PAR-2 befindet, und der nicht aktivierenden Spaltstelle, die sich an der Verbindungsstelle der Reste Lys-34 und Gly-35 von humanem PAR-2 befindet.
- 35 **7.** Isolierter humaner Antikörper oder Antigenbindungsfragment nach Anspruch 1, wobei der Antikörper oder das Antigenbindungsfragment ausgewählt ist aus der Gruppe bestehend aus: (a) einem Antikörper, der eine variable Region einer schweren Kette (HCVR) mit der Aminosäuresequenz von SEQ ID NO:714 und eine variable Region einer leichten Kette (LCVR) mit der Aminosäuresequenz von SEQ ID NO:692 umfasst; und (b) einem Antikörper, der eine HCVR mit der Aminosäuresequenz von SEQ ID NO:98 und eine LCVR mit der Aminosäuresequenz von SEQ ID NO:106 umfasst.
- 40 **8.** Pharmazeutische Zusammensetzung, die den Antikörper oder das Antigenbindungsfragment nach einem der Ansprüche 1 bis 7 umfasst, und ein pharmazeutisch verträglicher Träger oder Verdünnungsmittel.
- 45 **9.** Isolierter humaner Antikörper oder Antigenbindungsfragment nach einem der Ansprüche 1 bis 7 oder pharmazeutische Zusammensetzung nach Anspruch 8 zur Verwendung in einem Verfahren zum Behandeln eines Patienten, wobei der Patient ein oder mehrere Symptome oder Zeichen einer durch PAR-2-Aktivität verursachten Erkrankung oder Störung aufweist, wobei die durch PAR-2-Aktivität verursachte Erkrankung oder Störung eine Erkrankung oder Störung ist, die ausgewählt ist aus der Gruppe bestehend aus Schmerzen, Pruritus, Asthma, rheumatoider Arthritis, Fibrose, atopischer Dermatitis, entzündlicher Darmerkrankung, Colitis ulcerosa, Bauchspeicheldrüsenentzündung, Geschwür, Morbus Crohn, Krebs und Netherton-Krankheit.
- 50 **10.** Isolierter Antikörper, Antigenbindungsfragment oder Zusammensetzung nach Anspruch 9 zur Verwendung nach Anspruch 9, wobei das Verfahren weiter das Verabreichen von mindestens einer zusätzlichen therapeutisch wirksamen Komponente an den Patienten umfasst, die ausgewählt ist aus der Gruppe bestehend aus einem IL-1-Inhibitor, einem IL-18-Inhibitor, einem IL-4-Inhibitor, einem IL-4-Rezeptorinhibitor, einem IL-6-Inhibitor, einem IL-6-Rezeptorinhibitor, einem Nervenwachstumsfaktor- (NGF) -Inhibitor, einem Tumornekrosefaktor- (TNF) - Inhibitor, einem TNF-Rezeptorinhibitor, einem Harnsäuresynthese-Inhibitor und einem Corticosteroid.
- 55 **11.** Verwenden des isolierten Antikörpers oder Antigenbindungsfragments nach einem der Ansprüche 1 bis 7 oder der pharmazeutischen Zusammensetzung nach Anspruch 8 bei der Herstellung von einem Arzneimittel zur Verwendung beim Behandeln eines Patienten, der ein oder mehrere Symptome oder Zeichen einer durch PAR-2-Aktivität verursachten Erkrankung oder Störung aufweist, wobei die durch PAR-2-Aktivität verursachte Erkrankung oder Störung

eine Erkrankung oder Störung ist, die ausgewählt ist aus der Gruppe bestehend aus Schmerzen, Pruritus, Asthma, rheumatoider Arthritis, Fibrose, atopischer Dermatitis, entzündlicher Darmerkrankung, Colitis ulcerosa, Bauchspeicheldrüsenentzündung, Geschwür, Morbus Crohn, Krebs und Netherton-Krankheit.

12. Nukleinsäuremolekül, das einen Antikörper oder ein Antigenbindungsfragment davon nach einem der Ansprüche 1 bis 7, einen rekombinanten Expressionsvektor, der die Nukleinsäure trägt, oder eine Wirtszelle, in die der Vektor eingeführt wurde, codiert.
13. Verfahren zum Herstellen eines Antikörpers oder Antigenbindungsfragments davon nach einem der Ansprüche 1 bis 7, wobei das Verfahren das Züchten einer Wirtszelle nach Anspruch 12 unter Bedingungen, welche die Herstellung der Antikörper erlauben, und Wiedergewinnen der hergestellten Antikörper umfasst.

Revendications

1. Anticorps humain isolé ou un de ses fragments de liaison à un antigène qui se lie spécifiquement au PAR-2 humain (SEQ ID n° 851) et interagit avec Val-42 et Asp-43 du PAR-2 humain, l'anticorps ou son fragment de liaison à un antigène comprenant les régions déterminant la complémentarité (CDR), comprenant les séquences d'acides aminés HCDR1-HCDR2-HCDR3 / LCDR1-LCDR2-LCDR3, choisies dans le groupe constitué par : (a) SEQ ID n° 100-102-104 / 108-110-112 ; et (b) SEQ ID n° 700-702-704 / 708-710-712.
2. Anticorps humain isolé ou fragment de liaison à un antigène selon la revendication 1, lequel anticorps ou fragment de liaison à un antigène interagissant aussi avec un ou plusieurs résidus choisis dans le groupe constitué par Ser-37, Leu-38, Ile-39, Gly-40 et Gly-44 du PAR-2 humain.
3. Anticorps humain isolé ou fragment de liaison à un antigène selon la revendication 1 ou 2, lequel anticorps ou fragment de liaison à un antigène n'interagissant pas avec Lys-41 du PAR-2 humain.
4. Anticorps humain isolé ou fragment de liaison à un antigène selon l'une quelconque des revendications 1 à 3, lequel anticorps ou fragment de liaison à un antigène interagissant avec Ser-37, Leu-38, Ile-39, Gly-40, Val-42 et Asp-43 du PAR-2 humain, mais n'interagissant pas avec Lys-41 du PAR-2 humain.
5. Anticorps humain isolé ou fragment de liaison à un antigène selon l'une quelconque des revendications 1 à 4, lequel anticorps ou fragment de liaison à un antigène bloquant le clivage de la trypsine du PAR-2 humain au niveau du site de clivage activant situé à la jonction des résidus Arg-36 et Ser-37 du PAR-2 humain.
6. Anticorps humain isolé ou fragment de liaison à un antigène selon la revendication 5, lequel anticorps ou fragment de liaison à un antigène ne bloquant pas le clivage de la trypsine du PAR-2 humain au niveau d'un ou de plusieurs sites de clivage non activateurs choisis parmi le site de clivage non activateur situé à la jonction des résidus Arg-31 et Ser-32 du PAR-2 humain et le site de clivage non activateur situé à la jonction des résidus Lys-34 et Gly-35 du PAR-2 humain.
7. Anticorps humain isolé ou fragment de liaison à un antigène selon la revendication 1, lequel anticorps ou fragment de liaison à un antigène étant choisi dans le groupe constitué par : (a) un anticorps comprenant une région variable de chaîne lourde (HCVR) ayant la séquence d'acides aminés de SEQ ID n° 714 et une région variable de chaîne légère (LCVR) ayant la séquence d'acides aminés de SEQ ID n° 692 ; et (b) un anticorps comprenant une HCVR ayant la séquence d'acides aminés de SEQ ID n° 98, et une LCVR ayant la séquence d'acides aminés de SEQ ID n° 106.
8. Composition pharmaceutique comprenant l'anticorps ou le fragment de liaison à un antigène selon l'une quelconque des revendications 1 à 7, et un support ou un diluant pharmaceutiquement acceptable.
9. Anticorps ou fragment de liaison à un antigène selon l'une quelconque des revendications 1 à 7, ou composition pharmaceutique selon la revendication 8, en vue d'une utilisation dans une méthode de traitement d'un patient, ledit patient présentant un ou plusieurs symptômes ou indices d'une maladie ou d'un trouble causé par l'activité du PAR-2, ladite maladie ou ledit trouble causé par l'activité du PAR-2 étant une maladie ou un trouble choisi dans le groupe constitué par la douleur, le prurit, l'asthme, la polyarthrite rhumatoïde, la fibrose, la dermatite atopique, la maladie intestinale inflammatoire, la rectocolite hémorragique, la pancréatite, un ulcère, la maladie de Crohn, le cancer et

le syndrome de Netherton.

- 5 10. Anticorps humain isolé, fragment de liaison à un antigène ou composition selon la revendication 9, en vue d'une utilisation selon la revendication 9, la méthode comprenant également l'administration au patient d'au moins un composant thérapeutiquement actif supplémentaire choisi dans le groupe constitué par un inhibiteur de IL-1, un inhibiteur de IL-18, un inhibiteur de IL-4, un inhibiteur du récepteur de IL-4, un inhibiteur de IL-6, un inhibiteur du récepteur de IL-6, un inhibiteur du facteur de croissance du tissu nerveux (NGF), un inhibiteur du facteur de nécrose tumorale (TNF), un inhibiteur du récepteur de TNF, un inhibiteur de la synthèse d'acide urique et un corticostéroïde.
- 10 11. Utilisation de l'anticorps isolé ou du fragment de liaison à un antigène selon l'une quelconque des revendications 1 à 7, ou de la composition pharmaceutique selon la revendication 8, dans la fabrication d'un médicament utilisé pour traiter un patient présentant un ou plusieurs symptômes ou indices d'une maladie ou d'un trouble causé par l'activité du PAR-2, ladite maladie ou ledit trouble causé par l'activité du PAR-2 étant une maladie ou un trouble
15 choisi dans le groupe constitué par la douleur, le prurit, l'asthme, la polyarthrite rhumatoïde, la fibrose, la dermatite atopique, la maladie intestinale inflammatoire, la colite ulcéreuse, la pancréatite, un ulcère, la maladie de Crohn, le cancer et le syndrome de Netherton.
- 20 12. Molécule d'acide nucléique codant pour un anticorps ou un de ses fragments de liaison à un antigène selon l'une quelconque des revendications 1 à 7, vecteur d'expression recombinant porteur de l'acide nucléique, ou cellule hôte dans laquelle le vecteur a été introduit.
- 25 13. Méthode de production d'un anticorps ou d'un de ses fragments de liaison à un antigène selon l'une quelconque des revendications 1 à 7, ladite méthode comprenant la culture d'une cellule hôte selon la revendication 12 dans des conditions permettant de produire des anticorps, et la récupération des anticorps produits.

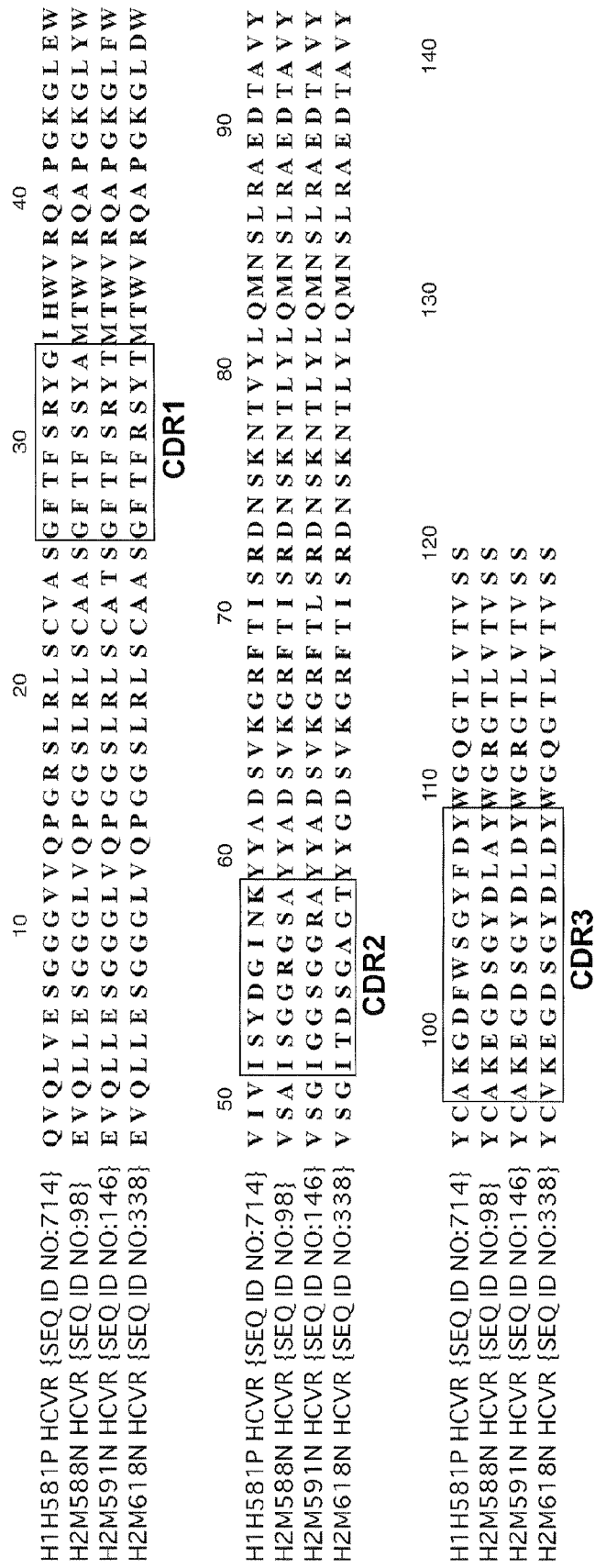


Fig. 1

H1H581P LCVR (SEQ ID NO:692)	D I V M T Q T P L S S P V T L G Q P A S I S C R S S	Q S L V H S D G N T Y	L S W L H Q
H2M588N LCVR (SEQ ID NO:106)	D I Q M T Q S P S S L S A S V G D R V T I T C R A R	Q G I S N N - - - -	L A W L Q Q
H2M591N LCVR (SEQ ID NO:154)	D I Q M T Q Y P S S L S A S V G D R V T I T C R A R	Q G I S N Y - - - -	L A W L Q Q
H2M618N LCVR (SEQ ID NO:346)	D I Q M T Q S P S S L S A S V G D R V T I T C R A S	Q G I S T Y - - - -	L A W L Q Q
CDR1			
H1H581P LCVR (SEQ ID NO:692)	R P G Q P P R L L I Y K I S	N R F S G V P D R F S G S G A G T D F T L Q I S R V E A E	
H2M588N LCVR (SEQ ID NO:106)	K P G K A P K S L I Y A A S	S S L Q S G I P S K F S G S G S G T Y F T L T I S S L Q P E	
H2M591N LCVR (SEQ ID NO:154)	K P G K A P K S L I Y A A S	S S L Q R G V P S K F S G S G S G T D F T L T I S S L Q P E	
H2M618N LCVR (SEQ ID NO:346)	K P G K A P K S L I Y A T S	S S L Q S G V P S K F S G S R S G T D F T L T I S S L Q P E	
CDR2			
H1H581P LCVR (SEQ ID NO:692)	D V G I Y Y C	M Q A T Q F P - T	F G G G T K V E I K
H2M588N LCVR (SEQ ID NO:106)	D F A T Y Y C	Q Q Y K S S P L T	F G G G T K V E I K
H2M591N LCVR (SEQ ID NO:154)	D S A T Y Y C	Q Q Y K I S P L T	F G G G T K V E I K
H2M618N LCVR (SEQ ID NO:346)	D F A T Y Y C	Q Q Y K S S P L T	F G G G T K V E I K
CDR3			

Fig. 2

(A)

	C-terminal Biotin	N-terminal Biotin
No Cleavage	① ② GTNRSSKGRSLIGKVDGT-B 2501 kDa	① ② B-GTNRSSKGRSLIGKVDGT 2373 kDa
Cleavage @ ①	2073 kDa	988 kDa
Cleavage @ ②	1558 kDa	N/A

(B)

Antibody	Time	2501 kDa	2073 kDa	1558 kDa	2373 kDa	988 kDa
Neg Ctrl	0	X			X	
Neg Ctrl	5			X		X
Neg Ctrl	15			X		N/D
H4H581P	0	X			X	
H4H581P	5		X			X
H4H581P	15		X			N/D
H4H588N	0	X			X	
H4H588N	5			X		X
H4H588N	15			X		N/D

Fig. 3

(A)	Mouse		Rat		Human	
	①	② ③	② ③	① ② ③	① ② ③	
	GRNSKGRSLIGRLRLETQPPI		GPNSKGRSLIGRLDTP		GTNRSSKGRSLIGKVDGT	
	No Cleavage	2556 kDa	2337 kDa	2502 kDa	2074 kDa	1558 kDa
	Cleavage @ ①	2342 kDa	N/A	1772 kDa	1558 kDa	
	Cleavage @ ②	1898 kDa	1853 kDa			
	Cleavage @ ③	1686 kDa	1640 kDa			

(B)	Antibody	Time	2556 kDa	2342 kDa	1898 kDa	1686 kDa	2337 kDa	1853 kDa	1640 kDa	2502 kDa	2074 kDa	1772 kDa	1558 kDa
	Neg Ctrl	0	X				X			X			
	Neg Ctrl	5				X			X				X
	H4H581P	0	X				X			X			
	H4H581P	5				X	X		X		X		
	H4H588N	0	X				X			X			
	H4H588N	5				X			X			X	X
	Comp. Ab	0	X				X			X			
	Comp. Ab	5				X			X	X			

Fig. 4

	▽ ▽ ▼	(28)(29)(30)(31)(32)(33)(34)(35)(36)(37)(38)(39)(40)(41)(42)(43)(44)(45)	
		GTNRSSKGRSLIGKVDGT	
Comparator 1:		280.11861.544282.5137152126135	
Comparator 3:		1097721797895120128118	
H4H581P:		11810650.20.12456120121112	
H4H588N:		1771408571220.5840.54.5164	

Fig. 5

REFERENCES CITED IN THE DESCRIPTION

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**MAGAS EMBERI PROTEÁZAKTIVÁLT RECEPTOR-2 AFFINITÁSÚ EMBERI ANTITESTEK
SZABADALMI IGÉNYPONTOK**

1. Izolált emberi antitest vagy annak antigénkötő fragmentuma, amely kifejezetten kötődik az emberi PAR-2-höz (szekvencia-azonosító: 851) és kölcsönhatásba lép az emberi PAR-2 Val-42 és Asp-43 peptidekkel, ahol az antitest vagy antigénkötő fragmentum tartalmazza azokat a komplementaritást meghatározó régiókat (CDR-ek), amelyek olyan HCDR1-HCDR2-HCDR3 / LCDR1-LCDR2-LCDR3 aminosav-szekvenciákat tartalmaznak, amelyek a következő csoportból kiválasztottak: (a) szekvencia-azonosítók: 100-102-104 / 108-110-112; és (b) szekvencia-azonosítók: 700-702-704 / 708-710-712.
2. Az izolált emberi antitest vagy antigénkötő fragmentum az 1-es igénypont szerint, ahol az antitest vagy antigénkötő fragmentum kölcsönhatásba lép továbbá egy vagy több maradvánnyal, amely az emberi PAR-2 Ser-37, Leu-38, Ile-39, Gly-40, és Gly-44 peptideket tartalmazó csoportból kiválasztott.
3. Az izolált emberi antitest vagy antigénkötő fragmentum az 1-es vagy 2-es igénypont szerint, ahol the antitest vagy antigénkötő fragmentum nem lép kölcsönhatásba az emberi PAR-2 Lys-41 peptidjével.
4. Az izolált emberi antitest vagy antigénkötő fragmentum az 1-3 igénypontok bármelyike szerint, ahol az antitest vagy antigénkötő fragmentum kölcsönhatásba lép az emberi PAR-2 Ser-37, Leu-38, Ile-39, Gly-40, Val-42 és Asp-43 peptidjeivel, viszont nem lép kölcsönhatásba az emberi PAR-2 Lys-41 peptidjével.
5. Az izolált emberi antitest vagy antigénkötő fragmentum az 1-4 igénypontok bármelyike szerint, ahol az antitest vagy antigénkötő fragmentum blokkolja az emberi PAR-2 tripszin peptidkötés-hasítását az emberi PAR-2 Arg-36 és Ser-37 csomópontjánál található aktiváló hasítási helyen.
6. Az izolált emberi antitest vagy antigénkötő fragmentum az 5-ös igénypont szerint, ahol az antitest vagy antigénkötő fragmentum nem blokkolja az emberi PAR-2 tripszin peptidkötés-hasítását egy vagy több olyan nem-aktiváló hasítási helyen, amelyek az emberi PAR-2 Arg-31 és Ser-32 maradványok csomópontjánál található nem-aktiváló hasítási hely vagy az emberi PAR-2 Lys-34 és Gly-35 maradványok csomópontjánál található nem aktiváló hasítási hely közül kiválasztottak.
7. Az izolált emberi antitest vagy antigénkötő fragmentum az 1-es igénypont szerint, ahol az antitest vagy antigénkötő fragmentum a következőket tartalmazó csoportból kiválasztott: (a) antitest, amely tartalmaz szekvencia-azonosító: 714 aminosav-szekvenciát tartalmazó nehézlánc variábilis régiót (HCVR) és szekvencia-azonosító: 692 aminosav-szekvenciát tartalmazó könnyűlánc variábilis régiót (LCVR); és (b) antitest, amely tartalmaz szekvencia-azonosító: 98 aminosav-szekvenciát tartalmazó HCVR-t és szekvencia-azonosító: 106 aminosav-szekvenciát tartalmazó LCVR-t.
8. Gyógyszerészeti összetétel, amely tartalmazza az antitestet vagy antigénkötő fragmentumot az 1-7 igénypontok bármelyike szerint és egy gyógyszerészetileg elfogadható hordozót vagy diluenset.



9. Az izolált emberi antitest vagy antigénkötő fragmentum az 1-7 igénypontok bármelyike szerint vagy a gyógyszerészeti összetétel a 8-as igénypont szerint beteg kezelésében történő felhasználásra, ahol a beteg PAR-2 aktivitás által előidézett megbetegedés vagy rendellenesség tüneteit vagy kialakulásának jeleit mutatja, ahol a PAR-2 aktivitás által előidézett megbetegedés vagy rendellenesség a következőket tartalmazó csoportból kiválasztott: fájdalom, viszketés, asztma, idült sokizületi gyulladás (rheumatoid arthritis), fibrózis, atópiás bőrgyulladás, gyulladásos bélbetegség, fekélyes vastagbélgyulladás, hasnyálmirigy-gyulladás, fekély, Crohn-betegség, rák és Neitherton betegség.

10. Az izolált antitest, antigénkötő fragmentum vagy összetétel a 9-es igénypontra, ahol továbbá a módszer tartalmazza legalább egy további terápiásan aktív komponens adagolását a beteg számára, amely a következőket tartalmazó csoportból kiválasztott: IL-1-gátló, IL-18-gátló, IL-4 gátló, IL-4 receptorgátló, IL-6-gátló, IL-6 receptorgátló, ideg növekedési faktorgátló (NGF), tumor nekrosis faktorgátló (TNF), TNF receptorgátló, húgysav szintézisgátló és kortikoszteroid.

11. Az 1-7 igénypontok bármelyike szerinti izolált antitest vagy antigénkötő fragmentum vagy a 8-as igénypont szerinti gyógyszerészeti összetétel felhasználása olyan gyógyszer gyártásában, amellyel olyan beteg kezelésében használnak fel, aki PAR-2 aktivitás által előidézett megbetegedés vagy rendellenesség tüneteit vagy kialakulásának jeleit mutatja, ahol a PAR-2 aktivitás által előidézett megbetegedés vagy rendellenesség a következőket tartalmazó csoportból kiválasztott: fájdalom, viszketés, asztma, idült sokizületi gyulladás (rheumatoid arthritis), fibrózis, atópiás bőrgyulladás, gyulladásos bélbetegség, fekélyes vastagbélgyulladás, hasnyálmirigy-gyulladás, fekély, Crohn-betegség, rák és Neitherton betegség.

12. A 1-7 igénypontok szerinti antitestet vagy annak antigénkötő fragmentumát kódoló nukleinsav molekula, a nukleinsavat hordozó rekombináns expressziós vektor vagy gazdasejt, amelybe a vektort juttatták.

13. Módszer az 1-7 igénypontok bármelyike szerinti antitest vagy annak antigénkötő fragmentumának gyártására, a módszer tartalmazza a 12-es igénypont szerinti gazdasejt tenyésztését az antitestek termelését lehetővé tévő körülmények között és a termelt antitestek begyűjtését.