



(11)

EP 3 330 288 A1

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:
06.06.2018 Bulletin 2018/23

(51) Int Cl.:
C07K 16/18 (2006.01)

(21) Application number: **17208690.2**

(22) Date of filing: **17.12.2012**

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR
Designated Extension States:
BA

(30) Priority: **21.12.2011 US 201161578458 P**

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
12821311.3 / 2 794 656

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Remarks:

This application was filed on 19-12-2017 as a divisional application to the application mentioned under INID code 62.

(54) **COMPOSITIONS AND METHODS FOR ANTIBODIES TARGETING FACTOR P**

(57) The present invention relates to antibodies or antigen binding fragments thereof that bind to complement Factor P and used thereof as well as combinations of anti-Factor P antibodies with antibodies or antigen binding fragments thereof that bind to complement component 5 (C5).

FIG 1A

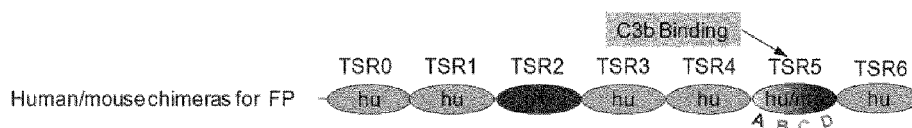
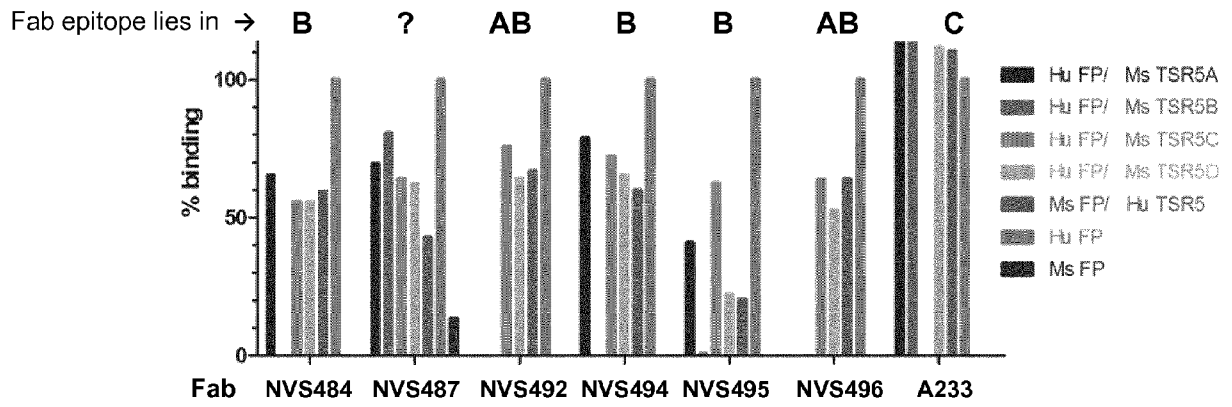


FIG 1B



FIG 1C



Description**BACKGROUND OF THE INVENTION**

[0001] Age related macular degeneration (AMD) is a progressive disease and a leading cause of vision loss and blindness in Americans aged 65 and older. AMD primarily affects the macula; a part of the retina responsible for high visual acuity needed to read or drive. The majority of AMD patients suffer from an early stage of the disease which is characterized by the presence of extracellular retinal deposits called drusen. Drusen are extracellular retinal deposits of cell debris, inflammatory mediators, and extracellular matrix components. The late stages of AMD manifest as a dry or wet form, both are associated with vision loss. Dry AMD, also known as geographic atrophy, appears on ophthalmoscopic examination as clearly demarcated regions corresponding to local areas of retinal pigmented epithelium (RPE) loss. Wet AMD is associated with neo-vascularization of the choroid, causing a loss of integrity in Bruch's membrane and vessel growth in the retina, where they can often hemorrhage. This leakage causes permanent damage to retinal cells which die off and create blind spots in the central vision.

[0002] The innate human system is composed of the complement pathway. The complement pathway serves to defend against pyogenic bacterial infection bridging innate and adaptive immunity; and disposing of products of immune complexes and inflammatory injury. The complement is a system of more than 30 proteins involved in cascade reactions in plasma and cell surfaces. The complement system and its complement components are involved in various immune processes. For example, complement C5b-9 complex, also termed the terminal complex or the membrane attack complex (MAC), plays an important role in cell death by inducing membrane permeability damages.

[0003] There are three known complement activation pathways: the classical, lectin, and alternative pathways. All three pathways lead to the cleavage of C3 by C3 convertase and subsequent cleavage of C5 by the C5 convertase, releasing C3a, C5a, and C5b. Factor P is a key regulator of the alternative complement pathway. It is proposed to have two major functions *in vivo*. First, Factor P stabilizes the C3 and C5 convertases by binding to C3b of the convertase enzyme and thereby prolongs the half life of C3 convertase. Second, Factor P may determine which cells will be lysed by attaching to a cell surface and functioning as a template on which convertases can form, leading to activation of the alternative complement pathway and lysis of the cell.

[0004] Recent work has demonstrated that complement components C3 and C5 are principal constituents of drusen in patients with AMD. Mulling, R.F. et al. (2000) FASEB J 14, 835-46 Their presence as well as that of the membrane attack complex (MAC) C5b-9 and other acute phase reactant proteins in RPE cells overlying drusen has been speculated to be involved in the process that can trigger complement activation and formation of MAC. Johnson, L et al. (2001) Exp Eye Res 73, 887-896. Thus, there is growing evidence that complement components are more than mere mediators of innate immunity.

[0005] Nutritional intervention has been prescribed to inhibit progression of dry AMD to wet AMD. At present the only FDA approved treatments for wet AMD include photodynamic therapy (PDT), an anti-VEGF aptamer, such as pegaptanib, and anti-VEGF antibodies, ranibizumab. These drugs or therapies are typically administered to patients who have already suffered substantial vision loss.

[0006] There remains a need to develop an effective treatment for AMD, particularly dry AMD to replace or supplement current treatments. Particularly, there is a need for treatments which can provide early detection, prevention or restoration of vision loss.

SUMMARY OF THE INVENTION

[0007] The present invention relates to an isolated antibody, or antigen binding fragment thereof, that binds to human or cynomolgus Factor P, wherein said antibody binds to the TSR5 domain (SEQ ID NO: 406). For example, the antibodies, or antigen binding fragments described herein bind to a region of the TSR5 domain comprising the sequence of SEQ ID NO: 407, more specifically said antibodies also bind a region of the Factor P TSR5 domain comprising the amino acid sequence KSISC (SEQ ID NO: 408). In certain embodiments, the isolated antibodies, or antigen binding fragments thereof, bind to a Factor P epitope comprising the amino acid sequence of SEQ ID NO: 407. In other embodiments, the isolated antibodies, or antigen binding fragments thereof, bind to a Factor P epitope comprising the amino acid sequence of SEQ ID NO: 408.

[0008] The isolated antibodies, or antigen binding fragments, described herein bind Factor P, with a KD of less than or equal to 1.2 nM. For example, the isolated antibodies or antigen binding fragments described herein may bind to human or cynomolgus Factor P with a KD of less than or equal to 1.1 nM, less than or equal to 1nM, less than or equal to 600pM, less than or equal to 500 pM, less than or equal to 400 pM, less than or equal to 300 pM, less than or equal to 200 pM, less than or equal to 100 pM, less than or equal to 75 pM, less than or equal to 50 pM, less than or equal to 40pM, less than or equal to 30 pM, less than or equal to 20 pM, or less than or equal to 10pM.

[0009] The binding affinity of isolated antibodies and antigen binding fragments described herein can be determined

by solution equilibrium titration (SET). Methods for SET are known in the art and are described in further detail below. Alternatively, binding affinity of the isolated antibodies, or fragments, described herein can be determined by Biacore assay. Methods for Biacore kinetic assays are known in the art and are described in further detail below.

[0010] The isolated antibodies and antigen binding fragments described herein can be used to inhibit the alternative complement pathway. For example, an isolated antibody or antigen binding fragment thereof can inhibit the alternative complement pathway as measured by an *in vitro* hemolytic assay with an IC₅₀ of less than or equal to 25 nM, less than or equal to 20 nM, less than or equal to 16 nM, less than or equal to 15 nM, less than or equal to 14 nM, less than or equal to 13 nM, less than or equal to 12 nM, less than or equal to 11 nM, less than or equal to 10 nM, less than or equal to 9 nM, less than or equal to 8 nM, less than or equal to 7 nM. More specifically, an isolated antibody or antigen binding fragment thereof as described herein can inhibit the alternative complement pathway in human as measured by an *in vitro* hemolytic assay with an IC₅₀ of less than or equal to 16 nM, or less than or equal to 9 nM.

[0011] An isolated antibody or antigen binding fragment thereof as described herein can inhibit the alternative complement pathway as measured by an *in vitro* C3b deposition assay with an IC₅₀ of less than or equal to 10 nM, less than or equal to 7 nM, less than or equal to 6 nM, less than or equal to 5 nM, less than or equal to 4 nM, less than or equal to 3 nM, less than or equal to 2 nM, less than or equal to 1 nM, less than or equal to 15 nM, less than or equal to 1 nM, less than or equal to 0.5 nM, or less than or equal to 0.1 nM. More specifically, an isolated antibody or antigen binding fragment thereof as described herein can inhibit the alternative complement pathway in human as measured by an *in vitro* C3b deposition assay with an IC₅₀ of less than or equal to 3 nM, or less than or equal to 2 nM.

[0012] An isolated antibody or antigen binding fragment thereof as described herein can inhibit the alternative complement pathway with an IC₅₀ of less than or equal to 25 nM, less than or equal to 20 nM, less than or equal to 15 nM, less than or equal to 10 nM, less than or equal to 9 nM, less than or equal to 8 nM, less than or equal to 7 nM, or less than or equal to 6 nM, as measured by deposition of the complement membrane attack complex. More specifically, an isolated antibody or fragment thereof as described herein can inhibit the alternative complement pathway in human with an IC₅₀ of less than or equal to 25 nM, or less than or equal to 7.5 nM, as measured by deposition of the complement membrane attack complex.

[0013] An isolated antibody or antigen binding fragment thereof as described herein can inhibit the alternative complement pathway with an IC₅₀ of less than or equal to 80 nM, less than or equal to 50 nM, less than or equal to 45 nM, or less than or equal to 35 nM, as measured by generation of C3a.

[0014] An isolated antibody or antigen binding fragment thereof as described herein may also inhibit the alternative complement pathway with an IC₅₀ of less than or equal to 80 nM, less than or equal to 50 nM, less than or equal to 45 nM, or less than or equal to 35 nM, as measured by generation of iC3b.

[0015] An isolated antibody or antigen binding fragment thereof as described herein may also inhibit the alternative complement pathway with an IC₅₀ of less than or equal to 80 nM, less than or equal to 50 nM, less than or equal to 45 nM, or less than or equal to 35 nM, as measured by generation of C5a.

[0016] An isolated antibody or antigen binding fragment thereof as described herein may also inhibit the alternative complement pathway with an IC₅₀ of less than or equal to 80 nM, less than or equal to 50 nM, less than or equal to 45 nM, or less than or equal to 35 nM, as measured by generation of C5b.

[0017] An isolated antibody or antigen binding fragment thereof as described herein may also inhibit the alternative complement pathway by destabilizing and/or blocking the activity of C3 and/or C5 convertase, as measured by a decrease in production of C3a, C3b, iC3b, C5a, and/or C5b.

[0018] An isolated antibody or antigen binding fragment thereof as described herein may also inhibit the generation of C5a with an IC₅₀ of less than or equal to 80 nM, less than or equal to 50 nM, less than or equal to 45 nM, or less than or equal to 35 nM.

[0019] The isolated antibodies, or antigen binding fragment thereof, may also block Factor P binding to C3b and/or prevent Factor P binding to the cell surface or to DNA or oligonucleotides.

[0020] Another aspect of the invention includes an isolated antibody, or antigen binding fragment thereof, that specifically binds to human, cynomolgus, rat and/or rabbit Factor P. In a further aspect, the isolated antibody, or antigen binding fragment, competes for binding with an antibody, or antigen binding fragment, described in Table 1.

[0021] The isolated antibodies, or antigen binding fragments thereof, as described herein can be a monoclonal antibodies, a human or humanized antibodies, a chimeric antibodies, single chain antibodies, Fab fragments, Fv fragments, F(ab')₂ fragments, or ScFv fragments, and/or IgG isotypes.

[0022] The isolated antibodies, or antigen binding fragments thereof, as described herein can also include a framework in which an amino acid has been substituted into the antibody framework from the respective human VH or VL germline sequences.

[0023] Another aspect of the invention includes an isolated antibody or antigen binding fragment thereof having the heavy and light chain sequences of Fabs described in Table 1. For example, the isolated antibody or antigen binding fragment thereof can have the heavy and light chain sequences of Fab NVS962, NVS963, NVS964, NVS965, NVS966, NVS967, NVS962-G, NVS962-S, NVS962-T, NVS962-Q, NVS962-S31A, NVS965-Q, NVS965-S, NVS965-T, NVS804,

NVS805, NVS806, NVS807, or NVS808.

[0024] A further aspect of the invention includes an isolated antibody or antigen binding fragment thereof having the heavy and light chain variable domain sequences of Fabs described in Table 1. For example, the isolated antibody or antigen binding fragment thereof can have the heavy and light chain variable domain sequence of Fab NVS962, NVS963, NVS964, NVS965, NVS966, NVS967, NVS962-G, NVS962-S, NVS962-T, NVS962-Q, NVS962-S31A, NVS965-Q, NVS965-S, NVS965-T, NVS804, NVS805, NVS806, NVS807, or NVS808.

[0025] The invention also relates to an isolated antibody or antigen binding fragment thereof that includes a heavy chain CDR1 selected from the group consisting of SEQ ID NOs 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169, 183, 197, 211, 225, 239, 253, and 267; a heavy chain CDR2 selected from the group consisting of SEQ ID NOs: 2, 16, 30, 44, 58, 72, 86, 100, 114, 128, 142, 156, 170, 184, 198, 212, 226, 240, 254, and 268; and a heavy chain CDR3 selected from the group consisting of SEQ ID NOs: 3, 17, 31, 45, 59, 73, 87, 101, 115, 129, 143, 157, 171, 185, 199, 213, 227, 241, 255, and 269, wherein the isolated antibody or antigen binding fragment thereof binds to human Factor P. In another aspect, the isolated antibody or antigen binding fragment thereof further includes a light chain CDR1 selected from the group consisting of SEQ ID NOs: 4, 18, 32, 46, 60, 74, 88, 102, 116, 130, 144, 158, 172, 186, 200, 214, 228, 242, 256, and 270; a light chain CDR2 selected from the group consisting of SEQ ID NOs 5, 19, 33, 47, 61, 75, 89, 103, 117, 131, 145, 159, 173, 187, 201, 215, 229, 243, 257, and 271; and a light chain CDR3 selected from the group consisting of SEQ ID NOs 6, 20, 34, 48, 62, 76, 90, 104, 118, 132, 146, 160, 174, 188, 202, 216, 230, 244, 258, and 272.

[0026] The invention also relates to an isolated antibody or antigen binding fragment thereof that includes a light chain CDR1 selected from the group consisting of SEQ ID NOs: 4, 18, 32, 46, 60, 74, 88, 102, 116, 130, 144, 158, 172, 186, 200, 214, 228, 242, 256, and 270; a light chain CDR2 selected from the group consisting of SEQ ID NOs 5, 19, 33, 47, 61, 75, 89, 103, 117, 131, 145, 159, 173, 187, 201, 215, 229, 243, 257, and 271; and a light chain CDR3 selected from the group consisting of SEQ ID NOs 6, 20, 34, 48, 62, 76, 90, 104, 118, 132, 146, 160, 174, 188, 202, 216, 230, 244, 258, and 272, wherein the isolated antibody or antigen binding fragment thereof binds to human Factor P.

The invention also relates to an isolated antibody or antigen binding fragment thereof that binds Factor P having HCDR1, HCDR2, HCDR3 and LCDR1, LCDR2, LCDR3, wherein HCDR1, HCDR2, HCDR3 comprises SEQ ID NOs: 1, 2, 3, and LCDR1, LCDR2, LCDR3 comprises SEQ ID NOs: 4, 5, 6; or HCDR1, HCDR2, HCDR3 and LCDR1, LCDR2, LCDR3, wherein HCDR1, HCDR2, HCDR3 comprises SEQ ID NOs 15, 16, 17, and LCDR1, LCDR2, LCDR3 comprises SEQ ID NOs: 18, 19, 20; or HCDR1, HCDR2, HCDR3 and LCDR1, LCDR2, LCDR3, wherein HCDR1, HCDR2, HCDR3 comprises SEQ ID NOs 29, 30, 31, and LCDR1, LCDR2, LCDR3 comprises SEQ ID NOs: 32, 33, 34; or HCDR1, HCDR2, HCDR3 and LCDR1, LCDR2, LCDR3, wherein HCDR1, HCDR2, HCDR3 comprises SEQ ID NOs 43, 44, 45, and LCDR1, LCDR2, LCDR3 comprises SEQ ID NOs: 46, 47, 48; or HCDR1, HCDR2, HCDR3 and LCDR1, LCDR2, LCDR3, wherein HCDR1, HCDR2, HCDR3 comprises SEQ ID NOs 57, 58, 59, and LCDR1, LCDR2, LCDR3 comprises SEQ ID NOs: 60, 61, 62; or HCDR1, HCDR2, HCDR3 and LCDR1, LCDR2, LCDR3, wherein HCDR1, HCDR2, HCDR3 comprises SEQ ID NOs 71, 72, 73, and LCDR1, LCDR2, LCDR3 comprises SEQ ID NOs: 74, 75, 76; or HCDR1, HCDR2, HCDR3 and LCDR1, LCDR2, LCDR3, wherein HCDR1, HCDR2, HCDR3 comprises SEQ ID NOs 85, 86, 87, and LCDR1, LCDR2, LCDR3 comprises SEQ ID NOs: 88, 89, 90; or HCDR1, HCDR2, HCDR3 and LCDR1, LCDR2, LCDR3, wherein HCDR1, HCDR2, HCDR3 comprises SEQ ID NOs 99, 100, 101, and LCDR1, LCDR2, LCDR3 comprises SEQ ID NOs: 102, 103, 104; or HCDR1, HCDR2, HCDR3 and LCDR1, LCDR2, LCDR3, wherein HCDR1, HCDR2, HCDR3 comprises SEQ ID NOs 113, 114, 115, and LCDR1, LCDR2, LCDR3 comprises SEQ ID NOs: 116, 117, 118; or HCDR1, HCDR2, HCDR3 and LCDR1, LCDR2, LCDR3, wherein HCDR1, HCDR2, HCDR3 comprises SEQ ID NOs 127, 128, 129, and LCDR1, LCDR2, LCDR3 comprises SEQ ID NOs: 130, 131, 132; or HCDR1, HCDR2, HCDR3 and LCDR1, LCDR2, LCDR3, wherein HCDR1, HCDR2, HCDR3 comprises SEQ ID NOs 141, 142, 143, and LCDR1, LCDR2, LCDR3 comprises SEQ ID NOs: 144, 145, 146; or HCDR1, HCDR2, HCDR3 and LCDR1, LCDR2, LCDR3, wherein HCDR1, HCDR2, HCDR3 comprises SEQ ID NOs 155, 156, 157, and LCDR1, LCDR2, LCDR3 comprises SEQ ID NOs: 158, 159, 160; or HCDR1, HCDR2, HCDR3 and LCDR1, LCDR2, LCDR3, wherein HCDR1, HCDR2, HCDR3 comprises SEQ ID NOs 169, 170, 171, and LCDR1, LCDR2, LCDR3 comprises SEQ ID NOs: 172, 173, 174; or HCDR1, HCDR2, HCDR3 and LCDR1, LCDR2, LCDR3, wherein HCDR1, HCDR2, HCDR3 comprises SEQ ID NOs 183, 184, 185, and LCDR1, LCDR2, LCDR3 comprises SEQ ID NOs: 186, 187, 188; or HCDR1, HCDR2, HCDR3 and LCDR1, LCDR2, LCDR3, wherein HCDR1, HCDR2, HCDR3 comprises SEQ ID NOs 197, 198, 199, and LCDR1, LCDR2, LCDR3 comprises SEQ ID NOs: 200, 201, 202; or HCDR1, HCDR2, HCDR3 and LCDR1, LCDR2, LCDR3, wherein HCDR1, HCDR2, HCDR3 comprises SEQ ID NOs 211, 212, 213, and LCDR1, LCDR2, LCDR3 comprises SEQ ID NOs: 214, 215, 216; or HCDR1, HCDR2, HCDR3 and LCDR1, LCDR2, LCDR3, wherein HCDR1, HCDR2, HCDR3 comprises SEQ ID NOs 225, 226, 227, and LCDR1, LCDR2, LCDR3 comprises SEQ ID NOs: 228, 229, 230; or HCDR1, HCDR2, HCDR3 and LCDR1, LCDR2, LCDR3, wherein HCDR1, HCDR2, HCDR3 comprises SEQ ID NOs 239, 240, 241, and LCDR1, LCDR2, LCDR3 comprises SEQ ID NOs: 242, 243, 244; or HCDR1, HCDR2, HCDR3 and LCDR1, LCDR2, LCDR3, wherein HCDR1, HCDR2, HCDR3 comprises SEQ ID NOs 253, 254, 255, and LCDR1, LCDR2, LCDR3 comprises SEQ ID NOs: 256, 257, 258; or HCDR1, HCDR2, HCDR3 and LCDR1, LCDR2, LCDR3, wherein HCDR1, HCDR2, HCDR3 comprises SEQ ID NOs

267, 268, 269, and LCDR1, LCDR2, LCDR3 comprises SEQ ID NOs: 270, 271, 272.

[0027] In one embodiment of the invention the isolated antibody or antigen binding fragment thereof includes a heavy chain variable domain sequence selected from the group consisting of SEQ ID NOs: 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175, 189, 203, 217, 231, 245, 259 and 273. In another embodiment, the isolated antibody or antigen binding fragment further comprises a light chain variable domain sequence wherein the heavy chain variable domain and light chain variable domain combine to form an antigen binding site for Factor P. In a further embodiment the isolated antibody or antigen binding fragment further includes a light chain variable domain sequence selected from SEQ ID NOs: 8, 22, 36, 50, 64, 78, 92, 106, 120, 134, 148, 162, 176, 190, 204, 218, 232, 246, 260, and 274 wherein said isolated antibody or antigen binding fragment thereof binds Factor P.

[0028] The invention also relates to an isolated antibody or antigen binding fragment thereof that includes a light chain variable domain sequence selected from the group consisting of SEQ ID NOs: 8, 22, 36, 50, 64, 78, 92, 106, 120, 134, 148, 162, 176, 190, 204, 218, 232, 246, 260, and 274, wherein said isolated antibody or antigen binding fragment thereof binds to human Factor P. In one embodiment, the isolated antibody or antigen binding fragment further comprises a heavy chain variable domain sequence wherein the light chain variable domain and heavy chain variable domain combine to form an antigen binding site for Factor P.

[0029] In another embodiment of the invention, the isolated antibody or antigen binding fragment thereof that binds Factor P, may have heavy and light chain variable domains comprising the sequences of SEQ ID NOs: 7 and 8; 21 and 22; 35 and 36; 49 and 50; 63 and 64; 77 and 78; 91 and 92; 104 and 105; 118 and 119; 132 and 133; 146 and 147; 160 and 161; 174 and 175; 188 and 189; 202 and 203; 216 and 217; 230 and 231; 244 and 245; 258 and 259; or 272 and 273, respectively.

[0030] The invention further relates to an isolated antibody or antigen binding fragment thereof, that includes a heavy chain variable domain having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175, 189, 203, 217, 231, 245, 259 and 273, wherein said antibody binds to Factor P. In one aspect, the isolated antibody or antigen binding fragment thereof also includes a light chain variable domain having at least 95% sequence identity to a sequence selected from the group consisting of SEQ ID NOs 8, 22, 36, 50, 64, 78, 92, 106, 120, 134, 148, 162, 176, 190, 204, 218, 232, 246, 260, and 274.

[0031] In another embodiment the isolated antibody or antigen binding fragment thereof, may include a light chain variable domain having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NOs 8, 22, 36, 50, 64, 78, 92, 106, 120, 134, 148, 162, 176, 190, 204, 218, 232, 246, 260, and 274, wherein said antibody binds Factor P.

[0032] In another embodiment the isolated antibody, or antigen binding fragment thereof, that binds to Factor P may have a heavy chain comprising the sequence of SEQ ID NO: 9, 23, 37, 51, 65, 79, 93, 107, 121, 135, 149, 163, 177, 191, 205, 219, 233, 247, 261 or 275. In a further embodiment, the isolated antibody also includes a light chain that can combine with the heavy chain to form an antigen binding site to human Factor P. In a further embodiment, the isolated antibody or antigen binding fragment thereof includes a light chain having a sequence comprising SEQ ID NO: 10, 24, 38, 52, 66, 80, 94, 108, 122, 136, 150, 164, 178, 192, 206, 220, 234, 248, 262, or 276.

[0033] The invention still further relates to an isolated antibody or antigen binding fragment thereof that includes a heavy chain having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NOs 9, 23, 37, 51, 65, 79, 93, 107, 121, 135, 149, 163, 177, 191, 205, 219, 233, 247, 261 and 275, wherein said antibody binds to Factor P. In one aspect, the isolated antibody or antigen binding fragment thereof also includes a light chain having at least 95% sequence identity to a sequence selected from the group consisting of SEQ ID NOs 10, 24, 38, 52, 66, 80, 94, 108, 122, 136, 150, 164, 178, 192, 206, 220, 234, 248, 262, and 276.

[0034] The invention still further relates to an isolated antibody or antigen binding fragment thereof that includes a light chain having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NOs 9, 23, 37, 51, 65, 79, 93, 107, 121, 135, 149, 163, 177, 191, 205, 219, 233, 247, 261 and 275, wherein said antibody binds Factor P.

[0035] The invention also relates to compositions comprising the isolated antibody, or antigen binding fragment thereof, described herein. As well as, antibody compositions in combination with a pharmaceutically acceptable carrier. Specifically, the invention further includes pharmaceutical compositions comprising an antibody or antigen binding fragment thereof of Table 1, such as, for example antibody NVS962, NVS963, NVS964, NVS965, NVS966, NVS967, NVS962-G, NVS962-S, NVS962-T, NVS962-Q, NVS962-S31A, NVS965-Q, NVS965-S, NVS965-T, NVS804, NVS805, NVS806, NVS807, or NVS808. The invention also relates to pharmaceutical compositions comprising a combination of two or more of the isolated antibodies or antigen binding fragments thereof of Table 1.

[0036] The invention also relates to an isolated nucleic acid comprising a sequence encoding a polypeptide that includes a heavy chain variable domain having at least 90% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175, 189, 203, 217, 231, 245, 259 and 273.

[0037] The invention also relates to an isolated nucleic acid comprising a sequence encoding a polypeptide that includes a light chain variable domain having at least 90% sequence identity to a sequence selected from the group

consisting of SEQ ID NOs 8, 22, 36, 50, 64, 78, 92, 106, 120, 134, 148, 162, 176, 190, 204, 218, 232, 246, 260, and 274.

[0038] The invention also relates to a vector that includes one or more of the nucleic acid molecules described herein.

[0039] The invention also relates to an isolated host cell that includes a recombinant DNA sequence encoding a heavy chain of the antibody described above, and a second recombinant DNA sequence encoding a light chain of the antibody described above, wherein said DNA sequences are operably linked to a promoter and are capable of being expressed in the host cell. It is contemplated that the antibody can be a human monoclonal antibody. It is also contemplated that the host cell is a non-human mammalian cell.

[0040] The invention also relates to a method of inhibiting the complement mediated cell death wherein the method includes the step of contacting a cell with an effective amount of a composition comprising the isolated antibody or antigen binding fragments thereof described herein. It is contemplated that the cell is a human cell. It is further contemplated that the cell is in a subject. It is still further contemplated that the subject is human.

[0041] The invention still further relates to a method of inhibiting the alternative complement pathway in a cell wherein the method includes the step of contacting the cell with an effective amount of a composition comprising the isolated antibody or antigen binding fragments thereof described herein. In one aspect, it is contemplated that the cell is a human cell. It is further contemplated that the cell is in a subject. It is still further contemplated that the subject is human.

[0042] The invention also relates to a method of inhibiting the formation of membrane attack complex in a cell wherein the method includes the step of contacting the cell with an effective amount of a composition comprising the isolated antibody or antigen binding fragments thereof described herein. It is contemplated that the cell is a human cell. It is further contemplated that the cell is in a subject. It is still further contemplated that the subject is human.

[0043] Any of the foregoing isolated antibodies or antigen binding fragments thereof may be a monoclonal antibody or antigen binding fragment thereof.

[0044] In one aspect, the invention provides a first antibody, or antigen binding fragment thereof, that binds Factor P, and a second antibody, or antigen binding fragment thereof, that binds C5, wherein said combination inhibits the alternative complement pathway. In one aspect the first and second antibodies can be in combination as a composition.

[0045] Such a combination can be used to inhibit ocular inflammation. Ocular inflammation can be determined by measuring neutrophil accumulation and/or macrophage recruitment in the retina.

[0046] In one aspect, such a combination can be used to inhibit neutrophil accumulation in the retina, or macrophage recruitment in the retina.

[0047] In one aspect, the antibody in such a combination that binds Factor P, binds a region of Factor P comprising SEQ ID NO: 408. Alternatively or in combination, such an antibody binds a region of Factor P comprising SEQ ID NO: 407.

[0048] In a further aspect, the combination of antibodies or binding fragments thereof that bind Factor P and C5 include a first antibody or antigen binding fragment selected from Table 1 and a second antibody or antigen-binding fragment selected from Table 2. In one aspect, the first antibody, or antigen binding fragment thereof binds the same epitope as is an antibody described in Table 1 and the second antibody, or antigen binding fragment thereof, binds the same epitope as is an antibody described in Table 2.

[0049] In one aspect, the invention provides a first antibody, or antigen binding fragment thereof that comprises a heavy chain CDR1, 2, 3, and a light chain CDR1, 2, 3, selected from the group consisting of a) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 1, 2, and 3, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 4, 5, and 6, respectively; b) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 15, 16, and 17, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 18, 19, and 20, respectively; c) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 29, 30, and 31, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 32, 33, and 34, respectively; d) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 43, 44, and 45, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 46, 47, and 48, respectively; e) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 57, 58, and 59, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 60, 61, and 62, respectively; f) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 71, 72, and 73, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 74, 75, and 76, respectively; g) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 85, 86, and 87, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 88, 89, and 90, respectively; h) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 99, 100, and 101, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 102, 103, and 104, respectively; i) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 113, 114, and 115, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 116, 117, and 118, respectively; j) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 127, 128, and 129, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 130, 131, and 132, respectively; k) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 141, 142, and 143, respectively,

and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 144, 145, and 146, respectively; l) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 155, 156, and 157, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 158, 159, and 160, respectively; m) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 169, 170, and 171, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 172, 173, and 174, respectively; n) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 183, 184, and 185, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 186, 187, and 188, respectively; o) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 197, 198, and 199, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 200, 201, and 202, respectively; p) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 211, 212, and 213, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 214, 215, and 216, respectively; q) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 225, 226, and 227, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 228, 229, and 230, respectively; r) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 239, 240, and 241, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 242, 243, and 244, respectively; s) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 253, 254, and 255, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 256, 257, and 258, respectively; and t) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 267, 268, and 269, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 270, 271, and 272, respectively, and wherein the second antibody or antigen binding fragment thereof comprises a heavy chain CDR1, 2, 3 and light chain CDR1, 2, 3 selected from the group consisting of: a) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 410, 411, and 412, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 413, 414, and 415, respectively; b) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 426, 427, and 428, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 429, 430, and 431, respectively; c) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 442, 443, and 444, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 445, 446, and 447, respectively; d) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 426, 458, and 428, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 429, 430, and 459, respectively; and e) a heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 470, 471, and 472, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 473, 474 and 475, respectively.

[0050] In one aspect, the invention relates to a first and second antibody or antigen binding fragment thereof (which may be in combination as a composition) where the first antibody or antigen binding fragment thereof includes heavy and light chain variable regions having amino acid sequences at least 90% identical to SEQ ID NOs: 7 and 8; SEQ ID NOs: 21 and 22; SEQ ID NOs: 35 and 36; SEQ ID NOs: 49 and 50; SEQ ID NOs: 63 and 64; SEQ ID NOs: 77 and 78; SEQ ID NOs: 91 and 92; SEQ ID NOs: 105 and 106; SEQ ID NOs: 119 and 120; SEQ ID NOs: 133 and 134; SEQ ID NOs: 147 and 148; SEQ ID NOs: 161 and 162; SEQ ID NOs: 175 and 176; SEQ ID NOs: 189 and 190; SEQ ID NOs: 203 and 204; SEQ ID NOs: 217 and 218; SEQ ID NOs: 231 and 232; SEQ ID NOs: 245 and 246; SEQ ID NOs: 259 and 260; or SEQ ID NOs: 273 and 274, respectively, and wherein the second antibody or antigen binding fragment thereof includes heavy and light chain variable regions having amino acid sequences at least 90% identical to SEQ ID NOs: 416 and 417; SEQ ID NOs: 432 and 433; SEQ ID NOs: 448 and 449; SEQ ID NOs: 460 and 461; or SEQ ID NOs: 476 and 477, respectively.

[0051] In one aspect, the invention relates to a first and second antibody or antigen binding fragment thereof (which may be in combination as a composition) where the first antibody or antigen binding fragment thereof includes heavy and light chain variable regions having amino acid sequences selected from SEQ ID NOs: 7 and 8; SEQ ID NOs: 21 and 22; SEQ ID NOs: 35 and 36; SEQ ID NOs: 49 and 50; SEQ ID NOs: 63 and 64; SEQ ID NOs: 77 and 78; SEQ ID NOs: 91 and 92; SEQ ID NOs: 105 and 106; SEQ ID NOs: 119 and 120; SEQ ID NOs: 133 and 134; SEQ ID NOs: 147 and 148; SEQ ID NOs: 161 and 162; SEQ ID NOs: 175 and 176; SEQ ID NOs: 189 and 190; SEQ ID NOs: 203 and 204; SEQ ID NOs: 217 and 218; SEQ ID NOs: 231 and 232; SEQ ID NOs: 245 and 246; SEQ ID NOs: 259 and 260; or SEQ ID NOs: 273 and 274, respectively, and wherein the second antibody or antigen binding fragment thereof includes heavy and light chain variable regions having amino acid sequences selected from SEQ ID NOs: 416 and 417; SEQ ID NOs: 432 and 433; SEQ ID NOs: 448 and 449; SEQ ID NOs: 460 and 461; or SEQ ID NOs: 476 and 477, respectively.

[0052] In a further aspect, the invention includes a first and second antibody or antigen binding fragment thereof (which may be in combination as a composition) in which (a) the first antibody, or antigen binding fragment thereof includes a heavy chain variable region comprising SEQ ID NO: 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175, 189, 203, 217, 231, 245, 259, or 273 and further includes a light chain variable region, wherein said heavy chain variable region and said light chain variable region combine to form an antigen binding site to Factor P and (b) wherein the second antibody or antigen binding fragment thereof includes a heavy chain variable region comprising SEQ ID NO: 416, 432,

448, 460 or 476 and further includes a light chain variable region, wherein said heavy chain variable region and said light chain variable region combine to form an antigen binding site to C5. In a further aspect, the first antibody or antigen binding fragment thereof includes the light chain variable region sequence of SEQ ID NO: 8, 22, 36, 50, 64, 78, 92, 106, 120, 134, 148, 162, 176, 190, 204, 218, 232, 246, 260, or 274, and the second antibody or antigen binding fragment thereof includes the light chain variable region sequence of SEQ ID NO: 417, 433, 449, 461 or 477.

[0053] In a further aspect, the invention includes a first and second antibody or antigen binding fragment thereof (which may be in combination as a composition) in which (a) the first antibody or antigen binding fragment thereof includes a light chain variable domain comprising SEQ ID NO: 8, 22, 36, 50, 64, 78, 92, 106, 120, 134, 148, 162, 176, 190, 204, 218, 232, 246, 260, or 274 and further includes a heavy chain variable domain, wherein the light chain variable domain and the heavy chain variable domain combine to form an antigen binding site to Factor P and (b) wherein the second antibody or antigen binding fragment thereof includes a light chain variable region comprises a light chain variable domain includes SEQ ID NO: 417, 433, 449, 461 or 477 and further comprises a heavy chain variable domain, wherein the light chain variable domain and the heavy chain variable domain combine to form an antigen binding site to C5.

[0054] In one aspect, the invention includes a first and second antibody or antigen binding fragment thereof (which may be in combination as a composition) in which (a) the first antibody, or antigen binding fragment thereof includes a heavy chain of SEQ ID NO: 9, 23, 37, 51, 65, 79, 93, 107, 121, 135, 149, 163, 177, 191, 205, 219, 233, 247, 261 or 275 and further includes a light chain, wherein the heavy chain and the light chain combine to form an antigen binding site to Factor P and (b) wherein the second antibody or antigen binding fragment thereof includes a heavy chain of SEQ ID NO: 418, 434, 450, 462, or 478 and further includes a light chain, wherein the heavy chain and the light chain combine to form an antigen binding site to C5. In a further aspect, the first antibody or antigen binding fragment thereof includes a light chain of SEQ ID NO: 10, 24, 38, 52, 66, 80, 94, 108, 122, 136, 150, 164, 178, 192, 206, 220, 234, 248, 262 or 276, and wherein the second antibody or antigen binding fragment thereof includes a light chain of SEQ ID NO: 419, 435, 451, 463, or 479.

[0055] In one aspect, the invention includes a first and second antibody or antigen binding fragment thereof (which may be in combination as a composition) in which (a) the first antibody, or antigen binding fragment thereof includes a light chain of SEQ ID NO: 10, 24, 38, 52, 66, 80, 94, 108, 122, 136, 150, 164, 178, 192, 206, 220, 234, 248, 262 or 276 and further includes a heavy chain, wherein the light chain and the heavy chain combine to form an antigen binding site to Factor P and (b) wherein the second antibody or antigen binding fragment thereof includes a light chain of SEQ ID NO: 419, 435, 451, 463, or 479 and further includes a heavy chain, wherein the light chain and the heavy chain combine to form an antigen binding site to C5.

[0056] In one aspect, the invention includes a first and second antibody or antigen binding fragment thereof (which may be in combination as a composition) wherein the first antibody, or antigen binding fragment thereof includes a heavy chain with an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 9, 23, 37, 51, 65, 79, 93, 107, 121, 135, 149, 163, 177, 191, 205, 219, 233, 247, 261 or 275 and further includes a light chain with an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 10, 24, 38, 52, 66, 80, 94, 108, 122, 136, 150, 164, 178, 192, 206, 220, 234, 248, 262 or 276 and wherein the second antibody or antigen binding fragment thereof includes a heavy chain with an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 418, 434, 450, 462, or 478 and further includes a light chain with an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 419, 435, 451, 463, or 479.

[0057] In a further aspect, the invention includes a first and second antibody or antigen binding fragment thereof (which may be in combination as a composition) wherein the first antibody, or antigen binding fragment thereof includes a heavy chain with an amino acid sequence selected from SEQ ID NO: 9, 23, 37, 51, 65, 79, 93, 107, 121, 135, 149, 163, 177, 191, 205, 219, 233, 247, 261 or 275 and further includes a light chain with an amino acid sequence selected from SEQ ID NO: 10, 24, 38, 52, 66, 80, 94, 108, 122, 136, 150, 164, 178, 192, 206, 220, 234, 248, 262 or 276 and wherein the second antibody or antigen binding fragment thereof includes a heavy chain with an amino acid sequence selected from SEQ ID NO: 418, 434, 450, 462, or 478 and further includes a light chain with an amino acid sequence selected from SEQ ID NO: 419, 435, 451, 463, or 479.

[0058] In a further aspect, the invention includes a first and second antibody or antigen binding fragment thereof (which may be in combination as a composition) wherein the first antibody, or antigen binding fragment thereof includes a heavy chain and a light chain with an amino acid sequence having at least 90% sequence identity, respectively, to SEQ ID NO: 9 and 10, 23 and 24, 37 and 38, 51 and 52, 65 and 66, 79 and 80, 93 and 94, 107 and 108, 121 and 122, 135 and 136, 149 and 150, 163 and 164, 177 and 178, 191 and 192, 205 and 206, 219 and 220, 233 and 234, 247 and 248, 261 and 262, or 275 and 276; and wherein the second antibody or antigen binding fragment thereof includes a heavy chain and a light chain with an amino acid sequence having at least 90% sequence identity, respectively, to SEQ ID NOs: 418 and 419, 434 and 435; 450 and 451; 462 and 463; or 478 and 479.

[0059] In a still further aspect, the invention includes a first and second antibody or antigen binding fragment thereof (which may be in combination as a composition) wherein the first antibody, or antigen binding fragment thereof includes a heavy chain and a light chain with an amino acid sequence, respectively, selected from SEQ ID NO: 9 and 10, 23 and

24, 37 and 38, 51 and 52, 65 and 66, 79 and 80, 93 and 94, 107 and 108, 121 and 122, 135 and 136, 149 and 150, 163 and 164, 177 and 178, 191 and 192, 205 and 206, 219 and 220, 233 and 234, 247 and 248, 261 and 262, or 275 and 276; and wherein the second antibody or antigen binding fragment thereof includes a heavy chain and a light chain with an amino acid sequence, respectively, selected from SEQ ID NOs: 418 and 419, 434 and 435; 450 and 451; 462 and 463; or 478 and 479.

[0060] The invention further relates to an isolated nucleic acid molecule comprising a nucleotide sequence encoding the first and/or second antibody or antigen binding fragment thereof as described herein. Such a nucleic acid sequence can be included in a vector, which may, in turn be included in a host cell which, in one aspect, is capable of expressing such nucleic acid sequence.

[0061] The invention further relates to a method of treating age related macular degeneration in a subject comprising administering to said subject, an effective amount of a first and second antibody or antigen binding fragment thereof, either singly, or in combination as a composition. The subject may be a human.

[0062] The invention further relates to a method of inhibiting the alternative complement pathway in a subject comprising administering to said subject an effective amount of a first and second antibody or antigen binding fragment thereof, either singly, or in combination as a composition. The subject may be a human.

DEFINITIONS

[0063] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which this invention pertains.

[0064] The term "antibody" as used herein means a whole antibodies and any antigen binding fragment (*i. e.*, "antigen-binding portion") or single chains thereof. A whole antibody is a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (C1q) of the classical complement system.

[0065] The term "antigen binding portion" or "antigen binding fragment" of an antibody, as used herein, refers to one or more fragments of an intact antibody that retain the ability to specifically bind to a given antigen (*e.g.*, Factor P). Antigen binding functions of an antibody can be performed by fragments of an intact antibody. Examples of binding fragments encompassed within the term antigen binding portion or antigen binding fragment of an antibody include a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; a F(ab)₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; an Fd fragment consisting of the VH and CH1 domains; an Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a single domain antibody (dAb) fragment (Ward et al., 1989 Nature 341:544-546), which consists of a VH domain or a VL domain; and an isolated complementarity determining region (CDR).

[0066] Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by an artificial peptide linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv); see, *e.g.*, Bird et al., 1988 Science 242:423-426; and Huston et al., 1988 Proc. Natl. Acad. Sci. 85:5879-5883). Such single chain antibodies include one or more antigen binding portions or fragments of an antibody. These antibody fragments are obtained using conventional techniques known to those of skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

[0067] Antigen binding fragments can also be incorporated into single domain antibodies, maxibodies, minibodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv (see, *e.g.*, Hollinger and Hudson, 2005, Nature Biotechnology, 23, 9, 1126-1136). Antigen binding portions of antibodies can be grafted into scaffolds based on polypeptides such as Fibronectin type III (Fn3) (see U.S. Pat. No. 6,703,199, which describes fibronectin polypeptide monobodies).

[0068] Antigen binding fragments can be incorporated into single chain molecules comprising a pair of tandem Fv segments (VH-CH1-VH-CH1) which, together with complementary light chain polypeptides, form a pair of antigen binding regions (Zapata et al., 1995 Protein Eng. 8(10):1057-1062; and U.S. Pat. No. 5,641,870).

[0069] As used herein, the term "affinity" refers to the strength of interaction between antibody and antigen at single

antigenic sites. Within each antigenic site, the variable region of the antibody "arm" interacts through weak non-covalent forces with antigen at numerous sites; the more interactions, the stronger the affinity. As used herein, the term "high affinity" for an IgG antibody or fragment thereof (e.g., a Fab fragment) refers to an antibody having a KD of 10^{-8} M or less, 10^{-9} M or less, or 10^{-10} M, or 10^{-11} M or less, or 10^{-12} M or less, or 10^{-13} M or less for a target antigen. However,

high affinity binding can vary for other antibody isotypes. For example, high affinity binding for an IgM isotype refers to an antibody having a KD of 10^{-7} M or less, or 10^{-8} M or less.

[0070] The term "amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline, γ -carboxyglutamate, and O-phosphoserine. Amino acid analogs refer to compounds that have the same basic chemical structure as a naturally occurring amino acid, i.e., an alpha carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, e.g., homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid.

[0071] The term "binding specificity" as used herein refers to the ability of an individual antibody combining site to react with only one antigenic determinant.

[0072] The phrase "specifically (or selectively) binds" to an antibody (e.g., a Factor P-binding antibody) refers to a binding reaction that is determinative of the presence of a cognate antigen (e.g., a human Factor P or cynomolgus Factor P) in a heterogeneous population of proteins and other biologics. The phrases "an antibody recognizing an antigen" and "an antibody specific for an antigen" are used interchangeably herein with the term "an antibody which binds specifically to an antigen".

[0073] The term "conditions or disorders associated with macular degeneration" refers to any of a number of conditions in which the retinal macula degenerates or becomes dysfunctional, e.g., as a consequence of decreased growth of cells of the macula, increased death or rearrangement of the cells of the macula (e.g., RPE cells), loss of normal biological function, or a combination of these events. Macular degeneration results in the loss of integrity of the histoarchitecture of the cells and/or extracellular matrix of the normal macula and/or the loss of function of the cells of the macula. Examples of macular degeneration-related disorder include AMD, North Carolina macular dystrophy, Sorsby's fundus dystrophy, Stargardt's disease, pattern dystrophy, Best disease, dominant drusen, and malattia leventinese (radial drusen). The term also encompasses extramacular changes that occur prior to, or following dysfunction and/or degeneration of the macula. Thus, the term "macular degeneration-related disorder" also broadly includes any condition which alters or damages the integrity or function of the macula (e.g., damage to the RPE or Bruch's membrane). For example, the term encompasses retinal detachment, chorioretinal degenerations, retinal degenerations, photoreceptor degenerations, RPE degenerations, mucopolysaccharidoses, rod-cone dystrophies, cone-rod dystrophies and cone degenerations.

[0074] The term "complement component", "complement proteins" or "complement component proteins" refers to the molecules that are involved in activation of the complement system. The classical pathway components include, e.g., C1q, C1r, C1s, C4, C2, C3, C5, C6, C7, C8, C9, and C5b-9 complex (membrane attack complex: MAC). The alternative pathway components include, e.g., Factor B, Factor D, Factor H, Factor I and Properdin.

[0075] The term "cellular activities regulated by the complement pathway" include cell damage resulting from the C5b-9 attack complex, vascular permeability changes, contraction and migration of smooth muscle cells, T cell proliferation, immune adherence, aggregation of dendritic cells, monocytes, granulocyte and platelet, phagocytosis, migration and activation of neutrophils (PMN) and macrophages.

[0076] Further, activation of the complement pathways results in the increase of proinflammatory response contributed by the by-products within the complement pathway. Disorders associated with activation of the complement pathway include nephritis, asthma, reperfusion injury, hemodialysis, rheumatoid arthritis, systemic lupus, psoriasis, multiple sclerosis, transplantation, Alzheimer's disease, aHUS, MPGN II, or any other complement-mediated disease. Disorders associated with macular degeneration include AMD, North Carolina macular dystrophy, Sorsby's fundus dystrophy, Stargardt's disease, pattern dystrophy, Best disease, dominant drusen, and malattia leventinese (radial drusen), extramacular changes that occur prior to, or following dysfunction and/or degeneration of the macula, retinal detachment, chorioretinal degenerations, retinal degenerations, photoreceptor degenerations, RPE degenerations, mucopolysaccharidoses, rod-cone dystrophies, cone-rod dystrophies and cone degenerations.

[0077] The term "chimeric antibody" is an antibody molecule in which (a) the constant region, or a portion thereof, is altered, replaced or exchanged so that the antigen binding site (variable region) is linked to a constant region of a different or altered class, effector function and/or species, or an entirely different molecule which confers new properties to the chimeric antibody, e.g., an enzyme, toxin, hormone, growth factor, drug, etc.; or (b) the variable region, or a portion thereof, is altered, replaced or exchanged with a variable region having a different or altered antigen specificity. For example, a mouse antibody can be modified by replacing its constant region with the constant region from a human

immunoglobulin. Due to the replacement with a human constant region, the chimeric antibody can retain its specificity in recognizing the antigen while having reduced antigenicity in human as compared to the original mouse antibody.

The term "Factor P protein" or "Factor P antigen" or "Factor P" are used interchangeably, and refers to the Factor P protein in different species. For example, human Factor P has the sequence as set out in Table 1: SEQ ID NO: 401. Human Factor P can be obtained from Complement Tech, Tyler, TX. Cynomolgus Factor P can be purified from cynomolgus serum (protocol adapted from Nakano et al., (1986) J Immunol Methods 90:77-83). Examples of Factor P protein from other species are provided in Table 1, SEQ ID NOs: 402, 403, 404 or 405, as well as Factor P protein binding domains and fragments (e.g.: SEQ ID NOs: 406, 407 or 408). Factor P is also known in the art as "Properdin".

[0078] The term "conservatively modified variant" applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, conservatively modified variants refers to those nucleic acids which encode identical or essentially identical amino acid sequences, or where the nucleic acid does not encode an amino acid sequence, to essentially identical sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given protein. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations," which are one species of conservatively modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid that encodes a polypeptide is implicit in each described sequence.

[0079] For polypeptide sequences, "conservatively modified variants" include individual substitutions, deletions or additions to a polypeptide sequence which result in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the invention. The following eight groups contain amino acids that are conservative substitutions for one another: 1) Alanine (A), Glycine (G); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W); 7) Serine (S), Threonine (T); and 8) Cysteine (C), Methionine (M) (see, e.g., Creighton, Proteins (1984)). In some embodiments, the term "conservative sequence modifications" are used to refer to amino acid modifications that do not significantly affect or alter the binding characteristics of the antibody containing the amino acid sequence.

[0080] The term "epitope" means a protein determinant capable of specific binding to an antibody. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. Conformational and nonconformational epitopes are distinguished in that the binding to the former but not the latter is lost in the presence of denaturing solvents.

[0081] The term "human antibody", as used herein, is intended to include antibodies having variable regions in which both the framework and CDR regions are derived from sequences of human origin. Furthermore, if the antibody contains a constant region, the constant region also is derived from such human sequences, e.g., human germline sequences, or mutated versions of human germline sequences. The human antibodies of the invention may include amino acid residues not encoded by human sequences (e.g., mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*).

[0082] The term "human monoclonal antibody" refers to antibodies displaying a single binding specificity which have variable regions in which both the framework and CDR regions are derived from human sequences. In one embodiment, the human monoclonal antibodies are produced by a hybridoma which includes a B cell obtained from a transgenic nonhuman animal, e.g., a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell.

[0083] A "humanized" antibody is an antibody that retains the reactivity of a non-human antibody while being less immunogenic in humans. This can be achieved, for instance, by retaining the non-human CDR regions and replacing the remaining parts of the antibody with their human counterparts (*i.e.*, the constant region as well as the framework portions of the variable region). See, e.g., Morrison et al., Proc. Natl. Acad. Sci. USA, 81:6851-6855, 1984; Morrison and Oi, Adv. Immunol., 44:65-92, 1988; Verhoeven et al., Science, 239:1534-1536, 1988; Padlan, Molec. Immun., 28:489-498, 1991; and Padlan, Molec. Immun., 31:169-217, 1994. Other examples of human engineering technology include, but are not limited to Xoma technology disclosed in US 5,766,886.

[0084] The terms "identical" or percent "identity," in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same. Two sequences are "substantially identical" if two sequences have a specified percentage of amino acid residues or nucleotides that are the same (*i.e.*, 60% identity, optionally 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identity over a specified region, or, when not specified, over the entire sequence), when compared and aligned for maximum correspondence over a comparison window, or desig-

nated region as measured using one of the following sequence comparison algorithms or by manual alignment and visual inspection. Optionally, the identity exists over a region that is at least about 50 nucleotides (or 10 amino acids) in length, or more preferably over a region that is 100 to 500 or 1000 or more nucleotides (or 20, 50, 200 or more amino acids) in length.

[0085] For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are entered into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. Default program parameters can be used, or alternative parameters can be designated. The sequence comparison algorithm then calculates the percent sequence identities for the test sequences relative to the reference sequence, based on the program parameters.

[0086] A "comparison window", as used herein, includes reference to a segment of any one of the number of contiguous positions selected from the group consisting of from 20 to 600, usually about 50 to about 200, more usually about 100 to about 150 in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequences for comparison are well known in the art. Optimal alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith and Waterman (1970) *Adv. Appl. Math.* 2:482c, by the homology alignment algorithm of Needleman and Wunsch, *J. Mol. Biol.* 48:443, 1970, by the search for similarity method of Pearson and Lipman, *Proc. Nat'l. Acad. Sci. USA* 85:2444, 1988, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by manual alignment and visual inspection (see, e.g., Brent et al., *Current Protocols in Molecular Biology*, John Wiley & Sons, Inc. (Ringbou ed., 2003)).

[0087] Two examples of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al., *Nuc. Acids Res.* 25:3389-3402, 1977; and Altschul et al., *J. Mol. Biol.* 215:403-410, 1990, respectively. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length *W* in the query sequence, which either match or satisfy some positive-valued threshold score *T* when aligned with a word of the same length in a database sequence. *T* is referred to as the neighborhood word score threshold (Altschul *et al.*, *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters *M* (reward score for a pair of matching residues; always > 0) and *N* (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity *X* from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters *W*, *T*, and *X* determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (*W*) of 11, an expectation (*E*) or 10, *M*=5, *N*=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength of 3, and expectation (*E*) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff, *Proc. Natl. Acad. Sci. USA* 89:10915, 1989) alignments (*B*) of 50, expectation (*E*) of 10, *M*=5, *N*=-4, and a comparison of both strands.

[0088] The BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, e.g., Karlin and Altschul, *Proc. Natl. Acad. Sci. USA* 90:5873-5787, 1993). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (*P(N)*), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.2, more preferably less than about 0.01, and most preferably less than about 0.001.

[0089] The percent identity between two amino acid sequences can also be determined using the algorithm of E. Meyers and W. Miller (*Comput. Appl. Biosci.*, 4:11-17, 1988) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch (*J. Mol. Biol.* 48:444-453, 1970) algorithm which has been incorporated into the GAP program in the GCG software package (available on the world wide web at gcg.com), using either a Blossom 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

[0090] Other than percentage of sequence identity noted above, another indication that two nucleic acid sequences or polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross reactive with the antibodies raised against the polypeptide encoded by the second nucleic acid, as described below. Thus, a polypeptide is typically substantially identical to a second polypeptide, for example, where the two peptides differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical

is that the two molecules or their complements hybridize to each other under stringent conditions, as described below. Yet another indication that two nucleic acid sequences are substantially identical is that the same primers can be used to amplify the sequence.

[0091] The term "inhibit (or inhibits) the alternative complement pathway" refers to the ability of Factor P antibodies to interfere with activation of the alternative complement pathway. Specifically, "inhibit" refers to a statistically significant decrease (i.e., $p < 0.05$) in alternative complement activation as measured by one or more assays as described herein, including MAC formation, hemolytic assay, or C3b deposition assay in a cell or subject following contact with an anti-Factor P antibody or fragment thereof as described herein relative to a control. As used herein, "inhibit (or inhibits) the alternative complement pathway" can also refer to a clinically relevant improvement in visual function or retinal anatomy following treatment with an anti-Factor P antibody described herein in a patient diagnosed with age related macular degeneration as described below.

[0092] The term "isolated antibody" refers to an antibody that is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody that specifically binds Factor P is substantially free of antibodies that specifically bind antigens other than Factor P). An isolated antibody that specifically binds Factor P may, however, have cross-reactivity to other antigens. Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[0093] The term "isotype" refers to the antibody class (e.g., IgM, IgE, IgG such as IgG1 or IgG4) that is provided by the heavy chain constant region genes. Isotype also includes modified versions of one of these classes, where modifications have been made to alter the Fc function, for example, to enhance or reduce effector functions or binding to Fc receptors.

[0094] The term "Kassoc" or "Ka", as used herein, is intended to refer to the association rate of a particular antibody-antigen interaction, whereas the term "Kdis" or "Kd," as used herein, is intended to refer to the dissociation rate of a particular antibody-antigen interaction. The term " K_D ", as used herein, is intended to refer to the dissociation constant, which is obtained from the ratio of Kd to Ka (i.e. K_D/K_a) and is expressed as a molar concentration (M). K_D values for antibodies can be determined using methods well established in the art. Methods for determining the K_D of an antibody include measuring surface plasmon resonance using a biosensor system such as a Biacore® system, or measuring affinity in solution by solution equilibrium titration (SET).

[0095] The terms "monoclonal antibody" or "monoclonal antibody composition" as used herein refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope.

[0096] The term "nucleic acid" is used herein interchangeably with the term "polynucleotide" and refers to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form. The term encompasses nucleic acids containing known nucleotide analogs or modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring, which have similar binding properties as the reference nucleic acid, and which are metabolized in a manner similar to the reference nucleotides. Examples of such analogs include, without limitation, phosphorothioates, phosphoramidates, methyl phosphonates, chiral-methyl phosphonates, 2-O-methyl ribonucleotides, peptide-nucleic acids (PNAs).

[0097] Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions) and complementary sequences, as well as the sequence explicitly indicated. Specifically, as detailed below, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer et al., Nucleic Acid Res. 19:5081, 1991; Ohtsuka et al., J. Biol. Chem. 260:2605-2608, 1985; and Rossolini et al., Mol. Cell. Probes 8:91-98, 1994).

[0098] The term "operably linked" refers to a functional relationship between two or more polynucleotide (e.g., DNA) segments. Typically, the term refers to the functional relationship of a transcriptional regulatory sequence to a transcribed sequence. For example, a promoter or enhancer sequence is operably linked to a coding sequence if it stimulates or modulates the transcription of the coding sequence in an appropriate host cell or other expression system. Generally, promoter transcriptional regulatory sequences that are operably linked to a transcribed sequence are physically contiguous to the transcribed sequence, i.e., they are cis-acting. However, some transcriptional regulatory sequences, such as enhancers, need not be physically contiguous or located in close proximity to the coding sequences whose transcription they enhance.

[0099] As used herein, the term, "optimized" means that a nucleotide sequence has been altered to encode an amino acid sequence using codons that are preferred in the production cell or organism, generally a eukaryotic cell, for example, a cell of Pichia, a Chinese Hamster Ovary cell (CHO) or a human cell. The optimized nucleotide sequence is engineered to retain completely or as much as possible the amino acid sequence originally encoded by the starting nucleotide sequence, which is also known as the "parental" sequence. The optimized sequences herein have been engineered to have codons that are preferred in mammalian cells. However, optimized expression of these sequences in other eukaryotic cells or prokaryotic cells is also envisioned herein. The amino acid sequences encoded by optimized nucleotide

sequences are also referred to as optimized.

[0100] The terms "polypeptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer. Unless otherwise indicated, a particular polypeptide sequence also implicitly encompasses conservatively modified variants thereof.

[0101] The term "recombinant human antibody", as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies isolated from an animal (e.g., a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom, antibodies isolated from a host cell transformed to express the human antibody, e.g., from a transfectoma, antibodies isolated from a recombinant, combinatorial human antibody library, and antibodies prepared, expressed, created or isolated by any other means that involve splicing of all or a portion of a human immunoglobulin gene, sequences to other DNA sequences. Such recombinant human antibodies have variable regions in which the framework and CDR regions are derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies can be subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[0102] The term "recombinant host cell" (or simply "host cell") refers to a cell into which a recombinant expression vector has been introduced. It should be understood that such terms are intended to refer not only to the particular subject cell but to the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein.

[0103] The term "subject" includes human and non-human animals. Non-human animals include all vertebrates (e.g.: mammals and non-mammals) such as, non-human primates (e.g.: cynomolgus monkey), sheep, dog, cow, chickens, amphibians, and reptiles. Except when noted, the terms "patient" or "subject" are used herein interchangeably. As used herein, the terms "cyno" or "cynomolgus" refer to the cynomolgus monkey (*Macaca fascicularis*).

[0104] As used herein, the term "treating" or "treatment" of any disease or disorder (i.e., AMD) refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In yet another embodiment, "treating" or "treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder. "Prevention" as it relates to AMD means any action that prevents or slows a worsening in visual function, retinal anatomy, and/or an AMD disease parameter, as described below, in a patient at risk for said worsening. More specifically, "treatment" of AMD means any action that results in the improvement or preservation of visual function and/or retinal anatomy. Methods for assessing treatment and/or prevention of disease are known in the art and described hereinbelow.

[0105] The term "vector" is intended to refer to a polynucleotide molecule capable of transporting another polynucleotide to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. Another type of vector is a viral vector, such as an adeno-associated viral vector (AAV, or AAV2), wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "recombinant expression vectors" (or simply, "expression vectors"). In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

BRIEF DESCRIPTION OF THE DRAWINGS

[0106]

Figure 1 Depicts the Factor P binding site. Figure 1A illustrates the relative position TSR5 domain of Factor P and

the TSR5 sequence fragments: A, B, C and D. Figure 1B shows the human TSR5 sequence aligned with the mouse sequence. Brackets indicate the sequence fragments of TSR5. Figure 1C illustrates the antibodies bind to region B of TSR5.

Figure 2 shows the results of a hemolytic assay demonstrating inhibition of the alternative complement pathway in 20% human serum.

Figure 3 shows an isobologram generated using the data from the hemolytic assay depicted in Figure 2.

Figure 4 shows the % inhibition of macrophage infiltrates in a mouse poly-IC model, comparing the inhibition of anti-FactorP and anti-C5 antibodies singly and in combination.

Figure 5 shows an isobologram generated using the data from the poly-IC results depicted in Figure 4.

DETAILED DESCRIPTION

[0107] The present invention is based, in part, on the discovery of antibody molecules that specifically bind to both human and cynomolgus Factor P. The invention relates to both full IgG format antibodies as well as antigen binding fragments thereof, such as Fab fragments (e.g., see antibodies NVS965-S, NVS962-S, NVS804 and NVS807).

[0108] Accordingly, the present invention provides antibodies that specifically bind to Factor P (e.g., human Factor P, cynomolgus Factor P, rat Factor P, rabbit Factor P), pharmaceutical compositions, production methods, and methods of use of such antibodies and compositions.

Factor P Antibodies & Antigen Binding Fragments

[0109] The present invention provides antibodies that specifically bind to Factor P. In some embodiments, the present invention provides antibodies that specifically bind to human, cynomolgus, rat and/or rabbit Factor P. Antibodies of the invention include, but are not limited to, the human monoclonal antibodies and Fabs, isolated as described in the Examples.

The present invention provides antibodies that specifically bind a Factor P protein (e.g., human and/or cynomolgus Factor P), wherein the antibodies comprise a VH domain having an amino acid sequence of SEQ ID NO: 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175, 189, 203, 217, 231, 245, 259 or 273. The present invention also provides antibodies that specifically bind to a Factor P protein, wherein the antibodies comprise a VH CDR having an amino acid sequence of any one of the VH CDRs listed in Table 1, *infra*. In particular, the invention provides antibodies that specifically bind to a Factor P protein (e.g., human and/or cynomolgus Factor P), wherein the antibodies comprise (or alternatively, consist of) one, two, three, or more VH CDRs having an amino acid sequence of any of the VH CDRs listed in Table 1, *infra*.

[0110] The present invention provides antibodies that specifically bind to a Factor P protein, said antibodies comprising a VL domain having an amino acid sequence of SEQ ID NO: 8, 22, 36, 50, 64, 78, 92, 106, 120, 134, 148, 162, 176, 190, 204, 218, 232, 246, 260, or 274. The present invention also provides antibodies that specifically bind to a Factor P protein (e.g., human and/or cynomolgus Factor P), said antibodies comprising a VL CDR having an amino acid sequence of any one of the VL CDRs listed in Table 1, *infra*. In particular, the invention provides antibodies that specifically bind to a Factor P protein (e.g., human and/or cynomolgus Factor P), said antibodies comprising (or alternatively, consisting of) one, two, three or more VL CDRs having an amino acid sequence of any of the VL CDRs listed in Table 1, *infra*.

[0111] Other antibodies of the invention include amino acids that have been mutated, yet have at least 60, 70, 80, 85, 90 or 95 percent identity in the CDR regions with the CDR regions depicted in the sequences described in Table 1. In some embodiments, it includes mutant amino acid sequences wherein no more than 1, 2, 3, 4 or 5 amino acids have been mutated in the CDR regions when compared with the CDR regions depicted in the sequence described in Table 1.

[0112] The present invention also provides nucleic acid sequences that encode VH, VL, the full length heavy chain, and the full length light chain of the antibodies that specifically bind to a Factor P protein (e.g., human and/or cynomolgus Factor P). Such nucleic acid sequences can be optimized for expression in mammalian cells (for example, Table 1 shows the optimized nucleic acid sequences for the heavy chain and light chain of antibodies of the invention).

Table 1 Examples of Factor P Antibodies, Fabs and Factor P Proteins

AMINO ACID SEQUENCE OR POLYNUCLEOTIDE (PN)	SEQUENCE IDENTIFIER (SEQ.ID.NO:)AND SEQUENCE
NVS962	
CDRH1	1/281 SYAIS (Kabat)/ GGTFNSY (Chothia)
CDRH2	2/282 RIIPFGTANYAQKFQG (Kabat)/ IPIFGT (Chothia)
CDRH3	3/283 HGGYSFDS (Kabat)/ HGGYSFDS (Chothia)
CDRL1	4/284 SGDNLGSKYVD (Kabat)/ DNLGSKY (Chothia)
CDRL2	5/285 SDNNRPS (Kabat)/ SDN (Chothia)
CDRL3	6/286 QTYTSGNNYL (Kabat)/ YTSGNNYL (Chothia)
VH	7 EVQLVQSGAEVKKPGSSVKVSKASGGTFNSYAI SWVRQAPGQGLEWM GRIIPFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYC ARHGGYSFDSWGQGT LVTVSS
VL	8 SYELTQPPSVSVAPGQTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYCYQTYTSGNNY LVFGGGTKLTVL
HEAVY CHAIN	9 EVQLVQSGAEVKKPGSSVKVSKASGGTFNSYAI SWVRQAPGQGLEWM GRIIPFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYC ARHGGYSFDSWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKRVEPKSC
LIGHT CHAIN	10 SYELTQPPSVSVAPGQTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYCYQTYTSGNNY LVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCOVTHEGSTVEKTVAPTECS
PN ENCODING SEQ.ID.NO: 7	11 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCAACAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTCGGCACCGCCAAC TACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACC GCCTAC ATGGAAGTGAAGCAGCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGCACGGCGGCTACAGCTTCGATAGCTGGGGCCAGGGCACCCCTG
	GTGACCGTGAGCTCA

(continued)

AMINO ACID SEQUENCE OR POLYNUCLEOTIDE (PN)	SEQUENCE IDENTIFIER (SEQ.ID.NO:;)AND SEQUENCE
NVS962	
PN ENCODING SEQ.ID.NO: 8	12 AGCTACGAGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCCAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTACGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCGAG GACGAGGCCGACTACTACTGCCAGACCTACACCAGCGGCAACAACCTAC CTGGTGTTTCGGAGGCGGAACAAAGTTAACCGTCCTA
PN ENCODING SEQ.ID.NO: 9	13 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCAACAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC ATGGAAGTGCAGCAGCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGGCACGGCGGCTACAGCTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTG GCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGC CTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGCTGTGGAAGTCA GGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCC TCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAAC ACCAAGGTGGACAAGAGAGTTGAGCCCCAATCTTGT
PN ENCODING SEQ.ID.NO: 10	14 AGCTACGAGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCCAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTACGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCGAG GACGAGGCCGACTACTACTGCCAGACCTACACCAGCGGCAACAACCTAC CTGGTGTTTCGGAGGCGGAACAAAGTTAACCGTCCTAGGTCAGCCCAAG GCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAA GCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGA GCCGTGACAGTGCCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGA GTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCC AGCAGCTATCTGAGCCTGACGCTGAGCAGTGGAAGTCCCACAGAAGC TACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGAGAGAAGACAGTG GCCCCCTACAGAATGTTCA
NVS963	
CDRH1	15/287 SYAIS (Kabat)/ GGTFFSY (Chothia)
CDRH2	16/288 PINPYYGDAIYAQKFQG (Kabat)/ NPYYGD (Chothia)
CDRH3	17/289 YYSYMDY (Kabat)/ YYSYMDY (Chothia)

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(continued)

NVS963	
CDRL1	18/290 TGSSSNIGAGYDVH (Kabat)/ SSSNIGAGYD (Chothia)
CDRL2	19/291 DNSHRPS (Kabat)/ DNS (Chothia)
CDRL3	20/292 ASYDESAHS (Kabat)/ YDESAHS (Chothia)
VH	21 EVQLVQSGAEVKKPGSSVKVSKASGGTFSSYAI SWVRQAPGQGLEWM GPINPYYGDAIYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYC
	ARYYSDYMDYWGQGT LVTVSS
VL	22 QSVLTQPPSVSGAPGQ RVTISCTGSSSNIGAGYDVHWYQQLPGTAPKL LIHDNSHRPSGVPDRFSGSKSGTSASLAITGLQSEDEADYYCASYDES AHSVFGGGTKLTVL
HEAVY CHAIN	23 EVQLVQSGAEVKKPGSSVKVSKASGGTFSSYAI SWVRQAPGQGLEWM GPINPYYGDAIYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYC ARYYSDYMDYWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKRVEPKSC
LIGHT CHAIN	24 QSVLTQPPSVSGAPGQ RVTISCTGSSSNIGAGYDVHWYQQLPGTAPKL LIHDNSHRPSGVPDRFSGSKSGTSASLAITGLQSEDEADYYCASYDES AHSVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFY PGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSH RSYSCQVTHEGSTVEKTVAPTECS
PN ENCODING SEQ.ID.NO: 21	25 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTTAGCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCAGGACAGGGCCTGGAATGGATG GGCCCCATCAACCCCTACTACGGCGACGCCATCTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC ATGGAAGTGAAGCAGCTGAGAAGCGAGGACACCGCCGTGTACTACTGC GCCCCGTACTACAGCGACTACATGGACTACTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCA
PN ENCODING SEQ.ID.NO: 22	26 CAGTCAGTGCTGACCCAGCCTCCCTCTGTGTCTGGCGCCCCCTGGCCAG AGAGTGACCATCAGCTGCACCGGCTCCAGCAGCAACATCGGAGCTGGA TACGACGTGCACTGGTATCAGCAGCTGCCCGGCACAGCCCCTAAGCTG CTGATCCACGACAACAGCCACAGACCCAGCGGCGTGCCCGATAGATTTC AGCGGCAGCAAGAGCGGCACCAGCGCCAGCCTGGCCATCACCGGCCTG CAGAGCGAGGACGAGGCCGACTACTACTGCGCCAGCTACGACGAGAGC GCCACAGCGTGTTTCGAGGCGGAACAAAGTTAACCGTCCTA

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NVS963	
PN ENCODING SEQ.ID.NO: 23	27 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTTAGCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCAGGACAGGGCCTGGAATGGATG GGCCCCATCAACCCCTACTACGGCGACGCCATCTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGC GCCCCGTACTACAGCGACTACATGGACTACTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTG GCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGC CTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGGAAGTCA GGCGCCCTGACCAGCGCGTGCACACCTTCCCGGCTGTCTACAGTCC TCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAAGCCCAGCAAC ACCAAGGTGGACAAGAGAGTTGAGCCCCAAATCTTGT
PN ENCODING SEQ.ID.NO: 24	28 CAGTCAGTGCTGACCCAGCCTCCCTCTGTGTCTGGCGCCCCCTGGCCAG AGAGTGACCATCAGCTGCACCGGCTCCAGCAGCAACATCGGAGCTGGA TACGACGTGCACTGGTATCAGCAGCTGCCCGGCACAGCCCCCTAAGCTG CTGATCCACGACAACAGCCACAGACCCAGCGGCGTGCCCGATAGATTCT AGCGGCAGCAAGAGCGGCACCAGCGCCAGCCTGGCCATCACCAGCCTG CAGAGCGAGGACGAGGCCGACTACTACTGCGCCAGCTACGACGAGAGC
	GCCACAGCGTGTTTCGGAGGCGGAACAAAGTTAACCGTCCTAGGTCAG CCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAG CTTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTAC CCGGGAGCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAG GCGGGAGTGAGACCACCAACCCCTCCAAACAAAGCAACAACAAGTAC GCGGCCAGCAGCTATCTGAGCCTGACGCTGAGCAGTGGAAGTCCCAC AGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAG ACAGTGGCCCCCTACAGAATGTTCA
NVS964	
CDRH1	29/293 SHYMH (Kabat)/ GYTFTSH (Chothia)
CDRH2	30/294 KINADLGDNTYAQKFQG (Kabat)/ NADLGD (Chothia)
CDRH3	31/295 DGIEHGGHYYWGYLFDI (Kabat)/ DGIEHGGHYYWGYLFDI (Chothia)
CDRL1	32/296 SGDSIREYYVH (Kabat)/ DSIREYY (Chothia)
CDRL2	33/297 DDTNRPS (Kabat)/ DDT (Chothia)
CDRL3	34/298 AAWDFSPA (Kabat)/ WDFSPA (Chothia)
VH	35

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NVS964	
5	EVQLVQSGAEVKKPGASVKVSCKASGYTFTSHYMHWVRQAPGQGLEWM GKINADLGDNTNYAQKFQGRVTMTRDTSISTAYMELSSLRSEDTAVYYC ARDGIEHGGHYWGYLFDIWGQGLTVTVSS
10	VL 36 SYELTQPPSVSVAPGQTARISCSGDSIREYYVHWYQQKPGQAPVLVIG DDTNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCAAWDFSPAI VFGGGTKLTVL
15	HEAVY CHAIN 37 EVQLVQSGAEVKKPGASVKVSCKASGYTFTSHYMHWVRQAPGQGLEWM GKINADLGDNTNYAQKFQGRVTMTRDTSISTAYMELSSLRSEDTAVYYC ARDGIEHGGHYWGYLFDIWGQGLTVTVSSASTKGPSVFPLAPSSKST SGGTAALGCLVKDYFPEPVTVSWNSGALTSKVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC
20	LIGHT CHAIN 38 SYELTQPPSVSVAPGQTARISCSGDSIREYYVHWYQQKPGQAPVLVIG DDTNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCAAWDFSPAI VFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGA VTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSY SCQVTHEGSTVEKTVAPTECS
30	PN ENCODING SEQ.ID.NO: 39 35 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCTGGCGCC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCTACACCTTCACCAGCCAC TACATGCACTGGGTGCGCCAGGCTCCAGGACAGGGCCTGGAATGGATG GGCAAGATCAACGCCGACCTGGGCGACACCAACTACGCCCAGAAATTC CAGGGCAGAGTGACCATGACCCGGGACACCAGCATCAGCACCGCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGC GCCAGGGACGGCATCGAGCACGGCGGCCACTACTACTGGGGCTACCTG TTCGACATCTGGGGCCAGGGCACCCCTGGTGACCGTGAGCTCA
40	PN ENCODING SEQ.ID.NO: 40 36 AGCTACGAGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCCAG ACCGCCAGAATCAGCTGCAGCGGCGACAGCATCCGGGAGTACTACGTG CACTGGTATCAGCAGAAGCCCGGCCAGGCTCCTGTGCTGGTGATCGGC
45	GACGACACCAACAGACCCAGCGGCATCCCCGAGAGATTACGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCGAG GACGAGGCCGATTACTACTGCGCCGCTGGGACTTCAGCCCTGCCATC GTGTTTCGGAGGCGGAACAAAGTTAACCGTCCTA

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NVS964	
PN ENCODING SEQ.ID.NO: 37	41 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCTGGCGCC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCTACACCTTCACCAGCCAC TACATGCACTGGGTGCGCCAGGCTCCAGGACAGGGCCTGGAATGGATG GGCAAGATCAACGCCGACCTGGGCGACACCAACTACGCCAGAAATTC CAGGGCAGAGTGACCATGACCCGGGACACCAGCATCAGCACCGCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGC GCCAGGGACGGCATCGAGCACGGCGGCCACTACTACTGGGGCTACCTG TTCGACATCTGGGGCCAGGGCACCCCTGGTGACCGTGAGCTCAGCATCC ACCAAGGGTCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACC TCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCC GAACCGGTGACGGTGTCGTGGAAGTCAAGCGCCCTGACCAGCGGCGTG CACACCTTCCCCGGCTGTCTTACAGTCTCAGGACTCTACTCCCTCAGC AGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATC TGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTT GAGCCCAAATCTTGT
PN ENCODING SEQ.ID.NO: 38	42 AGCTACGAGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCCAG ACCGCCAGAATCAGCTGCAGCGGCGACAGCATCCGGGAGTACTACGTG CACTGGTATCAGCAGAAGCCCGGCCAGGCTCCTGTGCTGGTGATCGGC GACGACACCAACAGACCCAGCGGCATCCCCGAGAGATTCAGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCGAG GACGAGGCCGATTACTACTGCGCCGCTGGGACTTCAGCCCTGCCATC GTGTTTCGGAGGCGGAACAAAGTTAACCGTCCTAGGTCAGCCCAAGGCT GCCCCCTCGGTCACTCTGTCTCCCGCCCTCCTCTGAGGAGCTTCAAGCC AACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCC GTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTG GAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGC AGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCACAGAAGCTAC AGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA
NVS966	
CDRH1	43/299 NYWIG (Kabat)/ GYSFTNY (Chothia)
CDRH2	44/300 RIDPGESLTNYAPSFQG (Kabat)/ DPGESL (Chothia)
CDRH3	45/301 TGVADVDMPPFAH (Kabat)/ TGVADVDMPPFAH (Chothia)
CDRL1	46/302 SGDNLGSYYVN (Kabat)/ DNLGSYY (Chothia)
CDRL2	47/303 GDSERPS (Kabat)/ GDS (Chothia)
CDRL3	48/304 GSWDITSF (Kabat)/ WDITSF (Chothia)
VH	49

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NVS966	
5	EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYWIGWVRQMPGKGLEWM GRIDPGESLTNYAPSFQGGQVTISADKSISTAYLQWSSLKASDTAMYCY ARTGVADVDMPPFAHWGOGTLTVSS
10	VL 50 SYVLTQPPSVSVAPGKTARISCSGDNLGSYYVNWYQQKPGQAPVLIY
	GDSERPSGIPERFSGSNSGNTATLTISRAGQAGDEADYCGSWDITSFV FGGGTKLTVL
15	HEAVY CHAIN 51 EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYWIGWVRQMPGKGLEWM GRIDPGESLTNYAPSFQGGQVTISADKSISTAYLQWSSLKASDTAMYCY ARTGVADVDMPPFAHWGOGTLTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTV PSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC
20	LIGHT CHAIN 52 SYVLTQPPSVSVAPGKTARISCSGDNLGSYYVNWYQQKPGQAPVLIY GDSERPSGIPERFSGSNSGNTATLTISRAGQAGDEADYCGSWDITSFV FGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAV TVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRSYS CQVTHEGSTVEKTVAPTECS
30	PN ENCODING SEQ.ID.NO: 49 53 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAGCCTGGCGAG AGCCTGAAGATCAGCTGCAAGGGCAGCGGCTACAGCTTCACCAACTAC TGGATCGGCTGGGTGCGCCAGATGCCTGGCAAGGGCCTGGAATGGATG GGCAGAATCGACCCCGGCGAGTCCCTGACCAACTACGCCCCAGCTTC CAGGGCCAGGTGACAATCAGCGCCGACAAGAGCATCAGCACCGCCTAT CTGCAGTGGAGCAGCCTGAAGGCCAGCGACACCGCCATGTACTACTGC GCCAGAACC GGCGTGGCCGACGTGGACATGCCTTTTGCCCACTGGGGC CAGGGCACCCCTGGTGACCGTGAGCTCA
40	PN ENCODING SEQ.ID.NO: 50 54 AGCTACGTGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCAAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCTACTACGTG AACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC GGCGACAGCGAGAGGCCTAGCGGCATCCCCGAGCGGTTAGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCTCTAGAGCCCAGGCCGGC GACGAGGCCGATTACTACTGCGGCTCCTGGGACATCACCAGCTTCGTG TTCGGAGGCGGAACAAAGTTAACCGTCCTA

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NVS966	
PN ENCODING SEQ.ID.NO: 51	55 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAGCCTGGCGAG AGCCTGAAGATCAGCTGCAAGGGCAGCGGCTACAGCTTCACCAACTAC TGGATCGGCTGGGTGCGCCAGATGCCTGGCAAGGGCCTGGAATGGATG GGCAGAATCGACCCCGGCGAGTCCCTGACCAACTACGCCCCAGCTTC CAGGGCCAGGTGACAATCAGCGCCGACAAGAGCATCAGCACCGCCTAT CTGCAGTGGAGCAGCCTGAAGGCCAGCGACACCGCCATGTACTACTGC GCCAGAACC GGCGTGGCCGACGTGGACATGCCTTTTGCCCACTGGGGC CAGGGCACCCCTGGTGACCGTGAGCTCAGCCTCCACCAAGGGTCCATCG GTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGGGGCACAGCG GCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTG TCGTGGAACCTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGT GTCTTACAGTCCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTG CCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCAC AAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGT
PN ENCODING SEQ.ID.NO: 52	56 AGCTACGTGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCAAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCTACTACGTG AACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC GGCGACAGCGAGAGGCCTAGCGGCATCCCCGAGCGGTTACGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCTCTAGAGCCCAGGCCGGC GACGAGGCCGATTACTACTGCGGCTCCTGGGACATCACCAGCTTCGTG TTCGGAGGCGGAACAAAGTTAACCGTCCTAGGTCAGCCCAAGGCTGCC CCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAAC
	AAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTG ACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAG ACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGC TATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGC TGCCAGGTACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCCT ACAGAAATGTTCA
NVS965	
CDRH1	57/305 SYAIS (Kabat)/ GGTFNSY (Chothia)
CDRH2	58/306 RIIPFGTANYAQKFQG (Kabat)/ IPIFGT (Chothia)
CDRH3	59/307 HGGYSFDS (Kabat)/ HGGYSFDS (Chothia)
CDRL1	60/308 SGDNLGSKYVD (Kabat)/ DNLGSKY (Chothia)
CDRL2	61/309 SDNNRPS (Kabat)/ SDN (Chothia)
CDRL3	62/310 ATYDSSPRTE (Kabat)/ YDSSPRTE (Chothia)

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NVS965	
VH	63 EVQLVQSGAEVKKPGSSVKVSCKASGGTFNSYAI SWVRQAPGQGLEWM GRIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC ARHGGYSFDSWGQGT LVTVSS
VL	64 SYVLTQPPSVSVAPGKTARISCSGDNLGSKYVDWYQQKPGQAPVLIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCATYDSSPRT EVFGGGTKLTVL
HEAVY CHAIN	65 EVQLVQSGAEVKKPGSSVKVSCKASGGTFNSYAI SWVRQAPGQGLEWM GRIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC ARHGGYSFDSWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKRVEPKSC
LIGHT CHAIN	66 SYVLTQPPSVSVAPGKTARISCSGDNLGSKYVDWYQQKPGQAPVLIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCATYDSSPRT EVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNKNYAASSYLSLTPEQWKSHRS YSCQVTHEGSTVEKTVAPTECS
PN ENCODING SEQ.ID.NO: 63	67 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCAACAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACCTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC ATGGAAGTGAAGCAGCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCGGCACGGCGGCTACAGCTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCA
PN ENCODING SEQ.ID.NO: 64	68 AGCTACGTGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCAAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCCAGCGGCATCCCTGAGCGGTTACGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCATG
	GACGAGGCCGACTACTACTGCGCCACCTACGACAGCAGCCCCAGAACC GAGGTGTTTCGGAGGCGGAACAAAGTTAACCGTCCTA

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NVS965	
PN ENCODING SEQ.ID.NO: 65	69 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCAACAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACACTACGCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGGCACGGCGGCTACAGCTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTG GCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGC CTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGGAAGTCA GGCGCCCTGACCAGCGGCTGCACACCTTCCCGGCTGTCTACAGTCC TCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAAGCCCAGCAAC ACCAAGGTGGACAAGAGAGTTGAGCCCCAAATCTTGT
PN ENCODING SEQ.ID.NO: 66	70 AGCTACGTGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCAAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTACGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCATG GACGAGGCCGACTACTACTGCGCCACCTACGACAGCAGCCCCAGAACC GAGGTGTTTCGGAGGCGGAACAAAGTTAACCGTCTCTAGGTGAGCCCAAG GCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAA GCCAACAAGGCCACACTGGTGTGTCTCATAAGTGAAGTCTACCCGGGA GCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGA GTGGAGACCACCACACCTCCAAACAAGCAACAACAAGTACGCGGCC AGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCACAGAAGC TACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAAGAAGACAGTG GCCCCACAGAATGTTCA
NVS967	
CDRH1	71/311 SHYMH (Kabat)/ GYTFTSH (Chothia)
CDRH2	72/312 NINPVDGGTEYAQKFQG (Kabat)/ NPVDGG (Chothia)
CDRH3	73/313 DGIEHGGHYYWGYLFDI (Kabat)/ DGIEHGGHYYWGYLFDI (Chothia)
CDRL1	74/314 SGDSIREYYVH (Kabat)/ DSIREYY (Chothia)
CDRL2	75/315 DDTNRPS (Kabat)/ DDT (Chothia)
CDRL3	76/316 AAWDFSPAI (Kabat)/ WDFSPAI (Chothia)
VH	77 EVQLVQSGAEVKKPGASVKVSCKASGYTFTSHYMHWVRQAPGQGLEWM GNINPVDGGTEYAQKFQGRVTMTDRDTSISTAYMELSSLRSEDTAVYYC ARDGIEHGGHYYWGYLFDIWGQGLTVTVSS

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NVS967	
5 VL	78 SYVLTQPPSVSVAPGKTARISCSGDSIREYYVHWYQQKPGQAPVLVIG DDTNRPSGIPERFSGSNSGNTATLTISRAGDEADYYCAAWDFSPAI VFGGGTKLTVL
10 HEAVY CHAIN	79 EVQLVQSGAEVKKPGASVKVSCKASGYTFTSHYMHVVRQAPGQGLEWM GNINPVDGGTEYAQKFQGRVTMTRDTSISTAYMELSSLRSEDTAVYYC ARDGIEHGGHYWGYLFDIWGQGLVTVSSASTKGPSVFPLAPSSKST 15 SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS SVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC
20 LIGHT CHAIN	80 SYVLTQPPSVSVAPGKTARISCSGDSIREYYVHWYQQKPGQAPVLVIG DDTNRPSGIPERFSGSNSGNTATLTISRAGDEADYYCAAWDFSPAI VFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGA VTVAWKADSSPVKAGVETTTPSKQSNKYAASSYLSLTPEQWKSHRSY SCQVTHEGSTVEKTVAPTECS
25 PN ENCODING SEQ.ID.NO: 77	81 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCTGGCGCC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCTACACCTTCACCAGCCAC TACATGCACTGGGTGCGCCAGGCTCCAGGACAGGGCCTGGAATGGATG GGCAACATCAACCCCGTGGACGGCGGCACCGAGTACGCCCAGAAATTC 30 CAGGGCAGAGTGACCATGACCCGGGACACCAGCATCAGCACCGCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGC GCCAGGGACGGCATCGAGCACGGCGGCCACTACTACTGGGGCTACCTG TTCGACATCTGGGGCCAGGGCACCCCTGGTGACCGTGAGCTCA
35 PN ENCODING SEQ.ID.NO: 78	82 TCTTACGTGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCAAG ACCGCCAGAATCAGCTGCAGCGGCGACAGCATCCGGGAGTACTACGTG CACTGGTATCAGCAGAAGCCCGGCCAGGCTCCTGTGCTGGTGATCGGC GACGACACCAACAGACCCAGCGGCATCCCCGAGAGATTAGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCTCTAGAGCCCAGGCCGCGC 40 GACGAGGCCGATTACTACTGCGCCGCGCTGGGACTTCAGCCCTGCCATC GTGTTCGGAGGCGGAACAAAGTTAACCGTCCTA

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NVS967	
PN ENCODING SEQ.ID.NO: 79	83 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCTGGCGCC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCTACACCTTCACCAGCCAC TACATGCACTGGGTGCGCCAGGCTCCAGGACAGGGCCTGGAATGGATG GGCAACATCAACCCCGTGGACGGCGGCACCGAGTACGCCCAGAAATTC CAGGGCAGAGTGACCATGACCCGGGACACCAGCATCAGCACCGCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGC GCCAGGGACGGCATCGAGCACGGCGGCCACTACTACTGGGGCTACCTG TTCGACATCTGGGGCCAGGGCACCCCTGGTGACCGTGAGCTCAGCCTCC ACCAAGGGTCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACC TCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCC GAACCGGTGACGGTGTCGTGGAAGTCAAGCGCCCTGACCAGCGGCGTG CACACCTTCCCCGGCTGTCTTACAGTCTCAGGACTCTACTCCCTCAGC AGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATC TGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTT GAGCCCAATCTTGT
PN ENCODING SEQ.ID.NO: 80	84 TCTTACGTGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCAAG ACCGCCAGAATCAGCTGCAGCGGCGACAGCATCCGGGAGTACTACGTG CACTGGTATCAGCAGAAGCCCGGCCAGGCTCCTGTGCTGGTGATCGGC GACGACACCAACAGACCCAGCGGCATCCCCGAGAGATTACGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCTCTAGAGCCCAGGCCGGC GACGAGGCCGATTACTACTGCGCCGCTGGGACTTCAGCCCTGCCATC GTGTTTCGAGAGCGGAACAAAGTTAACCCTCCTAGGTGAGCCCAAGGCT GCCCCCTCGGTCACTCTGTTCCCCGCCCTCCTCTGAGGAGCTTCAAGCC AACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCC GTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTG GAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGC
	AGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTAC AGCTGCCAGGTACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA
NVS807	
CDRH1	85/317 SYAIS (Kabat)/ GGTFFSY (Chothia)
CDRH2	86/318 RIIPFGTANYAQKFQG (Kabat)/ IPIFGT (Chothia)
CDRH3	87/319 HGGYSYFDS (Kabat)/ HGGYYFDS (Chothia)
CDRL1	88/320 SGDNLGSKYVD (Kabat)/ DNLGSKY (Chothia)
CDRL2	89/321 SDNNRPS (Kabat)/ SDN (Chothia)
CDRL3	90/322 QTYTSGNNYL (Kabat)/ YTSGNNYL (Chothia)

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NVS807	
VH	91 EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWM GRIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC ARHGGYYFDSWGOGTLVTVSS
VL	92 SYELTQPPSVSVAPGQTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQTYTSGNNY LVFGGGTKLTVL
HEAVY CHAIN	93 EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWM GRIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC ARHGGYYFDSWGOGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKRVEPKSC
LIGHT CHAIN	94 SYELTQPPSVSVAPGQTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQTYTSGNNY LVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCQVTHEGSTVEKTVAPTECS
PN ENCODING SEQ.ID.NO: 91	95 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCAGCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCGGCACGGCGGCTACTACTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCA
PN ENCODING SEQ.ID.NO: 92	96 AGCTACGAGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCCAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTTCAGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCGAG GACGAGGCCGACTACTACTGCCAGACCTACACCGCGGCAACAACCTAC CTGGTGTTTCGGAGGCGGAACAAAGTTAACCGTCCTA
PN ENCODING SEQ.ID.NO: 93	97 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC

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NVS807	
5	AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCAGCAGCTAC
10	GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG
	GGCCGGATCATCCCCATCTTCGGCACCGCCAACTACGCCCAGAAATTC
	CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC
	ATGGAAGTGAAGCAGCTGAGAAGCGAGGACACCGCCGTGTACTACTGT
	GCCCCGGCACGGCGGCTACTACTTCGATAGCTGGGGCCAGGGCACCCCTG
	GTGACCGTGAGCTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTG
15	GCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGC
	CTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGGAAGTCA
	GGCGCCCTGACCAGCGGCTGCACACCTTCCCGGCTGTCTACAGTCC
	TCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC
	TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAAGCCCAGCAAC
	ACCAAGGTGGACAAGAGAGTTGAGCCCCAAATCTTGT
20	PN ENCODING SEQ.ID.NO: 98
	94
25	AGCTACGAGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCCAG
	ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG
	GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC
	AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTACGCGGCAGC
	AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCGAG
	GACGAGGCCGACTACTACTGCCAGACCTACACCAGCGGCAACAACCTAC
	CTGGTGTTCGGAGGCGGAACAAAGTTAACCGTCTAGGTGAGCCCAAG
30	GCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAA
	GCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGA
	GCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGA
	GTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCC
	AGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCACAGAAGC
	TACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTG
	GCCCCCTACAGAATGTTCA
35	NVS808
	CDRH1 99/323 SYAIS (Kabat)/ GGTFFSY (Chothia)
40	CDRH2 100/324 RIIPFGTANYAQKFQG (Kabat)/ IPIFGT (Chothia)
	CDRH3 101/325 HGGYIFDS (Kabat)/ HGGYIFDS (Chothia)
45	CDRL1 102/326 SGDNLGSKYVD (Kabat)/ DNLGSKY (Chothia)
	CDRL2 103/327 SDNNRPS (Kabat)/ SDN (Chothia)
50	CDRL3 104/328 QTYTSGNNYL (Kabat)/ YTSGNNYL (Chothia)
55	VH 105 EVQLVQSGAEVKKPGSSVKVSKASGGTFSSYAIWVRQAPGQGLEWM GRIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC ARHGGYIFDSWGQGLTVVSS

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NVS808	
5 VL	106 SYELTQPPSVSVAPGQTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQTYTSGNNY LVFGGGTKLTVL
10 HEAVY CHAIN	107 EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAI SWVRQAPGQGLEWM GRIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC ARHGGYIFDSWGQGLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKRVEPKSC
15 LIGHT CHAIN	108 SYELTQPPSVSVAPGQTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQTYTSGNNY LVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCOVTHEGSTVEKTVAPTECS
20 PN ENCODING SEQ.ID.NO: 105	109 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCAGCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACCTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGGCACGGCGGCTACATTTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCA
25 PN ENCODING SEQ.ID.NO: 106	110 AGCTACGAGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCCAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCCAGCGGCATCCCTGAGCGGTTACGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCGAG GACGAGGCCGACTACTACTGCCAGACCTACACCAGCGGCAACAACCTAC CTGGTGTTTCGGAGGCGGAACAAAGTTAACCGTCCTA
30 PN ENCODING SEQ.ID.NO: 107	111 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCAGCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACCTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGGCACGGCGGCTACATTTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTG GCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGC CTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGGAACCTCA GGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCTACAGTCC TCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAAC ACCAAGGTGGACAAGAGAGTTGAGCCCCAAATCTTGT

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NVS808	
PN ENCODING SEQ.ID.NO: 108	112 AGCTACGAGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCCAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTTCAGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCGAG GACGAGGCCGACTACTACTGCCAGACCTACACCAGCGGCAACAACCTAC CTGGTGTTTCGGAGGCGGAACAAAGTTAACCCTCCTAGGTCAGCCCAAG GCTGCCCCCTCGGTCACTCTGTTCCTCGCCCTCCTCTGAGGAGCTTCAA GCCAACAAGGCCACACTGGTGTGTCTCATAAGTGAAGTCTACCCGGGA GCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGA GTGGAGACCACCACACCTCCAAACAAAGCAACAACAAGTACGCGGCC
	AGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCACAGAAGC TACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGAGAAGACAGTG GCCCCCTACAGAATGTTCA
NVS806	
CDRH1	113/329 SYAIS (Kabat) / GGTFSY (Chothia)
CDRH2	114/330 RIIPFGTANYAQKFQG (Kabat) / IPIFGT (Chothia)
CDRH3	115/331 HGGYVFDS (Kabat) / HGGYVFDS (Chothia)
CDRL1	116/332 SGDNLGSKYVD (Kabat) / DNLGSKY (Chothia)
CDRL2	117/333 SDNNRPS (Kabat) / SDN (Chothia)
CDRL3	118/334 QTYTSGNNYL (Kabat) / YTSGNNYL (Chothia)
VH	119 EVQLVQSGAEVKKPGSSVKVSKASGGTFSSYAI SWVRQAPGQGLEWM GRIIPFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYC ARHGGYVFDSWGQGLTVTVSS
VL	120 SYELTQPPSVSVAPGQTARISCSGDNLGSKYVDWYQQKPGQAPVLIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQTYTSGNNY LVFGGGTKLTVL
HEAVY CHAIN	121 EVQLVQSGAEVKKPGSSVKVSKASGGTFSSYAI SWVRQAPGQGLEWM GRIIPFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYC ARHGGYVFDSWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKRVEPKSC

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NVS806	
LIGHT CHAIN	122 SYELTQPPSVSVAPGQTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYQCQTYTSGNNY LVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCQVTHEGSTVEKTVAPTECS
PN ENCODING SEQ.ID.NO: 119	123 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCAGCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGGCACGGCGGCTACGTCTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCA
PN ENCODING SEQ.ID.NO: 120	124 AGCTACGAGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCCAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTACGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCGAG GACGAGGCCGACTACTACTGCCAGACCTACACCAGCGGCAACAACCTAC CTGGTGTTTCGAGGCGGAACAAAGTTAACCGTCCTA
PN ENCODING SEQ.ID.NO: 121	125 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC
	AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCAGCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGGCACGGCGGCTACGTCTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTG GCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGC CTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAAGTCA GGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCCTACAGTCC TCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAAC ACCAAGGTGGACAAGAGAGTTGAGCCCCAAATCTTGT

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NVS804	
5 LIGHT CHAIN	136 SYVLTQPPSVSVAPGKTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCATYDSSPRT EVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCQVTHEGSTVEKTVAPTECS
10 PN ENCODING SEQ.ID.NO: 133	137 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCAGCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGGCACGGCGGCTACATTTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCA
15 PN ENCODING SEQ.ID.NO: 134	138 AGCTACGTGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCAAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTACGCGGCAGC AACAGCGGCAATAACCGCCACCCTGACCATCAGCGGCACCCAGGGCATG GACGAGGCCGACTACTACTGCGCCACCTACGACAGCAGCCCCAGAACC GAGGTGTTTCGGAGGCGGAACAAAGTTAACCGTCCTA
20 PN ENCODING SEQ.ID.NO: 135	139 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCAGCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGGCACGGCGGCTACATTTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTG GCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGC CTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAAGTCA GGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCCTACAGTCC TCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAAC ACCAAGGTGGACAAGAGAGTTGAGCCCCAAATCTTGT

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NVS804	
PN ENCODING SEQ.ID.NO: 136	140 AGCTACGTGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCAAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTTCAGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCATG GACGAGGCCGACTACTACTGCGCCACCTACGACAGCAGCCCCAGAACC GAGGTGTTCTGGAGGCGGAACAAAGTTAACCGTCTTAGGTTCAGCCCAAG GCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAA GCCAACAAGGCCACACTGGTGTGTCTCATAAGTGAAGTCTTACCCGGGA GCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGA GTGGAGACCACCACCCCTCCAAACAAAGCAACAACAAGTACGCGGCC AGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGC TACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTG GCCCCCTACAGAATGTTCA
NVS809	
CDRH1	141/341 SYAIS (Kabat)/ GGTFFSY (Chothia)
CDRH2	142/342 RIIPIFGTANYAQKFQG (Kabat)/ IPIFGT (Chothia)
CDRH3	143/343 HGGYYFDS (Kabat)/ HGGYYFDS (Chothia)
CDRL1	144/344 SGDNLGSKYVD (Kabat)/ DNLGSKY (Chothia)
CDRL2	145/345 SDNNRPS (Kabat)/ SDN (Chothia)
CDRL3	146/346 ATYDSSPRTE (Kabat)/ YDSSPRTE (Chothia)
VH	147 EVQLVQSGAEVKKPGSSVKVSCASGGTFSSYAIWVRQAPGQGLEWM GRIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYC ARHGGYYFDSWGQGT LVT VSS
VL	148 SYVLTQPPSVSVAPGKTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCATYDSSPRTE EVFGGGTKLTVL
HEAVY CHAIN	149 EVQLVQSGAEVKKPGSSVKVSCASGGTFSSYAIWVRQAPGQGLEWM GRIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYC ARHGGYYFDSWGQGT LVT VSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSS LGTQTYICNVNHKPSNTKVDKRVEPKSC

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NVS809	
LIGHT CHAIN	150 SYVLTQPPSVSVAPGKTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCATYDSSPRT EVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCQVTHEGSTVEKTVAPTECS
PN ENCODING SEQ.ID.NO: 147	151 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCAGCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGGCACGGCGGCTACTACTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCA
PN ENCODING SEQ.ID.NO: 148	152 AGCTACGTGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCAAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCCAGCGGCATCCCTGAGCGGTTACGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGGCCATG GACGAGGCCGACTACTACTGCGCCACCTACGACAGCAGCCCCAGAACC GAGGTGTTTCGGAGGCGGAACAAAGTTAACCGTCCTA
PN ENCODING SEQ.ID.NO: 149	153 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCAGCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC
	ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGGCACGGCGGCTACTACTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTG GCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGC CTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAATCA GGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCTTACAGTCC TCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAAGCCCAGCAAC ACCAAGGTGGACAAGAGAGTTGAGCCCCAAATCTTGT

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NVS805	
5	LIGHT CHAIN 164 SYVLTQPPSVSVAPGKTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCATYDSSPRT EVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG
10	AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCQVTHEGSTVEKTVAPTECS
15	PN ENCODING SEQ.ID.NO: 161 165 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCAGCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACCTACGCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACC GCCTAC ATGGAAGTGAAGCAGCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGGCACGGCGGCTACGTCTTCGATAGCTGGGGCCAGGGCACCTG GTGACCGTGAGCTCA
20	
25	PN ENCODING SEQ.ID.NO: 162 166 AGCTACGTGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCAAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTACGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCATG GACGAGGCCGACTACTACTGCGCCACCTACGACAGCAGCCCCAGAACC GAGGTGTTTCGGAGGCGGAACAAAGTTAACCGTCTCTA
30	
35	PN ENCODING SEQ.ID.NO: 163 167 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCAGCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACCTACGCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACC GCCTAC ATGGAAGTGAAGCAGCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGGCACGGCGGCTACGTCTTCGATAGCTGGGGCCAGGGCACCTG GTGACCGTGAGCTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTG GCACCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGC CTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAAGTCA GGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCTTACAGTCC TCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAAC ACCAAGGTGGACAAGAGAGTTGAGCCCCAAATCTTGT
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NVS805	
PN ENCODING SEQ.ID.NO: 164	168 AGCTACGTGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCAAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTTCAGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCATG GACGAGGCCGACTACTACTGCGCCACCTACGACAGCAGCCCCAGAACC GAGGTGTTTCGAGGCGGAACAAAGTTAACCGTCCTAGGTTCAGCCCAAG GCTGCCCCCTCGGTCACTCTGTTCCTCGCCCTCCTCTGAGGAGCTTCAA GCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGA GCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGA GTGGAGACCACACCCCTCCAAACAAAGCAACAACAAGTACGCGGCC AGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGC TACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAAGAAGACAGTG GCCCCACAGAATGTTCA
NVS962-S	
CDRH1	169/353 SYAIS (Kabat)/ GGTFFSY (Chothia)
CDRH2	170/354 RIIPIFGTANYAQKFQG (Kabat)/ IPIFGT (Chothia)
CDRH3	171/355 HGGYSFDS (Kabat)/ HGGYSFDS (Chothia)
CDRL1	172/356 SGDNLGSKYVD (Kabat)/ DNLGSKY (Chothia)
CDRL2	173/357 SDNNRPS (Kabat)/ SDN (Chothia)
CDRL3	174/358 QTYTSGNNYL (Kabat)/ YTSGNNYL (Chothia)
VH	175 EVQLVQSGAEVKKPGSSVKVSKASGGTFSSYAI SWVRQAPGQGLEWM GRIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYC ARHGGYSFDSWGQGT LVTVSS
VL	176 SYELTQPPSVSVAPGQTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQTYTSGNNY LVFGGGTKLTVL
HEAVY CHAIN	177 EVQLVQSGAEVKKPGSSVKVSKASGGTFSSYAI SWVRQAPGQGLEWM GRIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYC ARHGGYSFDSWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKRVEPKSC

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NVS962-S	
5 LIGHT CHAIN	178 SYELTQPPSVSVAPGQTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYCYCQTYTSGNNY LVFGGGTKLTLVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCOVTHEGSTVEKTVAPTECS
10 PN ENCODING SEQ.ID.NO: 175	179 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCAGCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACCTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGGCACGGCGGCTACAGCTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCA
15 PN ENCODING SEQ.ID.NO: 176	180 AGCTACGAGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCCAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTACGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCGAG GACGAGGCCGACTACTACTGCCAGACCTACACCAGCGGCAACAACCTAC CTGGTGTTTCGAGGCGGAACAAAGTTAACCGTCCTA
20 PN ENCODING SEQ.ID.NO: 177	181 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCAGCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACCTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGGCACGGCGGCTACAGCTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTG GCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGC
25 CTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAAGTCA GGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCCTACAGTCC TCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAAC ACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGT	

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NVS962-S	
PN ENCODING SEQ.ID.NO: 178	182 AGCTACGAGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCCAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTTCAGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCGAG GACGAGGCCGACTACTACTGCCAGACCTACACCAGCGGCAACAACCTAC CTGGTGTTTCGGAGGCGGAACAAAGTTAACCGTCTTAGGTTCAGCCCAAG GCTGCCCCCTCGGTCACTCTGTTCCTCGCCCTCCTCTGAGGAGCTTCAA GCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGA GCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGA GTGGAGACCACCACCCCTCCAAACAAAGCAACAACAAGTACGCGGCC AGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCACAGAAGC TACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTG GCCCTACAGAATGTTCA
NVS962-Q	
CDRH1	183/359 SYAIS (Kabat)/ GGTFAQSY (Chothia)
CDRH2	184/360 RIIPFGTANYAQKFQG (Kabat)/ IPIFGT (Chothia)
CDRH3	185/361 HGGYSFDS (Kabat)/ HGGYSFDS (Chothia)
CDRL1	186/362 SGDNLGSKYVD (Kabat)/ DNLGSKY (Chothia)
CDRL2	187/363 SDNNRPS (Kabat)/ SDN (Chothia)
CDRL3	188/364 QTYTSGNNYL (Kabat)/ YTSGNNYL (Chothia)
VH	189 EVQLVQSGAEVKKPGSSVKVCKASGGTFQSYAISWVRQAPGQGLEWM GRIIPFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDYAVYYC ARHGGYSFDSWGQGLTVTVSS
VL	190 SYELTQPPSVSVAPGQTARISCSGDNLGSKYVDWYQQKPGQAPVLIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQTYTSGNNY LVFGGGTKLTVL
HEAVY CHAIN	191 EVQLVQSGAEVKKPGSSVKVCKASGGTFQSYAISWVRQAPGQGLEWM GRIIPFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDYAVYYC ARHGGYSFDSWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSS LGTQTYICNVNHKPSNTKVDKRVEPKSC

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NVS962-Q	
LIGHT CHAIN	192 SYELTQPPSVSVAPGQTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYQCQTYTSGNNY LVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCQVTHEGSTVEKTVAPTECS
PN ENCODING	193
SEQ.ID.NO:189	GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCCAAAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACCTACGCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACC GCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGGCACGGCGGCTACAGCTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCA
PN ENCODING SEQ.ID.NO: 190	194 AGCTACGAGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCCAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTACGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCGAG GACGAGGCCGACTACTACTGCCAGACCTACACCAGCGGCAACAACCTAC CTGGTGTTTCGGAGGCGGAACAAAGTTAACCGTCTCA
PN ENCODING SEQ.ID.NO: 191	195 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCCAAAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACCTACGCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACC GCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGGCACGGCGGCTACAGCTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTG GCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGC CTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAAGTCA GGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCCTACAGTCC TCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAAC ACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGT

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NVS962-Q	
PN ENCODING SEQ.ID.NO: 192	196 AGCTACGAGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCCAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTTCAGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCGAG GACGAGGCCGACTACTACTGCCAGACCTACACCAGCGGCAACAACACTAC CTGGTGTTTCGGAGGCGGAACAAAGTTAACCGTCCTAGGTCAGCCCAAG GCTGCCCCCTCGGTCACTCTGTTCCTCGCCCTCCTCTGAGGAGCTTCAA GCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGA GCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGA GTGGAGACCACACCCCTCCAAACAAAGCAACAACAAGTACGCGGCC AGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCACAGAAGC TACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTG GCCCCACAGAATGTTCA
NVS962-S31A	
CDRH1	197/365 SYAIS (Kabat)/ GGTFNAY (Chothia)
CDRH2	198/366 RIIPIFGTANYAQKFQG (Kabat)/ IPIFGT (Chothia)
CDRH3	199/367 HGGYSFDS (Kabat)/ HGGYSFDS (Chothia)
CDRL1	200/368 SGDNLGSKYVD (Kabat)/ DNLGSKY (Chothia)
CDRL2	201/369 SDNNRPS (Kabat)/ SDN (Chothia)
CDRL3	202/370 QTYTSGNNYL (Kabat)/ YTSGNNYL (Chothia)
VH	203 EVQLVQSGAEVKKPGSSVKVSKASGGTFNAYAISWVRQAPGQGLEWM GRIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYC ARHGGYSFDSWGQGT LVTVSS
VL	204 SYELTQPPSVSVAPGQTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQTYTSGNNY LVFGGGTKLTVL
HEAVY CHAIN	205 EVQLVQSGAEVKKPGSSVKVSKASGGTFNAYAISWVRQAPGQGLEWM GRIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYC ARHGGYSFDSWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYIICNVNHNKPSNTKVDKRVEPKSC

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NVS962-S31A	
5 10	LIGHT CHAIN 206 SYELTQPPSVSVAPGQTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYQCQTYTSGNNY LVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCQVTHEGSTVEKTVAPTECS
15 20	PN ENCODING SEQ.ID.NO: 203 207 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCAACGCCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCGGCACGGCGGCTACAGCTTCGATAGCTGGGGCCAGGGCACCCTG GTGACCGTGAGCTCA
25 30	PN ENCODING SEQ.ID.NO: 204 208 AGCTACGAGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCCAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCCAGCGGCATCCCTGAGCGGTTACGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCGAG GACGAGGCCGACTACTACTGCCAGACCTACACCAGCGGCAACAACCTAC CTGGTGTTTCGGAGGCGGAACAAAGTTAACCGTCCTA
35 40 45	PN ENCODING SEQ.ID.NO: 205 209 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCAACGCCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCGGCACGGCGGCTACAGCTTCGATAGCTGGGGCCAGGGCACCCTG GTGACCGTGAGCTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTG GCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGC CTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAAGTCA GGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCCTACAGTCC TCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAAGCCCAGCAAC ACCAAGGTGGACAAGAGAGTTGAGCCCCAAATCTTGT

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NVS962-S31A	
PN ENCODING SEQ.ID.NO: 206	210 AGCTACGAGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCCAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTTCAGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCGAG GACGAGGCCGACTACTACTGCCAGACCTACACCAGCGGCAACAACACTAC CTGGTGTTCGGAGGCGGAACAAAGTTAACCGTCCTAGGTCAGCCCAAG GCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAA GCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGA GCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGA GTGGAGACCACCACCCCTCCAAACAAAGCAACAACAAGTACGCGGCC AGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGC TACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTG GCCCCTACAGAATGTTCA
NVS962-G	
CDRH1	211/371 SYAIS (Kabat)/ GGTFGSY (Chothia)
CDRH2	212/372 RIIPIFGTANYAQKFQG (Kabat)/ IPIFGT (Chothia)
CDRH3	213/373 HGGYSFDS (Kabat)/ HGGYSFDS (Chothia)
CDRL1	214/374 SGDNLGSKYVD (Kabat)/ DNLGSKY (Chothia)
CDRL2	215/375 SDNNRPS (Kabat)/ SDN (Chothia)
CDRL3	216/376 QTYTSGNNYL (Kabat)/ YTSGNNYL (Chothia)
VH	217 EVQLVQSGAEVKKPGSSVKVSKASGGTFGSYAI SWVRQAPGQGLEWM GRIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYC ARHGGYSFDSWGQGLTVTVSS
VL	218 SYELTQPPSVSVAPGQTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQTYTSGNNY LVFGGGTKLTVL
HEAVY CHAIN	219 EVQLVQSGAEVKKPGSSVKVSKASGGTFGSYAI SWVRQAPGQGLEWM GRIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYC ARHGGYSFDSWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSS LGTQTYICNVNHKPSNTKVDKRVEPKSC

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NVS962-S31A	
5 10	LIGHT CHAIN 220 SYELTQPPSVSVAPGQTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQTYTSGNNY LVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCQVTHEGSTVEKTVAPTECS
15	PN ENCODING SEQ.ID.NO: 217 221 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCGGCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC
20	ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCGGCACGGCGGCTACAGCTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCA
25 30	PN ENCODING SEQ.ID.NO: 218 222 AGCTACGAGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCCAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTACGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCGAG GACGAGGCCGACTACTACTGCCAGACCTACACCAGCGGCAACAACCTAC CTGGTGTTTCGGAGGCGGAACAAAGTTAACCGTCCTA
35 40 45	PN ENCODING SEQ.ID.NO: 219 223 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCGGCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCGGCACGGCGGCTACAGCTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTG GCACCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGC CTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACCTCA GGCGCCCTGACCAGCGGCTGCACACCTTCCCGGCTGTCCTACAGTCC TCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAAC ACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGT

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NVS962-S31A	
PN ENCODING SEQ.ID.NO: 220	224 AGCTACGAGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCCAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTTCAGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCGAG GACGAGGCCGACTACTACTGCCAGACCTACACCAGCGGCAACAACACTAC CTGGTGTTTCGGAGGCGGAACAAAGTTAACCGTCTCTAGGTTCAGCCCAAG GCTGCCCCCTCGGTCACTCTGTTCCTCGCCCTCCTCTGAGGAGCTTCAA GCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGA GCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGA GTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCC AGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCACAGAAAGC TACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTG GCCCTACAGAATGTTCA
NVS962-T	
CDRH1	225/377 SYAIS (Kabat)/ GGTFTSY (Chothia)
CDRH2	226/378 RIIPFGTANYAQKFQG (Kabat)/ IPIFGT (Chothia)
CDRH3	227/379 HGGYSFDS (Kabat)/ HGGYSFDS (Chothia)
CDRL1	228/380 SGDNLGSKYVD (Kabat)/ DNLGSKY (Chothia)
CDRL2	229/381 SDNNRPS (Kabat)/ SDN (Chothia)
CDRL3	230/382 QTYTSGNNYL (Kabat)/ YTSGNNYL (Chothia)
VH	231 EVQLVQSGAEVKKPGSSVKVSKASGGTFTSYAISWVRQAPGQGLEWM GRIIPFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC ARHGGYSFDSWGQGLTVTVSS
VL	232 SYELTQPPSVSVAPGQTARISCSGDNLGSKYVDWYQQKPGQAPVLIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQTYTSGNNY LVFGGGTKLTVL
HEAVY CHAIN	233 EVQLVQSGAEVKKPGSSVKVSKASGGTFTSYAISWVRQAPGQGLEWM GRIIPFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC ARHGGYSFDSWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKRVEPKSC

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NVS962-T	
5 LIGHT CHAIN	234 SYELTQPPSVSVAPGQTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCQTYTSGNNY LVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCQVTHEGSTVEKTVAPTECS
10 PN ENCODING SEQ.ID.NO: 231	235 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCACCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGGCACGGCGGCTACAGCTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCA
15 PN ENCODING SEQ.ID.NO: 232	236 AGCTACGAGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCCAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCCAGCGGCATCCCTGAGCGGTTACGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCGAG GACGAGGCCGACTACTACTGCCAGACCTACACCAGCGGCAACAACCTAC CTGGTGTTTCGGAGGCGGAACAAAGTTAACCGTCCTA
20 PN ENCODING SEQ.ID.NO: 233	237 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCACCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGGCACGGCGGCTACAGCTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTG GCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGC CTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACCTCA GGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCCTACAGTCC TCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAAC ACCAAGGTGGACAAGAGAGTTGAGCCCCAAATCTTGT
25 PN ENCODING SEQ.ID.NO: 234	238 AGCTACGAGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCCAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCCAGCGGCATCCCTGAGCGGTTACGCGGCAGC

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NVS962-T	
5	AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCGAG GACGAGGCCGACTACTACTGCCAGACCTACACCAGCGGCAACAACACTAC CTGGTGTTCGGAGGCGGAACAAAGTTAACCGTCCTAGGTCAGCCCAAG GCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAA 10GCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGA GCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGA GTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCC AGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGC TACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGAGAGAAGACAGTG 15GCCCCCTACAGAATGTTCA
NVS965-T	
CDRH1	239/383 SYAIS (Kabat)/ GGTFTSY (Chothia)
CDRH2	240/384 RIIPFGTANYAQKFQG (Kabat)/ IPIFGT (Chothia)
CDRH3	241/385 HGGYSFDS (Kabat)/ HGGYSFDS (Chothia)
CDRL1	242/386 SGDNLGSKYVD (Kabat)/ DNLGSKY (Chothia)
CDRL2	243/387 SDNNRPS (Kabat)/ SDN (Chothia)
CDRL3	244/388 ATYDSSPRTE (Kabat)/ YDSSPRTE (Chothia)
VH	245 EVQLVQSGAEVKKPGSSVKVSKASGGTFTSYAISWVRQAPGQGLEWM 35GRIIPFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYC ARHGGYSFDSWGQGT LVTVSS
VL	246 SYVLTQPPSVSVAPGKTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY 40SDNNRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCATYDSSPRT EVFGGGTKLTVL
HEAVY CHAIN	247 EVQLVQSGAEVKKPGSSVKVSKASGGTFTSYAISWVRQAPGQGLEWM 45GRIIPFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYC ARHGGYSFDSWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKRVEPKSC
LIGHT CHAIN	248 SYVLTQPPSVSVAPGKTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY 50SDNNRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCATYDSSPRT EVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTPSKQSNNKYAASSYLSLTPEQWKSHRS 55YSCQVTHEGSTVEKTVAPTECS

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NVS965-T	
5 10 15 PN ENCODING SEQ.ID.NO: 245	249 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCACCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACC GCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCGCGGCACGGCGGCTACAGCTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCA
15 PN ENCODING SEQ.ID.NO: 246	250 AGCTACGTGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCAAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG
20	GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTACAGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCATG GACGAGGCCGACTACTACTGCGCCACCTACGACAGCAGCCCCAGAACC GAGGTGTTTCGGAGGCGGAACAAAGTTAACCGTCCTA
25 30 35 40 PN ENCODING SEQ.ID.NO: 247	251 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCACCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACC GCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCGCGGCACGGCGGCTACAGCTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTG GCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGC CTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAATCA GGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTCCTACAGTCC TCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAAC ACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGT
45 50 55 PN ENCODING SEQ.ID.NO: 248	252 AGCTACGTGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCAAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTACAGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCATG GACGAGGCCGACTACTACTGCGCCACCTACGACAGCAGCCCCAGAACC GAGGTGTTTCGGAGGCGGAACAAAGTTAACCGTCCTAGGTCAGCCCAAG GCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAA GCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGA GCCGTGACAGTGCCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGA GTGGAGACCACACACCTCCAAACAAGCAACAACAAGTACGCGGCC AGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGC TACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGAGAGAAGACAGTG GCCCCACAGAATGTTCA

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	NVS965-Q	
5	CDRH1	253/389 SYAIS (Kabat)/ GGTFQSY (Chothia)
	CDRH2	254/390 RIIPIFGTANYAQKFQG (Kabat)/ IPIFGT (Chothia)
10	CDRH3	255/391 HGGYSFDS (Kabat)/ HGGYSFDS (Chothia)
	CDRL1	256/392 SGDNLGSKYVD (Kabat)/ DNLGSKY (Chothia)
15	CDRL2	257/393 SDNNRPS (Kabat)/ SDN (Chothia)
	CDRL3	258/394 ATYDSSPRTE (Kabat)/ YDSSPRTE (Chothia)
20	VH	259 EVQLVQSGAEVKKPGSSVKVSCASGGTFQSYAISWVRQAPGQGLEWM GRIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYC ARHGGYSFDSWGQGT LVTVSS
25	VL	260 SYVLTQPPSVSVAPGKTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCATYDSSPRT
		EVFGGGTKLTVL
30	HEAVY CHAIN	261 EVQLVQSGAEVKKPGSSVKVSCASGGTFQSYAISWVRQAPGQGLEWM GRIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYC ARHGGYSFDSWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTQTYICNVNHKPSNTKVDKRVEPKSC
35		
	LIGHT CHAIN	262 SYVLTQPPSVSVAPGKTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCATYDSSPRT EVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCOVTHEGSTVEKTVAPTECS
40		
45	PN ENCODING SEQ.ID.NO: 259	263 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCCAAAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTCGGCACCGCCAAC TACGCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACC GCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGCACGGCGGCTACAGCTTCGATAGCTGGGGCCAGGGCACCCTG GTGACCGTGAGCTCA
50		
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NVS965-Q	
PN ENCODING SEQ.ID.NO: 260	264 AGCTACGTGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCAAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTTACGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCATG GACGAGGCCGACTACTACTGCGCCACCTACGACAGCAGCCCCAGAACC GAGGTGTTTCGGAGGCGGAACAAAGTTAACCGTCCTA
PN ENCODING SEQ.ID.NO: 261	265 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCCAAAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC ATGGAAGTGCAGCAGCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGGCACGGCGGCTACAGCTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTG GCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGC CTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAAGTCA GGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCTTACAGTCC TCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAAC ACCAAGGTGGACAAGAGAGTTGAGCCCCAAATCTTGT
PN ENCODING SEQ.ID.NO: 262	266 AGCTACGTGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCAAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTTACGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCATG GACGAGGCCGACTACTACTGCGCCACCTACGACAGCAGCCCCAGAACC GAGGTGTTTCGGAGGCGGAACAAAGTTAACCGTCTAGGTCAGCCCAAG GCTGCCCCCTCGGTCACTCTGTTCCTCGCCCTCCTCTGAGGAGCTTCAA GCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGA GCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGA
	GTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCC AGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCACAGAAGC TACAGCTGCCAGGTACGCATGAAGGGAGCACCGTGAGAGAAGACAGTG GCCCCTACAGAATGTTCA
NVS965-S	
CDRH1	267/395 SYAIS (Kabat)/ GGTFSSY (Chothia)
CDRH2	268/396 RIIPIFGTANYAQKFQG (Kabat)/ IPIFGT (Chothia)
CDRH3	269/397 HGGYSFDS (Kabat)/ HGGYSFDS (Chothia)
CDRL1	270/398 SGDNLGSKYVD (Kabat)/ DNLGSKY (Chothia)

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NVS965-S	
CDRL2	271/399 SDNNRPS (Kabat)/ SDN (Chothia)
CDRL3	272/400 ATYDSSPRTE (Kabat)/ YDSSPRTE (Chothia)
VH	273 EVQLVQSGAEVKKPGSSVKVSCASGGTFSSYAI SWVRQAPGQGLEWM GRI IPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC ARHGGYSFDSWGQGT LVTVSS
VL	274 SYVLTQPPSVSVAPGKTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGI PERFSGSNSGNTATLTISGTQAMDEADYYCATYDSSPRT EVFGGGTKLTVL
HEAVY CHAIN	275 EVQLVQSGAEVKKPGSSVKVSCASGGTFSSYAI SWVRQAPGQGLEWM GRI IPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC ARHGGYSFDSWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSS LGTOTYICNVNHKPSNTKVDKRVEPKSC
LIGHT CHAIN	276 SYVLTQPPSVSVAPGKTARISCSGDNLGSKYVDWYQQKPGQAPVLVIY SDNNRPSGI PERFSGSNSGNTATLTISGTQAMDEADYYCATYDSSPRT EVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPG AVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRS YSCQVTHEGSTVEKTVAPTECS
PN ENCODING SEQ.ID.NO: 273	277 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCTTGCAAGGCCAGCGGCGGCACCTTCAGCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGGCACGGCGGCTACAGCTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCA
PN ENCODING SEQ.ID.NO: 274	278 AGCTACGTGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCAAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTACGCGGCAGC AACAGCGGCAATAACCGCCACCCTGACCATCAGCGGCACCCAGGCCATG GACGAGGCCGACTACTACTGCGCCACCTACGACAGCAGCCCCAGAACC GAGGTGTTTCGAGGCGGAACAAAGTTAACCGTCCCTA
PN ENCODING	279

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NVS965-S	
5 10 15 20 25 30 35	SEQ.ID.NO:275 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAAGTGAAGAAACCCGGCAGC AGCGTGAAGGTGTCCTGCAAGGCCAGCGGCGGCACCTTCAGCAGCTAC GCCATCAGCTGGGTGCGCCAGGCTCCTGGACAGGGCCTGGAATGGATG GGCCGGATCATCCCCATCTTCGGCACCGCCAACTACGCCCAGAAATTC CAGGGCAGAGTGACCATCACCGCCGACGAGAGCACCAGCACCGCCCTAC ATGGAAGTGAAGCAGCCTGAGAAGCGAGGACACCGCCGTGTACTACTGT GCCCCGCACGGCGGCTACAGCTTCGATAGCTGGGGCCAGGGCACCCCTG GTGACCGTGAGCTCAGCCTCCACCAAGGGTCCATCGGTCTTCCCCCTG GCACCCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGC CTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAAGTCA GGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCTTACAGTCC TCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGC TTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAAGCCCAGCAAC ACCAAGGTGGACAAGAGAGTTGAGCCCCAAATCTTGT
20 25 30 35	PN ENCODING SEQ.ID.NO: 280 276 AGCTACGTGCTGACTCAGCCCCCTTCTGTGTCTGTGGCCCCCTGGCAAG ACCGCCAGAATCAGCTGCAGCGGCGACAACCTGGGCAGCAAATACGTG GACTGGTATCAGCAGAAGCCCGGCCAGGCTCCCGTGCTGGTGATCTAC AGCGACAACAACCGGCCAGCGGCATCCCTGAGCGGTTTACGCGGCAGC AACAGCGGCAATACCGCCACCCTGACCATCAGCGGCACCCAGGCCATG GACGAGGCCGACTACTACTGCGCCACCTACGACAGCAGCCCCAGAACC GAGGTGTTTCGGAGGCGGAACAAAGTTAACCGTCTCTAGGTCTAGCCCCAAG GCTGCCCCCTCGGTCACTCTGTTCCTCGCCCTCCTCTGAGGAGCTTCAA GCCAACAAGGCCACACTGGTGTGTCTCATAAGTGAAGTCTTACCCGGGA GCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGA GTGGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGGCC AGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCACAGAAGC TACAGCTGCCAGGTACGCATGAAGGGAGCACCGTGGAGAAGACAGTG GCCCCTACAGAATGTTCA
40 45	Human Factor P NP_ 401 001138724.1 PVLCFTQYEESSGKCKGLLGGSVVEDCCLNTAFAYQKRSGGLCQPCR SPRWSLWSTWAPCSVTCSEGSQLRYRRCVGNWNGQCSGKVAPGTLEWQL QACEDQCCPEMGGWSGWGPWEPCSVTCSKGTRTRRRACNHPAPKCGG HCPGQAQESEACDTQQVCPTHGAWATWGPWTPCSASCHGGPHEPKETR SRKCSAPEPSQKPPGKPCPLAYEQRRCTGLPPCPVAGGWGPWGPVSP CPVTCGLGQTMEQRTCNHPVPQHGGPFCAGDATRTHICNTAVPCPVDG EWDSWGWEWSPCIRNMKSI SCQEIPGQQSRGRTCRGRKFDGHRACAGQQ QDIRHCYSIQHCPLKGSWSEWSTWGLCMPPCGPNPTRARQRLCTPLLP KYPPTVSMVEGQGEKNVTFWGRPLPRCEELQGQKLVEEKRPLHVPAC CKDPEEEEL

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NVS965-S	
5 Chimpanzee Factor P XP_ 001136665.1	402 MITEGAQAPCLLLPPLLLLLLTLPATGSDPVLCTQYEESSGKCKGLLG GGVSVKDCCLNNTAYAYQERNGLGCQPCRSRWSLWSTWAPCSVTCSEG SQLRYRRCVGNWQCSE ~~R~~ VALGTLEWQLQACEDKQCCPEMGGWSDWGP WEPCSVTCSKGMRRRRAC ~~N~~ HAPKCGGHCPGEAQESEAEDTQQVCPT 10 HGAWAAGWPWSPCSGSGHGGPHEPKETRSTCSAPEPSQKPPGKPCPG PAYEHRKCTGLPPCPVAGGWGPWGPVSPCVTCGLGQTIERRTCNRPV PQHGGPSCAGDATRTHICNTA ~~A~~ PCPVDGEWDLWGQWSTCVRRNMKSIS CEEIPGQQSRWRTCKGRKFDGHRCTGQQQDIRHCYSIQHCPLKGSWSE 15 WSTWGLCMPPCGPNPTRARQRLCTPLLPKYPPTVSMVEGQGEKNVTFW GRPLPRCEELQGQKLVEEKRPCLVHPACKDPEEEKL
20 Rat Factor P NP_ 001100227.1	403 MPVGMQAPQWLLLLLLILPTTGSDDPVLCTQYEEPSGRCKGLLGRDIR VEDCCLNNTAYAFQEHGGLGCQSCRSPQWSAWSSWGPCSVCSEGSQLR HRRCVGRGGQCSEKAAPGTLEWQLQACEDQLCCPEMGGWSEWGPWGPC SVTCSKGTQTRQRLCDNPAPKCGGHCPGEAQSSQACDTQKICPTHGAW
25	ASWGPWSACSGSCLGGAQEPKETRSRSCSAPAPSHQPPGKPCSGTAYE HRGCSGLPPCPVAGGWGPWGPSSPCPVTCGLGQTLERRTCDHPVPRHG GPFCAAGDATRKHVCNTAMPVNGEWEAWGKWSHCSRVRMKSISCDEI PGQQSRSRSCGGRKFDGQPCGTGLQDIRHCYDIHNVCVLKGSWSQWSTW GLCTPPCGPNPTRVRQRLCTPLLPKYSPTVSMVEGQGEKNVTFWGI PR PLCEVLQGQKLVEEKRPCLVHPACRDPEEKPP
30 Rabbit Factor P XP_ 002719931.1	404 MPAQAPPLPLLLLPLLLTLPATGADPVVCFTEYDEPSGKCKGLLGGG VSVEHCCLNAAAYAFQEPGSLCHACRSPLWSPWSAWAPCSVTCSEGSQ LRHRCVGGGQGPCSEKAAPGTLQWQLQACEDQPCPEIGWSDWGPWR PCSVTCSKGTQTRQACDRPAPKCGGRCPGEAQESEAEDTKQVCPHGH 35 LWAAWGPWSPCSGSGHGGPQVPKETRSRTCSAPEPSQKPPGKPCSGPA YEEQSCAGLPPCPVAGGWGPWGPVSSCSVTCGLGKTLEKRTCDHPVPQ HGGPFCTGDATRTHICNTAVPCPVNGEWEAWGEWSECSRPRKSISCE EVPQQRRTRVCKGRKFDGQRCAGEYQDIRHCYNIQRCRLKGSWLEWS 40 SWGLCTPPCGPSPTRTRQRLCTALLPKFPPTISLVEGQGEKNVTFWGK PWPQCEQLQGQKLVEEKRPCLVHPACKDPEEKPP
45 Mouse Factor P NP_ 032849.2	405 MPAEMQAPQWLLLLLVILPATGSDPVLCTQYEESSGRCKGLLGRDIR VEDCCLNAAAYAFQEHGGLGCQACRSPOWSAWSLWGPCSVCSEGSQLR HRRCVGRGGQCSENVAPGTLEWQLQACEDQPCPEMGGWSEWGPWGPC SVTCSKGTQIRQVCDNPAPKCGGHCPGEAQSSQACDTQKTCPTHGAW ASWGPWSPCSGSLGGAQEPKETRSRSCSAPAPSHQPPGKPCSGPAYE HKACSGLPPCPVAGGWGPWSPLSPCSVTCGLGQTLQRTCDHPAPRHG 50 GPFCAAGDATRNQMCNKAVPCPVNGEWEAWGKWSDCSRLRMSINCEGTP GQQSRSRSCGGRKFNGKPCAGKLQDIRHCYNIHNICIMKGSWSQWSTWS LCTPPCSPNATRVRQRLCTPLLPKYPPTVSMVEGQGEKNVTFWGTFRP LCEALQGQKLVEEKRSCLVHPVCKDPEEKPP
55 TSR5 Domain of SEQ ID NO: 401	406 VDGEWDSWGEWSPCIRRNMKSISCQEIPGQQSRGRTCRGRKFDGHRCAQQQD IRHCYSIQHCP

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NVS965-S		
5	Region B of TSR 5 domain	407 PCIRRNMKISISCQEIPGQQSRGR
	Region of TSR 5 binding domain	408 KSISC
10	TSR5 Domain of mouse SEQ ID NO: 405	409 VNGEWEAWGKWSDCSRLRMSINCEGTPGQQSRSRSCGGRKFNGKPCAGKLQDI RHCYNIHNCI

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Table 2 Examples of C5 Antibodies, Fabs and C5 Proteins

Antibody 8109	Sequence Identifier (SEQ ID NO:)
CDRH1	410 SYAIS
CDRH2	411 GIGPFFGTANYAQKFQG
CDRH3	412 DTPYFDY
CDRL1	413 SGDSIPNYYVY
CDRL2	414 DDSNRPS
CDRL3	415 QSFDSSSLNAEV
VH	416 EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYISWVRQAPGQGLEWMGGIGPFFGTANYAQKFQG RVITADESTSTAYMELSSLRSEDTAVYYCARDTPYFDYWGGGTLTVSS
VL	417 SYELTQPLSVSVLALGQTARITCSGDSIPNYYVYVYQQKPGQAPVLVYDDSNRPSGIPERFSGSNSGN TATLTISRAQAGDEADYYCQSFDSSSLNAEVFGGGTKLTVL
Heavy chain	418 EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYISWVRQAPGQGLEWMGGIGPFFGTANYAQKFQG RVITADESTSTAYMELSSLRSEDTAVYYCARDTPYFDYWGGGTLTVSSASTKGPSVFPLAPSSKST SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVN HKPSNTKVDKRVPEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDITLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKA KGQPREPQVYVTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSPGK

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Antibody 8109	Sequence Identifier (SEQ ID NO:)
Light chain	419 SYELTQPLSVSVALGQTARITCSGDSIPNYYVYQKPGQAPVLVYDDSNRSPGIPERFSGSNSGN TATLTISRAGAGDEADYYCQSFDSLSNAEVFGGKLTVLGQPKAAPSVTLFPPSSEELQANKATLVC LISDFYPGAVTVAWKADSPVKAGVETTTTPSKQSNKNKYAASSYLSLTPEQWKSHRSYSCQVTHEGST VEKTVAPTECS
PN encoding SEQ ID NO:416	420 GAGGTGCAATTGGTTTCAGTCTGGCGCGGAAGTGAAAAAACCGGGCAGCAGCGTGAAAGTGAGCT GCAAAGCCTCCGGAGGCACATTTTTC TTCTTATGCCATTTCTTGGGTGCGCCAAAGCCCTGGGCAG GGTCTCGAGTGGATGGCGGTATCGGTCCGTTTTTTGGCACTGCGAATTACGCGCAGAAGTTTCA GGCCCGGGTGACCA TTACCGCGGATGAAAGCACCAGCAGCCGCGTATATGGAAC TGACGAGCAGCCTG CGTAGCGAAGATACGGCCGTGTA TTA TTGCGCGGTGATACTCC TTA TTTT GATTAT TGGGGGCCA AGGCACCCCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO:417	421 TCCTATGAACTCACACAGCCCCCTGAGCGTGAGCGTGGCCCTGGGCCAGACCCCGGATCACCT GCTCCGGCGACAGCATCCCCAACTACTACGTGTA CTGGTACCAGCAGAA GCCCGGCCAGGCCCC CGTGCTGGTGATCTACGACGACAGCAACCGGCCAGCGGCATCCCCGAGCGGTTTCAGCGGCAG CAACAGCGGCAACACCGCCACCCTGACCATTCCAGAGCACAGGCGGCGACGAGGCCGACTA CTACTGCCAGAGCTTCGACAGCAGCCTGAACGCCGAGGTGTTGCGCGGAGGACCAAGTTAACCC GTCCTA

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Antibody 8109 PN encoding SEQ ID NO:418	Sequence Identifier (SEQ ID NO:)
	422 GAGGTGCAATTGGTTCAAGTCTGGCGCGAAGTGAATAAACCAGGCGAGCAGCGTGAAAGTGAGCT GCAAAGCCCTCCGGAGGCACCTTTTCTTATGCCATTTCTGGGTGCGCAAGCCCTGGGCAG GGTCTGAGTGGATGGCGGTATCGGTCCGTTTTTGGCACTGCGAATTACGGCAGAAAGTTTCA GGCCCGGGTGACCAATTACCGCGGATGAAAGCACCAGCAGCCGATATGAACTGAGCAGCCTG CGTAGCGAAGATACGGCCGTGATTATTGCGCGGTGATACTCCTATTTTATTATTTGGGGCCA AGCACCCCTGGTACGGTTAGCTCAGCCTCACCAGGGTCCATCGGTCTTCCCCCTGGCACCC TCCTCAAAGAGCACCTCTGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCG AACCGGTACGGTGTGCGGAACTCAGGCGCCCTGACAGCGCGGTGCACACCTTCCCGGCTG TCCTACAGTCCCTCAGGACTCTACTCCTCAGCAGCGGTGACCGTGCCCTCCAGCAGCTTGGG CACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGCAACACCAAGGTGGACAAGAGAGTT GAGCCCAAATCTTGACAAAACCTACACATGCCACCCGTGCCAGCACCTGAAGCAGCGGGGG GACCGTCAGTCTTCTCTTCCCGCCAAAACCAAGGACACCTCATGATCTCCCGGACCCCTGAG GTCACATGCGTGGTGGAGCTGAGCCACGAGACCCCTGAGGTCAAGTTCAACTGGTACGTGG ACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCCGGGAGGAGCAGTACAACAGCACGTACC GGGTGGTCAAGCTCCTCAGCGTCTGACCCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAA GGTCTCCAAACAAAGCCCTCCAGCGCCCTCATCGAATAACCATCTCCAAAGCCAAAGGGCAGCCC CGAGAACCCACAGGTGTACACCCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCCAGGTACGCC TGACCTGCCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCA GCCGGAGAACAACTACAAGACCAACGCTCCCGTGTGACTCCGACGGCTCTTCTTCTCTTAC AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGCTTCTCATGCTCCGTGATGC ATGAGGCTCTGCACAACCACTACACGCAAGAGCCCTCTCCCTGTCTCCGGGTAAA

(continued)

Antibody 8109	Sequence Identifier (SEQ ID NO:)
PN encoding SEQ ID NO:419	423 TCCTATGAACTCACACAGCCCCCTGAGCGTGAGCGTGCCCTGGCCAGACCCCGGATCACCT GCTCCGGCGACAGCATCCCCAACTACTACGTGTACTGGTACCAGCAGAAAGCCCGGCCAGGCCCC CGTGTGGTGATCTACGACGACAGCAACCGGGCCAGCGGCATCCCCGAGCGGTTTCAGCGGCAG CAACAGCGGCAACACCCGCCACCCTGACCATTTCAGAGCACAGGCAGGCACGAGGCCGACTA CTACTGCCAGAGCTTCGACAGCAGCCTGAACGCCGAGGTGTTCCGGCGAGGACCAAGTTAACC GTCCTAGGTCAGCCCCAAGGTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTC AAGCCAAAGGCCACACTGGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGC CTGGAAGGCAGATAGCAGCCCCGTCAAGCGGGAGTGGAGACCAACACCCCTCCAAACAAAG CAACAACAAGTACGGGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCACAGA AGCTACAGCTGCCAGGTACGCGATGAAGGAGACCCGTGGAGAGACAGTGGCCCTACAGAAT GTTCA

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Antibody 8109 Optimized PN encoding SEQ ID NO:418	Sequence Identifier (SEQ ID NO:)
	424 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAGAACCCGGTAGCAGCGTCAAGGTGTCC TGCAAGGCCAGCGCGGCACCTTCAGCAGCTACGCCATCAGTGGTGCAGGAGGCCCCAGGC CAGGCCCTGGAGTGGATGGGCGGCATCGGCCATTCTTGGCACCGCCAACTACGCCCCAGAAG TTCAGGGCAGGGTCACCATCACCGCCGACAGAGACACAGCACCCCTACTATGGAGCTGTCCA GCCTGAGAAGCGAGGACACCGCCGTGTACTACTGCGCCAGAGACACCCCTACTTCGACTACTG GGCCAGGGCACCCCTGGTACCGTGAGCAGCGCTAGCACAGGGCCCCAGCGTGTCCCCCT GGCCCCAGCAGCAAGACACCTCCGGCGGCACAGCCGCCCTGGGCTGCCGTGGTGAAGGACTA CTTCCCGAGCCCGTGACCGTGTCTTGGAAACAGCGGAGCCCTGACCGCGGTGCACACCTT CCCCCGCTGTCAGAGACGCGGCCTGTACAGCCTGTCCAGCGTGGTGACAGTGGCCAGCAG CAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCAAGCCAGCAACACCAAGGTGGAC AAGAGAGTGGAGCCCAAGAGCTGCGACAAGACCCACACCTGCCCCCTGCCAGCCCCCGAA GCTGCAGGGGCCCTTCCGTGTTCCGTGTTCCCGCCCAAGCCCAAGGACACCCCTGATGATCAGCA GGACCCCGAGGTGACCTGCGTGGTGGTGACGTGAGCCACGACCAAGCCCAAGGAGGAGTACA ACTGGTACGTGGACGGCGTGAGGTGCACAACGCCAAGACCAAGCCCAAGGAGGAGCAGTACA ACAGCACCTACAGGGTGGTGTCCGTGCTGACCGTGTGCACCCAGGACTGGGTGAACGGCAAAGA ATACAAAGTCAAGGTCTCCAAAGGCCCTGCCTGCCCCCATCGAAAAGACCATCAGCAAGGCC AAGGGCCAGCCACGGGAGCCCGAGGTGTACACCCCTGCCCCCTTCTCGGGAGGAGATGACCAAAG AACCAGGTGCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCGAGCGACATCGCCGTGGAGTGGG AGAGCAACGGCCAGCCCGAGAACTACAAAGACCCACCCCGCCAGTGTGGACAGCGACGGCA GCTTCTTCTGTACAGCAAGCTGACCGTGGACAAAGAGGAGGTGGCAGCAGGGCAACGTGTTGAG CTGCAGCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAGAGCCTGAGCCTGTCAACC GGCAAG

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Antibody 8109	Sequence Identifier (SEQ ID NO:)
Optimized PN encoding SEQ ID NO:419	425 AGCTACGAGCTGACCCAGCCCCCTGAGCGTGAGCGTGGCCCTGGCCAGACCCGCGGATCACC TGCAGCGCGACAGCATCCCCAACTACTACGTGTACTGGTATCAGCAGAAGCCCGGCCAGGCC CCGTGCTGGTGATCTACGACGACAGCAACAGGCCCGGCGCATCCCCGAGAGGTTTACGCGGCA GCAACAGCGGCAACACCCGCAACCTGACCATCAGCAGAGCCCGGCGGCGACGAGGCCGACT ACTACTGCCAGAGCTTCGACAGCTCACTGAACGCCGAGGTGTTCCGCGGAGGACCAAGCTGAC CGTGTGGGCCAGCCTAAGGCTGCCCCCAGCGTGACCGTGTCCCCCAGCAGCGGAGGAGCT GCAGGCCAACAAAGCCACCTGGTGTGCCTGATCAGCGACTTCTACCCAGGCGCGGTGACCGTG GCCTGGAAGGCCGACAGACGCCCCGTGAAGGCCGCGTGAGAGCCACACCCCCCAGCAAGCAG AGCAACAAGTACGCCGCCAGCAGCTACCTGAGCCTGACCCCGGAGCGAGTGGAGAGGCCACA GGTCCTACAGCTGCCAGGTGACCCACGAGGGCAGCACCGTGGAAAAAGACCCGTGGCCCCAACCCG AGTGCAGC
Antibody 8110	Sequence Identifier (SEQ ID NO:) and Sequence or comments
CDRH1	426 NYIS
CDRH2	427 IIDPDDSYTEYSPSFQG
CDRH3	428 YEYGGFDI
CDRL1	429 SGDNIGNSYVH
CDRL2	430 KDNDRPS
CDRL3	431 GTYDI ESYV
VH	432 EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVRQMPKGLEWMGIIDPDDSYTEYSPFQGV TISADKSI STAYLQWSSLKASD TAMYCARYEYGGFDI WGGTLVTVSS

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Antibody 8110	Sequence Identifier (SEQ ID NO:) and Sequence or comments
VL	433 SYELTQPPSVVAPGQTARISCGDNIGNSVHWYQKPGQAPVLVIKDNDRPSGIPERFSGNSG NTATLTISGTQAEDEADYYCGTYDIESVVFGGGKLTVL
Heavy chain	434 EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVRQMPGKGLEWMGIIDPDSDSYTEYSPFQGGV TISADKISITAYLQWSSLKASDTAMYYCARYEYGGFDIWGGTLVTVSSASTKGPSVFLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQYICNVNH KPSNTKVDKRVKPEKSCDKTHITCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGGSFFLY SKLTVDKSRWQQGNV/FSCSVMEALHNHYTQKSLSLSPGK
Light chain	435 SYELTQPPSVVAPGQTARISCGDNIGNSVHWYQKPGQAPVLVIKDNDRPSGIPERFSGNSG NTATLTISGTQAEDEADYYCGTYDIESVVFGGGKLTVLGPKAAPSVTLPSPSEELQANKATLVCLIS DFYPGAVTVAWKADSSPVKAGVETTTPSKQSNKYYASSYLSLTPEQWKSHRYSYSCQVTHEGSTE KTVAPTECS
PN encoding SEQ ID NO:432	436 GAGGTGCAATTGGTTCAGAGCGGCGGGAAGTGAAAAACCGGGCGAAGCCTGAAAAATTAGCT GCAAGGTTCCGGATATTCCTTTACTAATTATATTTCTGGGTGCGCCAGATGCTGGGAAGGGT CTCGAGTGGATGGCATTATTGATCCTGATGATTCTTATACTAGTATTCTCCTCTTTTCAGGGT CAGGTACCATTAGCGCGGATAAAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGC GAGCGATACGGCCATGATTATTGCGCGGCTTATGAGTATGGTGGTTTTGATATTTGGGGCCCAAG GCACCCCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO:434	437 AGTTACGAACTGACCCAGCGCCCTTCAAGTACGCGTTGCACCAGGTGACACCGCGCGTATCTCGT GTAGCGGCGATAATATTGGTAATTCTTATGTTCAATGGTACCAGCAGAAACCCGGGCGGCGCCA GTTCTTGATTTATAAGGATAATGATCGTCCCTCAGGCATCCCGAACGCTTTAGCGGATCCCAAC AGCGGCAACACCGCGACCCCTGACCATTAGCGGCACTCAGCGGAAAGACGAGGATTTATTATT GCGGTACTTATGATATTGAGTCTTATGTGTTTGGCGGCGCACGAAGTTAACCGTCCTA

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Antibody 8110	Sequence Identifier (SEQ ID NO:) and Sequence or comments
PN encoding SEQ ID	438
NO:435	GAGGTGCAATTGGTTTCAGAGCGGCGGGAAGTGAATAAACCGGGGAAAGCCTGAAAATTAGCT GCAAAGGTTCCGGATATTCCTTACTAATTATATTTCTTGGTGCGCCAGATGCCTGGGAAGGGT CTCGAGTGGATGGGCAATTATTGATCCTGATGATTCCTTATACTAGTATTCTCCTCTTTTCAGGGT CAGGTACCAATTAGCGCGGATAAAAGCAATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGC GAGCGATACGGCCATGATATTATTGCGCGCTTATGAGTATGGTGGTTTGATATTTGGGGCCAAAG GCACCTGGTGACGGTTAGCTCAGCCTCCACCAAGGTCCA TCGGTCTTCCCCCTGGCACCCCTC CTCCAAGAGCACCTCTGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAA CCGGTGACGGTGTCGTGGAACCTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTC CTACAGTCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCA CCCAGACCTACATCTGCAACGTGAATCACAAGCCCCAGCAACACCAAGGTGGACAAGAGATTGA GCCCAAATCTTGTGACAAAACCTCACACATGCCACCCGTGCCCCAGCACCTGAAGCAGCGGGGGA CCGTCACTCTTCTCTTCCCCCAAAACCCAAAGGACACCTCATGATCTCCCGGACCCCTGAGGT CACATGCGTGGTGGACGTGAGCCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGGAC GGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGAGGAGCAGTACAACAGCACGTACCCG GTGGTCAGCGTCTCACCCTCCTGCACCAAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGG TCTCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCG AGAACCAAGGTGTACACCTGCCCCCATCCCCGGGAGGAGATGACCAAGAACCAGGTACGCTG ACCTGCCCTGGTCAAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGC CGGAGAACAACTACAAGACCAACGCTCCCGTGGTGGACTCCGACGGCTCCTTCTCCTCTACAG CAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGGAACGCTTCTCATGCTCCCGTGATGCAT GAGGCTCTGCACAACCACTACACGCAGAAAGAGCCTCTCCCTGTCTCCGGGTAAA

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Antibody 8110	Sequence Identifier (SEQ ID NO:) and Sequence or comments
PN encoding SEQ ID NO:436	439 AGTTACGAAGTACCCAGCCGCTTCAGTGAGCGTTGCACCAAGTCAAGCCGCGTATCTCGT GTAGCGGCGATAATATTGGTAATCTTATGTTTATTGTTACAGCAGAAACCCGGGCGGCGCA GTTCTTGTGATTTAAGGATAATGATCGTCCCTCAGGCTCCGGAAAGCTTTAGCGGATCCAAAC AGCGGCAACACCCGACCTGACCATTAAGCGGCACTCAGCGGAAAGACGAAAGCGGATTAATT GCGGTACTTATGATAATTGAGTCTTATGTGTTTGGCGGCGACGAAGTTAACCGTCTAGGTGAG CCCAAGGCTGCCCCCTGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCCAACAAGG CCACACTGGTGTCTCATAAAGTGAATCTTACCCGGAGCCGTGACAGTGGCCTGGAAGGCAGA TAGCAGCCCCGTCAAGCGGGAGTGGAGACCACACACCTCCAAACAAAGCAACAAGTAC GCGGCCAGCAGCTATCTGAGCCTGACGCTGAGCAGTGAAGTCCACAGAAAGTACAGCTGCC AGGTACGCATGAAGGAGCACCCGTGGAGAAGACAGTGGCCCTACAGAATGTTCA
Optimized PN encoding SEQ ID NO:434	440 GAGGTGAGCTGGTGCAGAGCGGAGCCGAGGTGAAAAAGCCCGTGAGAGCCTGAAGATCAGC TGCAAGGGCAGCGGCTACAGCTTACCAACTACATCAGCTGGTGCGGAGATGCCCGGCAAG GGCCTGGAGTGGATGGGCATCATGACCCCGACGACAGTACACCGAGTACAGCCCCAGCTTCC AGGCCAGGTGACCATCAGCGCCGACAAGAGCATCAGCACCGCTACCTGCAAGTGGAGCAGCC TGAAGGCCAGCGACACCCCATGTACTGCGCCAGATACGAGTACGGCGGCTTCGACATCTG GGGCCAGGGCACCCCTGGTACCCTGAGCTCAGTACAGTACCAAGGGCCCCAGCGTGTCCCGCT GGCCCCCAGCAGCAAGAGCACCTCCGGCGGCACAGCCCGCTGGGCTGCCCTGGTGAAGGACTA CTTCCCGAGCCGTGACCGTGTCTGGAACAGCGAGCGGCCCTGACCGCGGTGCACACCTT CCCCCTGCTGTCAGAGCAGCGGCTGTACAGCCTGTCCAGCGTGTGACAGTGGCCAGCAG CAGCCTGGCACCCAGACCTTACATCTGCAACGTGAACCCACAAAGCCCAAGCAACCAAGGTGGAC AAGAGAGTGGAGCCCAAGAGCTGCGACAAGACCCACACCTGCCCGCTGCCAGCCCCCGAA GCTGCAGGGCGGCTTCCGTGTTCTGTTCCCGCCCCAAGCCCCAAGGACACCTGATGATCAGCA GGACCCCGAGGTGACCTGCGTGGTGGTGGAGCTGAGCCACGAGACCCAGAGGTGAAGTTCA ACTGGTACGTGGACCGGTGGAGGTGCACAACGCCAAGACCAAGCCCAAGAGAGGAGCAGTACA ACAGCACCTACAGGGTGTCCGTGCTGACCGTGTGCACCGAGGACTGGCTGAACGGCAAGA ATACAAAGTCAAGGTCTCCAAACAAGGCCCTGCTGCCCGCCATCGAAAAGACCATCAGCAAGGCC AAGGGCCAGCCACGGGAGCCCCAGGTGTACACCTGCCCGCTTCTCGGGAGGAGATGACCAAG AACCAGGTGCTCCTGACCTGTCTGTTGAAGGGCTTCTACCCCGAGCGACATGCCCGTGGAGTGGG

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Antibody 8110	Sequence Identifier (SEQ ID NO:) and Sequence or comments
	AGAGCAACGGCCAGCCCGAGAACAACTACAAAGACACCCCGCCAGTCTGGACAGCGGCA GCTTCTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGGTGGCAGCAGGGCAACGTTTCAG CTGACGGTGTATGCACGAGGGCCCTGCACAACCACTACACCCAGAGGCCTGAGCCTGTCACCC GGCAAG
Optimized PN encoding SEQ ID NO:435	441 AGCTACGAGCTGACCCAGCCCCCAGCGTGAGCGTGCGCCAGGCCAGCCGCGGATCAGC TGCAGCGCGACAAACATCGGCAACAGCTACGTGCACTGGTATCAGCAGAAAGCCCGCCAGGCC CCCGTGCTGTGATCTACAAGGACAAACAGACAGGCCCAAGCGCATCCCCAGAGGTTCAAGCGGC AGCAACTCCGGCAACACCGCCACCCCTGACCATCAGCGGCACCCAGGCCGAGGACGAGGCCGAC TACTACTGCGGCACCTACGACATCGAGTCATACGTGTTCCGCGGAGGACCAAGCTGACCGTGC TGGCCAGCCTAAGGCTGCCCCCAGCGTGACCCCTGTTCCCCCCCCAGCAGCAGGAGCTGCAGG CCAACAAGGCCACCCCTGGTGTGCTGTATCAGCGACTTCTACCCAGGCGCCGTGACCGTGGCCTG GAAGGCCGACAGCAGCCCCGTGAAGGCCGCGTGGAGACCACCCACCCAGCAAGCAGAGCAA CAACAAGTACGCCCGCAGCAGCTACCTGAGCCTGACCCCGCAGCAGTGGAAGAGCCACAGGTC CTACAGCTGCCAGGTGACCCACGAGGGCAGCACCGTGAAAAAGACCCGTGGCCCCCAACCGAGTG CAGC
Antibody 8111	Sequence Identifier (SEQ ID NO:) and Sequence or comments
CDRH1	442 TSGGGVS
CDRH2	443 NIDDADIKDYSPSLKS
CDRH3	444 GPYGFDS
CDRL1	445 TGTSSDIGTYNYVS
CDRL2	446 DDSNRPS
CDRL3	447 QSYDSQSIV

(continued)		Sequence Identifier (SEQ ID NO:) and Sequence or comments
Antibody 8111		
VH	448	EVTLKESGPALVKPTQTLTLTCTFSGFSLSTSGGGVSWIRPPGKALEWLANIDDADIKDYSPSLKSRL TISKDTSKNQVVLMTNMDPVDATYYCARGPYGFDSWGQGLVTYSS
VL	449	ESALTQPASVSGSPGQSITISCTGTSSDIGTYNYVSWYQQHPGKAPKLMYDDSNRPSGVSNRFGSK SGNTASLTISGLQAEDEADYYCQSYDSQSIVFGGGTKLTVL
Heavy chain	450	EVTLKESGPALVKPTQTLTLTCTFSGFSLSTSGGGVSWIRPPGKALEWLANIDDADIKDYSPSLKSRL TISKDTSKNQVVLMTNMDPVDATYYCARGPYGFDSWGQGLVTYSSASTKGPSVFPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQTYICNVNH KPSNTKVDKRVPEPKSCDKTHITCPPCPAPEAAGGPSVFLFPPKPKDITLMISRTPEVTCVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFCFSCVMHEALHNHYTQKSLSLSPGK
Light chain	451	ESALTQPASVSGSPGQSITISCTGTSSDIGTYNYVSWYQQHPGKAPKLMYDDSNRPSGVSNRFGSK SGNTASLTISGLQAEDEADYYCQSYDSQSIVFGGGTKLTVLGGPKAAPSVTLFPPSSEELQANKATLV CLISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNKNKYAASSYLSTPEQWKSHRSYSCQVTHEGS TVEKTVAPTECS
PN encoding SEQ ID	452	GAGGTGACATTGAAAGAAAGCGGCCCGGCCCTGGTGAAACCGACCCAAACCCCTGACCCTGACCT GTACCTTTCCGGATTAGCCTGTCTACTTCTGGTGGTGTGTCTGGATTGCCAGCCGCGCT GGGAAAGCCCTCGAGTGGCTGCTAATAATTGATGCTGATGCTGATTAAGGATTAATCTCCTTCTCTT AAGTCTCGTCTGACCATTAGCAAAAGATACCTCGAAAAATCAGGTGGTCTGACTATGACCAACATG GACCCGGTGGATACGGCCACCTATTATTGCGCGCGTGGTCTTATGTTTTGATTTTGGGGGCA AGGCACCCCTGGTGACGGTTAGCTCA
NO:448		

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Antibody 8111	Sequence Identifier (SEQ ID NO:) and Sequence or comments
PN encoding SEQ ID NO:449	453 GAAAGCGCACTGACCCAGCCAGCTTCAGTGAGCGGGCTACCAGGTCAGAGCAATTACCATCTCGT GTACGGGTACTAGCAGCGATATTGGTACTTATAATTATGTCTTGGTACGAGCATCCCGGG AAGGCGCGAACTTATGATTATGATGATTCTAATGTCCTCAGGCGTGAGCAACCGTTTATAGC GGATCCAAAAGCGGCAACACCGCGAGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCG GATTATTGCCAGTCTTATGATTCTCAGTCTATTGTGTTGGCGGCGACGAAGTTAACCGTC CTA
PN encoding SEQ ID NO:450	454 GAGGTGACATTGAAAGAAAGCGGCCCGCCCTGGTGAAACCGACCCAAACCCCTGACCCCT GTACCTTTTCCGGATTTAGCCTGTCTACTTCTGGTGGTGTGCTTGGATTGCGCCAGCCGCCT GGGAAAGCCCTCGAGTGGCTGGCTAATATTGATGATGCTGATATTAGGATTATTCTCTCTCTT AAGTCTCGTCTGACCATTAGCAAAAGATACTTCGAAAAATCAGGTGGTGTGACTATGACCAACATG GACCCGGTGGATACGGCCACCTATTATTGCGCGCGTGGTCTTATGGTTTTGATTCTTGGGGCCA AGGACCCCTGGTGACGGTTAGTCAAGCTCCACCAAGGTTCCATCGGTCTTCCCCCTGGCACCC TCCTCAAAGAGCACCTCTGGGGCACAGCGGCCCTGGGCTGCCTGCTCAAGGACTACTTCCCCCG AACCGGTACGGTGTGGAACCTCAGGCGCCCTGACAGCGGCGTGCACACCTTCCCGGCTG TCCTACAGTCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGG CACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAAGCAACCAAGGTGGACAAGAGATT GAGCCCAAATCTTGTGACAAAACCTACACATGCCACCGTGCCCCAGCACCTGAAGCAGCGGGG GACCGTCAGTCTTCTCTTCCCCCAAAACCAAGGACACCTCATGATCTCCCGGACCCCTGAG GTCACATGCGTGGTGGACGTGAGCCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTGG ACGCGTGGAGGTGCATAATGCCAAGACAAAAGCGCGGGAGGAGAGTACAACAGCACGTACC GGGTGGTCAGCGTCTACCGTCTCTGCAACGAGTGGCTGAATGGCAAGGAGTACAAGTGCAA GGTTCTCAAACAAAAGCCCTCCAGCCCCCATCGAGAAAACCATCTCAAAGCCAAAGGGCAGCCC CGAGAACCACAGGTGTACACCTGCCCCCATCCCCGGGAGGAGATGACCAAGAACCAGGTCAGCC TGACCTGCCTGGTCAAAAGCTTCTATCCCAAGCAGCATCGCCGTGGAGTGGGAGAGCAATGGGCA GCCGGAGAACAACCTACAAGACCAACCGCTCCCGTGTGGACTCCGACGGCTCTTCTCTCTCTAC AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGCTTCTCATGCTCCCGTGATGC ATGAGGCTCTGCACAACCACTACACGCAAGAGCCTCTCCCTGTCTCCGGGTAA

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Antibody 8111	Sequence Identifier (SEQ ID NO:) and Sequence or comments
PN encoding SEQ ID NO:451	455 GAAAGCGCACTGACCCAGCCAGCTTCAGTGAGCGGCTCACAGGTGAGCATTACCATCTCGT GTACGGGTACTAGCAGCGGATTTGGTACTTATAATTATGTCTTGGTACCAGCAGCATCCCGGG AAGCGCCGAACTTATGATTTATGATGATTCTAATCGTCCCTCAGGCGTGAGCAACCGTTTAGC GGATCCAAAAGCGGCAACACCGCAGCCTGACCATTAGCGGCCCTGCAAGCGGAAGACGAAGCG GATTATTGCCAGTCTTATGATTCTCAGTCTATTGTGTTTGGCGGCGCACGAAAGTTAACCGTC CTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAG CCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTG GAAGGCAGATAGCAGCCCCGTCAAGCGGGAGTGGAGACCACACACCCCTCCAAACAAAGCAAC AACAAGTAGCGGGCCAGCAGCTATCTAGCCTGACGCCCTGAGCAGTGGAAAGTCCACACAGAAGCT ACAGCTGCCAGGTCACGCATGAAGGGAGCACCCGTGGAGAAACAGAGTGGCCCCCTACAGAAATGTTCA A
Optimized PN encoding SEQ ID NO:448	456 GAGGTGACCCCTGAAGGAGAGCGGGCCAGCCCTGGTGAAGCCCAACCCAGACCCCTGACCCCTGACT TGCACCTTCAGCGGCTTCAGCCTGAGCACCGGAGGGGGCGGTGAGCTGGATCAGGCAGCCCC CCAGGTAAGGCCCTGGAGTGGCTGGCCCAATATCGACGACGCCCGATATCAAGGACTACAGCCCCCA

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Antibody 8111	Sequence Identifier (SEQ ID NO:) and Sequence or comments
	GCCTGAAGAGCAGGCTGACCATCAGCAAGGACACAGCAAGAACCCAGGTGGTGTGACCATGAC CAATATGGACCCCGTGGACACCGCCACCTACTACTGCGCCAGAGGCCCTACGGCTTCGACAGC TGGGCCAGGGCACCCCTGGTGACCGTCAGCTCAGCTAGCAGCAAGGGCCCCCAGCGTGTCCCC CTGGCCCCCAGCAGCAAGAGACACCTCCGGCGGCACAGCCGCCCTGGGCTGCCCTGGTGAAGGAC TACTTCCCCGAGCCCCGTGACCGTGTCTGTGAACAGCGGAGCCCTGACAGCGCGCTGCACACCT TCCCCGCCGTGCTGCAGAGCAGCGGCCCTGTACAGCCTGTCCAGCGTGGTGACAGTGCCCCAGCA GCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCCACAAGCCCCAGCAACACCAAGGTGGA CAAGAGGTGGAGCCCAAGAGCTGCGACAAGACCCACACCTGCCCCCCTGCCAGCCCCCGA AGCTGCAGGGCGGCCCTTCCGTGTTCCCTGTTCCCCCAGCCCAAGGACACCCCTGATGATCAGC AGGACCCCGAGGTGACCTGCGTGGTGGTGGACGTGAGCCACGAGGACCCAGAGGTGAAGTTC AACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCCAAGAGGAGGAGCAGTAC AACAGCACCTACAGGGTGGTGCCGTGCTGACCGTGTGCACCCAGGACTGGCTGAACGGCAAAG AATACAAGTGCAAGGTCTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATCAGCAAGGC CAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCCTGCCCCCTTCTCGGGAGGAGATGACCAA GAACCAAGGTGCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCCAGCGACATCGCCGTGGAGTGG GAGAGCAACGGCCAGCCCGAGAACAACTACAAGACACCCCCCAGTGTGGACAGCGACCGGC AGCTTCTTCTGTACAGCAAGCTGACCCGTGGACAGAGCAGGTGGCAGGGCAACCGTGTTC GCTGCAGCGTGTGACAGAGGGCCCTGCACAACCCACTACACCCAGAGAGCCCTGAGCCCTGTCACC CGGCAAG

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Antibody 8111	Sequence Identifier (SEQ ID NO:) and Sequence or comments
Optimized PN encoding SEQ ID NO:449	457 GAGAGCGCCCTGACCCAGCCCGCAGCGTGAGCGGCAGGCCAGGCGCTATCACAATCAGC TGCACCGGCACCTCCAGCGATATCGGCACCTACAACCTACGTAGCTGGTATCAGCAGCACCCCG GCAAGGCCCCCAAGCTGATGATCTACGACGACGACAACAGGCCGCGTGAGCAACAGGTT CAGCGGACGCAAGAGCGGCAACACCCGACCTGACAATCAGCGGCTGCAGGCCGAGGACGA GGCCGACTACTACTGCCAGAGCTACGACAGCCAGTCAATCGTGTTCGGCGGAGGACCAAGCTG ACCGTGCTGGGCCAGCCTAAGGCTGCCCCCAGCGTGACCTGTTCCTCCCGCAGCAGCGAGGAG CTGACGGCCAAAGGCCACCCCTGGTGTGCCTGATCAGCGACTTCTACCCAGGCGCCGTGACCG TGGCCTGGAAGGCCGACAGCAGCCCCCGTGAAGGCCGCGTGAGAGCCACACCCCCAGCAAGC AGAGCAACAACAGTACGCCGCCAGCAGCTACCTGAGCCTGACCCCCGAGCAGTGGAAGAGCCA CAGGTCCTACAGCTGCCAGGTGACCCACAGGCGCAGCACCGTGGAAGAACCGTGCCCCCAAC CGAGTGCAGC
Antibody 8113	Sequence Identifier (SEQ ID NO:) and Sequence or comments
CDRH1	SEQ ID NO:426
CDRH2	458 IDPDDSYTRYSPSFQG
CDRH3	SEQ ID NO:428
CDRL1	SEQ ID NO:429
CDRL2	SEQ ID NO:430
CDRL3	459 ATWGSQV
VH	460 EVQLVQSGAEVKPGESLKISCKGSGYSFTNYISWVRQMPGKGLEWMGIIDPDDSYTRYSPFQGV TISADKSISTAYLQWSSLKASDTAMYYCARYEYGGFDIWGGQTLVTVSS
VL	461 SYELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQKPGQAPVLVIYKNDNRPSGIPERFSGNSG NTATLTISGTQAEDEADYYCATWGSQVFGGGTKLTVL

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Antibody 8113	Sequence Identifier (SEQ ID NO:) and Sequence or comments
Heavy chain	462 EVQLVQSGAEVKKPGESLKISKCKSGYSFTNYSWVRQMPGKGLEWMGIDPDDSYTRYSPSFQGGV TISADKSISTAYLQWSSLKASDTAMYICARYEYGGFDIWGGTLVTVSSASTKGPSVFPPLAPSSKSTS GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSWTVPSSSLGTQTYICNVNH KPSNTKVDKRVKPEKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLY SKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
Light chain	463 SYELTQPPSVVAPGQTARISCSGDNIGNSVHWYQQKPKQAPVLVIYKDNDRPSGIPERFSGNSG NTATLTISGTQAEDEADYYCATWGEDQVFGGGTKLTVLGQPKAAPSVTLPFPSSEELQANKATLVCL ISDFYPGAVTVAWKADSSPVKAGVETTTTPSKQSNKNKYAASSLSLTPEQWKSHRSYSCQVTHEGSTV EKTVAPTES
PN encoding SEQ ID NO:460	464 GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACC GGCGGAAAGCCTGAAAAATTAGCT GCAAAGGTTCCGGATATTCCTTTACTAATTATATTTCTGGGTGCGCCAGATGCCTGGGAAGGGT CTCGAGTGGATGGGATTATCGATCCGGATGATAGCTATACCCGTTATTCCTCGAGCTTTCAGGG ACAGGTGACCATTAGCGCGGATAAAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAG CGAGCGATACGGCCATGTATTATTGCGCGCGTTATGAGTATGGTGGTTTTGATATTTGGGGCCAA GGCACCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO:461	465 AGTTACGAACTGACCCAGCCGCTTCAGTGAGCGTTGCACCAGGTGACACCGCGGTATCTCGT GTAGCGGCGATAATATTGGTAATTCCTTATGTTCA TTGGTACAGCAGAAACCCGGGCGGCGCCA GTTCTTGATTTATAAGGATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAAAC AGCGGCAACACCGCGACCCGTGACCATTAGCGGCACTCAGCGGAAACGAGCGGATTTATTATT GCGCTACTTGGGGTTCTGAGGATCAGGTGTTTGGCGGCGGACGAAAGTTAACCGTCCTA

(continued)

Antibody 8113	Sequence Identifier (SEQ ID NO:) and Sequence or comments
PN encoding SEQ ID NO:462	466 GAGGTGCAATTGGTTTCAGAGCGGCGGAAGTGAAAAACCGGGCGAAAGCCTGAAAAATTAGCT GCAAAGGTTCCGGATATTCTTTACTAATTATATTTCTGGTGCGCCAGATGCCTGGGAAGGGT CTCGAGTGGATGGGCATTATCGATCCGGATAGTAGCTATACCCGTTATTCGCCGAGCTTTCAGGG ACAGGTGACCATAGCGCGGATAAAAGCATTAGCACCGCTATCTTCAATGGAGCAGCCTGAAAG CGAGCGATACGGCCATGTATTATTCGCGCGTTATGAGTATGGTGGTTTGATATTTGGGGCCAA GGCACCTGGTGACGGTTAGCTCAGCCTCCACCAAGGTCATCGGTCTTCCCCCTGGCACCCCT CCTCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGCTGCCTGGTCAAGGACTACTTCCCCG AACCGGTGACGGTGTGGAACCTCAGGCGCCCTGACAGCGCGGTGCACACCTTCCCGGCTG TCCTACAGTCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGG CACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGCAACCAAGGTGGACAAGAGATT GAGCCCAATCTTGTGACAAAACTCACACATGCCACCGTGCCCCAGCACCTGAAGCAGCGGGG GACCGTCAGTCTTCTCTTCCGCCAAAACCCAAAGGACACCTCATGATCTCCCGGACCCCTGAG GTCACATGCGTGGTGACGTGAGCCACGAAGACCTGAGGTCAAGTTCAACTGGTACGTGG ACGGCGTGGAGGTGCATAATGCCAAGACAAAGCGCGGGAGGAGCAGTACAACAGCACGTACC GGGTGGTCAGGTCCTACCGTCTCTGCCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAA GGTCCTCAACAAAGCCCTCCCAGCCCCCATCGAGAAAAACCATCTCAAAAGCCAAAGGGCAGCCC CGAGAACCACAGGTGTACACCTGCCCCCATCCCCGGAGGAGATGACCAAGAACAGGTGACGCC TGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCA GCCGGAGAACAACTACAAGACCAACGCCTCCCGTGTGGACTCCGACGGCTCCTTCTCCTCTAC AGCAAGCTCACCGTGGACAAAGACAGGTGGCAGCAGGGGGAACGTCTTCTCATGCTCCCGTGATGC ATGAGGCTCTGCACAACCACTACACGGAAGAGCCTCTCCCTGTCTCCGGGTAAA
PN encoding SEQ ID NO:463	467 AGTTACGAACTGACCCAGCCGCTTTCAGTGAGCGTTGCACCAGGTGACACCGCGCGTATCTCGT GTAGCGGCGATAATATTGGTAATTCTTATGTTTCA TTGGTACCAGCAGAAACCCGGGCGAGCGCCA GTTCTTGTGATTTATAAGGATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAAAC AGCGGCAACACCGCGACCTGACCATTAGCGGCACTCAGGCGGAAGACGAAAGCGGATTATTATT GCGCTACTTGGGGTTCTGAGGATCAGGTGTTTGGCGGCGGCACGAAGTTAACCGTCTCCTAGGTCA

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Antibody 8113	Sequence Identifier (SEQ ID NO:) and Sequence or comments
	GCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAAACAAAG GCCACACTGGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAGGCAG ATAGCAGCCCCGTCAAGGGGGAGTGGAGACCACACACCCTCCAAACAAAGCAACAAGTA CGGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGAAGTCCACAGAAAGCTACAGCTGC CAGGTCACGCATGAAGGGAGCACCCGTGGAGAAGACAGTGGCCCCCTACAGAATGTTCA
Optimized PN encoding SEQ ID NO:462	468 GAGGTGACGCTGGTGACAGCGGAGCCGAGGTGAAAAAGCCCGGTGAGAGCCTGAAGATCAGC TGCAAGGGCAGCGGTACAGCTTCAACCAATACATCAGCTGGGTGCGGAGATGCCCCGGCAAG GGCCTGGAGTGGATGGGCATCATCGACCCCGACAGCATACACAGGTACAGCCCCAGCTTCC AGGCCAGGTGACCATCAGCGCCGACAAGAGCATCAGCACCCCTACCTGCAGTGGAGCAGCC TGAAGGCCAGCAGACCCCATGTACTTGCAGCATACGAGTACGGCGGCTTCGACATCTG GGCCAGGGCACCCCTGGTGACCGTCAGCTCAGCTAGCAGCAAGGCCCCCAGCGTGTTCGCCCT GGCCCCCAGCAGCAAGAGCACCTCCGGCGGCACAGCCGCCCTGGCTGGCTGGTGAAGGACTA CTTCCCCAGCCCGTGACCGTGTCTCTGGAACAGCGGAGCCCTGACCAAGCGCGTGCACACCTT CCCCGCGTGTGCAGAGCAGCGGCTGTACAGCCTGTCCAGCGTGTGACAGTGCACAGTGCACAGCAG CAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCAAGCCCAAGCCAGCAACACCAAGGTGGAC AAGAGTGGAGCCCAAGAGCTGCGACAAGACCAACACACCTGCCGCCCTGCCAGCCCCCGAA GCTGCAGGGCGCCCTTCCGTGTTCCGTGTTCCGCCCAAGCCCAAGGACACCCCTGATGATCAGCA GGACCCCGAGGTGACCTGCGTGGTGGACGTGAGCCACGAGGACCCAGAGGTGAAGTTCA ACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAGACCAAGCCCAAGAGGAGCAGTACA ACAGCACCTACAGGGTGGTCCGTGCTGACCGTGTGCACCCAGGACTGGCTGAACGGCAAAGA ATACAAGTCAAGGTCTCCAAACAGGCCCTGCCTGCCCCCATCGAAAAGACCATCAGCAAGGCC AAGGCCAGCCACGGGAGCCCAAGGTGTACACCTGCCCTTCTCGGGAGGAGATGACCAAG AACCAGGTGTCCTGACCTGTCTGGTGAAGGGCTTCTACCCAGCGACATCGCCGTGGAGTGGG AGAGCAACGGCCAGCCGAGAACAACTACAAGACCCACCCCTGCTGGACAGCGACGGCA GCTTCTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGTGGCAGCAGGGCAACGTGTTTCA CTGCAGCGTGATGCAGGAGGCCCTGCACAACCACTACACCCAGAGAGCCTGAGCCTGTCAACC GGCAAG

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Antibody 8113	Sequence Identifier (SEQ ID NO:) and Sequence or comments
Optimized PN encoding SEQ ID NO:463	469 AGCTACGAGCTGACCCAGCCCCCAGCGTGAGCGTGGCCCCAGGCCAGACCGCCAGGATCAGC TGCAGCGGCGACAATATCGGCAACAGCTACGTGCACTGGTATCAGCAGAAGCCCGCCAGGCCCC CCGTGCTGGTGATCTACAAGGACACGACAGGCCAGCGGCA TCCCCGAGAGGTTTACAGCGGCA GCAACTCCGGCAACACCGCCACCCTGACAAATCAGCGGCACCCAGGCCGAGGACGAGGCCGACT ACTACTGCCCCACCTGGGGCTCAGAGGACCAGGTGTTCCGGCGAGGACCAAGCTGACCGTGC TGGGCCAGCCTAAGGCTGCCCCCAGCGTGACCCCTGTTCCCCCCCAGCAGCGAGGAGCTGCAGG CCAACAAGGCCACCCCTGGTGTGCCTGATCAGCGACTTCTACCCAGGCGCCGTGACCCGTGGCCTG GAAGGCCGACAGCAGCCCCGTGAAGGCCGCGTGGAGACCACCCACCCAGCAAGCAGAGCAA CAACAAGTACGCCGCCAGCAGCTACCTGAGCCTGACCCCCGAGCAGTGGAAGAGAGCCACAGGTC CTACAGCTGCCAGGTGACCCACAGAGGGCAGCACCGTGGAAGAAGACCCGTGGCCCCCAACCCGAGTG CAGC
Antibody 8114	Sequence Identifier (SEQ ID NO:) and Sequence or comments
CDRH1	470 SYIIG
CDRH2	471 IIDPTDSQTAYSPSFQG
CDRH3	472 YMMRGFDH
CDRL1	473 SGDSLGDYYAY
CDRL2	474 KDNNRPS
CDRL3	475 QTWDTGESGV
VH	476 EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYIIGWVRQMPGKGLEWMGIIDPTDSQTAYSPSFQGG VTISADKSIISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSS

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Antibody 8114	Sequence Identifier (SEQ ID NO:) and Sequence or comments
VL	477 SYELTQPPSVAPGQTARISCGDSLGDYYAYWYQQKPGQAPVLIYKDNRRPSGIPERFSGNSG NTATLTISGTQAEDEADYYCQTWDTGESGVFGGGTKLTVL
Heavy chain	478 EVQLVQSGAEVKPGESLKISKCKSGSYFTSYIGWVRQMPGKLEWMGIIDPTDSQTAYSPSFQGG VTISADKSIISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGLTVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNV NHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVLFPPKPKDTLMISRTPEVTCVVVDVSH DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVSVLTVLHQDWLNGKEYCKVSNKALPAIEKTI SKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKLSLSPGK
Light chain	479 SYELTQPPSVAPGQTARISCGDSLGDYYAYWYQQKPGQAPVLIYKDNRRPSGIPERFSGNSG NTATLTISGTQAEDEADYYCQTWDTGESGVFGGGTKLTVLGPKAAPSVTLPFPSSEELQANKATLV CLISDFYPGAVTVAWKADSSPVKAGVETTPPSKQSNKYYASSYLSLTPEQWKSHRYSYSCQVTHEGS TVEKTVAPTECS
PN encoding SEQ ID NO:476	480 GAGGTGCAATTGGTTCAGAGCGGCGGGAAGTGAAAAACCGGGCGAAAGCCTGAAAAATTAGCT GCAAAGGTTCCGGATATTCCTTTACTTCTTATTATTATTGTTGGTGCGCCAGATGCCTGGGAAG GGTCTCGAGTGGATGGGCAATTATGATCCTACTGATTCAGACTGCTTATTCCTCTTTTCAG GGTCAGGTGACCAATTAGCGCGGATAAAAGCATTAGCACCGCTATCTTCAATGGAGCAGCCTGAA AGCGAGCGATACGGCCATGATTATTGCGCGGCTTATGATGCGTGGTTTGATCATTTGGGGCC AAGGCACCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO:478	481 AGTTACGAACTGACCCAGCCGCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGGTATCTCGT GTAGCGGCGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCGGCGCCA GTTCTTGATTTATAAGGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAAC AGCGGCAACACCGGACCCCTGACCAATTAGCGGCACTCAGCGGAGACGAAAGCGGATTATTATT GCCAGACTTGGGATACTGGTGAGTCTGGTGTGTTGGCGGCGGCACGAAAGTTAACCGTCCTA

Antibody 8114	Sequence Identifier (SEQ ID NO:) and Sequence or comments
PN encoding SEQ ID NO:479	482 GAGGTGCAATTGGTTCAGAGCGCGCGGAAGTGAAAAACGGCGAAAGCCTGAAAAATTAGCT GCAAAGGTTCCGGATATCCTTTACTTCTTATTATATTGGTTGGTGGCCAGATGCCTGGGAAG GGTCTGAGTGGATGGCATATTGATCCTACTGATTTCTCAGACTGCTTATTCTCCTCTTTTCAG GGTCAGGTGACCATTAGCGCGGATAAAAGCATTAGCACCCGCTATCTTCAATGGAGCAGCCTGAA AGCGAGGATACGGCCATGTATTATTGCGCGCTTATATGATGCGTGGTTTTTGATCATTTGGGGCC AAGGCACCCTGGTGACGGTTAGCTCAGCTCCACCAAGGTTCCATCGGTCTTCCCCCTGGCACC CTCTCCAAAGAGCACCTCTGGGGGCACAGCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCC GAACGGTGACGGTGTGCGTGAACCTCAGGCGCCCTGACCAGCGGGCGTGCACACCTTCCGGGCT GTCCTACAGTCCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCCCTCCAGCAGCTTGG GCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCGACACACCAAGGTGGACAAGAGAGT TGAGCCCAAAATCTTTGTACAAAACCTCACACATGCCACCGTGCCCCAGCACCTGAAGCAGCGGGG GGACCGTCAGTCTTCCCTCTTCCCCCAAAACCCCAAGGACACCCCTCATGATCTCCCGGACCCCTGA GGTCACATGCGTGGTGGACGTGAGCCACGAAGACCCCTGAGGTCAAGTTCAACTGGTACGTG GACGGCGTGGAGGTGCATAATGCCAAGACAAAAGCCGCGGAGGAGCAGTACAACACGACCGTAC CGGGTGGTCAGCGTCTCACCCTCTGACCCAGGACTGGCTGAA TGGCAAGGAGTACAAGTGCA AGGTCTCCAACAAAGCCCTCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGCGAGCC CCGAGAACCCACAGGTGTACACCCCTGCCCCCATCCCGGAGGAGATGACCAAGAACCCAGGTACGC CTGACCTGCCCTGGTCAAAGGCTTCTATCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC AGCCGGAGAACAACTACAAGACCAACCGCTCCCGTGTCTGGACTCCGACGGCTCTTCTTCTCTA CAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGGAACGCTTCTCATGCTCCGTGATG CATGAGGCTCTGCACAACCACTACACGCAGAAGACGCTCTCCCTGTCTCCGGGGTAA

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Antibody 8114	Sequence Identifier (SEQ ID NO:) and Sequence or comments
PN encoding SEQ ID NO:480	483 AGTTACGAACTGACCCAGCCGCCCTTCAGTGAGCGTTGCACAGGTCAGACCGCGGTATCTCGT GTAGCGGCGATTCTCTGGTGATTATTATGCTTATTGTTACCAGCAGAAACCCGGCAGGCGCCA GTTCTTGATTTATAAGGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAAC AGCGGCAACACCGGACCCCTGACCAATTAGCGGCACTCAGGCGAAGACGAAAGCGGATTATTATT GCCAGACTTGGGATACTGGTGAGTCTGGTGTTTGGCGGCGGCACGAAAGTTAACCGTCCTAGG TCAGCCCAAGGTCGCCCCCTCGGTCACTCTGTCCCGCCCTCCCTCTGAGGAGCTTCAAGCCAAAC AAGGCCACACTGGTGTCTCATAAGTGACTTTACCCGGGAGCCGTGACAGTGGCCTGGAAGG CAGATAGCAGCCCCGTCAAGCGGGAGTGAGAGCCACACACCCCTCCAAACAAAGCAACAACAA GTACGGGGCCAGCAGCTATCTGAGCCTGACGCTGAGCAGTGGAGTCCACAGAAGCTACAGC TGCCAGGTACGCAATGAAGGGAGCACCCGTGGAGAAAGACAGTGGCCCCCTACAGAAATGTTCA

Antibody 8114	Sequence Identifier (SEQ ID NO:) and Sequence or comments
Optimized PN encoding SEQ ID NO:479	484 GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAAAAGCCCGGTGAGAGCCTGAAGATCAGC TGCAAGGGCAGCGCTACAGCTTACCAGCTACTACATCGGCTGGTGCGGCAGATGCCCGGC AAGGGCCTGGAGTGGATGGCATCATCGACCCACCGACAGCCAGCCCTACAGCCCCAGC TTCCAGGGCCAGGTGACCATCAGCGCCGACAAGAGGATCAGCACCGCTACCTGCAGTGGAGCA GCCTGAAGGCCAGCGACACCGCATGTACTACTGCGCCCGGTACATGATGAGGGGCTTCGACCA CTGGGGTCAGGGCACCCCTGGTGACCGTCAGCTCAGCTAGCACCAAGGGCCCCAGCGTGTCCC CCTGGCCCCCAGCAGCAAGAGCACCTCGGGCGGCACAGCGCCCTGGGCTGCCTGGTGAAGGA CTACTTCCCGAGCCCCGTGACCGTGTCTCTGGAACAGCGGAGCCCTGACCAAGCGCGTGCACAC CTTCCCCCGCCGTGCTGCAGAGCAGCGGCCCTGTACAGCCTGTCCAGCGTGGTGACAGTGGCCAG CAGCAGCCTGGGCACCCAGACCTACATCTGCAACGTGAACCAAGCCAGCCAGCAACACCAAGGTG GACAAGAGAGTGGAGCCCCAAGAGCTGCGACAAGACCACACCTGCCCCCCCCCTGCCAAGCCCCC GAAGCTGCAGGGGCCCCCTCCCGTGTCTCTGTTCCCCCCCCAAGCCCCAAGACACCCCTGATGATCA GCAGGACCCCCGAGGTGACCTGGCTGGTGGTGGACGTGAGCCACGAGGACCCAGAGGTGAAGT TCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCAAGACCAAGCCCCAGAGAGGAGCAGT ACAAACAGCACCTACAGGGTGGTGTCCGTGCTGACCGTGTGCACCAGGACTGGCTGAACGGCAA AGAAATACAAAGTCAAGGTCTCCAACAAGGCCCTGCCTGCCCCCATCGAAAAGACCATCAGCAAG GCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCCTGCCCCCTTCTCGGGAGGAGATGACC AAGAACCAGGTGTCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCGCGACATCGCCCGTGGAGT GGGAGAGCAACGGCCAGCCCCGAGAACTACAAGACACCCCCCCCCAGTGCTGGACAGCGACG GCAGCTTCTTCTCTGTACAGCAAGCTGACCGTGGACAAAGAGCAGGTGGCAGCAGGGCAACGTGTT CAGCTGCAGCGTGTGCACGAGGGCCCTGCACAACCCACTACACCCAGAAAGAGCCTGAGCCTGTCA CCCCGCAAG

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Antibody 8114	Sequence Identifier (SEQ ID NO:) and Sequence or comments
Optimized PN encoding SEQ ID NO:480	485 AGCTACGAGCTGACCCAGCCCCCAGCGTGAGCGTGCGCCCGAGGCCAGACCCGAGGATCAGC TGCAGCGGCGACAGCCTGGGCGACTACTACGCTACTGGTATCAGCAGAGAAGCCCGCCAGGCC CCCGTGCTGTGATCTACAAGGACAAACAGGCCCGAGCGGCA TCCCCGAGAGGTTTCAGCGGCA GCAACAGCGGCAACACCGCCACCCCTGACAATCAGCGGCACCCAGGCCGAGGACGAGGCCGACT ACTACTGCCAGACCTGGGACACCGGCGAGTCAGGCGTGTTCGGCGGAGGGACCAAGCTGACCG TGCTGGGTACGCTAAGGCTGCCCCCAGCGTGACCTGT TCCCCCCCAGCAGCGAGGAGCTGC AGGCCAACAAAGGCCACCCCTGGTGTGCTGATCAGCGACTTCTACCCAGGCCCGTGACCCGTGGC
	CTGGAAGGCCGACAGCAGCCCCCGTGAAGGCCCGCGTGGAGACCCACCAACCCCGAGCAAGCAGAG CAACAACAAGTACGCCGCCAGCAGCTACCTGAGCCTGACCCCGAGCAGTGGAAGAGCCACAG GTCCTACAGCTGCCAGGTGACCCACGAGGGCAGCACCGTGGAAGAGACCCGTGGCCCCAACCCGA GTGCAGC

[0113] Other antibodies of the invention include those where the amino acids or nucleic acids encoding the amino acids have been mutated, yet have at least 60, 65, 70, 75, 80, 85, 90, or 95 percent identity to the sequences described in Table 1. Some embodiments include mutant amino acid sequences wherein no more than 1, 2, 3, 4 or 5 amino acids have been mutated in the variable regions when compared with the variable regions depicted in the sequence described in Table 1, while retaining substantially the same antigen binding activity.

[0114] Since each of these antibodies can bind to Factor P, the VH, VL, full length light chain, and full length heavy chain sequences (amino acid sequences and the nucleotide sequences encoding the amino acid sequences) can be "mixed and matched" to create other Factor P-binding antibodies of the invention. Such "mixed and matched" Factor P-binding antibodies can be tested using the binding assays known in the art (e.g., ELISAs, and other assays described in the Example section). When these chains are mixed and matched, a VH sequence from a particular VH/VL pairing should be replaced with a structurally similar VH sequence. Likewise a full length heavy chain sequence from a particular full length heavy chain / full length light chain pairing should be replaced with a structurally similar full length heavy chain sequence. Likewise, a VL sequence from a particular VH/VL pairing should be replaced with a structurally similar VL sequence. Likewise a full length light chain sequence from a particular full length heavy chain / full length light chain pairing should be replaced with a structurally similar full length light chain sequence. Accordingly, in one aspect, the invention provides an isolated antibody or antigen binding region thereof having: a heavy chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175, 189, 203, 217, 231, 245, 259 and 273, and a light chain variable domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 22, 36, 50, 64, 78, 92, 106, 120, 134, 148, 162, 176, 190, 204, 218, 232, 246, 260, and 274 wherein the antibody specifically binds to Factor P (e.g., human and/or cynomolgus Factor P).

[0115] In another aspect, the invention provides (i) an isolated antibody having: a full length heavy chain comprising an amino acid sequence that has been optimized for expression in a mammalian cell selected from the group consisting of SEQ ID NOs: 9, 23, 37, 51, 65, 79, 93, 107, 121, 135, 149, 163, 177, 191, 205, 219, 233, 247, 261 and 275, and a full length light chain comprising an amino acid sequence that has been optimized for expression in a mammalian cell selected from the group consisting of SEQ ID NOs: 10, 24, 38, 52, 66, 80, 94, 108, 122, 136, 150, 164, 178, 192, 206, 220, 234, 248, 262 and 276; or (ii) a functional protein comprising an antigen binding portion thereof.

[0116] The terms "complementarity determining region," and "CDR," as used herein refer to the sequences of amino acids within antibody variable regions which confer antigen specificity and binding affinity. In general, there are three CDRs in each heavy chain variable region (HCDR1, HCDR2, HCDR3) and three CDRs in each light chain variable region (LCDR1, LCDR2, LCDR3).

[0117] The precise amino acid sequence boundaries of a given CDR can be readily determined using any of a number of well-known schemes, including those described by Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD ("Kabat" numbering scheme), Al-Lazikani et al., (1997) JMB 273,927-948 ("Chothia" numbering scheme).

[0118] For example, under Kabat, the CDR amino acid residues in the heavy chain variable domain (VH) are numbered 31-35 (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3); and the CDR amino acid residues in the light chain variable domain (VL) are numbered 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3). Under Chothia the CDR amino acids in the VH are numbered 26-32 (HCDR1), 52-56 (HCDR2), and 95-102 (HCDR3); and the amino acid residues in VL are numbered 26-32 (LCDR1), 50-52 (LCDR2), and 91-96 (LCDR3). By combining the CDR definitions of both Kabat and Chothia, the CDRs consist of amino acid residues 26-35 (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3) in human VH and amino acid residues 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3) in human VL.

[0119] In another aspect, the present invention provides Factor P binding antibodies that comprise the heavy chain and light chain CDR1s, CDR2s, and CDR3s as described in Table 1, or combinations thereof. The amino acid sequences of the VH CDR1s of the antibodies are shown in SEQ ID NOs: 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169, 183, 197, 211, 225, 239, 253, or 267. The amino acid sequences of the VH CDR2s of the antibodies are shown in SEQ ID NOs: 2, 16, 30, 44, 58, 72, 86, 100, 114, 128, 142, 156, 170, 184, 198, 212, 226, 240, 254, or 268. The amino acid sequences of the VH CDR3s of the antibodies are shown in SEQ ID NOs: 3, 17, 31, 45, 59, 73, 87, 101, 115, 129, 143, 157, 171, 185, 199, 213, 227, 241, 255, or 269. The amino acid sequences of the VL CDR1s of the antibodies are shown in SEQ ID NOs: 4, 18, 32, 46, 60, 74, 88, 102, 116, 130, 144, 158, 172, 186, 200, 214, 228, 242, 256, or 270. The amino acid sequences of the VL CDR2s of the antibodies are shown in SEQ ID NOs: 5, 19, 33, 47, 61, 75, 89, 103, 117, 131, 145, 159, 173, 187, 201, 215, 229, 243, 257, or 271. The amino acid sequences of the VL CDR3s of the antibodies are shown in SEQ ID NOs: 6, 20, 34, 48, 62, 76, 90, 104, 118, 132, 146, 160, 174, 188, 202, 216, 230, 244, 258, or 272. These CDR regions are delineated using the Kabat system.

[0120] Alternatively, as defined using the Chothia system (Al-Lazikani et al., (1997) JMB 273,927-948) the amino acid sequences of the VH CDR1s of the antibodies are shown in SEQ ID NOs: 281, 287, 293, 299, 305, 311, 317, 323, 329, 335, 341, 347, 353, 359, 365, 371, 377, 383, 389, or 395. The amino acid sequences of the VH CDR2s of the antibodies are shown in SEQ ID NOs: 282, 288, 294, 300, 306, 312, 318, 324, 330, 336, 342, 348, 354, 360, 366, 372, 378,

384, 390, or 396. The amino acid sequences of the VH CDR3s of the antibodies are shown in SEQ ID NOs: 283, 289, 295, 301, 307, 313, 319, 325, 331, 337, 343, 349, 355, 361, 367, 373, 379, 385, 391, or 397. The amino acid sequences of the VL CDR1s of the antibodies are shown in SEQ ID NOs: 284, 290, 296, 302, 308, 314, 320, 326, 332, 338, 344, 350, 356, 362, 368, 374, 380, 386, 392, or 398. The amino acid sequences of the VL CDR2s of the antibodies are shown in SEQ ID NOs: 285, 291, 297, 303, 309, 315, 321, 327, 333, 339, 345, 351, 357, 363, 369, 375, 381, 387, 393, or 399. The amino acid sequences of the VL CDR3s of the antibodies are shown in SEQ ID NOs: 286, 292, 298, 304, 310, 316, 322, 328, 334, 340, 346, 352, 358, 364, 370, 376, 382, 388, 394, or 400.

[0121] Given that each of these antibodies can bind to Factor P and that antigen-binding specificity is provided primarily by the CDR1, 2 and 3 regions, the VH CDR1, 2 and 3 sequences and VL CDR1, 2 and 3 sequences can be "mixed and matched" (*i.e.*, CDRs from different antibodies can be mixed and matched, although each antibody preferably contains a VH CDR1, 2 and 3 and a VL CDR1, 2 and 3 to create other Factor P binding molecules of the invention. Such "mixed and matched" Factor P binding antibodies can be tested using the binding assays known in the art and those described in the Examples (*e.g.*, ELISAs, SET, Biacore). When VH CDR sequences are mixed and matched, the CDR1, CDR2 and/or CDR3 sequence from a particular VH sequence should be replaced with a structurally similar CDR sequence(s). Likewise, when VL CDR sequences are mixed and matched, the CDR1, CDR2 and/or CDR3 sequence from a particular VL sequence should be replaced with a structurally similar CDR sequence(s). It will be readily apparent to the ordinarily skilled artisan that novel VH and VL sequences can be created by substituting one or more VH and/or VL CDR region sequences with structurally similar sequences from the CDR sequences shown herein for monoclonal antibodies of the present invention. In addition to the foregoing, in one embodiment, the antigen binding fragments of the antibodies described herein can comprise a VH CDR1, 2, and 3, or a VL CDR 1, 2, and 3, wherein the fragment binds to Factor P as a single variable domain.

[0122] In certain embodiments of the invention, the antibodies or antigen binding fragments thereof may have the heavy and light chain sequences of the Fabs described in Table 1. More specifically, the antibody or antigen binding fragment thereof may have the heavy and light sequence of Fab NVS962, NVS963, NVS964, NVS965, NVS966, NVS967, NVS805, NVS806, NVS807, NVS808, NVS809, NVS962-S, NVS962-Q, NVS962-S31A, NVS962-G, NVS962-T, NVS965-S, NVS965-T, or NVS965-Q.

[0123] In other embodiments of the invention the antibody or antigen binding fragment in that specifically binds Factor P comprises a heavy chain variable region CDR1, a heavy chain variable region CDR2, a heavy chain variable region CDR3, a light chain variable region CDR1, a light chain variable region CDR2, and a light chain variable region CDR3 as defined by Kabat and described in Table 1. In still other embodiments of the invention the antibody or antigen binding fragment in that specifically binds Factor P comprises a heavy chain variable region CDR1, a heavy chain variable region CDR2, a heavy chain variable region CDR3, a light chain variable region CDR1, a light chain variable region CDR2, and a light chain variable region CDR3 as defined by Chothia and described in Table 1.

[0124] In a specific embodiment, the invention includes an antibody that specifically binds to Factor P comprising a heavy chain variable region CDR1 of SEQ ID NO: 1; a heavy chain variable region CDR2 of SEQ ID NO: 2; a heavy chain variable region CDR3 of SEQ ID NO: 3; a light chain variable region CDR1 of SEQ ID NO: 4; a light chain variable region CDR2 of SEQ ID NO: 5; and a light chain variable region CDR3 of SEQ ID NO: 6. In another specific embodiment, the invention includes an antibody that specifically binds to Factor P comprising a heavy chain variable region CDR1 of SEQ ID NO: 15; a heavy chain variable region CDR2 of SEQ ID NO: 16; a heavy chain variable region CDR3 of SEQ ID NO: 17; a light chain variable region CDR1 of SEQ ID NO: 18; a light chain variable region CDR2 of SEQ ID NO: 19; and a light chain variable region CDR3 of SEQ ID NO: 20. In another specific embodiment, the invention includes an antibody that specifically binds to Factor P comprising a heavy chain variable region CDR1 of SEQ ID NO: 29; a heavy chain variable region CDR2 of SEQ ID NO: 30; a heavy chain variable region CDR3 of SEQ ID NO: 31; a light chain variable region CDR1 of SEQ ID NO: 32; a light chain variable region CDR2 of SEQ ID NO: 33; and a light chain variable region CDR3 of SEQ ID NO: 34. In another specific embodiment, the invention includes an antibody that specifically binds to Factor P comprising a heavy chain variable region CDR1 of SEQ ID NO: 43; a heavy chain variable region CDR2 of SEQ ID NO: 44; a heavy chain variable region CDR3 of SEQ ID NO: 45; a light chain variable region CDR1 of SEQ ID NO: 46; a light chain variable region CDR2 of SEQ ID NO: 47; and a light chain variable region CDR3 of SEQ ID NO: 48. In another specific embodiment, the invention includes an antibody that specifically binds to Factor P comprising a heavy chain variable region CDR1 of SEQ ID NO: 57; a heavy chain variable region CDR2 of SEQ ID NO: 58; a heavy chain variable region CDR3 of SEQ ID NO: 59; a light chain variable region CDR1 of SEQ ID NO: 60; a light chain variable region CDR2 of SEQ ID NO: 61; and a light chain variable region CDR3 of SEQ ID NO: 62. In another specific embodiment, the invention includes an antibody that specifically binds to Factor P comprising a heavy chain variable region CDR1 of SEQ ID NO: 71; a heavy chain variable region CDR2 of SEQ ID NO: 72; a heavy chain variable region CDR3 of SEQ ID NO: 73; a light chain variable region CDR1 of SEQ ID NO: 74; a light chain variable region CDR2 of SEQ ID NO: 75; and a light chain variable region CDR3 of SEQ ID NO: 76. In another specific embodiment, the invention includes an antibody that specifically binds to Factor P comprising a heavy chain variable region CDR1 of SEQ ID NO: 85; a heavy chain variable region CDR2 of SEQ ID NO: 86; a heavy chain variable region CDR3 of SEQ ID NO: 87; a

[illegible]

[0125] In another specific embodiment, the invention includes an antibody that specifically binds to Factor P comprising a heavy chain variable region CDR1 of SEQ ID NO: 281; a heavy chain variable region CDR2 of SEQ ID NO: 282; a heavy chain variable region CDR3 of SEQ ID NO: 283; a light chain variable region CDR1 of SEQ ID NO: 284; a light chain variable region CDR2 of SEQ ID NO: 285; and a light chain variable region CDR3 of SEQ ID NO: 286. In another specific embodiment, the invention includes an antibody that specifically binds to Factor P comprising a heavy chain variable region CDR1 of SEQ ID NO: 287; a heavy chain variable region CDR2 of SEQ ID NO: 288; a heavy chain

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CDR3 of SEQ ID NO: 379; a light chain variable region CDR1 of SEQ ID NO: 380; a light chain variable region CDR2 of SEQ ID NO: 381; and a light chain variable region CDR3 of SEQ ID NO: 382. In another specific embodiment, the invention includes an antibody that specifically binds to Factor P comprising a heavy chain variable region CDR1 of SEQ ID NO: 383; a heavy chain variable region CDR2 of SEQ ID NO: 384; a heavy chain variable region CDR3 of SEQ ID NO: 385; a light chain variable region CDR1 of SEQ ID NO: 386; a light chain variable region CDR2 of SEQ ID NO: 387; and a light chain variable region CDR3 of SEQ ID NO: 388. In another specific embodiment, the invention includes an antibody that specifically binds to Factor P comprising a heavy chain variable region CDR1 of SEQ ID NO: 389; a heavy chain variable region CDR2 of SEQ ID NO: 390; a heavy chain variable region CDR3 of SEQ ID NO: 391; a light chain variable region CDR1 of SEQ ID NO: 392; a light chain variable region CDR2 of SEQ ID NO: 393; and a light chain variable region CDR3 of SEQ ID NO: 394. In another specific embodiment, the invention includes an antibody that specifically binds to Factor P comprising a heavy chain variable region CDR1 of SEQ ID NO: 395; a heavy chain variable region CDR2 of SEQ ID NO: 396; a heavy chain variable region CDR3 of SEQ ID NO: 397; a light chain variable region CDR1 of SEQ ID NO: 398; a light chain variable region CDR2 of SEQ ID NO: 399; and a light chain variable region CDR3 of SEQ ID NO: 400.

[0126] In certain embodiments, the invention includes antibodies or antigen binding fragments that specifically binds to Factor P as described in Table 1. In a preferred embodiment, the antibody, or antigen binding fragment, that binds Factor P is Fab NVS962, NVS963, NVS964, NVS965, NVS966, NVS967, NVS804, NVS805, NVS806, NVS807, NVS808, NVS809, NVS962-S, NVS962-Q, NVS962-G, NVS962-T, NVS962-S31A, NVS965-T, NVS965-Q, or NVS965-S.

[0127] As used herein, a human antibody comprises heavy or light chain variable regions or full length heavy or light chains that are "the product of" or "derived from" a particular germline sequence if the variable regions or full length chains of the antibody are obtained from a system that uses human germline immunoglobulin genes. Such systems include immunizing a transgenic mouse carrying human immunoglobulin genes with the antigen of interest or screening a human immunoglobulin gene library displayed on phage with the antigen of interest. A human antibody that is "the product of" or "derived from" a human germline immunoglobulin sequence can be identified as such by comparing the amino acid sequence of the human antibody to the amino acid sequences of human germline immunoglobulins and selecting the human germline immunoglobulin sequence that is closest in sequence (*i.e.*, greatest % identity) to the sequence of the human antibody. A human antibody that is "the product of" or "derived from" a particular human germline immunoglobulin sequence may contain amino acid differences as compared to the germline sequence, due to, for example, naturally occurring somatic mutations or intentional introduction of site-directed mutations. However, in the VH or VL framework regions, a selected human antibody typically is at least 90% identical in amino acids sequence to an amino acid sequence encoded by a human germline immunoglobulin gene and contains amino acid residues that identify the human antibody as being human when compared to the germline immunoglobulin amino acid sequences of other species (*e.g.*, murine germline sequences). In certain cases, a human antibody may be at least 60%, 70%, 80%, 90%, or at least 95%, or even at least 96%, 97%, 98%, or 99% identical in amino acid sequence to the amino acid sequence encoded by the germline immunoglobulin gene. Typically, a recombinant human antibody will display no more than 10 amino acid differences from the amino acid sequence encoded by the human germline immunoglobulin gene in the VH or VL framework regions. In certain cases, the human antibody may display no more than 5, or even no more than 4, 3, 2, or 1 amino acid difference from the amino acid sequence encoded by the germline immunoglobulin gene. Examples of human germline immunoglobulin genes include, but are not limited to the variable domain germline fragments described below, as well as DP47 and DPK9.

Homologous antibodies

[0128] In yet another embodiment, the present invention provides an antibody, or an antigen binding fragment thereof, comprising amino acid sequences that are homologous to the sequences described in Table 1, and the antibody binds to a Factor P protein (*e.g.*, human and/or cynomolgus Factor P), and retains the desired functional properties of those antibodies described in Table 1.

[0129] For example, the invention provides an isolated antibody, or a functional antigen binding fragment thereof, comprising a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain comprises an amino acid sequence that is at least 80%, at least 90%, or at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175, 189, 203, 217, 231, 245, 259 and 273; the light chain variable domain comprises an amino acid sequence that is at least 80%, at least 90%, or at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 22, 36, 50, 64, 78, 92, 106, 120, 134, 148, 162, 176, 190, 204, 218, 232, 246, 260, and 274; and the antibody specifically binds to Factor P (*e.g.*, human and/or cynomolgus Factor P).

[0130] In other embodiments, the VH and/or VL amino acid sequences may be 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to the sequences set forth in Table 1. In other embodiments, the VH and/or VL amino acid sequences may be identical except for an amino acid substitution in no more than 1,2,3,4 or 5 amino acid positions.

An antibody having VH and VL regions having high (*i. e.*, 80% or greater) identity to the VH and VL regions of those described in Table 1 can be obtained by mutagenesis (*e.g.*, site-directed or PCR-mediated mutagenesis) of nucleic acid molecules encoding SEQ ID NOs: 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175, 189, 203, 217, 231, 245, 259 or 273 and SEQ ID NOs: 8, 22, 36, 50, 64, 78, 92, 106, 120, 134, 148, 162, 176, 190, 204, 218, 232, 246, 260, or 274, respectively, followed by testing of the encoded altered antibody for retained function using the functional assays described herein.

[0131] In other embodiments, the full length heavy chain and/or full length light chain amino acid sequences may be 50% 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to the sequences set forth in Table 1. An antibody having a full length heavy chain and full length light chain having high (*i.e.*, 80% or greater) identity to the full length heavy chains of any of SEQ ID NOs : 9, 23, 37, 51, 65, 79, 93, 107, 121, 135, 149, 163, 177, 191, 205, 219, 233, 247, 261 or 275, and full length light chains of any of SEQ ID NOs 10, 24, 38, 52, 66, 80, 94, 108, 122, 136, 150, 164, 178, 192, 206, 220, 234, 248, 262, or 276, can be obtained by mutagenesis (*e.g.*, site-directed or PCR-mediated mutagenesis) of nucleic acid molecules encoding such polypeptides, followed by testing of the encoded altered antibody for retained function using the functional assays described herein.

[0132] In other embodiments, the full length heavy chain and/or full length light chain nucleotide sequences may be 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to the sequences set forth in Table 1.

[0133] In other embodiments, the variable regions of heavy chain and/or the variable regions of light chain nucleotide sequences may be 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to the sequences set forth in Table 1.

[0134] As used herein, the percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity equals number of identical positions/total number of positions x 100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm, as described in the non-limiting examples below.

[0135] Additionally or alternatively, the protein sequences of the present invention can further be used as a "query sequence" to perform a search against public databases to, for example, identify related sequences. For example, such searches can be performed using the BLAST program (version 2.0) of Altschul, et al., 1990 J.Mol. Biol. 215:403-10.

Antibodies with Conservative Modifications

[0136] In certain embodiments, an antibody of the invention has a heavy chain variable region comprising CDR1, CDR2, and CDR3 sequences and a light chain variable region comprising CDR1, CDR2, and CDR3 sequences, wherein one or more of these CDR sequences have specified amino acid sequences based on the antibodies described herein or conservative modifications thereof, and wherein the antibodies retain the desired functional properties of the Factor P-binding antibodies of the invention. Accordingly, the invention provides an isolated antibody, or a antigen binding fragment thereof, consisting of a heavy chain variable region comprising CDR1, CDR2, and CDR3 sequences and a light chain variable region comprising CDR1, CDR2, and CDR3 sequences, wherein: the heavy chain variable region CDR1 amino acid sequences are selected from the group consisting of SEQ ID NOs: 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169, 183, 197, 211, 225, 239, 253, and 267, and conservative modifications thereof; the heavy chain variable region CDR2 amino acid sequences are selected from the group consisting of SEQ ID NOs: 2, 16, 30, 44, 58, 72, 86, 100, 114, 128, 142, 156, 170, 184, 198, 212, 226, 240, 254, and 268, and conservative modifications thereof; the heavy chain variable region CDR3 amino acid sequences are selected from the group consisting of SEQ ID NOs: 3, 17, 31, 45, 59, 73, 87, 101, 115, 129, 143, 157, 171, 185, 199, 213, 227, 241, 255, and 269, and conservative modifications thereof; the light chain variable regions CDR1 amino acid sequences are selected from the group consisting of SEQ ID NOs: 4, 18, 32, 46, 60, 74, 88, 102, 116, 130, 144, 158, 172, 186, 200, 214, 228, 242, 256, and 270, and conservative modifications thereof; the light chain variable regions CDR2 amino acid sequences are selected from the group consisting of SEQ ID NOs: 5, 19, 33, 47, 61, 75, 89, 103, 117, 131, 145, 159, 173, 187, 201, 215, 229, 243, 257, and 271, and conservative modifications thereof; the light chain variable regions of CDR3 amino acid sequences are selected from the group consisting of SEQ ID NOs: 6, 20, 34, 48, 62, 76, 90, 104, 118, 132, 146, 160, 174, 188, 202, 216, 230, 244, 258, and 272, and conservative modifications thereof; and the antibody or antigen binding fragment thereof specifically binds to Factor P.

[0137] In other embodiments, the antibody of the invention is optimized for expression in a mammalian cell has a full length heavy chain sequence and a full length light chain sequence, wherein one or more of these sequences have specified amino acid sequences based on the antibodies described herein or conservative modifications thereof, and wherein the antibodies retain the desired functional properties of the Factor P binding antibodies of the invention. Accordingly, the invention provides an isolated antibody optimized for expression in a mammalian cell consisting of a full length heavy chain and a full length light chain wherein the full length heavy chain has amino acid sequences selected from the group of SEQ ID NOs: 9, 23, 37, 51, 65, 79, 93, 107, 121, 135, 149, 163, 177, 191, 205, 219, 233, 247, 261 and 275, and conservative modifications thereof; and the full length light chain has amino acid sequences selected from

the group of SEQ ID NOs: 10, 24, 38, 52, 66, 80, 94, 108, 122, 136, 150, 164, 178, 192, 206, 220, 234, 248, 262, and 276, and conservative modifications thereof; and the antibody specifically binds to Factor P (e.g., human and/or cynomolgus Factor P).

5 Antibodies That Bind to the Same Epitope

[0138] The present invention provides antibodies that bind to the same epitope as the Factor P binding antibodies described in Table 1. Additional antibodies can therefore be identified based on their ability to compete (e.g., to competitively inhibit the binding of, in a statistically significant manner) with other antibodies of the invention in Factor P binding assays (such as those described in the Examples). The ability of a test antibody to inhibit the binding of antibodies of the present invention to a Factor P protein demonstrates that the test antibody can compete with that antibody for binding to Factor P; such an antibody may, according to non-limiting theory, bind to the same or a related (e.g., a structurally similar or spatially proximal) epitope on the Factor P protein as the antibody with which it competes. In a certain embodiment, the antibody that binds to the same epitope on Factor P as the antibodies of the present invention is a human monoclonal antibody. Such human monoclonal antibodies can be prepared and isolated as described herein. As used herein, an antibody "competes" for binding when the competing antibody inhibits Factor P binding of an antibody or antigen binding fragment of the invention by more than 50%, in the presence of an equimolar concentration of competing antibody.

[0139] In other embodiments the antibodies or antigen binding fragments of the invention bind the Thrombospondin type 5 repeat (TSR 5) domain of Factor P (SEQ ID NO: 406). In other embodiments the antibodies or antigen binding fragments of the invention bind a region of the Factor P TSR5 domain comprising SEQ ID NO: 407. Still in other embodiments the region comprises SEQ ID NO: 408.

[0140] In other embodiments of the invention the isolated antibodies or antigen binding fragments bind an epitope comprising SEQ ID NO: 407, and in other embodiments the epitope comprises SEQ ID NO: 408. In other embodiments of the invention, the antibodies or antigen binding fragments bind a peptide according to SEQ ID NO: 407 and in still other embodiments the Factor P epitope includes SEQ ID NO: 408.

Engineered and Modified Antibodies

[0141] An antibody of the invention further can be prepared using an antibody having one or more of the VH and/or VL sequences shown herein as starting material to engineer a modified antibody, which modified antibody may have altered properties from the starting antibody. An antibody can be engineered by modifying one or more residues within one or both variable regions (*i. e.*, VH and/or VL), for example within one or more CDR regions and/or within one or more framework regions. Additionally or alternatively, an antibody can be engineered by modifying residues within the constant region(s), for example to alter the effector function(s) of the antibody.

[0142] One type of variable region engineering that can be performed is CDR grafting. Antibodies interact with target antigens predominantly through amino acid residues that are located in the six heavy and light chain complementarity determining regions (CDRs). For this reason, the amino acid sequences within CDRs are more diverse between individual antibodies than sequences outside of CDRs. Because CDR sequences are responsible for most antibody-antigen interactions, it is possible to express recombinant antibodies that mimic the properties of specific naturally occurring antibodies by constructing expression vectors that include CDR sequences from the specific naturally occurring antibody grafted onto framework sequences from a different antibody with different properties (see, e.g., Riechmann, L. et al., 1998 Nature 332:323-327; Jones, P. et al., 1986 Nature 321:522-525; Queen, C. et al., 1989 Proc. Natl. Acad., U.S.A. 86:10029-10033; U.S. Patent No. 5,225,539 to Winter, and U.S. Patent Nos. 5,530,101; 5,585,089; 5,693,762 and 6,180,370 to Queen et al.)

[0143] Accordingly, another embodiment of the invention pertains to an isolated antibody, or an antigen binding fragment thereof, comprising a heavy chain variable region comprising CDR1 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169, 183, 197, 211, 225, 239, 253, and 267; CDR2 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 16, 30, 44, 58, 72, 86, 100, 114, 128, 142, 156, 170, 184, 198, 212, 226, 240, 254, and 268; CDR3 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 17, 31, 45, 59, 73, 87, 101, 115, 129, 143, 157, 171, 185, 199, 213, 227, 241, 255, and 269, respectively; and a light chain variable region having CDR1 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 18, 32, 46, 60, 74, 88, 102, 116, 130, 144, 158, 172, 186, 200, 214, 228, 242, 256, and 270; CDR2 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 19, 33, 47, 61, 75, 89, 103, 117, 131, 145, 159, 173, 187, 201, 215, 229, 243, 257, and 271; and CDR3 sequences consisting of an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 20, 34, 48, 62, 76, 90, 104, 118, 132, 146, 160, 174, 188, 202, 216, 230, 244, 258, and 272, respectively. Thus, such antibodies contain the VH and VL CDR sequences of monoclonal antibodies, yet may

contain different framework sequences from these antibodies.

[0144] Alternatively, another embodiment of the invention pertains to an isolated antibody, or an antigen binding fragment thereof, comprising a heavy chain variable region comprising CDR1 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 281, 287, 293, 299, 305, 311, 317, 323, 329, 335, 341, 347, 353, 359, 365, 371, 377, 383, 389, and 395; CDR2 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 282, 288, 294, 300, 306, 312, 318, 324, 330, 336, 342, 348, 354, 360, 366, 372, 378, 384, 390, and 396; CDR3 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 283, 289, 295, 301, 307, 313, 319, 325, 331, 337, 343, 349, 355, 361, 367, 373, 379, 385, 391, and 397, respectively; and a light chain variable region having CDR1 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 284, 290, 296, 302, 308, 314, 320, 326, 332, 338, 344, 350, 356, 362, 368, 374, 380, 386, 392, and 398; CDR2 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 285, 291, 297, 303, 309, 315, 321, 327, 333, 339, 345, 351, 357, 363, 369, 375, 381, 387, 393, and 399; and CDR3 sequences consisting of an amino acid sequence selected from the group consisting of SEQ ID NOs: 286, 292, 298, 304, 310, 316, 322, 328, 334, 340, 346, 352, 358, 364, 370, 376, 382, 388, 394, and 400, respectively. Thus, such antibodies contain the VH and VL CDR sequences of monoclonal antibodies, yet may contain different framework sequences from these antibodies.

[0145] Such framework sequences can be obtained from public DNA databases or published references that include germline antibody gene sequences. For example, germline DNA sequences for human heavy and light chain variable region genes can be found in the "VBase" human germline sequence database (available on the world wide web at mrc-cpe.cam.ac.uk/vbase), as well as in Kabat, E. A., et al., 1991 Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; Tomlinson, I. M., et al., 1992 J. Mol. Biol. 227:776-798; and Cox, J. P. L. et al., 1994 Eur. J Immunol. 24:827-836; the contents of each of which are expressly incorporated herein by reference.

[0146] An example of framework sequences for use in the antibodies of the invention are those that are structurally similar to the framework sequences used by selected antibodies of the invention, e.g., consensus sequences and/or framework sequences used by monoclonal antibodies of the invention. The VH CDR1, 2 and 3 sequences, and the VL CDR1, 2 and 3 sequences, can be grafted onto framework regions that have the identical sequence as that found in the germline immunoglobulin gene from which the framework sequence derive, or the CDR sequences can be grafted onto framework regions that contain one or more mutations as compared to the germline sequences. For example, it has been found that in certain instances it is beneficial to mutate residues within the framework regions to maintain or enhance the antigen binding ability of the antibody (see e.g., U.S. Patent Nos. 5,530,101; 5,585,089; 5,693,762 and 6,180,370 to Queen et al). Frameworks that can be utilized as scaffolds on which to build the antibodies and antigen binding fragments described herein include, but are not limited to VH1A, VH1B, VH3, Vk1, VI2, and Vk2. Additional frameworks are known in the art and may be found, for example, in the vBase data base on the world wide web at vbase.mrc-cpe.cam.ac.uk/index.php?&MMN_position=1:1.

[0147] Accordingly, an embodiment of the invention relates to isolated Factor P binding antibodies, or antigen binding fragments thereof, comprising a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175, 189, 203, 217, 231, 245, 259 and 273, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions in the framework region of such sequences, and further comprising a light chain variable region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 22, 36, 50, 64, 78, 92, 106, 120, 134, 148, 162, 176, 190, 204, 218, 232, 246, 260, and 274, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions in the framework region of such sequences.

[0148] Another type of variable region modification is to mutate amino acid residues within the VH and/or VL CDR1, CDR2 and/or CDR3 regions to thereby improve one or more binding properties (e.g., affinity) of the antibody of interest, known as "affinity maturation." Site-directed mutagenesis or PCR-mediated mutagenesis can be performed to introduce the mutation(s) and the effect on antibody binding, or other functional property of interest, can be evaluated in *in vitro* or *in vivo* assays as described herein and provided in the Examples. Conservative modifications (as discussed above) can be introduced. The mutations may be amino acid substitutions, additions or deletions. Moreover, typically no more than one, two, three, four or five residues within a CDR region are altered.

[0149] Accordingly, in another embodiment, the invention provides isolated Factor P-binding antibodies, or antigen binding fragments thereof, consisting of a heavy chain variable region having a VH CDR1 region consisting of an amino acid sequence selected from the group having SEQ ID NOs: 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169, 183, 197, 211, 225, 239, 253, and 267 or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169, 183, 197, 211, 225, 239, 253, or 267; a VH CDR2 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 16, 30, 44, 58, 72, 86, 100, 114, 128, 142, 156, 170, 184, 198, 212, 226, 240, 254, and 268 or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ

ID NOs: 2, 16, 30, 44, 58, 72, 86, 100, 114, 128, 142, 156, 170, 184, 198, 212, 226, 240, 254, or 268; a VH CDR3 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 17, 31, 45, 59, 73, 87, 101, 115, 129, 143, 157, 171, 185, 199, 213, 227, 241, 255, and 269, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 3, 17, 31, 45, 59, 73, 87, 101, 115, 129, 143, 157, 171, 185, 199, 213, 227, 241, 255, or 269; a VL CDR1 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 18, 32, 46, 60, 74, 88, 102, 116, 130, 144, 158, 172, 186, 200, 214, 228, 242, 256, and 270, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 4, 18, 32, 46, 60, 74, 88, 102, 116, 130, 144, 158, 172, 186, 200, 214, 228, 242, 256, or 270; a VL CDR2 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 19, 33, 47, 61, 75, 89, 103, 117, 131, 145, 159, 173, 187, 201, 215, 229, 243, 257, and 271, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 5, 19, 33, 47, 61, 75, 89, 103, 117, 131, 145, 159, 173, 187, 201, 215, 229, 243, 257, or 271; and a VL CDR3 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 20, 34, 48, 62, 76, 90, 104, 118, 132, 146, 160, 174, 188, 202, 216, 230, 244, 258, and 272, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 6, 20, 34, 48, 62, 76, 90, 104, 118, 132, 146, 160, 174, 188, 202, 216, 230, 244, 258, or 272.

[0150] Accordingly, in another embodiment, the invention provides isolated Factor P-binding antibodies, or antigen binding fragments thereof, consisting of a heavy chain variable region having a VH CDR1 region consisting of an amino acid sequence selected from the group having SEQ ID NOs: 281, 287, 293, 299, 305, 311, 317, 323, 329, 335, 341, 347, 353, 359, 365, 371, 377, 383, 389, and 395 or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 281, 287, 293, 299, 305, 311, 317, 323, 329, 335, 341, 347, 353, 359, 365, 371, 377, 383, 389, or 395; a VH CDR2 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 282, 288, 294, 300, 306, 312, 318, 324, 330, 336, 342, 348, 354, 360, 366, 372, 378, 384, 390, and 396 or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 282, 288, 294, 300, 306, 312, 318, 324, 330, 336, 342, 348, 354, 360, 366, 372, 378, 384, 390, or 396; a VH CDR3 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 283, 289, 295, 301, 307, 313, 319, 325, 331, 337, 343, 349, 355, 361, 367, 373, 379, 385, 391, and 397, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 283, 289, 295, 301, 307, 313, 319, 325, 331, 337, 343, 349, 355, 361, 367, 373, 379, 385, 391, or 397; a VL CDR1 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 284, 290, 296, 302, 308, 314, 320, 326, 332, 338, 344, 350, 356, 362, 368, 374, 380, 386, 392, and 398, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 284, 290, 296, 302, 308, 314, 320, 326, 332, 338, 344, 350, 356, 362, 368, 374, 380, 386, 392, or 398; a VL CDR2 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 285, 291, 297, 303, 309, 315, 321, 327, 333, 339, 345, 351, 357, 363, 369, 375, 381, 387, 393, and 399, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 285, 291, 297, 303, 309, 315, 321, 327, 333, 339, 345, 351, 357, 363, 369, 375, 381, 387, 393, or 399; and a VL CDR3 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 286, 292, 298, 304, 310, 316, 322, 328, 334, 340, 346, 352, 358, 364, 370, 376, 382, 388, 394, and 400, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 286, 292, 298, 304, 310, 316, 322, 328, 334, 340, 346, 352, 358, 364, 370, 376, 382, 388, 394, or 400.

Grafting Antigen-binding Domains Into Alternative Frameworks or Scaffolds

[0151] A wide variety of antibody/ immunoglobulin frameworks or scaffolds can be employed so long as the resulting polypeptide includes at least one binding region which specifically binds to Factor P. Such frameworks or scaffolds include the 5 main idiotypes of human immunoglobulins, or fragments thereof, and include immunoglobulins of other animal species, preferably having humanized aspects. Single heavy-chain antibodies such as those identified in camelids are of particular interest in this regard. Novel frameworks, scaffolds and fragments continue to be discovered and developed by those skilled in the art.

[0152] In one aspect, the invention pertains to generating non-immunoglobulin based antibodies using non-immunoglobulin scaffolds onto which CDRs of the invention can be grafted. Known or future non-immunoglobulin frameworks and scaffolds may be employed, as long as they comprise a binding region specific for the target Factor P protein. Known non-immunoglobulin frameworks or scaffolds include, but are not limited to, fibronectin (Compound Therapeutics, Inc., Waltham, MA), ankyrin (Molecular Partners AG, Zurich, Switzerland), domain antibodies (Domantis, Ltd., Cambridge, MA, and Ablynx nv, Zwijnaarde, Belgium), lipocalin (Pieris Proteolab AG, Freising, Germany), small modular immunopharmaceuticals (Trubion Pharmaceuticals Inc., Seattle, WA), maxybodies (Avidia, Inc., Mountain View, CA), Protein A (Affibody AG, Sweden), and affilin (gamma-crystallin or ubiquitin) (Scil Proteins GmbH, Halle, Germany).

[0153] The fibronectin scaffolds are based on fibronectin type III domain (*e.g.*, the tenth module of the fibronectin type III (10 Fn3 domain)). The fibronectin type III domain has 7 or 8 beta strands which are distributed between two beta sheets, which themselves pack against each other to form the core of the protein, and further containing loops (analogous to CDRs) which connect the beta strands to each other and are solvent exposed. There are at least three such loops at each edge of the beta sheet sandwich, where the edge is the boundary of the protein perpendicular to the direction of the beta strands (see US 6,818,418). These fibronectin-based scaffolds are not an immunoglobulin, although the overall fold is closely related to that of the smallest functional antibody fragment, the variable region of the heavy chain, which comprises the entire antigen recognition unit in camel and llama IgG. Because of this structure, the non-immunoglobulin antibody mimics antigen binding properties that are similar in nature and affinity to those of antibodies. These scaffolds can be used in a loop randomization and shuffling strategy *in vitro* that is similar to the process of affinity maturation of antibodies *in vivo*. These fibronectin-based molecules can be used as scaffolds where the loop regions of the molecule can be replaced with CDRs of the invention using standard cloning techniques.

[0154] The ankyrin technology is based on using proteins with ankyrin derived repeat modules as scaffolds for bearing variable regions which can be used for binding to different targets. The ankyrin repeat module is a 33 amino acid polypeptide consisting of two anti-parallel α -helices and a β -turn. Binding of the variable regions is mostly optimized by using ribosome display.

[0155] Avimers are derived from natural A-domain containing protein such as LRP-1. These domains are used by nature for protein-protein interactions and in human over 250 proteins are structurally based on A-domains. Avimers consist of a number of different "A-domain" monomers (2-10) linked via amino acid linkers. Avimers can be created that can bind to the target antigen using the methodology described in, for example, U.S. Patent Application Publication Nos. 20040175756; 20050053973; 20050048512; and 20060008844.

[0156] Affibody affinity ligands are small, simple proteins composed of a three-helix bundle based on the scaffold of one of the IgG-binding domains of Protein A. Protein A is a surface protein from the bacterium *Staphylococcus aureus*. This scaffold domain consists of 58 amino acids, 13 of which are randomized to generate affibody libraries with a large number of ligand variants (See *e.g.*, US 5,831,012). Affibody molecules mimic antibodies, they have a molecular weight of 6 kDa, compared to the molecular weight of antibodies, which is 150 kDa. In spite of its small size, the binding site of affibody molecules is similar to that of an antibody.

[0157] Anticalins are products developed by the company Pieris ProteoLab AG. They are derived from lipocalins, a widespread group of small and robust proteins that are usually involved in the physiological transport or storage of chemically sensitive or insoluble compounds. Several natural lipocalins occur in human tissues or body liquids. The protein architecture is reminiscent of immunoglobulins, with hypervariable loops on top of a rigid framework. However, in contrast with antibodies or their recombinant fragments, lipocalins are composed of a single polypeptide chain with 160 to 180 amino acid residues, being just marginally bigger than a single immunoglobulin domain. The set of four loops, which makes up the binding pocket, shows pronounced structural plasticity and tolerates a variety of side chains. The binding site can thus be reshaped in a proprietary process in order to recognize prescribed target molecules of different shape with high affinity and specificity. One protein of lipocalin family, the bilin-binding protein (BBP) of *Pieris Brassicae* has been used to develop anticalins by mutagenizing the set of four loops. One example of a patent application describing anticalins is in PCT Publication No. WO 199916873.

[0158] Affilin molecules are small non-immunoglobulin proteins which are designed for specific affinities towards proteins and small molecules. New affilin molecules can be very quickly selected from two libraries, each of which is based on a different human derived scaffold protein. Affilin molecules do not show any structural homology to immunoglobulin proteins. Currently, two affilin scaffolds are employed, one of which is gamma crystalline, a human structural eye lens protein and the other is "ubiquitin" superfamily proteins. Both human scaffolds are very small, show high temperature stability and are almost resistant to pH changes and denaturing agents. This high stability is mainly due to the expanded beta sheet structure of the proteins. Examples of gamma crystalline derived proteins are described in WO200104144 and examples of "ubiquitin-like" proteins are described in WO2004106368.

[0159] Protein epitope mimetics (PEM) are medium-sized, cyclic, peptide-like molecules (MW 1-2kDa) mimicking beta-hairpin secondary structures of proteins, the major secondary structure involved in protein-protein interactions.

[0160] The present invention provides fully human antibodies that specifically bind to a Factor P protein. Compared to the chimeric or humanized antibodies, the human Factor P-binding antibodies of the invention have further reduced antigenicity when administered to human subjects.

Camelid antibodies

[0161] Antibody proteins obtained from members of the camel and dromedary (*Camelus bactrianus* and *Camelus dromaderius*) family including new world members such as llama species (*Lama paccos*, *Lama glama* and *Lama vicugna*) have been characterized with respect to size, structural complexity and antigenicity for human subjects. Certain IgG antibodies from this family of mammals as found in nature lack light chains, and are thus structurally distinct from the

typical four chain quaternary structure having two heavy and two light chains, for antibodies from other animals. See PCT/EP93/02214 (WO 94/04678 published 3 March 1994).

[0162] A region of the camelid antibody which is the small single variable domain identified as VHH can be obtained by genetic engineering to yield a small protein having high affinity for a target, resulting in a low molecular weight antibody-derived protein known as a "camelid nanobody". See U.S. patent number 5,759,808 issued June 2, 1998; see also Stijlemans, B. et al., 2004 J Biol Chem 279: 1256-1261; Dumoulin, M. et al., 2003 Nature 424: 783-788; Pleschberger, M. et al. 2003 Bioconjugate Chem 14: 440-448; Cortez-Retamozo, V. et al. 2002 Int J Cancer 89: 456-62; and Lauwereys, M. et al. 1998 EMBO J 17: 3512-3520. Engineered libraries of camelid antibodies and antibody fragments are commercially available, for example, from Ablynx, Ghent, Belgium. As with other antibodies of non-human origin, an amino acid sequence of a camelid antibody can be altered recombinantly to obtain a sequence that more closely resembles a human sequence, *i.e.*, the nanobody can be "humanized". Thus the natural low antigenicity of camelid antibodies to humans can be further reduced.

[0163] The camelid nanobody has a molecular weight approximately one-tenth that of a human IgG molecule, and the protein has a physical diameter of only a few nanometers. One consequence of the small size is the ability of camelid nanobodies to bind to antigenic sites that are functionally invisible to larger antibody proteins, *i.e.*, camelid nanobodies are useful as reagents detect antigens that are otherwise cryptic using classical immunological techniques, and as possible therapeutic agents. Thus yet another consequence of small size is that a camelid nanobody can inhibit as a result of binding to a specific site in a groove or narrow cleft of a target protein, and hence can serve in a capacity that more closely resembles the function of a classical low molecular weight drug than that of a classical antibody.

[0164] The low molecular weight and compact size further result in camelid nanobodies being extremely thermostable, stable to extreme pH and to proteolytic digestion, and poorly antigenic. Another consequence is that camelid nanobodies readily move from the circulatory system into tissues, and even cross the blood-brain barrier and can treat disorders that affect nervous tissue. Nanobodies can further facilitated drug transport across the blood brain barrier. See U.S. patent application 20040161738 published August 19, 2004. These features combined with the low antigenicity to humans indicate great therapeutic potential. Further, these molecules can be fully expressed in prokaryotic cells such as *E. coli* and are expressed as fusion proteins with bacteriophage and are functional.

[0165] Accordingly, a feature of the present invention is a camelid antibody or nanobody having high affinity for Factor P. In certain embodiments herein, the camelid antibody or nanobody is naturally produced in the camelid animal, *i.e.*, is produced by the camelid following immunization with Factor P or a peptide fragment thereof, using techniques described herein for other antibodies. Alternatively, the Factor P-binding camelid nanobody is engineered, *i.e.*, produced by selection for example from a library of phage displaying appropriately mutagenized camelid nanobody proteins using panning procedures with Factor P as a target as described in the examples herein. Engineered nanobodies can further be customized by genetic engineering to have a half life in a recipient subject of from 45 minutes to two weeks. In a specific embodiment, the camelid antibody or nanobody is obtained by grafting the CDRs sequences of the heavy or light chain of the human antibodies of the invention into nanobody or single domain antibody framework sequences, as described for example in PCT/EP93/02214.

Bispecific Molecules and Multivalent Antibodies

[0166] In another aspect, the present invention features bispecific or multispecific molecules comprising a Factor P-binding antibody, or a fragment thereof, of the invention. An antibody of the invention, or antigen-binding regions thereof, can be derivatized or linked to another functional molecule, *e.g.*, another peptide or protein (*e.g.*, another antibody or ligand for a receptor) to generate a bispecific molecule that binds to at least two different binding sites or target molecules. The antibody of the invention may in fact be derivatized or linked to more than one other functional molecule to generate multi-specific molecules that bind to more than two different binding sites and/or target molecules; such multi-specific molecules are also intended to be encompassed by the term "bispecific molecule" as used herein. To create a bispecific molecule of the invention, an antibody of the invention can be functionally linked (*e.g.*, by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other binding molecules, such as another antibody, antibody fragment, peptide or binding mimetic, such that a bispecific molecule results.

[0167] Accordingly, the present invention includes bispecific molecules comprising at least one first binding specificity for Factor P and a second binding specificity for a second target epitope. For example, the second target epitope is another epitope of Factor P different from the first target epitope.

[0168] Additionally, for the invention in which the bispecific molecule is multi-specific, the molecule can further include a third binding specificity, in addition to the first and second target epitope.

[0169] In one embodiment, the bispecific molecules of the invention comprise as a binding specificity at least one antibody, or an antibody fragment thereof, including, *e.g.*, a Fab, Fab', F(ab')₂, Fv, or a single chain Fv. The antibody may also be a light chain or heavy chain dimer, or any minimal fragment thereof such as a Fv or a single chain construct as described in Ladner et al. U.S. Patent No. 4,946,778.

[0170] Diabodies are bivalent, bispecific molecules in which VH and VL domains are expressed on a single polypeptide chain, connected by a linker that is too short to allow for pairing between the two domains on the same chain. The VH and VL domains pair with complementary domains of another chain, thereby creating two antigen binding sites (see e.g., Holliger et al., 1993 Proc. Natl. Acad. Sci. USA 90:6444-6448; Poljak et al., 1994 Structure 2:1121-1123). Diabodies can be produced by expressing two polypeptide chains with either the structure VHA-VLB and VHB-VLA (VH-VL configuration), or VLA-VHB and VLB-VHA (VL-VH configuration) within the same cell. Most of them can be expressed in soluble form in bacteria. Single chain diabodies (scDb) are produced by connecting the two diabody-forming polypeptide chains with linker of approximately 15 amino acid residues (see Holliger and Winter, 1997 Cancer Immunol. Immunother., 45(3-4):128-30; Wu et al., 1996 Immunotechnology, 2(1):21-36). scDb can be expressed in bacteria in soluble, active monomeric form (see Holliger and Winter, 1997 Cancer Immunol. Immunother., 45(34): 128-30; Wu et al., 1996 Immunotechnology, 2(1):21-36; Pluckthun and Pack, 1997 Immunotechnology, 3(2): 83-105; Ridgway et al., 1996 Protein Eng., 9(7):617-21). A diabody can be fused to Fc to generate a "di-diabody" (see Lu et al., 2004 J. Biol. Chem., 279(4):2856-65).

[0171] Other antibodies which can be employed in the bispecific molecules of the invention are murine, chimeric and humanized monoclonal antibodies.

[0172] Bispecific molecules can be prepared by conjugating the constituent binding specificities, using methods known in the art. For example, each binding specificity of the bispecific molecule can be generated separately and then conjugated to one another. When the binding specificities are proteins or peptides, a variety of coupling or cross-linking agents can be used for covalent conjugation. Examples of cross-linking agents include protein A, carbodiimide, N-succinimidyl-S-acetyl-thioacetate (SATA), 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB), o-phenylenedimaleimide (oPDM), N-succinimidyl-3-(2-pyridyldithio)propionate (SPDP), and sulfosuccinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (sulfo-SMCC) (see e.g., Karpovsky et al., 1984 J. Exp. Med. 160:1686; Liu, MA et al., 1985 Proc. Natl. Acad. Sci. USA 82:8648). Other methods include those described in Paulus, 1985 Behring Ins. Mitt. No. 78,118-132; Brennan et al., 1985 Science 229:81-83), and Glennie et al., 1987 J. Immunol. 139: 2367-2375). Conjugating agents are SATA and sulfo-SMCC, both available from Pierce Chemical Co. (Rockford, IL).

[0173] When the binding specificities are antibodies, they can be conjugated by sulfhydryl bonding of the C-terminus hinge regions of the two heavy chains. In a particularly embodiment, the hinge region is modified to contain an odd number of sulfhydryl residues, for example one, prior to conjugation.

[0174] Alternatively, both binding specificities can be encoded in the same vector and expressed and assembled in the same host cell. This method is particularly useful where the bispecific molecule is a mAb x mAb, mAb x Fab, Fab x F(ab')₂ or ligand x Fab fusion protein. A bispecific molecule of the invention can be a single chain molecule comprising one single chain antibody and a binding determinant, or a single chain bispecific molecule comprising two binding determinants. Bispecific molecules may comprise at least two single chain molecules. Methods for preparing bispecific molecules are described for example in U.S. Patent Number 5,260,203; U.S. Patent Number 5,455,030; U.S. Patent Number 4,881,175; U.S. Patent Number 5,132,405; U.S. Patent Number 5,091,513; U.S. Patent Number 5,476,786; U.S. Patent Number 5,013,653; U.S. Patent Number 5,258,498; and U.S. Patent Number 5,482,858.

[0175] Binding of the bispecific molecules to their specific targets can be confirmed by, for example, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (REA), FACS analysis, bioassay (e.g., growth inhibition), or Western Blot assay. Each of these assays generally detects the presence of protein-antibody complexes of particular interest by employing a labeled reagent (e.g., an antibody) specific for the complex of interest.

[0176] In another aspect, the present invention provides multivalent compounds comprising at least two identical or different antigen-binding portions of the antibodies of the invention binding to Factor P. The antigen-binding portions can be linked together via protein fusion or covalent or non covalent linkage. Alternatively, methods of linkage have been described for the bispecific molecules. Tetravalent compounds can be obtained for example by cross-linking antibodies of the antibodies of the invention with an antibody that binds to the constant regions of the antibodies of the invention, for example the Fc or hinge region.

[0177] Trimerizing domain are described for example in Borean patent EP 1 012 280B1. Pentamerizing modules are described for example in PCT/EP97/05897.

Antibodies with Extended Half Life

[0178] The present invention provides for antibodies that specifically bind to Factor P protein which have an extended half-life *in vivo*.

[0179] Many factors may affect a protein's half life *in vivo*. For examples, kidney filtration, metabolism in the liver, degradation by proteolytic enzymes (proteases), and immunogenic responses (e.g., protein neutralization by antibodies and uptake by macrophages and dendritic cells). A variety of strategies can be used to extend the half life of the antibodies of the present invention. For example, by chemical linkage to polyethyleneglycol (PEG), reCODE PEG, antibody scaffold, polysialic acid (PSA), hydroxyethyl starch (HES), albumin-binding ligands, and carbohydrate shields; by genetic fusion

to proteins binding to serum proteins, such as albumin, IgG, FcRn, and transferring; by coupling (genetically or chemically) to other binding moieties that bind to serum proteins, such as nano-boies, Fabs, DARPinS, avimers, affibodies, and anticalins; by genetic fusion to rPEG, albumin, domain of albumin, albumin-binding proteins, and Fc; or by incorporation into nanocarriers, slow release formulations, or medical devices.

[0180] To prolong the serum circulation of antibodies *in vivo*, inert polymer molecules such as high molecular weight PEG can be attached to the antibodies or a fragment thereof with or without a multifunctional linker either through site-specific conjugation of the PEG to the N- or C-terminus of the antibodies or via epsilon-amino groups present on lysine residues. To pegylate an antibody, the antibody, or fragment thereof, typically is reacted with polyethylene glycol (PEG), such as a reactive ester or aldehyde derivative of PEG, under conditions in which one or more PEG groups become attached to the antibody or antibody fragment. The pegylation can be carried out by an acylation reaction or an alkylation reaction with a reactive PEG molecule (or an analogous reactive water-soluble polymer). As used herein, the term "polyethylene glycol" is intended to encompass any of the forms of PEG that have been used to derivatize other proteins, such as mono (C1-C10) alkoxy- or aryloxy-polyethylene glycol or polyethylene glycol-maleimide. In certain embodiments, the antibody to be pegylated is an aglycosylated antibody. Linear or branched polymer derivatization that results in minimal loss of biological activity will be used. The degree of conjugation can be closely monitored by SDS-PAGE and mass spectrometry to ensure proper conjugation of PEG molecules to the antibodies. Unreacted PEG can be separated from antibody-PEG conjugates by size-exclusion or by ion-exchange chromatography. PEG-derivatized antibodies can be tested for binding activity as well as for *in vivo* efficacy using methods well-known to those of skill in the art, for example, by immunoassays described herein. Methods for pegylating proteins are known in the art and can be applied to the antibodies of the invention. See for example, EP 0 154 316 by Nishimura et al. and EP 0 401 384 by Ishikawa et al.

[0181] Other modified pegylation technologies include reconstituting chemically orthogonal directed engineering technology (ReCODE PEG), which incorporates chemically specified side chains into biosynthetic proteins via a reconstituted system that includes tRNA synthetase and tRNA. This technology enables incorporation of more than 30 new amino acids into biosynthetic proteins in *E. coli*, yeast, and mammalian cells. The tRNA incorporates a nonnative amino acid any place an amber codon is positioned, converting the amber from a stop codon to one that signals incorporation of the chemically specified amino acid.

[0182] Recombinant pegylation technology (rPEG) can also be used for serum half-life extension. This technology involves genetically fusing a 300-600 amino acid unstructured protein tail to an existing pharmaceutical protein. Because the apparent molecular weight of such an unstructured protein chain is about 15-fold larger than its actual molecular weight, the serum half-life of the protein is greatly increased. In contrast to traditional PEGylation, which requires chemical conjugation and repurification, the manufacturing process is greatly simplified and the product is homogeneous.

[0183] Polysialylation is another technology, which uses the natural polymer polysialic acid (PSA) to prolong the active life and improve the stability of therapeutic peptides and proteins. PSA is a polymer of sialic acid (a sugar). When used for protein and therapeutic peptide drug delivery, polysialic acid provides a protective microenvironment on conjugation. This increases the active life of the therapeutic protein in the circulation and prevents it from being recognized by the immune system. The PSA polymer is naturally found in the human body. It was adopted by certain bacteria which evolved over millions of years to coat their walls with it. These naturally polysialylated bacteria were then able, by virtue of molecular mimicry, to foil the body's defense system. PSA, nature's ultimate stealth technology, can be easily produced from such bacteria in large quantities and with predetermined physical characteristics. Bacterial PSA is completely non-immunogenic, even when coupled to proteins, as it is chemically identical to PSA in the human body.

[0184] Another technology includes the use of hydroxyethyl starch ("HES") derivatives linked to antibodies. HES is a modified natural polymer derived from waxy maize starch and can be metabolized by the body's enzymes. HES solutions are usually administered to substitute deficient blood volume and to improve the rheological properties of the blood. Hesylation of an antibody enables the prolongation of the circulation half-life by increasing the stability of the molecule, as well as by reducing renal clearance, resulting in an increased biological activity. By varying different parameters, such as the molecular weight of HES, a wide range of HES antibody conjugates can be customized.

[0185] Antibodies having an increased half-life *in vivo* can also be generated introducing one or more amino acid modifications (*i.e.*, substitutions, insertions or deletions) into an IgG constant domain, or FcRn binding fragment thereof (preferably a Fc or hinge Fc domain fragment). See, *e.g.*, International Publication No. WO 98/23289; International Publication No. WO 97/34631; and U.S. Patent No. 6,277,375.

[0186] Further, antibodies can be conjugated to albumin (*e.g.*, human serum albumin; HSA) in order to make the antibody or antibody fragment more stable *in vivo* or have a longer half life *in vivo*. The techniques are well-known in the art, see, *e.g.*, International Publication Nos. WO 93/15199, WO 93/15200, and WO 01/77137; and European Patent No. EP 413,622. In addition, in the context of a bispecific antibody as described above, the specificities of the antibody can be designed such that one binding domain of the antibody binds to Factor P while a second binding domain of the antibody binds to serum albumin, preferably HSA.

[0187] The strategies for increasing half life is especially useful in nanobodies, fibronectin-based binders, and other antibodies or proteins for which increased *in vivo* half life is desired.

Antibody Conjugates

[0188] The present invention provides antibodies or fragments thereof that specifically bind to a Factor P protein recombinantly fused or chemically conjugated (including both covalent and non-covalent conjugations) to a heterologous protein or polypeptide (or fragment thereof, preferably to a polypeptide of at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90 or at least 100 amino acids) to generate fusion proteins. In particular, the invention provides fusion proteins comprising an antigen-binding fragment of an antibody described herein (e.g., a Fab fragment, Fd fragment, Fv fragment, F(ab)₂ fragment, a VH domain, a VH CDR, a VL domain or a VL CDR) and a heterologous protein, polypeptide, or peptide. Methods for fusing or conjugating proteins, polypeptides, or peptides to an antibody or an antibody fragment are known in the art. See, e.g., U.S. Patent Nos. 5,336,603, 5,622,929, 5,359,046, 5,349,053, 5,447,851, and 5,112,946; European Patent Nos. EP 307,434 and EP 367,166; International Publication Nos. WO 96/04388 and WO 91/06570; Ashkenazi et al., 1991, Proc. Natl. Acad. Sci. USA 88: 10535-10539; Zheng et al., 1995, J. Immunol. 154:5590-5600; and Vil et al., 1992, Proc. Natl. Acad. Sci. USA 89:11337-11341.

[0189] Additional fusion proteins may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to alter the activities of antibodies of the invention or fragments thereof (e.g., antibodies or fragments thereof with higher affinities and lower dissociation rates). See, generally, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458; Patten et al., 1997, Curr. Opin. Biotechnol. 8:724-33; Harayama, 1998, Trends Biotechnol. 16(2):76-82; Hansson, et al., 1999, J. Mol. Biol. 287:265-76; and Lorenzo and Blasco, 1998, Biotechniques 24(2):308-313 (each of these patents and publications are hereby incorporated by reference in its entirety). Antibodies or fragments thereof, or the encoded antibodies or fragments thereof, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. A polynucleotide encoding an antibody or fragment thereof that specifically binds to a Factor P protein may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

[0190] Moreover, the antibodies or fragments thereof can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., 1989, Proc. Natl. Acad. Sci. USA 86:821-824, for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin ("HA") tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., 1984, Cell 37:767), and the "flag" tag.

[0191] In other embodiments, antibodies of the present invention or fragments thereof conjugated to a diagnostic or detectable agent. Such antibodies can be useful for monitoring or prognosing the onset, development, progression and/or severity of a disease or disorder as part of a clinical testing procedure, such as determining the efficacy of a particular therapy. Such diagnosis and detection can be accomplished by coupling the antibody to detectable substances including, but not limited to, various enzymes, such as, but not limited to, horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; prosthetic groups, such as, but not limited to, streptavidin/biotin and avidin/biotin; fluorescent materials, such as, but not limited to, umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; luminescent materials, such as, but not limited to, luminol; bioluminescent materials, such as but not limited to, luciferase, luciferin, and aequorin; radioactive materials, such as, but not limited to, iodine (131I, 125I, 123I, and 121I), carbon (14C), sulfur (35S), tritium (3H), indium (115In, 113In, 112In, and 111In), technetium (99Tc), thallium (201Tl), gallium (68Ga, 67Ga), palladium (103Pd), molybdenum (99Mo), xenon (133Xe), fluorine (18F), 153Sm, 177Lu, 159Gd, 149Pm, 140La, 175Yb, 166Ho, 90Y, 47Sc, 186Re, 188Re, 142Pr, 105Rh, 97Ru, 68Ge, 57Co, 65Zn, 85Sr, 32P, 153Gd, 169Yb, 51Cr, 54Mn, 75Se, 113Sn, and 117Tm; and positron emitting metals using various positron emission tomographies, and noradioactive paramagnetic metal ions.

[0192] The present invention further encompasses uses of antibodies or fragments thereof conjugated to a therapeutic moiety. An antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytotoxic agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells.

[0193] Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety or drug moiety that modifies a given biological response. Therapeutic moieties or drug moieties are not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein, peptide, or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, cholera toxin, or diphtheria toxin; a protein such as tumor necrosis factor, α -interferon, β -interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, an anti-angiogenic agent; or, a biological response modifier such as, for example, a lymphokine.

[0194] Moreover, an antibody can be conjugated to therapeutic moieties such as a radioactive metal ion, such as alph-

emitters such as ^{213}Bi or macrocyclic chelators useful for conjugating radiometal ions, including but not limited to, ^{131}In , ^{131}Lu , ^{131}Y , ^{131}Ho , ^{131}Sm , to polypeptides. In certain embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) which can be attached to the antibody via a linker molecule. Such linker molecules are commonly known in the art and described in Denardo et al., 1998, Clin Cancer Res. 4(10):2483-90; Peterson et al., 1999, Bioconjug. Chem. 10(4):553-7; and Zimmerman et al., 1999, Nucl. Med. Biol. 26(8):943-50, each incorporated by reference in their entireties.

[0195] Techniques for conjugating therapeutic moieties to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies 84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., 1982, Immunol. Rev. 62:119-58.

[0196] Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

Methods of Producing Antibodies of the Invention

Nucleic Acids Encoding the Antibodies

[0197] The invention provides substantially purified nucleic acid molecules which encode polypeptides comprising segments or domains of the Factor P-binding antibody chains described above. Some of the nucleic acids of the invention comprise the nucleotide sequence encoding the heavy chain variable region shown in SEQ ID NO: 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175, 189, 203, 217, 231, 245, 259 or 273, and/or the nucleotide sequence encoding the light chain variable region shown in SEQ ID NO: 8, 22, 36, 50, 64, 78, 92, 106, 120, 134, 148, 162, 176, 190, 204, 218, 232, 246, 260, or 274. In a specific embodiment, the nucleic acid molecules are those identified in Table 1. Some other nucleic acid molecules of the invention comprise nucleotide sequences that are substantially identical (e.g., at least 65, 80%, 95%, or 99%) to the nucleotide sequences of those identified in Table 1. When expressed from appropriate expression vectors, polypeptides encoded by these polynucleotides are capable of exhibiting Factor P antigen binding capacity.

[0198] Also provided in the invention are polynucleotides which encode at least one CDR region and usually all three CDR regions from the heavy or light chain of the Factor P-binding antibody set forth above. Some other polynucleotides encode all or substantially all of the variable region sequence of the heavy chain and/or the light chain of the Factor P-binding antibody set forth above. Because of the degeneracy of the code, a variety of nucleic acid sequences will encode each of the immunoglobulin amino acid sequences.

[0199] The nucleic acid molecules of the invention can encode both a variable region and a constant region of the antibody. Some of nucleic acid sequences of the invention comprise nucleotides encoding a mature heavy chain sequence that is substantially identical (e.g., at least 80%, 90%, or 99%) to the mature heavy chain sequence set forth in SEQ ID NO: 9, 23, 37, 51, 65, 79, 93, 107, 121, 135, 149, 163, 177, 191, 205, 219, 233, 247, 261 or 275. Some other nucleic acid sequences comprising nucleotide encoding a mature light chain sequence that is substantially identical (e.g., at least 80%, 90%, or 99%) to the mature light chain sequence set forth in SEQ ID NO: 10, 24, 38, 52, 66, 80, 94, 108, 122, 136, 150, 164, 178, 192, 206, 220, 234, 248, 262, or 276.

[0200] The polynucleotide sequences can be produced by de novo solid-phase DNA synthesis or by PCR mutagenesis of an existing sequence (e.g., sequences as described in the Examples below) encoding a Factor P-binding antibody or its binding fragment. Direct chemical synthesis of nucleic acids can be accomplished by methods known in the art, such as the phosphotriester method of Narang et al., 1979, Meth. Enzymol. 68:90; the phosphodiester method of Brown et al., Meth. Enzymol. 68:109, 1979; the diethylphosphoramidite method of Beaucage et al., Tetra. Lett., 22:1859, 1981; and the solid support method of U.S. Patent No. 4,458,066. Introducing mutations to a polynucleotide sequence by PCR can be performed as described in, e.g., PCR Technology: Principles and Applications for DNA Amplification, H.A. Erlich (Ed.), Freeman Press, NY, NY, 1992; PCR Protocols: A Guide to Methods and Applications, Innis et al. (Ed.), Academic Press, San Diego, CA, 1990; Mattila et al., Nucleic Acids Res. 19:967, 1991; and Eckert et al., PCR Methods and Applications 1:17, 1991.

[0201] Also provided in the invention are expression vectors and host cells for producing the Factor P-binding antibodies described above. Various expression vectors can be employed to express the polynucleotides encoding the Factor P-binding antibody chains or binding fragments. Both viral-based and nonviral expression vectors can be used to produce the antibodies in a mammalian host cell. Nonviral vectors and systems include plasmids, episomal vectors, typically with

an expression cassette for expressing a protein or RNA, and human artificial chromosomes (see, e.g., Harrington et al., Nat Genet 15:345, 1997). For example, nonviral vectors useful for expression of the Factor P-binding polynucleotides and polypeptides in mammalian (e.g., human) cells include pThioHis A, B & C, pcDNA3.1/His, pEBVHis A, B & C, (Invitrogen, San Diego, CA), MPSV vectors, and numerous other vectors known in the art for expressing other proteins.

Useful viral vectors include vectors based on retroviruses, adenoviruses, adenoassociated viruses, herpes viruses, vectors based on SV40, papilloma virus, HBP Epstein Barr virus, vaccinia virus vectors and Semliki Forest virus (SFV). See, Brent *et al.*, supra; Smith, Annu. Rev. Microbiol. 49:807, 1995; and Rosenfeld et al., Cell 68:143, 1992.

[0202] The choice of expression vector depends on the intended host cells in which the vector is to be expressed. Typically, the expression vectors contain a promoter and other regulatory sequences (e.g., enhancers) that are operably linked to the polynucleotides encoding a Factor P-binding antibody chain or fragment. In some embodiments, an inducible promoter is employed to prevent expression of inserted sequences except under inducing conditions. Inducible promoters include, e.g., arabinose, lacZ, metallothionein promoter or a heat shock promoter. Cultures of transformed organisms can be expanded under noninducing conditions without biasing the population for coding sequences whose expression products are better tolerated by the host cells. In addition to promoters, other regulatory elements may also be required or desired for efficient expression of a Factor P-binding antibody chain or fragment. These elements typically include an ATG initiation codon and adjacent ribosome binding site or other sequences. In addition, the efficiency of expression may be enhanced by the inclusion of enhancers appropriate to the cell system in use (see, e.g., Scharf et al., Results Probl. Cell Differ. 20:125, 1994; and Bittner et al., Meth. Enzymol., 153:516, 1987). For example, the SV40 enhancer or CMV enhancer may be used to increase expression in mammalian host cells.

[0203] The expression vectors may also provide a secretion signal sequence position to form a fusion protein with polypeptides encoded by inserted Factor P-binding antibody sequences. More often, the inserted Factor P-binding antibody sequences are linked to a signal sequences before inclusion in the vector. Vectors to be used to receive sequences encoding Factor P-binding antibody light and heavy chain variable domains sometimes also encode constant regions or parts thereof. Such vectors allow expression of the variable regions as fusion proteins with the constant regions thereby leading to production of intact antibodies or fragments thereof. Typically, such constant regions are human.

[0204] The host cells for harboring and expressing the Factor P-binding antibody chains can be either prokaryotic or eukaryotic. *E. coli* is one prokaryotic host useful for cloning and expressing the polynucleotides of the present invention. Other microbial hosts suitable for use include bacilli, such as *Bacillus subtilis*, and other enterobacteriaceae, such as *Salmonella*, *Serratia*, and various *Pseudomonas* species. In these prokaryotic hosts, one can also make expression vectors, which typically contain expression control sequences compatible with the host cell (e.g., an origin of replication). In addition, any number of a variety of well-known promoters will be present, such as the lactose promoter system, a tryptophan (*trp*) promoter system, a beta-lactamase promoter system, or a promoter system from phage lambda. The promoters typically control expression, optionally with an operator sequence, and have ribosome binding site sequences and the like, for initiating and completing transcription and translation. Other microbes, such as yeast, can also be employed to express Factor P-binding polypeptides of the invention. Insect cells in combination with baculovirus vectors can also be used.

[0205] In some preferred embodiments, mammalian host cells are used to express and produce the Factor P-binding polypeptides of the present invention. For example, they can be either a hybridoma cell line expressing endogenous immunoglobulin genes (e.g., the 1D6.C9 myeloma hybridoma clone as described in the Examples) or a mammalian cell line harboring an exogenous expression vector (e.g., the SP2/0 myeloma cells exemplified below). These include any normal mortal or normal or abnormal immortal animal or human cell. For example, a number of suitable host cell lines capable of secreting intact immunoglobulins have been developed including the CHO cell lines, various Cos cell lines, HeLa cells, myeloma cell lines, transformed B-cells and hybridomas. The use of mammalian tissue cell culture to express polypeptides is discussed generally in, e.g., Winnacker, FROM GENES TO CLONES, VCH Publishers, N.Y., N.Y., 1987. Expression vectors for mammalian host cells can include expression control sequences, such as an origin of replication, a promoter, and an enhancer (see, e.g., Queen, et al., Immunol. Rev. 89:49-68, 1986), and necessary processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites, and transcriptional terminator sequences. These expression vectors usually contain promoters derived from mammalian genes or from mammalian viruses. Suitable promoters may be constitutive, cell type-specific, stage-specific, and/or modulatable or regulatable. Useful promoters include, but are not limited to, the metallothionein promoter, the constitutive adenovirus major late promoter, the dexamethasone-inducible MMTV promoter, the SV40 promoter, the MRP polIII promoter, the constitutive MPSV promoter, the tetracycline-inducible CMV promoter (such as the human immediate-early CMV promoter), the constitutive CMV promoter, and promoter-enhancer combinations known in the art.

[0206] Methods for introducing expression vectors containing the polynucleotide sequences of interest vary depending on the type of cellular host. For example, calcium chloride transfection is commonly utilized for prokaryotic cells, whereas calcium phosphate treatment or electroporation may be used for other cellular hosts. (See generally Sambrook, *et al.*, supra). Other methods include, e.g., electroporation, calcium phosphate treatment, liposome-mediated transformation,

injection and microinjection, ballistic methods, virosomes, immunoliposomes, polycation:nucleic acid conjugates, naked DNA, artificial virions, fusion to the herpes virus structural protein VP22 (Elliot and O'Hare, Cell 88:223, 1997), agent-enhanced uptake of DNA, and ex vivo transduction. For long-term, high-yield production of recombinant proteins, stable expression will often be desired. For example, cell lines which stably express Factor P-binding antibody chains or binding fragments can be prepared using expression vectors of the invention which contain viral origins of replication or endogenous expression elements and a selectable marker gene. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth of cells which successfully express the introduced sequences in selective media. Resistant, stably transfected cells can be proliferated using tissue culture techniques appropriate to the cell type.

Generation of monoclonal antibodies of the invention

[0207] Monoclonal antibodies (mAbs) can be produced by a variety of techniques, including conventional monoclonal antibody methodology *e.g.*, the standard somatic cell hybridization technique of Kohler and Milstein, 1975 Nature 256: 495. Many techniques for producing monoclonal antibody can be employed *e.g.*, viral or oncogenic transformation of B lymphocytes.

[0208] An animal systems for preparing hybridomas include the murine, rat and rabbit systems. Hybridoma production in the mouse is a well established procedure. Immunization protocols and techniques for isolation of immunized splenocytes for fusion are known in the art. Fusion partners (*e.g.*, murine myeloma cells) and fusion procedures are also known.

[0209] Chimeric or humanized antibodies of the present invention can be prepared based on the sequence of a murine monoclonal antibody prepared as described above. DNA encoding the heavy and light chain immunoglobulins can be obtained from the murine hybridoma of interest and engineered to contain non-murine (*e.g.*, human) immunoglobulin sequences using standard molecular biology techniques. For example, to create a chimeric antibody, the murine variable regions can be linked to human constant regions using methods known in the art (see *e.g.*, U.S. Patent No. 4,816,567 to Cabilly *et al.*). To create a humanized antibody, the murine CDR regions can be inserted into a human framework using methods known in the art. See *e.g.*, U.S. Patent No. 5,225,539 to Winter, and U.S. Patent Nos. 5,530,101; 5,585,089; 5,693,762 and 6,180,370 to Queen *et al.*

[0210] In a certain embodiment, the antibodies of the invention are human monoclonal antibodies. Such human monoclonal antibodies directed against Factor P can be generated using transgenic or transchromosomal mice carrying parts of the human immune system rather than the mouse system. These transgenic and transchromosomal mice include mice referred to herein as HuMAb mice and KM mice, respectively, and are collectively referred to herein as "human Ig mice."

[0211] The HuMAb mouse® (Medarex, Inc.) contains human immunoglobulin gene miniloci that encode un-rearranged human heavy (μ and γ) and κ light chain immunoglobulin sequences, together with targeted mutations that inactivate the endogenous μ and κ chain loci (see *e.g.*, Lonberg, *et al.*, 1994 Nature 368(6474): 856-859). Accordingly, the mice exhibit reduced expression of mouse IgM or κ , and in response to immunization, the introduced human heavy and light chain transgenes undergo class switching and somatic mutation to generate high affinity human IgG κ monoclonal (Lonberg, N. *et al.*, 1994 *supra*; reviewed in Lonberg, N., 1994 Handbook of Experimental Pharmacology 113:49-101; Lonberg, N. and Huszar, D., 1995 Intern. Rev. Immunol.13: 65-93, and Harding, F. and Lonberg, N., 1995 Ann. N. Y. Acad. Sci. 764:536-546). The preparation and use of HuMAb mice, and the genomic modifications carried by such mice, is further described in Taylor, L. *et al.*, 1992 Nucleic Acids Research 20:6287-6295; Chen, J. *et al.*, 1993 International Immunology 5: 647-656; Tuailon *et al.*, 1993 Proc. Natl. Acad. Sci. USA 94:3720-3724; Choi *et al.*, 1993 Nature Genetics 4:117-123; Chen, J. *et al.*, 1993 EMBO J. 12: 821-830; Tuailon *et al.*, 1994 J. Immunol. 152:2912-2920; Taylor, L. *et al.*, 1994 International Immunology 579-591; and Fishwild, D. *et al.*, 1996 Nature Biotechnology 14: 845-851, the contents of all of which are hereby specifically incorporated by reference in their entirety. See further, U.S. Patent Nos. 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,789,650; 5,877,397; 5,661,016; 5,814,318; 5,874,299; and 5,770,429; all to Lonberg and Kay; U.S. Patent No. 5,545,807 to Surani *et al.*; PCT Publication Nos. WO 92103918, WO 93/12227, WO 94/25585, WO 97113852, WO 98/24884 and WO 99/45962, all to Lonberg and Kay; and PCT Publication No. WO 01/14424 to Korman *et al.*

[0212] In another embodiment, human antibodies of the invention can be raised using a mouse that carries human immunoglobulin sequences on transgenes and transchromosomes such as a mouse that carries a human heavy chain transgene and a human light chain transchromosome. Such mice, referred to herein as "KM mice", are described in detail in PCT Publication WO 02/43478 to Ishida *et al.*

[0213] Still further, alternative transgenic animal systems expressing human immunoglobulin genes are available in the art and can be used to raise Factor P-binding antibodies of the invention. For example, an alternative transgenic system referred to as the Xenomouse (Abgenix, Inc.) can be used. Such mice are described in, *e.g.*, U.S. Patent Nos. 5,939,598; 6,075,181; 6,114,598; 6,150,584 and 6,162,963 to Kucherlapati *et al.*

[0214] Moreover, alternative transchromosomal animal systems expressing human immunoglobulin genes are available in the art and can be used to raise Factor P -binding antibodies of the invention. For example, mice carrying both a human heavy chain transchromosome and a human light chain transchromosome, referred to as "TC mice" can be used; such mice are described in Tomizuka et al., 2000 Proc. Natl. Acad. Sci. USA 97:722-727. Furthermore, cows

carrying human heavy and light chain transchromosomes have been described in the art (Kuroiwa et al., 2002 Nature Biotechnology 20:889-894) and can be used to raise Factor P -binding antibodies of the invention.

[0215] Human monoclonal antibodies of the invention can also be prepared using phage display methods for screening libraries of human immunoglobulin genes. Such phage display methods for isolating human antibodies are established in the art or described in the examples below. See for example: U.S. Patent Nos. 5,223,409; 5,403,484; and 5,571,698 to Ladner et al.; U.S. Patent Nos. 5,427,908 and 5,580,717 to Dower et al.; U.S. Patent Nos. 5,969,108 and 6,172,197 to McCafferty et al.; and U.S. Patent Nos. 5,885,793; 6,521,404; 6,544,731; 6,555,313; 6,582,915 and 6,593,081 to Griffiths et al.

[0216] Human monoclonal antibodies of the invention can also be prepared using SCID mice into which human immune cells have been reconstituted such that a human antibody response can be generated upon immunization. Such mice are described in, for example, U.S. Patent Nos. 5,476,996 and 5,698,767 to Wilson et al.

Framework or Fc engineering

[0217] Engineered antibodies of the invention include those in which modifications have been made to framework residues within VH and/or VL, e.g. to improve the properties of the antibody. Typically such framework modifications are made to decrease the immunogenicity of the antibody. For example, one approach is to "backmutate" one or more framework residues to the corresponding germline sequence. More specifically, an antibody that has undergone somatic mutation may contain framework residues that differ from the germline sequence from which the antibody is derived. Such residues can be identified by comparing the antibody framework sequences to the germline sequences from which the antibody is derived. To return the framework region sequences to their germline configuration, the somatic mutations can be "backmutated" to the germline sequence by, for example, site-directed mutagenesis. Such "backmutated" antibodies are also intended to be encompassed by the invention.

[0218] Another type of framework modification involves mutating one or more residues within the framework region, or even within one or more CDR regions, to remove T cell - epitopes to thereby reduce the potential immunogenicity of the antibody. This approach is also referred to as "deimmunization" and is described in further detail in U.S. Patent Publication No. 20030153043 by Carr et al.

[0219] In addition or alternative to modifications made within the framework or CDR regions, antibodies of the invention may be engineered to include modifications within the Fc region, typically to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding, and/or antigen-dependent cellular cytotoxicity. Furthermore, an antibody of the invention may be chemically modified (e.g., one or more chemical moieties can be attached to the antibody) or be modified to alter its glycosylation, again to alter one or more functional properties of the antibody. Each of these embodiments is described in further detail below. The numbering of residues in the Fc region is that of the EU index of Kabat.

[0220] In one embodiment, the hinge region of CH1 is modified such that the number of cysteine residues in the hinge region is altered, e.g., increased or decreased. This approach is described further in U.S. Patent No. 5,677,425 by Bodmer et al. The number of cysteine residues in the hinge region of CH1 is altered to, for example, facilitate assembly of the light and heavy chains or to increase or decrease the stability of the antibody.

[0221] In another embodiment, the Fc hinge region of an antibody is mutated to decrease the biological half-life of the antibody. More specifically, one or more amino acid mutations are introduced into the CH2-CH3 domain interface region of the Fc-hinge fragment such that the antibody has impaired Staphylococcal protein A (SpA) binding relative to native Fc-hinge domain SpA binding. This approach is described in further detail in U.S. Patent No. 6,165,745 by Ward et al.

[0222] In another embodiment, the antibody is modified to increase its biological half-life. Various approaches are possible. For example, one or more of the following mutations can be introduced: T252L, T254S, T256F, as described in U.S. Patent No. 6,277,375 to Ward. Alternatively, to increase the biological half life, the antibody can be altered within the CH1 or CL region to contain a salvage receptor binding epitope taken from two loops of a CH2 domain of an Fc region of an IgG, as described in U.S. Patent Nos. 5,869,046 and 6,121,022 by Presta et al.

[0223] In yet other embodiments, the Fc region is altered by replacing at least one amino acid residue with a different amino acid residue to alter the effector functions of the antibody. For example, one or more amino acids can be replaced with a different amino acid residue such that the antibody has an altered affinity for an effector ligand but retains the antigen-binding ability of the parent antibody. The effector ligand to which affinity is altered can be, for example, an Fc receptor or the C1 component of complement. This approach is described in further detail in U.S. Patent Nos. 5,624,821 and 5,648,260, both by Winter *et al.*

[0224] In another embodiment, one or more amino acids selected from amino acid residues can be replaced with a

different amino acid residue such that the antibody has altered C1q binding and/or reduced or abolished complement dependent cytotoxicity (CDC). This approach is described in further detail in U.S. Patent Nos. 6,194,551 by Idusogie et al.

[0225] In another embodiment, one or more amino acid residues are altered to thereby alter the ability of the antibody to fix complement. This approach is described further in PCT Publication WO 94/29351 by Bodmer et al.

[0226] In yet another embodiment, the Fc region is modified to increase the ability of the antibody to mediate antibody dependent cellular cytotoxicity (ADCC) and/or to increase the affinity of the antibody for an Fc γ receptor by modifying one or more amino acids. This approach is described further in PCT Publication WO 00/42072 by Presta. Moreover, the binding sites on human IgG1 for Fc γ RI, Fc γ RII, Fc γ RIII and FcRn have been mapped and variants with improved binding have been described (see Shields, R.L. et al., 2001 J. Biol. Chem. 276:6591-6604).

[0227] In still another embodiment, the glycosylation of an antibody is modified. For example, an aglycosylated antibody can be made (*i.e.*, the antibody lacks glycosylation). Glycosylation can be altered to, for example, increase the affinity of the antibody for "antigen". Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence. For example, one or more amino acid substitutions can be made that result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site. Such aglycosylation may increase the affinity of the antibody for antigen. Such an approach is described in further detail in U.S. Patent Nos. 5,714,350 and 6,350,861 by Co et al.

[0228] Additionally or alternatively, an antibody can be made that has an altered type of glycosylation, such as a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNac structures. Such altered glycosylation patterns have been demonstrated to increase the ADCC ability of antibodies.

Such carbohydrate modifications can be accomplished by, for example, expressing the antibody in a host cell with altered glycosylation machinery. Cells with altered glycosylation machinery have been described in the art and can be used as host cells in which to express recombinant antibodies of the invention to thereby produce an antibody with altered glycosylation. For example, EP 1,176,195 by Hang et al. describes a cell line with a functionally disrupted FUT8 gene, which encodes a fucosyl transferase, such that antibodies expressed in such a cell line exhibit hypofucosylation. PCT Publication WO 03/035835 by Presta describes a variant CHO cell line, Lec13 cells, with reduced ability to attach fucose to Asn(297)-linked carbohydrates, also resulting in hypofucosylation of antibodies expressed in that host cell (see also Shields, R.L. et al., 2002 J. Biol. Chem. 277:26733-26740). PCT Publication WO 99/54342 by Umana et al. describes cell lines engineered to express glycoprotein-modifying glycosyl transferases (*e.g.*, beta(1,4)-N acetylglucosaminyltransferase III (GnTIII)) such that antibodies expressed in the engineered cell lines exhibit increased bisecting GlcNac structures which results in increased ADCC activity of the antibodies (see also Umana et al., 1999 Nat. Biotech. 17:176-180).

Methods of Engineering Altered Antibodies

[0229] As discussed above, the Factor P -binding antibodies having VH and VL sequences or full length heavy and light chain sequences shown herein can be used to create new Factor P-binding antibodies by modifying full length heavy chain and/or light chain sequences, VH and/or VL sequences, or the constant region(s) attached thereto. Thus, in another aspect of the invention, the structural features of a Factor P-binding antibody of the invention are used to create structurally related Factor P-binding antibodies that retain at least one functional property of the antibodies of the invention, such as binding to human Factor P and also inhibiting one or more functional properties of Factor P (*e.g.*, inhibiting MAC deposition in a MAC deposition assay, inhibit red blood cell lysis in a hemolytic assay).

[0230] For example, one or more CDR regions of the antibodies of the present invention, or mutations thereof, can be combined recombinantly with known framework regions and/or other CDRs to create additional, recombinantly-engineered, Factor P - binding antibodies of the invention, as discussed above. Other types of modifications include those described in the previous section. The starting material for the engineering method is one or more of the VH and/or VL sequences provided herein, or one or more CDR regions thereof. To create the engineered antibody, it is not necessary to actually prepare (*i.e.*, express as a protein) an antibody having one or more of the VH and/or VL sequences provided herein, or one or more CDR regions thereof. Rather, the information contained in the sequence(s) is used as the starting material to create a "second generation" sequence(s) derived from the original sequence(s) and then the "second generation" sequence(s) is prepared and expressed as a protein.

[0231] Accordingly, in another embodiment, the invention provides a method for preparing a Factor P-binding antibody consisting of a heavy chain variable region antibody sequence having a CDR1 sequence selected from the group consisting of SEQ ID NOs: 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, 169, 183, 197, 211, 225, 239, 253, and 267, a CDR2 sequence selected from the group consisting of SEQ ID NOs: 2, 16, 30, 44, 58, 72, 86, 100, 114, 128, 142, 156, 170, 184, 198, 212, 226, 240, 254, and 268, and/or a CDR3 sequence selected from the group consisting of SEQ ID NOs: 3, 17, 31, 45, 59, 73, 87, 101, 115, 129, 143, 157, 171, 185, 199, 213, 227, 241, 255, and 269; and a light chain variable region antibody sequence having a CDR1 sequence selected from the group consisting of SEQ ID NOs: 4, 18, 32, 46, 60, 74, 88, 102, 116, 130, 144, 158, 172, 186, 200, 214, 228, 242, 256, and 270, a CDR2 sequence selected from the group consisting of SEQ ID NOs: 5, 19, 33, 47, 61, 75, 89, 103, 117, 131, 145, 159, 173, 187, 201,

215, 229, 243, 257, and 271, and/or a CDR3 sequence selected from the group consisting of SEQ ID NOs: 6, 20, 34, 48, 62, 76, 90, 104, 118, 132, 146, 160, 174, 188, 202, 216, 230, 244, 258, and 272; altering at least one amino acid residue within the heavy chain variable region antibody sequence and/or the light chain variable region antibody sequence to create at least one altered antibody sequence; and expressing the altered antibody sequence as a protein.

[0232] Accordingly, in another embodiment, the invention provides a method for preparing a Factor P-binding antibody consisting of a heavy chain variable region antibody sequence having a CDR1 sequence selected from the group consisting of SEQ ID NOs: 281, 287, 293, 299, 305, 311, 317, 323, 329, 335, 341, 347, 353, 359, 365, 371, 377, 383, 389, and 395, a CDR2 sequence selected from the group consisting of SEQ ID NOs: 282, 288, 294, 300, 306, 312, 318, 324, 330, 336, 342, 348, 354, 360, 366, 372, 378, 384, 390, and 396, and/or a CDR3 sequence selected from the group consisting of SEQ ID NOs: 283, 289, 295, 301, 307, 313, 319, 325, 331, 337, 343, 349, 355, 361, 367, 373, 379, 385, 391, and 397; and a light chain variable region antibody sequence having a CDR1 sequence selected from the group consisting of SEQ ID NOs: 284, 290, 296, 302, 308, 314, 320, 326, 332, 338, 344, 350, 356, 362, 368, 374, 380, 386, 392, and 398, a CDR2 sequence selected from the group consisting of SEQ ID NOs: 285, 291, 297, 303, 309, 315, 321, 327, 333, 339, 345, 351, 357, 363, 369, 375, 381, 387, 393, and 399, and/or a CDR3 sequence selected from the group consisting of SEQ ID NOs: 286, 292, 298, 304, 310, 316, 322, 328, 334, 340, 346, 352, 358, 364, 370, 376, 382, 388, 394, and 400; altering at least one amino acid residue within the heavy chain variable region antibody sequence and/or the light chain variable region antibody sequence to create at least one altered antibody sequence; and expressing the altered antibody sequence as a protein.

[0233] Accordingly, in another embodiment, the invention provides a method for preparing a Factor P-binding antibody optimized for expression in a mammalian cell consisting of: a full length heavy chain antibody sequence having a sequence selected from the group of SEQ ID NOs: 9, 23, 37, 51, 65, 79, 93, 107, 121, 135, 149, 163, 177, 191, 205, 219, 233, 247, 261 and 275; and a full length light chain antibody sequence having a sequence selected from the group of SEQ ID NOs: 10, 24, 38, 52, 66, 80, 94, 108, 122, 136, 150, 164, 178, 192, 206, 220, 234, 248, 262, and 276; altering at least one amino acid residue within the full length heavy chain antibody sequence and/or the full length light chain antibody sequence to create at least one altered antibody sequence; and expressing the altered antibody sequence as a protein. In one embodiment, the alteration of the heavy or light chain is in the framework region of the heavy or light chain.

[0234] The altered antibody sequence can also be prepared by screening antibody libraries having fixed CDR3 sequences or minimal essential binding determinants as described in US2005025552 and diversity on CDR1 and CDR2 sequences. The screening can be performed according to any screening technology appropriate for screening antibodies from antibody libraries, such as phage display technology.

[0235] Standard molecular biology techniques can be used to prepare and express the altered antibody sequence. The antibody encoded by the altered antibody sequence(s) is one that retains one, some or all of the functional properties of the Factor P-binding antibodies described herein, which functional properties include, but are not limited to, specifically binding to human and/or cynomolgus Factor P; and the antibody inhibit red blood cell lysis in a hemolytic assay.

[0236] In certain embodiments of the methods of engineering antibodies of the invention, mutations can be introduced randomly or selectively along all or part of an Factor P-binding antibody coding sequence and the resulting modified Factor P-binding antibodies can be screened for binding activity and/or other functional properties as described herein. Mutational methods have been described in the art. For example, PCT Publication WO 02/092780 by Short describes methods for creating and screening antibody mutations using saturation mutagenesis, synthetic ligation assembly, or a combination thereof. Alternatively, PCT Publication WO 03/074679 by Lazar et al. describes methods of using computational screening methods to optimize physiochemical properties of antibodies.

[0237] In certain embodiments of the invention antibodies have been engineered to remove sites of deamidation. Deamidation is known to cause structural and functional changes in a peptide or protein. Deamidation can result in decreased bioactivity, as well as alterations in pharmacokinetics and antigenicity of the protein pharmaceutical. (Anal Chem. 2005 Mar 1;77(5): 1432-9).

[0238] The functional properties of the altered antibodies can be assessed using standard assays available in the art and/or described herein, such as those set forth in the Examples (e.g., ELISAs).

Prophylactic and Therapeutic Uses

[0239] Antibodies that binds Factor P as described herein, can be used at a therapeutically useful concentration for the treatment of a disease or disorder associated with increased complement activity by administering to a subject in need thereof an effective amount of the antibodies or antigen binding fragments of the invention. In a specific embodiment, the present invention provides a method of treating age-related macular degeneration (AMD) by administering to a subject in need thereof an effective amount of the antibodies of the invention.

[0240] The antibodies of the invention can be used, *inter alia*, to prevent progression of dry AMD to wet AMD, to slow and/or prevent progression of geographic atrophy, to treat or prevent macular edema, to reduce the frequency of Lucentis injection and to improve vision lost due to dry and wet AMD progression. It can also be used in combination with anti-

VEGF therapies for the treatment of wet AMD patients.

[0241] Treatment and/or prevention of ocular disease such as AMD can be determined by an ophthalmologist or health care professional using clinically relevant measurements of visual function and/or retinal anatomy. Treatment of AMD means any action (e.g., administration of an anti-Factor P antibody described herein) contemplated to improve or preserve visual function and/or retinal anatomy. In addition, prevention as it relates to AMD means any action (e.g., administration of an anti-Factor P antibody described herein) that prevents or slows a worsening in visual function, retinal anatomy, and/or an AMD disease parameter, as defined herein, in a patient at risk for said worsening.

[0242] Visual function may include, for example, visual acuity, visual acuity with low illumination, visual field, central visual field, peripheral vision, contrast sensitivity, dark adaptation, photostress recovery, color discrimination, reading speed, dependence on assistive devices (e.g., large typeface, magnifying devices, telescopes), facial recognition, proficiency at operating a motor vehicle, ability to perform one or more activities of daily living, and/or patient-reported satisfaction related to visual function. Thus, treatment of AMD can be said to occur where a subject has an at least 10% decrease or lack of a 10% or more increase in time to a pre-specified degree of dark adaptation. In addition, treatment of AMD can be said to occur where a subject exhibits at least a 10% reduction or lack of a 10% or more increase in total area of central visual scotoma expressed as a visual angle determined by a qualified health care professional (i.e., ophthalmologist).

[0243] Exemplary measures of visual function include Snellen visual acuity, ETDRS visual acuity, low-luminance visual acuity, Amsler grid, Goldmann visual field, Humphrey visual field, microperimetry, Pelli-Robson charts, SKILL card, Ishihara color plates, Farnsworth D15 or D100 color test, and validated tests for reading speed, facial recognition, driving simulations, and patient reported satisfaction. Thus, treatment of AMD can be said to be achieved upon a gain of or failure to lose 2 or more lines (or 10 letters) of vision on an ETDRS scale. In addition, treatment of AMD can be said to occur where a subject exhibits at least a 10% increase or lack of 10% decrease in reading speed (words per minute). In addition, treatment of AMD can be said to occur where a subject exhibits at least a 20% increase or lack of a 20% decrease in the proportion of correctly identified plates on an Ishihara test or sequenced disks on a Farnsworth test.

[0244] Undesirable aspects of retinal anatomy that may be treated or prevented include, for example, drusen, soft drusen, hard drusen, cuticular drusen, basal laminar drusen, confluent drusen, large drusen (e.g., greater than 125 microns in diameter), RPE atrophy, photoreceptor atrophy, geographic atrophy, choroidal neovascularization, subretinal neovascularization, retinal neovascularization, classic choroidal neovascularization, occult choroidal neovascularization, retinal angiomatous proliferation, chorioretinal anastomosis, an abnormality of choroidal anatomy, subretinal hemorrhage, intraretinal hemorrhage, vitreous hemorrhage, macular scar, subretinal fibrosis, and retinal fibrosis. Thus, treatment of, for example, geographic atrophy can be determined by a 20% or more reduction in lesion growth rate as compared to control or previously documented growth rate in the same subject in the same eye.

[0245] Exemplary means of assessing retinal anatomy include funduscopy, fundus photography, fluorescein angiography, indocyanine green angiography, ocular coherence tomography (OCT), spectral domain ocular coherence tomography, scanning laser ophthalmoscopy, confocal microscopy, adaptive optics, fundus autofluorescence, biopsy, necropsy, and immunohistochemistry. Thus, AMD can be said to be treated in a subject upon a 10% reduction in the measurement of macular thickness as determined by OCT, and/or a reduction of hyperfluorescence as determined by fluorescein angiography.

[0246] Exemplary measures of retinal anatomy include drusen area, drusen volume, geographic atrophy lesion area, geographic atrophy growth rate, and neovascular membrane area.

[0247] In some embodiments, the present invention provides methods of treating a complement related disease or disorder by administering to a subject in need thereof an effective amount of the antibodies of the invention. Examples of known complement related diseases or disorders include: neurological disorders, multiple sclerosis, stroke, Guillain Barre Syndrome, traumatic brain injury, Parkinson's disease, disorders of inappropriate or undesirable complement activation, hemodialysis complications, hyperacute allograft rejection, xenograft rejection, interleukin-2 induced toxicity during IL-2 therapy, inflammatory disorders, inflammation of autoimmune diseases, Crohn's disease, adult respiratory distress syndrome, thermal injury including burns or frostbite, post-ischemic reperfusion conditions, myocardial infarction, balloon angioplasty, post-pump syndrome in cardiopulmonary bypass or renal bypass, hemodialysis, renal ischemia, mesenteric artery reperfusion after aortic reconstruction, infectious disease or sepsis, immune complex disorders and autoimmune diseases, rheumatoid arthritis, systemic lupus erythematosus (SLE), SLE nephritis, proliferative nephritis, hemolytic anemia, and myasthenia gravis. In addition, other known complement related disease are lung disease and disorders such as dyspnea, hemoptysis, ARDS, asthma, chronic obstructive pulmonary disease (COPD), emphysema, pulmonary embolisms and infarcts, pneumonia, fibrogenic dust diseases, inert dusts and minerals (e.g., silicon, coal dust, beryllium, and asbestos), pulmonary fibrosis, organic dust diseases, chemical injury (due to irritant gasses and chemicals, e.g., chlorine, phosgene, sulfur dioxide, hydrogen sulfide, nitrogen dioxide, ammonia, and hydrochloric acid), smoke injury, thermal injury (e.g., burn, freeze), asthma, allergy, bronchoconstriction, hypersensitivity pneumonitis, parasitic diseases, Goodpasture's Syndrome, pulmonary vasculitis, and immune complex-associated inflammation.

[0248] In a specific embodiment, the present invention provides methods of treating a complement related disease or

disorder by administering to a subject in need thereof an effective amount of the antibodies of the invention, wherein said disease or disorder is asthma, arthritis (e.g., rheumatoid arthritis), autoimmune heart disease, multiple sclerosis, inflammatory bowel disease, ischemia-reperfusion injuries, Barraquer-Simons Syndrome, hemodialysis, systemic lupus, lupus erythematosus, psoriasis, multiple sclerosis, transplantation, diseases of the central nervous system such as

Alzheimer's disease and other neurodegenerative conditions, aHUS, glomerulonephritis, bullous pemphigoid or MPGN II. **[0249]** In a specific embodiment, the present invention provides methods of treating glomerulonephritis by administering to a subject in need thereof an effective amount of a composition comprising an antibody of the present invention. Symptoms of glomerulonephritis include, but not limited to, proteinuria; reduced glomerular filtration rate (GFR); serum electrolyte changes including azotemia (uremia, excessive blood urea nitrogen--BUN) and salt retention, leading to water retention resulting in hypertension and edema; hematuria and abnormal urinary sediments including red cell casts; hypoalbuminemia; hyperlipidemia; and lipiduria. In a specific embodiment, the present invention provides methods of treating paroxysmal nocturnal hemoglobinuria (PNH) by administering to a subject in need thereof an effective amount of a composition comprising an antibody of the present invention.

[0250] In a specific embodiment, the present invention provides methods of reducing the dysfunction of the immune and hemostatic systems associated with extracorporeal circulation by administering to a subject in need thereof an effective amount of a composition comprising an antibody of the present invention. The antibodies of the present invention can be used in any procedure which involves circulating the patient's blood from a blood vessel of the patient, through a conduit, and back to a blood vessel of the patient, the conduit having a luminal surface comprising a material capable of causing at least one of complement activation, platelet activation, leukocyte activation, or platelet-leukocyte adhesion. Such procedures include, but are not limited to, all forms of ECC, as well as procedures involving the introduction of an artificial or foreign organ, tissue, or vessel into the blood circuit of a patient.

[0251] Subjects to be treated with therapeutic agents of the present invention can also be administered other therapeutic agents with known methods of treating conditions associated with macular degeneration, such as antibiotic treatments as described in U.S. Pat. No. 6,218,368. In other treatments, immunosuppressive agents such as cyclosporine, are agents capable of suppressing immune responses. These agents include cytotoxic drugs, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), specific T-lymphocyte immunosuppressants, and antibodies or fragments thereof (see Physicians' Desk Reference, 53rd edition, Medical Economics Company Inc., Montvale, N.J. (1999). Immunosuppressive treatment is typically continued at intervals for a period of a week, a month, three months, six months or a year. In some patients, treatment is administered for up to the rest of a patient's life.

[0252] When the therapeutic agents of the present invention are administered together with another agent, the two can be administered sequentially in either order or simultaneously. In some aspects, an antibody of the present invention is administered to a subject who is also receiving therapy with a second agent (e.g., verteporfin). In other aspects, the binding molecule is administered in conjunction with surgical treatments.

[0253] Suitable agents for combination treatment with Factor P binding antibodies include agents known in the art that are able to modulate the activities of complement components (see, e.g., U.S. Pat. No. 5,808,109). Other agents have been reported to diminish complement-mediated activity. Such agents include: amino acids (Takada, Y. et al. Immunology 1978, 34, 509); phosphonate esters (Becker, L. Biochem. Biophys. Acta 1967, 147, 289); polyanionic substances (Conrow, R. B. et al. J. Med. Chem. 1980, 23, 242); sulfonyl fluorides (Hansch, C.; Yoshimoto, M. J. Med. Chem. 1974, 17, 1160, and references cited therein); polynucleotides (DeClercq, P. F. et al. Biochem. Biophys. Res. Commun. 1975, 67, 255); pimelic acids (Glovsky, M. M. et al. J. Immunol. 1969, 102, 1); porphines (Lapidus, M. and Tomasco, J. Immunopharmacol. 1981, 3, 137); several antiinflammatories (Burge, J. J. et al. J. Immunol. 1978, 120, 1625); phenols (Muller-Eberhard, H. J. 1978, in Molecular Basis of Biological Degradative Processes, Berlin, R. D. et al., eds. Academic Press, New York, p. 65); and benzamidines (Vogt, W. et al Immunology 1979, 36, 138). Some of these agents function by general inhibition of proteases and esterases. Others are not specific to any particular intermediate step in the complement pathway, but, rather, inhibit more than one step of complement activation. Examples of the latter compounds include the benzamidines, which block C1, C4 and C3b utilization (see, e.g., Vogt et al. Immunol. 1979, 36, 138).

[0254] Additional agents known in the art that can inhibit activity of complement components include K-76, a fungal metabolite from *Stachybotrys* (Corey et al., J. Amer. Chem. Soc. 104: 5551, 1982). Both K-76 and K-76 COOH have been shown to inhibit complement mainly at the C3b step (Hong et al., J. Immunol. 122: 2418, 1979; Miyazaki et al., Microbiol. Immunol. 24: 1091, 1980), and to prevent the generation of a chemotactic factor from normal human complement (Bumpers et al., Lab. Clin. Med. 102: 421, 1983). At high concentrations of K-76 or K-76 COOH, some inhibition of the reactions of C2, C3, C6, C7, and C9 with their respective preceding intermediaries is exhibited. K-76 or K-76 COOH has also been reported to inhibit the C3b inactivator system of complement (Hong et al., J. Immunol. 127: 104-108, 1981). Other suitable agents for practicing methods of the present invention include griseofulvin (Weinberg, in Principles of Medicinal Chemistry, 2d Ed., Foye, W. O., ed., Lea & Febiger, Philadelphia, Pa., p. 813, 1981), isopannarin (Djura et al., Aust. J. Chem. 36: 1057, 1983), and metabolites of *Siphonodictyon coralli-phagum* (Sullivan et al., Tetrahedron 37: 979, 1981).

[0255] A combination therapy regimen may be additive, or it may produce synergistic results (e.g., reductions in

complement pathway activity more than expected for the combined use of the two agents). In some embodiments, the present invention provide a combination therapy for preventing and/or treating AMD or another complement related disease as described above with a Factor P binding antibody of the invention and an anti-angiogenic, such as anti-VEGF agent, or another anti-complement antibody such as an antibody or antigen binding fragment thereof that binds to complement factor 5 (C5).

Combination of anti-complement antibodies

[0256] In one aspect, the invention provides combinations of any one or more of the anti-Factor P with an additional antibody that binds to and inhibits the activity of a different component of the complement pathway. In particular, the invention includes any one or more of the anti-Factor P antibodies or antigen binding fragments described herein in combination with an antibody or antigen binding fragment that binds complement component 5 (C5). Examples of antibodies or antigen binding fragments thereof that bind to C5 and inhibit complement activation can be found, for example in U.S. Patent 8,241,628 (incorporated herein by reference). More specifically, antibodies or antigen binding fragments thereof that bind to C5 and inhibit the complement pathway are shown and described in Table 2. In one aspect the invention includes a combination of an anti-Factor P antibody or antigen binding fragment thereof as shown and described in Table 1 with the anti-C5 antibody 8109 from Table 2. More specifically, one aspect of the invention relates to a combination of antibody NVS962 from Table 1 (or an antigen binding fragment thereof) with antibody 8109 from Table 2 (or an antigen binding fragment thereof).

[0257] In one aspect the combinations of anti-Factor P and anti-C5 antibodies described herein demonstrate a synergistic inhibition of the complement pathway, particularly the alternative complement pathway. Such inhibition can be demonstrated, for example, using the hemolytic or poly-IC assays described in the Examples below. Synergy in the inhibition of the alternative complement pathway, achieved using a combination of the anti-Factor-P and anti-C5 antibodies described herein can be determined using methods that are well known in the art. For example, a synergistic effect of the combination of anti-Factor P antibody and anti-C5 antibody can be determine relative to a merely additive effect using specific software, such as a Chalice Analyzer.

[0258] Briefly, Chalice Analyzer (Lehar et al, Nature Biotechnology 2009, 7:659) software can be used to determine whether the combination of complement inhibiting antibodies (e.g., anti-Factor P and anti-C5) acted synergistically to block complement activation. Combination effects can be characterized by comparing each data point's inhibition to that of a combination reference model that was derived from the single agent curves (Greco, Bravo, Parsons (1995). The search for synergy: a critical review from a response surface perspective. Pharmacol Rev 47(2): 331-85). In the Loewe additivity model (Loewe (1928). Die quantitativen Probleme der Pharmakologie. Ergebn. Physiol. 27: 47-187), $I_{\text{Loewe}}(C_X, C_Y)$ is the inhibition that satisfies $(C_X/IC_X) + (C_Y/IC_Y) = 1$, and $IC_{X,Y}$ are the effective concentrations at I_{Loewe} for the fitted single agent curves. Loewe additivity is the generally accepted reference for synergy (Greco et al.), as it represents the combination response generated if X and Y are the same compound.

[0259] Potency shifting is usually shown using an isobologram (Greco et al.) which shows how much less drug is required in combination to achieve a desired effect level, when compared to the single agent doses needed to reach that effect. The choice of effect level for the isobologram display and combination index calculations can either be manually or automatically selected in the Chalice Analyzer. The automatic iso-level selection algorithm finds the observed I_{data} with the the largest $I_{\text{data}} - I_{\text{Loewe}}$, excluding those points with I_{data} exceeding the lesser single agent's I_{max} . This exclusion is applied to ensure that the isobologram reflects the best synergy at levels covered by both single agents. Having selected an isobologram level I_{cut} , the isobologram is drawn by identifying the locus of concentrations that correspond to crossing the chosen iso-level. The isobologram shows the standard isobolographic analysis of synergy compared to the Loewe dose-additive "drug-with-itself" standard. For a specified isobologram level, the observed iso-effect contour (e.g., curved line in Figure 3) is displayed with the theoretical dose-additive contour (e.g., straight line in Figure 3), on an IC_{effect} -normalized linear concentration scale for both substances in the combination. The Dose-additive reference is always a line connecting the two IC_{effect} concentrations. The IC_{effect} crossing points are found by interpolating the fitted sigmoidal dose response curves.

[0260] Potency shifting is scored as the combination index (Chou, Talalay (1984). Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors. Adv Enzyme Regul 22: 27-55) CI. For a chosen iso-effect level I_{cut} , $CI = (C_X/EC_X)_I + (C_Y/EC_Y)_I$, where $(C_X/EC_X)_I$ for a particular data point is the ratio of the X compound's measured concentration to its effective concentration at the chosen inhibition level. The CI can be thought of as a rough estimate of how much drug was needed in combination relative to the single agent doses required to achieve the chosen effect level, and a value of 0.1 means that only a tenth of equivalent amounts of the single agents were needed for the combination to reach the same effect level. CI values in the range of 0.5-0.7 are typical for *in vitro* measurements of current clinical combinations (Greco et al.). A CI value of 1.0 is indicative of an additive effect of a combination of antibodies, while a CI value of less than 0.5 is indiciative of a strong synergistic effect resulting from the antibody combination. In the Chalice Analyzer, the best CI is reported from the many combination index values calculated for

each I_{cut} crossing concentration. Among all the measured CI values, the one with the largest signal-to-noise level is reported as the best combination index.

[0261] Combinations of anti-Factor P and anti-C5 antibodies as described herein can be administered singly or as a single composition. In addition, the relative dose of an anti-Factor P and anti-C5 antibody can be in a ratio of 1:1, or may be in a different ratio. The specific dose of an anti-Factor P antibody relative to an anti-C5 antibody may ultimately be determined by a treating physician or health care professional to achieve improvement in the pathological condition being treated. For example, when a combination as described herein is used to treat AMD, a physician or health care professional may tailor the relative doses of the anti-Factor P and anti-C5 antibodies so as to achieve optimal therapeutic benefit as determined using the measurements and criteria described herein.

Pharmaceutical Compositions

[0262] The invention provides pharmaceutical compositions comprising the Factor P-binding antibodies (intact or binding fragments) formulated together with a pharmaceutically acceptable carrier. The compositions can additionally contain one or more other therapeutic agents that are suitable for treating or preventing, for example, pathological angiogenesis or tumor growth. Pharmaceutically acceptable carriers enhance or stabilize the composition, or can be used to facilitate preparation of the composition. Pharmaceutically acceptable carriers include solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible.

[0263] A pharmaceutical composition of the present invention can be administered by a variety of methods known in the art. The route and/or mode of administration vary depending upon the desired results. It is preferred that administration be intravitreal, intravenous, intramuscular, intraperitoneal, or subcutaneous, or administered proximal to the site of the target. The pharmaceutically acceptable carrier should be suitable for intravitreal, intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (e.g., by injection or infusion). Depending on the route of administration, the active compound, *i.e.*, antibody, bispecific and multispecific molecule, may be coated in a material to protect the compound from the action of acids and other natural conditions that may inactivate the compound.

[0264] The composition should be sterile and fluid. Proper fluidity can be maintained, for example, by use of coating such as lecithin, by maintenance of required particle size in the case of dispersion and by use of surfactants. In many cases, it is preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol or sorbitol, and sodium chloride in the composition. Long-term absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

[0265] Pharmaceutical compositions of the invention can be prepared in accordance with methods well known and routinely practiced in the art. See, *e.g.*, Remington: The Science and Practice of Pharmacy, Mack Publishing Co., 20th ed., 2000; and Sustained and Controlled Release Drug Delivery Systems, J.R. Robinson, ed., Marcel Dekker, Inc., New York, 1978. Pharmaceutical compositions are preferably manufactured under GMP conditions. Typically, a therapeutically effective dose or efficacious dose of the Factor P-binding antibody is employed in the pharmaceutical compositions of the invention. The Factor P-binding antibodies are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art. Dosage regimens are adjusted to provide the optimum desired response (e.g., a therapeutic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

[0266] Actual dosage levels of the active ingredients in the pharmaceutical compositions of the present invention can be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. The selected dosage level depends upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors.

[0267] A physician or veterinarian can start doses of the antibodies of the invention employed in the pharmaceutical composition at levels lower than that required to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. In general, effective doses of the compositions of the present invention, for the treatment of an allergic inflammatory disorder described herein vary depending upon many different factors, including means of administration, target site, physiological state of the patient, whether the patient is human or an animal, other medications administered, and whether treatment is prophylactic or therapeutic. Treatment dosages need to be titrated

to optimize safety and efficacy. For systemic administration with an antibody, the dosage ranges from about 0.0001 to 100 mg/kg, and more usually 0.01 to 15 mg/kg, of the host body weight. For intravitreal administration with an antibody, the dosage may range from 0.1 mg/eye to 5mg/eye. For example, 0.1 mg/ml, 0.2 mg/ml, 0.3 mg/ml, 0.4 mg/ml, 0.5 mg/ml, 0.6 mg/ml, 0.7 mg/ml, 0.8 mg/ml, 0.9 mg/ml, 1.0 mg/ml, 1.1 mg/ml, 1.2 mg/ml, 1.3 mg/ml, 1.4 mg/ml, 1.5 mg/ml, 1.6 mg/ml, 1.7 mg/ml, 1.8 mg/ml, 1.9 mg/ml, 2.0 mg/ml, 2.1 mg/ml, 2.2 mg/ml, 2.3 mg/ml, 2.4 mg/ml, 2.5 mg/ml, 2.6 mg/ml, 2.7 mg/ml, 2.8 mg/ml, 2.9 mg/ml, 3.0 mg/ml, 3.1 mg/ml, 3.2 mg/ml, 3.3 mg/ml, 3.4 mg/ml, 3.5 mg/ml, 3.6 mg/ml, 3.7 mg/ml, 3.8 mg/ml, 3.9 mg/ml, 4.0 mg/ml, 4.1 mg/ml, 4.2 mg/ml, 4.3 mg/ml, 4.4 mg/ml, 4.5 mg/ml, 4.6 mg/ml, 4.7 mg/ml, 4.8 mg/ml, 4.9 mg/ml, or 5.0 mg/ml. An exemplary treatment regime entails systemic administration once per every two weeks or once a month or once every 3 to 6 months. An exemplary treatment regime entails systemic

[0268] Antibody is usually administered on multiple occasions. Intervals between single dosages can be weekly, monthly or yearly. Intervals can also be irregular as indicated by measuring blood levels of Factor P-binding antibody in the patient. In addition alternative dosing intervals can be determined by a physician and administered monthly or as necessary to be efficacious. Efficacy is based on lesion growth, rate of Lucentis rescue, retinal thickness as determined by Spectral Domain-optical Optical Coherence Tomography (SD-OCT), and secondary visual acuity. In some methods of systemic administration, dosage is adjusted to achieve a plasma antibody concentration of 1-1000 μ g/ml and in some methods 25-500 μ g/ml. Alternatively, antibody can be administered as a sustained release formulation, in which case less frequent administration is required. Dosage and frequency vary depending on the half-life of the antibody in the patient. In general, humanized antibodies show longer half life than that of chimeric antibodies and nonhuman antibodies. The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic. In prophylactic applications, a relatively low dosage is administered at relatively infrequent intervals over a long period of time. Some patients continue to receive treatment for the rest of their lives. In therapeutic applications, a relatively high dosage at relatively short intervals is sometimes required until progression of the disease is reduced or terminated, and preferably until the patient shows partial or complete amelioration of symptoms of disease. Thereafter, the patient can be administered a prophylactic regime.

EXAMPLES

[0269] The following examples are provided to further illustrate the invention but not to limit its scope. Other variants of the invention will be readily apparent to one of ordinary skill in the art and are encompassed by the appended claims.

Example 1: Generation of Affinity Matured Factor P Antibodies

[0270] A fully human phage display library was used to generate the Factor P binding antibodies described herein.

[0271] Biotinylated and non-biotinylated human and cynomolgus Factor P were used in solution and solid phase pannings. Standard panning were performed as well as RapMAT approaches (Prassler et al., (2009) Immunotherapy 1(4):571-583). Following affinity maturation (Knappik et al., (2000) J.Mol.Biol., 296:57-86) a set of 10 antibodies were subsequently chosen for conversion to a disulfide-bridged Fab format. The resulting disulfide bridged Fabs are shown in Table 1 (NVS962, NVS963, NVS964, NVS965, NVS966, NVS967).

Example 2: Further Antibody Optimization

[0272] The following example describes methods that may be used to further optimize antibodies described herein.

Removal of Deamidation Sites

[0273] Deamidation sites were identified by peptide mapping and size exclusion chromatography (SEC), run under reducing conditions. The deamidated material has decreased potency in a MAC deposition assay and decreased affinity for human and cyno FP as measured by Biacore and SET. The extent of deamidation increased over time (3 weeks), at higher temperatures (5 days at 37C), and under reducing conditions. Deamidation can be detected using an ion-exchange column resultin multiple peaks and observation of the additional, deamidated peak. Amino acid sequences that are most prone to deamidation are: SNG, LNG, LNN, ELN (Daugherty, A. and Mrsny, R. (2010) Current Trends in Monoclonal Antibody Development and Manufacturing. Springer. p103-129.). Accordingly, we engaged in a series of studies to remove the deamidation sites and test the modified antibodies for retained function.

[0274] Two Fabs, NVS962 and NVS965, were re-engineered to replace a deamidation site on the heavy chain, specifically occurring at an asparagine at position 30. The following new Fabs were generated to remove the deamidation site and corresponding amino acid replacements shown in Table 2.

Table 2: Deaminated Fabs

Deaminated Fab	N30 replaced with:	Modified Fab
NVS962	Serine	NVS962-S
	Glutamine	NVS962-Q
	Glycine	NVS962-G
	Threonine	NVS962-T
NVS965	Threonine	NVS965-T
	Glutamine	NVS965-Q
	Serine	NVS965-S

[0275] An additional Fab that was generated replaced serine 31 with an alanine in Fab NVS962, generating Fab NVS962-S31A. The sequences of the modified Fabs is shown in Table 1.

Removal of Cleavage Sites

[0276] Further optimization was conducted on NVS962-S and NVS965-S to remove a cleavage site in the heavy chain CDR3. Specifically the heavy chain was cleaved at Y102S103. The following table describes the amino acid substitutions that were made to destroy the cleavage site. The sequences of the modified Fabs is shown in Table 1.

Table 3: Modified Fabs

Clipped Fab	Y102 replaced with:	S103 replaced with:	Modified Fab
NVS962-S	F	I	NVS808
	K	V	NVS806
	S	Y	NVS807
NVS965-S	Y	I	NVS804
	Y	V	NVS805
	Y	Y	NVS809

Example 3: Characterization of Optimized Antibodies

[0277] The following example describes methods that may be used to measure antibody affinity. These and other methods of measuring binding affinity are known in the art.

Affinity Determination

[0278] Antibody affinity for Factor P was measured by surface plasmon resonance (SPR) using a Biacore T200 (Biacore) and solution equilibrium titration (SET). Explanations of each technology and corresponding mean results for Factor P binding are described below. Modelling assumptions take into account concentrations of Factor P in the system, kinetics of Factor P biosynthesis and half-life, as well as the desired dosing schedule, and suggest that a Fab with an affinity of greater than 500 pM for Factor P is sufficient to lower levels of free Factor P.

Biacore Determination

[0279] The kinetics of an interaction, i.e. the rates of complex formation (k_a) and dissociation (k_d), can be determined from the information in a sensorgram. If binding occurs as sample passes over a prepared sensor surface, the response in the sensorgram increases. If equilibrium is reached a constant signal will be seen. Replacing sample with buffer causes the bound molecules to dissociate and the response decreases. Biacore evaluation software generates the values of k_a and k_d by fitting the data to interaction models (Table 4).

[0280] Biacore kinetic experiments were done with the BIAcore T100 (GE Healthcare) using CM5 sensor chips (GE

Healthcare, BR-1005-30) at 25°C. The running buffer was HBS-EP(+) (GE Healthcare, BR-1001-88). Briefly, the following steps were carried out to determine binding affinity.

- Prepare anti-FP IgG immobilized sensor chip: Mouse anti-FP monoclonal antibody (Quidel, A235) (30ug/ml in acetate pH5.0 coupling buffer (GE Healthcare, BR-1003-51)) was coupled to two different flow cells (Fc1 and 2) on a CM5 chip at 10ul/min flow rate for 600 seconds by using amino-coupling procedure according to the supplier's instruction (GE Healthcare, BR-1000-50). The final immobilized level will be >7000RU.
- Capture FP on second flow cell: 1ug/ml of FP in running buffer was injected at 10ul/min on second flow cell (Fc2) to reach capture level -20 RU for Fab or ~7 RU for IgG kinetics analysis.
- Inject anti-FP Fab or IgG at different concentration on both flow cells: Inject anti-FP solution (0.3125nM~10nM in running buffer; at 1:2 serial dilutions) on both flow cells (Fc1 and 2) at 60ul/min for 240 seconds.
- Dissociation: Inject HBS-EP(+) running buffer at 60ul/min on both flow cells to monitor the dissociation between FP and anti-FP Fab/IgG. Dissociation time was set at 2400 seconds for 5nM and 2.5M Fab/IgG concentrations and at 300 seconds for all other concentrations including another 5nM Fab/IgG concentration.
- Regeneration: Regeneration was performed at the end of each cycle on both flow cells with 10 mM Glycine-HCl pH1.7 (provided by GE Healthcare)+ 0.05% P20 surfactant (GE Healthcare, BR-1000-54) at a flow rate of 60ul/min for 15 seconds twice.
- Kinetics analysis: Kinetic rate constants was obtained by applying 1:1 binding model with BIAevaluation 1.1 software, wherein the Rmax values were fit locally.

[0281] The results of the Biacore binding kinetics determination are shown in Table 4. As shown the antibodies described herein exhibit high affinity binding to human Factor P, with KD values typically less than or equal to 1 nM, and in many cases less than or equal to 200 pM. These antibodies also show very high affinity to cyno Factor P (binding affinity less than 500 pM).

SET Determination

[0282] In contrast to kinetic assays using sensor surfaces, such as SPR, SET is a method which determines affinities in solution. It is an equilibrium measurement that does not deliver kinetic data.

[0283] In SET, a constant amount of antibody is incubated with different concentrations of antigen until equilibrium is reached. The concentration of free antibody in the equilibrated solution is determined by applying the solution on an antigen coated MSD™ plate (Meso Scale Discovery™) followed by incubation with an ECL-labeled secondary antibody and measurement of signal intensity. At low antigen concentrations, a strong signal is achieved (high concentration of free antibody which binds to the antigen on the plate) whereas for high antigen concentration, the antibody is completely antigen-captured, resulting in a low signal. If a sufficient number of antigen concentrations in a matching range are available, the titration curve allows for a reasonable determination of the affinity, using the appropriate fit model. For a complete titration, antigen concentrations of at least 10-fold higher than the anticipated K_D have to be applied. The constant concentration of antibody applied in the assay should be in the range of, or below, the K_D (Table 4).

[0284] For K_D determination by solution equilibrium titration (SET), monomer fractions of antibody protein were used (at least 90% monomer content, analyzed by analytical SEC; Superdex75 (Amersham Pharmacia) for Fab, or Tosoh G3000SWXL (Tosoh Bioscience) for IgG, respectively).

[0285] Affinity determination in solution was basically performed as described in the literature (Friguet et al. 305-19). In order to improve the sensitivity and accuracy of the SET method, it was transferred from classical ELISA to ECL based technology (Haenel et al., 2005).

[0286] 1 mg/ml goat-anti-human (Fab)₂ fragment specific antibodies (Dianova) were labeled with MSD Sulfo-TAG™ NHS-Ester (Meso Scale Discovery, Gaithersburg, MD, USA) according to the manufacturer's instructions.

[0287] Human Factor P (Complement Technology cat#: A139) and Cyno Factor P purified from cyno serum (protocol adapted from Nakano, et al., (1986) J Immunol Methods 90:77-83) were coated on standard binding MSD plates (Meso Scale Discovery, 384-well: MSD cat#: L21XA, 96-well: MSD cat#: L15XA) at 0.2-0.3μg/ml in 25μl PBS and incubated overnight at 4°C. Factor P inhibitors were diluted to a fixed concentration (1pM or 10pM) in incubation buffer (PBS with 2% BSA (Sigma cat#: A4503) and 1% Tween20 and 1% Triton-X (Sigma cat#: 234729)), and added to a serial dilution of Factor P (human or cyno) in incubation buffer. Samples were allowed to reach equilibrium by incubation at RT overnight. Plates were washed 3x in wash buffer (PBS with 0.05% Tween20), and blocked with 100μl incubation buffer at RT for

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2hrs. Plates were washed 3x in wash buffer. Sample containing Factor P inhibitors and Factor P titration were added to the plate (25µl), and incubated at RT for 15min. Plates were washed 3x in wash buffer. 25µl detection antibody was added (Anti-Human (Goat) Sulfo-TAG, 1:1000 in incubation buffer, MSD cat#: R32AJ-1), and incubated at RT for 60min. Plates were washed 3x in wash buffer, and 50µl of 1x MSD Read buffer T was added (with surfactant, MSD cat#: R92TC-1). Plates were read on a MSD Spector Imager 6000. Data was analyzed using GraphPad Prism software v4, with background (an average of wells containing no Fab) subtracted from each value. X-axis values (concentration of Factor P in solution) were transformed into log10x. KD values (KD) were fitted from the following model:

Fab:

$$Y = \frac{\text{Top} - \left(\frac{\text{Top}}{2 \times \text{Fab}} \right) \times \left(\left((10^x) + \text{Fab} \right) + \text{KD} \right) - \left(\left(\left((10^x) + \text{Fab} \right) + \text{KD} \right) \times \left((10^x) + \text{Fab} \right) + \text{KD} \right)}{\left((4 \times (10^x) \times \text{Fab})^{0.5} \right)}$$

Top= signal at antigen concentration = 0

x= concentration of Factor P in solution

Fab= concentration of applied monovalent analyte (Fab)

Table 4: Affinity Binding of Factor P Antibodies

Factor P Antibody	Factor P Species	SET K _D (pM)	Biacore K _D (pM)	Biacore K _a (1/Ms)	Biacore K _d (1/s)
NVS962	Human	46	83	1.52 x 10 ⁶	1.25 x 10 ⁻⁴
	Cyno	47	182	1.53 x 10 ⁶	2.79 x 10 ⁻⁴
NVS965	Human	36	16	2.65 x 10 ⁶	4.10 x 10 ⁻⁵
	Cyno	14	28	2.24 x 10 ⁶	6.22 x 10 ⁻⁵
NVS963	Human	55	90	1 x 10 ⁶	1 x 10 ⁻⁴
	Cyno	115	170	1 x 10 ⁶	2 x 10 ⁻⁴
NVs966	Human	70	160	2 x 10 ⁶	3 x 10 ⁻⁴
	Cyno	40	210	1 x 10 ⁵	2 x 10 ⁻⁴
NVS964	Human	20	35	1 x 10 ⁶	4 x 10 ⁻⁵
	Cyno	190	160	1 x 10 ⁶	2 x 10 ⁻⁴
NVS967	Human	40	60	1 x 10 ⁶	9 x 10 ⁻⁵
	Cyno	280	315	1 x 10 ⁶	6 x 10 ⁻⁴
NVS962-Q	Human	1061	496	6.27 x 10 ⁵	3.11 x 10 ⁻⁴
	Cyno	930	475	5.55 x 10 ⁵	2.64x 10 ⁻⁴
NVS962-S	Human	156	161	7.3 x 10 ⁵	1.17 x 10 ⁻⁴
	Cyno	141	127	5.24 x 10 ⁵	6.66 x 10 ⁻⁵
NVS962-T	Human	251	131	6.39 x 10 ⁵	8.35 x 10 ⁻⁵
	Cyno	354	175	4.88 x 10 ⁵	8.56 x 10 ⁻⁵
NVS962-G	Human	953	1140	3.87 x 10 ⁵	4.4 x 10 ⁻⁴
	Cyno	567	1080	3.13 x 10 ⁵	3.39 x 10 ⁻⁴
NVS962-S31A	Human	189	225	5.04 x 10 ⁵	1.13 x 10 ⁻⁴
	Cyno	189	234	3.72 x 10 ⁵	8.7 x10 ⁻⁵
NVS965-Q	Human	301	138	2.65 x 10 ⁶	3.66 x 10 ⁻⁴
	Cyno	201	215	2.77 x 10 ⁶	5.94 x 10 ⁻⁴

(continued)

Factor P Antibody	Factor P Species	SET K _D (pM)	Biacore K _D (pM)	Biacore K _a (1/Ms)	Biacore K _d (1/s)
NVS965-S	Human	51	27	3.69 x 10 ⁶	9.9 x 10 ⁻⁵
	Cyno	36	60	2.71 x 10 ⁶	1.63 x 10 ⁻⁴
NVS965-T	Human	52	51.4	2.37 x 10 ⁶	1.03 x 10 ⁻⁴
	Cyno	44	74.6	2.17 x 10 ⁶	1.51 x 10 ⁻⁴
NVS808	Human	107	195	7.91 x 10 ⁵	1.54 x 10 ⁻⁴
	Cyno	ND	ND	ND	ND
NVS806	Human	18	52	4.34 x 10 ⁵	2.24 x 10 ⁻⁵
	Cyno	ND	ND	ND	ND
NVS807	Human	27	106	1.21 x 10 ⁶	1.23 x 10 ⁻⁴
	Cyno	ND	ND	ND	ND
NVS804	Human	0.8	5	2.72 x 10 ⁶	1.29 x 10 ⁻⁵
	Cyno	ND	ND	ND	ND
NVS805	Human	0.3	3	3.61 x 10 ⁶	9.88 x 10 ⁻⁶
	Cyno	ND	ND	ND	ND
NVS809	Human	4.2	24.7	4.25 x 10 ⁶	1.04 x 10 ⁻⁴
	Cyno	ND	ND	ND	ND

Example 4: Factor P Antibodies Inhibit the Alternative Complement Pathway

Hemolysis Assay

[0288] In hemolytic techniques, all of the complement components must be present and functional. Therefore hemolytic techniques can screen both functional integrity and deficiencies of the complement system (van et al., 1980; Minh et al., 1983; Tanaka et al., 1986). To measure the functional capacity of the classical pathway, sheep red blood cells coated with hemolysin (rabbit IgG to sheep red blood cells) or chicken red blood cells that are sensitized with rabbit anti-chicken antibodies are used as target cells (sensitized cells). These Ag-Ab complexes activate the classical pathway and result in lysis of the target cells when the components are functional and present in adequate concentration. To determine the functional capacity of the alternative pathway in human and cynomolgus sera, rabbit red blood cells are used as the target cell (see U.S. Pat. No. 6,087,120).

[0289] The hemolytic assay is a basic functional assay that tests for complement activation and has been used to evaluate the ability of anti-human FP mAbs and Fab molecules to block lysis of red blood cells (RBCs) by complement pathways. *In vitro* and *in vivo* inhibition of complement activity by a single-chain Fv fragment recognizing human C5 can be measured using a haemolytic assay (Thomas et al., 1996; Rinder et al., 1995; Rinder et al., 1995). Blockade of C5a and C5b-9 generation inhibits leukocyte and platelet activation during extracorporeal circulation. Briefly, for classical pathway assays, sensitized red blood cells (e.g., chicken RBCs) are used as targets for lysis by complement proteins present in serum. The following assay is of interest for the characterization and screening of Factor P antibodies for their inhibition of the alternative complement pathway.

[0290] This procedure was adapted from (Rinder et al., 1995; Thomas et al., 1996).

Reagents:

[0291]

- Rabbit red blood cells (Rb RBCs) - Lampire, Cat# 7246408
- Human serum - Novartis Blood Research Program; or Cyno serum - Alpha Genesis
- Gelatin veronal buffer (GVB) - Boston BioProducts, Cat# IBB-300
- EGTA - Boston BioProducts, Cat# BM-151

- MgCl₂
- U-bottom 96-well plate - Corning, Cat# 3795
- Flat-bottom 96-well plate - Corning, Cat# 3370
- NP-40 - Sigma, Cat# 74385

Protocol:

[0292] Rabbit red blood cells (RBCs) were washed and adjusted to 8.33×10^7 cells/ml in GVB/EGTA/Mg⁺⁺. 50 μ l Fab diluted in GVB was added to wells in a 96-well round bottom plate. 50 μ l serum diluted in GVB with EGTA and Mg⁺⁺ was then added. Control wells were prepared in the following manner: serum without Fab (negative control) and cells plus 0.1% NP-40 (100% lysis control), and NP-40 blank wells. Serum with and without Fab and controls were incubated at room temperature for 30 minutes. At that point, 30 μ l Rb RBCs were added to sample and control wells and 30 μ l of buffer was added to the blank wells. The cells were generally incubated for 30 minutes at 37°C and the plate centrifuged at 2000rpm for 5min. The supernatant was harvested and transferred to a flat-bottom plate. The absorbance of the supernatant was read at OD415 and OD570. Percent hemolysis was calculated using the formula below.

$$\% \text{Hemolysis} = \frac{(OD_{\text{sample}} - OD_{\text{serum blank}}) - (OD_{0\% \text{ lysis}} - OD_{\text{buffer blank}})}{(OD_{100\% \text{ lysis}} - OD_{\text{NP 40 blank}}) - (OD_{0\% \text{ lysis}} - OD_{\text{buffer blank}})}$$

Table 5 exemplifies of the ability of the Factor P antibodies and antigen binding fragments to inhibit hemolysis in 10% human or 20% cynomolgus serum. Each of the Factor P antibodies described herein inhibited hemolysis with an IC₅₀ of less than or equal to 50 nM.

[0293] In contrast, when the assay was performed using sensitized red blood cells in order to examine activation of the classical complement pathway, the Factor P antibodies described herein were found not to inhibit the classical complement pathway (data not shown).

C3b Deposition Assay

[0294] One method of measuring the inhibitor activity against the complement C3 in the alternative pathway is to measure its breakdown product, C3b, depositing on zymosan. This ELISA based assay was performed according to the following steps: 25 μ l of 1 mg/ml Zymosan A (Sigma Z4250) in carbonate buffer, pH 9.6 (Pierce Cat# 28382) was coated on Maxisorp 384-well ELISA plate (Nunc 464718) overnight at 4°C. On the following day, the zymosan-coated plate was aspirated and blocked with 100 μ l per well of ELISA blocking buffer, Synblock (AbD Serotec BUFO34C) for 2h at room temperature. In a separate reaction, the inhibitors, serially diluted in gelatin veronal buffer (Boston Bioproducts IBB320-10mM Barbitol, 145mM NaCl, 0.1% Gelatin, 0.5mM MgCl₂, 10mM EGTA) were added to 10% serum supplemented with MgCl₂ and EGTA for a final total reaction concentration of 1mM MgCl₂ and 10mM EGTA. The positive control contained no inhibitor and negative control had 25mM EDTA. The mixture was allowed to reach equilibrium by incubating at room temperature for 30min. To remove the blocking buffer, the buffer was aspirated and the plate was washed once with TBS/0.05% Tween-20. 25 μ l per well of the 10% serum containing the inhibitors or controls was added to the plate and incubated at 37°C for 30min (previously determined by time-course to be within the linear range of C3b deposition on zymosan.) After the 30min incubation, the plate was washed three times with TBS/0.05% Tween-20. To detect C3b deposition on zymosan, 25 μ l per well of chicken anti-human C3-HRP conjugated polyclonal antibody (Immunology Consultants Laboratory, Inc. Cat# CC3-80P-1) diluted according to manufacturer in PBS with 2% BSA Fraction V (Fisher Cat# ICN 16006980), 0.1% Tween20 (Sigma Cat# P1379), and 0.1% TritonX-100 (Sigma Cat# P234729) was added to the plate and incubate at room temperature for 1h. Afterward, the plate was washed three times with TBS/0.05% Tween-20 and then add 25 μ l of Ultra TMB Substrate Solution (Pierce Cat#34028.) When the solution in the well turned blue, the reaction was stopped with 15 μ l of 2N sulfuric acid. The plate was read at 450nm using the Spectromax with correction for the plastic plate at 570nm (OD_{450-570nm} reading.) The percentage of C3b deposition on zymosan was calculated using the following formula:

$$\% \text{ C3b Deposition} = 100 - 100 * \frac{[(OD_{\text{no inhibitor}} - OD_{25\text{mM EDTA}}) - (OD_{\text{sample}} - OD_{25\text{mM EDTA}})]}{(OD_{\text{no inhibitor}} - OD_{25\text{mM EDTA}})}$$

[0295] Each of the antibodies tested were shown to inhibit C3b deposition with an IC₅₀ of at least less than or equal

to 10 nM (Table 5).

MAC Deposition Assay

[0296] Another assay that was used to determine the ability of the Factor P antibodies to inhibit the alternative complement pathway was to measure the ability of the antibodies to inhibit the generation of the membrane attack complex (MAC), which is downstream of the C3 convertase and the activity of Factor P. Briefly, Zymosan A (Sigma) was coated on a plate at 1mg/ml in carbonate buffer, pH 9.5, to activate the Alternative Pathway. Fabs were pre-incubated with serum (20% serum, 5mM MgCl₂, 10mM EDTA), then added to the plate and incubated overnight at room temperature. After washing the plate three times with TBST, MAC was detected by incubation with anti-C5b-9-ALP (Diatec) for 1h, followed by three washes with TBST, and incubation with 4-methylumbelliferyl phosphate (Fisher) supplemented with 2mM MgCl₂ for 30 minutes. The reaction was stopped with 0.2M EDTA, and the plate was read at ex=355nm, em=460nm. Inhibition of MAC deposition was calculated for each sample relative to baseline (EDTA treated human serum) and positive control (human serum), and used to generate the IC50 curve with PRISM.

[0297] Table 5 shows data demonstrating the ability of the Factor P antibodies to inhibit the deposition of MAC, thus indicating that the antibodies inhibited the alternative complement pathway. Specifically, the antibodies inhibited MAC deposition with an IC50 of less than or equal to 25nM.

C3a Deposition Assay

[0298] Another method used to assess the ability of Factor P antibodies to inhibit the alternative complement pathway is to measure the ability of antibodies to inhibit the generation of C3a following cleavage of C3 by C3 convertase. The assay was carried out on zymosan-coated Maxisorp plates coated at 10 mg/ml and 10% and 20% human serum pre-incubated with anti-properdin Fab diluted in a 2ⁿ series. The serum was added to the plates for 30 minutes at which time the serum was collected for assessment of C3a generation.

[0299] Maxisorp plates were coated with anti-C3a des-arg neo antibody (1ug/ml) overnight, washed three times, and blocked with diluent for two hours at room temperature. Following aspiration of the diluent, serum was added for one hour. Plates were washed three times and a 100 uL/well detection antibody Mouse anti-Human C3a-Biotin 1:1000 diluted in diluent was added. Following an additional one hour incubation, a streptavidin-HRP secondary antibody diluted 1:5000 in diluent was added to the wells for one hour at room temperature. Plates were washed four times before the addition of TMB detection substrate. The reaction was stopped using standard stop solution and absorbance was read at 450-570 nm.

[0300] In parallel to the addition of the serum, a standard curve was produced using purified C3a des-arg diluted in serum. Starting at 5ug/ml, C3a des-arg was serially diluted 1:4 to generate a 7 point curve. The standard curve wells were treated, washed, and read as above.

Table 5: Functional Analysis of Factor P Antibodies

Factor P Antibody	Factor P Species	MAC Deposition, 20% Serum EC50 (nM)	Zymosan-C3b IC50 (nM), 10% serum	Hemolytic assay IC50 (nM), 10% serum	Inhibition of C3a generation, 20% human serum (nM)
NVS962	Human	18.79	2.63	13.18	78.42
	Cyno	12.08	9.91	16.14	ND
NVS965	Human	17.32	1.54	7.527	31.33
	Cyno	22.17	6.36	13.20	ND
NVS963	Human	ND	2.34	10.11	65.08
	Cyno	ND	9.75	14.53	ND
NVS966	Human	ND	1.66	7.154	41.11
	Cyno	ND	6.62	13.00	ND
NVS964	Human	ND	1.54	9.26	42.18
	Cyno	ND	6.59	13.41	ND
NVS967	Human	ND	2.53	9.61	43.53
	Cyno	ND	5.92	14.01	ND

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(continued)

Factor P Antibody	Factor P Species	MAC Deposition, 20% Serum EC50 (nM)	Zymosan-C3b IC50 (nM), 10% serum	Hemolytic assay IC50 (nM), 10% serum	Inhibition of C3a generation, 20% human serum (nM)
NVS962-Q	Human	23.12	0.64	15.27	ND
	Cyno	20.88	1.62	14.7	ND
NVS962-S	Human	6.53	1.53	8.21	ND
	Cyno	15.57	1.94	12.02	ND
NVS962-T	Human	6.61	1.75	9.31	ND
	Cyno	5.42	3.10	12.54	ND
NVS962-G	Human	12.68	1.18	13.39	ND
	Cyno	9.27	2.94	14.23	ND
NVS962-S31A	Human	9.96	1.15	12.79	ND
	Cyno	7.86	3.12	11.61	ND
NVS965-Q	Human	15.40	1.64	9.71	ND
	Cyno	9.39	3.30	14.71	ND
NVS965-S	Human	7.32	1.39	7.89	ND
	Cyno	8.12	1.57	12.02	ND
NVS965-T	Human	13.80	0.77	7.15	ND
	Cyno	10.98	1.91	12.54	ND
NVS808	Human	6.51	ND	13.28	ND
	Cyno	8.38	ND	15.53	ND
NVS806	Human	5.74	ND	10.14	ND
	Cyno	6.51	ND	13.93	ND
NVS807	Human	5.40	ND	12.91	ND
	Cyno	6.35	ND	12.57	ND
NVS804	Human	5.85	ND	12.38	ND
	Cyno	8.51	ND	14.44	ND
NVS805	Human	5.90	ND	12.82	ND
	Cyno	5.95	ND	22.11	ND
NVS809	Human	6.46	ND	12.1	ND
	Cyno	5.90	ND	12.78	ND
ND: Not Determined					

Example 5: Species Cross Reactivity

[0301] In order to determine whether, in addition to human and cynomolgus, the anti-Factor P antibodies described herein would bind to Factor P from other species, MAC deposition and hemolytic assays were carried out as described above. BIAcore analysis, or hemolytic assays were carried out as described above. The serum concentrations used for each species were as follows: 10 and 20% rabbit, 10 and 20% cynomolgus, and 10 and 20% human sera. Rat Factor P binding was assessed by BIAcore. As shown in Table 6 below, the Factor P antibodies were able to cross react with several species, including rabbit, rat and cynomolgus.

Table 6: Species cross-reactivity

Antibody	Human	Rat	Rabbit	Cyno
NVS962	X	X	X	X
NVS962-S	X	X	X	X
NVS801	X	X	X	X
NVS965	X	ND	ND	X
NVS965-S	X	ND	ND	X
NVS808	X	ND	X	X
NVS806	X	ND	X	X
ND: not determined				

Example 6: Epitope Mapping

[0302] Factor P is comprised of several Thrombospondin repeat domains (TSR 0-6). The TSR0 domain is also referred to as the N terminal domain. Epitope mapping of the Factor P Fabs was performed by creating mouse and human chimeras for each TSR. Previous functional assays showed that the Fabs do not bind to mouse Factor P (hemolytic assays), although each of the chimeras was functional in Factor P-depleted serum. Using this method it was determined that all of the Fabs bind to TSR 5 (SEQ ID NO: 406). Figure 1C shows the antibodies bind region B of TSR5. The commercially-available antibody, A233, was shown not to bind in this region. Binding can be assessed by ELISA or Biacore using standard methods. For one Ab, NVS487, the data was not conclusive due to cross reactivity to mouse Factor P. Sequence alignment between mouse and human Factor P TSR5 domain shows the epitope includes the amino acids of SEQ ID NO: 408.

Example 7: *In vivo* inhibition of the Alternative Complement Pathway

[0303] Experiments were performed in cynomolgus monkey with antibodies of the invention to determine their ability to inhibit the alternative complement pathway.

[0304] The test item, NVS962, was administered at the dose levels shown in Table 7. The route of administration was either intravitreal (IVT) or intravenous (IV).

Table 7: *In Vivo* Study Design

Group number	Group description	Dose level	Route of dosing	Dose volume (μL/ injection)	Animals/group	
					Male	Female
1	Control	0 (vehicle)	IVT IV	50/IVT injection 100/IV injection	1	1
2	Low IVT	1 mg/eye (2 mg/ monkey)	IVT	50/IVT injection	1	1
3	IV	10 mg/monkey	IV	100/IV injection	1	1
4	High IVT	5 mg/eye (10 mg/ monkey)	IVT	50/IVT injection	1	1

[0305] The test item and vehicle solutions (vehicle: 10 mM His/His-HCl; 10% trehalose; 0.02% Tween 20; pH 5.5) were administered intravitreally and intravenously on days 1, 15, and 29 of the study as indicated in Table 7.

[0306] Assessment of toxicity was based on mortality, clinical observations, body weights, pharmacodynamics (hemolytic analysis), ophthalmic examinations, intraocular pressure measurements, electroretinography, hematology, clinical chemistry, organ weights, and pathology.

[0307] There were no mortalities during the study and no test item related findings were seen after evaluation of clinical signs, body weights, ophthalmic examinations, intraocular pressure measurements, electroretinography, hematology, clinical chemistry, organ weights, and pathology.

[0308] Complement mediated hemolytic activity was measured using the hemolytic assay described above (see Example 4). Analysis of the hemolytic assay data showed that IV administration of NVS962 led to a complete or nearly complete but short-lived, inhibition of hemolytic complement activity immediately after administration. When administered by the IVT route at a dose of 1 mg/eye, the test item had little or no effect on serum hemolytic complement activity. At 5 mg/eye and in 10% cynomolgus serum, a complete or nearly complete inhibition of hemolytic complement activity was observed.

Example 8: Synergistic inhibition of the Alternative Complement Pathway by Antibody Combinations

Hemolysis Assay

[0309] Hemolytic assays using the Fab versions of the anti-C5 antibody 8109 from Table 2 and anti-Factor P antibody NVS962 from Table 1 were performed as described in Example 4.

[0310] Figure 2 exemplifies of the ability of the Factor P antibodies and antigen binding fragments in combinations with anti-C5 antibodies and antigen binding fragments to inhibit hemolysis in 20% human serum. 500nM anti-factor P and 500nM anti-C5 Fabs individually demonstrate no inhibition of hemolysis when incubated for 60 mins. In contrast, the combination of anti-factor P and anti-C5 antibodies at the same concentration and at concentrations as low as 167nM demonstrate near complete inhibition of hemolysis. In addition, the near complete inhibition of hemolysis lasts for up to 250 minutes.

[0311] Data from the hemolytic assay was used with Chalice Analyzer software to determine whether the combination of complement inhibiting antibodies acted synergistically to block complement activation. Combination effects can be characterized by comparing each data point's inhibition to that of a combination reference model that was derived from the single agent curves (Greco, Bravo, Parsons (1995). The search for synergy: a critical review from a response surface perspective. *Pharmacol Rev* 47(2): 331-85). In the Loewe additivity model (Loewe (1928). *Die quantitativen Probleme der Pharmakologie. Ergebn. Physiol.* 27: 47-187), $I_{\text{Loewe}}(C_X, C_Y)$ is the inhibition that satisfies $(C_X/IC_X) + (C_Y/IC_Y) = 1$, and $IC_{X,Y}$ are the effective concentrations at I_{Loewe} for the fitted single agent curves. Loewe additivity is the generally accepted reference for synergy (Greco et al.), as it represents the combination response generated if X and Y are the same compound.

[0312] Potency shifting is usually shown using an isobologram (Greco et al.) which shows how much less drug is required in combination to achieve a desired effect level, when compared to the single agent doses needed to reach that effect. The choice of effect level for the isobologram display and combination index calculations can either be manually or automatically selected in the Chalice Analyzer. The automatic iso-level selection algorithm finds the observed I_{data} with the the largest $I_{\text{data}} - I_{\text{Loewe}}$, excluding those points with I_{data} exceeding the lesser single agent's I_{max} . This exclusion is applied to ensure that the isobologram reflects the best synergy at levels covered by both single agents. Having selected an isobologram level I_{cut} , the isobologram is drawn by identifying the locus of concentrations that correspond to crossing the chosen iso-level. The isobologram shows the standard isobolographic analysis of synergy compared to the Loewe dose-additive "drug-with-itself" standard. For a specified isobologram level, the observed iso-effect contour (e.g., curved line in Figure 3) is displayed with the theoretical dose-additive contour (e.g., straight line in Figure 3), on an IC_{effect} -normalized linear concentration scale for both substances in the combination. The Dose-additive reference is always a line connecting the two IC_{effect} concentrations. The IC_{effect} crossing points are found by interpolating the fitted sigmoidal dose response curves.

[0313] Potency shifting is scored as the combination index (Chou, Talalay (1984). Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors. *Adv Enzyme Regul* 22: 27-55) CI. For a chosen iso-effect level I_{cut} , $CI = (C_X/EC_X)_I + (C_Y/EC_Y)_I$, where $(C_X/EC_X)_I$ for a particular data point is the ratio of the X compound's measured concentration to its effective concentration at the chosen inhibition level. The CI can be thought of as a rough estimate of how much drug was needed in combination relative to the single agent doses required to achieve the chosen effect level, and a value of 0.1 means that only a tenth of equivalent amounts of the single agents were needed for the combination to reach the same effect level. CI values in the range of 0.5-0.7 are typical for *in vitro* measurements of current clinical combinations (Greco et al.). A CI value of 1.0 is indicative of an additive effect of a combination of antibodies, while a CI value of less than 0.5 is indicative of a synergistic effect resulting from the antibody combination. In the Chalice Analyzer, the best CI is reported from the many combination index values calculated for each I_{cut} crossing concentration. Among all the measured CI values, the one with the largest signal-to-noise level is reported as the best combination index.

[0314] Data from the hemolytic assay were expressed as % inhibition and loaded into an 8x8 Excel table, in which the antibodies concentrations were expressed as uM values. The Excel template was uploaded to the Chalice software (Lehar et al. 2009) and the combination index was generated by creating an isobologram curve using IC20 for each antibody ($CI = C_X/IC_X + C_Y/IC_Y$, where IC_X and IC_Y are, respectively, the concentrations of anti-factor P antibody and anti-C5 antibody alone that result in a 20% inhibition effect and C_X and C_Y are the concentrations of each drug in the

mixture that yield 20 % inhibition). The combination index at 20% inhibition is 0.36, indicating synergy between anti-factor P antibody and anti-C5 antibody (Figure 3).

Macrophage Infiltration

[0315] The effect of anti-fP and anti-C5 Fabs individually or in combination were assessed *in vivo* using the poly-IC murine model of ocular inflammation. Mice were injected i.v. with synthetic dsRNA analog, poly I:C in 0.1ml PBS systemically into C57BL/6 mice along with anti-fP (antibody NVS962 from Table 1) and anti-C5 antibodies (antibody 8019 from Table 2) individually or in combination. Mice were euthanized at indicated time points. Eyes and retinas were collected and protein extracts were prepared for cytokine and chemokine analysis using a multiplex assay (Pierce). To determine retinal leukocyte infiltration, eyes were fixed in 4% paraformaldehyde and stained with Alexa Fluor-488 conjugated F4/80 antibody for macrophages. The retinas were flat mounted with the retinal vasculature orientated superiorly onto a glass slide and coverslipped with a drop of Vectashield mounting medium (Vector Laboratories Inc, Burlingame, CA). Fluorescent images of five (500um) regions on each retina were captured using the AxioCam MR3 camera on a Axio.ImageM1 microscope (Zeiss). The number of neutrophils and macrophages was quantified with Axiovision software (Version 4.5 Zeiss). Using optical coherence tomography (OCT), images of retinas were obtained and analysed from mice treated with poly I:C. These results (Figure 4) demonstrate that at the highest concentrations tested (20ug) no greater than 45% inhibition of macrophage infiltration was observed. In contrast, combinations of the anti-Factor P and C5 antibodies at concentrations as low as 2 ug demonstrated 79% inhibition and increasing the concentration achieved 100% inhibition (compared to only 13% and 32% inhibition respectively for the anti-C5 and anti-Factor P antibodies individually).

[0316] Data from *in vivo* poly-IC model (macrophage infiltration) described in the preceding paragraph were expressed as % inhibition and loaded into a 4x4 Excel table, in which the antibody doses were expressed as ug values. The Excel template was uploaded to the Chalice analyzer (described above) and the combination index was generated by creating an isobologram curve using IC50 for each antibody ($CI = C_X/IC_X + C_Y/IC_Y$, where IC_X and IC_Y are, respectively, the concentrations of anti-factor P antibody and anti-C5 antibody alone that result in a 50% inhibition effect and C_X and C_Y are the concentrations of each drug in the mixture that yield 50 % inhibition). The combination index at 50% inhibition is 0.42 (See Figure 5), indicating synergy between anti-factor P antibody and anti-C5 antibody.

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 BRANNETTI, BARBARA

<120> COMPOSITIONS AND METHODS FOR ANTIBODIES TARGETING FACTOR P

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30 Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

35 Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
210 215 220

<210> 24
<211> 216
40 <212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
45 polypeptide

<400> 24
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
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50 Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
20 25 30

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

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

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

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

Ala His Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
 100 105 110

15 Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
 115 120 125

20 Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
 130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
 145 150 155 160

25 Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
 165 170 175

30 Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
 180 185 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
 195 200 205

35 Thr Val Ala Pro Thr Glu Cys Ser
 210 215

40 <210> 25
 <211> 351
 <212> DNA
 <213> Artificial Sequence

45 <220>
 <223> Description of Artificial Sequence: Synthetic
 polynucleotide

<400> 25
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 ccaggacagg gcctggaatg gatgggcccc atcaaccctt actacggcga cgccatctac 180
 55 gccagaaaat tccagggcag agtgaccatc accgccgacg agagcaccag caccgcctac 240
 atggaactga gcagcctgag aagcgaggac accgccgtgt actactgcgc ccggtactac 300

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<210> 26

<211> 330

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 26

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agctgcaccg gctccagcag caacatcgga gctggatacg acgtgcactg gtatcagcag 120

ctgcccggca cagcccctaa gctgctgac cagacaaca gccacagacc cagcggcgtg 180

cccgatagat tcagcggcag caagagcggc accagcgcca gcctggccat caccggcctg 240

cagagcgagg acgagggcga ctactactgc gccagctacg acgagagcgc ccacagcgtg 300

ttcggaggcg gaacaaagtt aaccgtccta 330

<210> 27

<211> 660

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 27

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tcctgcaagg ccagcggcgg cacctttagc agctacgcca tcagctgggt gcgccaggct 120

ccaggacagg gcctggaatg gatgggcccc atcaaccctt actacggcga cgccatctac 180

gcccagaaat tccagggcag agtgaccatc accgcgcagc agagcaccag caccgcctac 240

atggaactga gcagcctgag aagcgaggac accgcctgtt actactgcgc ccggtactac 300

agcgactaca tggactactg gggccagggc accctggtga ccgtgagctc agcctccacc 360

aaggttccat cggctcttccc cctggcacc cctccaaga gcacctctgg gggcacagcg 420

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 480

ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcttc aggactctac 540

tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcaccagac ctacatctgc 600

aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt 660

<210> 28

<211> 648

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 28

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ctgcccggca cagcccctaa gctgctgatc cagcacaaca gccacagacc cagcggcgtg      180
cccgatagat tcagcggcag caagagcggc accagcgcca gcctggccat caccggcctg      240
cagagcgagg acgaggccga ctactactgc gccagctacg acgagagcgc ccacagcgtg      300
ttcggaggcg gaacaaagtt aaccgtccta ggtcagccca aggctgcccc ctcggtcact      360
ctgttccccg cctcctctga ggagcttcaa gccacaagg ccacactggg gtgtctcata      420
agtgaattct acccgggagc cgtgacagtg gcctggaagg cagatagcag ccccgtaag      480
gcgggagtg agaccaccac accctccaaa caaagcaaca acaagtacgc ggccagcagc      540
tatctgagcc tgacgcctga gcagtggaag tcccacagaa gctacagctg ccaggtcacg      600
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<210> 29

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 29

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Ser His Tyr Met His
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<210> 30

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 30

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Lys Ile Asn Ala Asp Leu Gly Asp Thr Asn Tyr Ala Gln Lys Phe Gln
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Gly

<210> 31

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<211> 17
<212> PRT
<213> Artificial Sequence

5

<220>
<223> Description of Artificial Sequence: Synthetic peptide

10

<400> 31
Asp Gly Ile Glu His Gly Gly His Tyr Tyr Trp Gly Tyr Leu Phe Asp
1 5 10 15

Ile

15

<210> 32
<211> 11
<212> PRT
<213> Artificial Sequence

20

<220>
<223> Description of Artificial Sequence: Synthetic peptide

25

<400> 32
Ser Gly Asp Ser Ile Arg Glu Tyr Tyr Val His
1 5 10

30

<210> 33
<211> 7
<212> PRT
<213> Artificial Sequence

35

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 33
Asp Asp Thr Asn Arg Pro Ser
1 5

40

<210> 34
<211> 9
<212> PRT
<213> Artificial Sequence

45

<220>
<223> Description of Artificial Sequence: Synthetic peptide

50

<400> 34
Ala Ala Trp Asp Phe Ser Pro Ala Ile
1 5

55

<210> 35
<211> 126
<212> PRT
<213> Artificial Sequence

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<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 35

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

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

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

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

Ala Arg Asp Gly Ile Glu His Gly Gly His Tyr Tyr Trp Gly Tyr Leu
100 105 110

Phe Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 36

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 36

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

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

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

Asp Asp Thr Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

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Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
 65 70 75 80
 5 Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Phe Ser Pro Ala Ile
 85 90 95
 10 Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105
 <210> 37
 <211> 229
 <212> PRT
 15 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: Synthetic
 polypeptide
 20 <400> 37
 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15
 25 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser His
 20 25 30
 30 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Lys Ile Asn Ala Asp Leu Gly Asp Thr Asn Tyr Ala Gln Lys Phe
 50 55 60
 35 Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 40 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 45 Ala Arg Asp Gly Ile Glu His Gly Gly His Tyr Tyr Trp Gly Tyr Leu
 100 105 110
 Phe Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
 115 120 125
 50 Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
 130 135 140
 55 Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
 145 150 155 160

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Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
165 170 175

5 His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

10 Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val
210 215 220

15 Glu Pro Lys Ser Cys
225

<210> 38
<211> 213
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
25 polypeptide

<400> 38
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15

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

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

40 Asp Asp Thr Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

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

45 Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Phe Ser Pro Ala Ile
85 90 95

50 Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
100 105 110

Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
115 120 125

55 Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala

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130

135

140

5

Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145 150 155 160

10

Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
165 170 175

15

Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
180 185 190

Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
195 200 205

20

Pro Thr Glu Cys Ser
210

25

<210> 39
<211> 378
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

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<400> 39
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tcctgcaagg ccagcggcta caccttcacc agccactaca tgcactgggt gcgccaggct 120

35

ccaggacagg gcctggaatg gatgggcaag atcaacgccg acctggggcga caccaactac 180

gccagaaat tccagggcag agtgaccatg acccgggaca ccagcatcag caccgcctac 240

atggaactga gcagcctgag aagcgaggac accgccgtgt actactgccc cagggacggc 300

40

atcgagcacg ggggccacta ctactggggc tacctgttcg acatctgggg ccagggcacc 360

ctggtgaccg tgagctca 378

45

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

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

50

<400> 40
agctacgagc tgactcagcc cccttctgtg tctgtggccc ctggccagac cgccagaatc 60

55

agctgcagcg ggcagacgat ccgggagtag tacgtgcact ggtatcagca gaagcccggc 120

caggctcctg tgctggtgat cggcgacgac accaacagac ccagcggcat ccccgagaga 180

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	ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccgag	240
	gacgaggccg attactactg cgccgcctgg gacttcagcc ctgccatcgt gttcggagggc	300
5	ggaacaaagt taaccgtcct a	321
	<210> 41	
	<211> 687	
10	<212> DNA	
	<213> Artificial Sequence	
	<220>	
	<223> Description of Artificial Sequence: Synthetic polynucleotide	
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20	ccaggacagg gcctggaatg gatgggcaag atcaacgccg acctgggcga caccaactac	180
	gccagaaat tccagggcag agtgaccatg acccgggaca ccagcatcag caccgcctac	240
25	atggaactga gcagcctgag aagcgaggac accgccgtgt actactgcgc cagggacggc	300
	atcgagcacg gcggccacta ctactggggc tacctgttcg acatctgggg ccagggcacc	360
	ctggtgaccg tgagctcagc atccaccaag ggtccatcgg tcttccccct ggcaccctcc	420
30	tccaagagca cctctggggg cacagcggcc ctgggctgcc tgggtcaagga ctacttcccc	480
	gaaccggtga cgggtgtcgtg gaactcaggc gccctgacca gcggcgtgca caccttcccc	540
	gctgtcctac agtcctcagg actctactcc ctcagcagcg tggtgaccgt gccctccagc	600
35	agcttgggca cccagaccta catctgcaac gtgaatcaca agcccagcaa caccaagggtg	660
	gacaagagag ttgagcccaa atcttgt	687
40	<210> 42	
	<211> 639	
	<212> DNA	
	<213> Artificial Sequence	
	<220>	
45	<223> Description of Artificial Sequence: Synthetic polynucleotide	
	<400> 42	
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	caggctcctg tgctgggtgat cggcgacgac accaacagac ccagcggcat ccccgagaga	180
55	ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccgag	240
	gacgaggccg attactactg cgccgcctgg gacttcagcc ctgccatcgt gttcggagggc	300

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ggaacaaagt taaccgtcct aggtcagccc aaggctgccc cctcggtcac tctgttcccg 360
 ccctcctctg aggagcttca agccaacaag gccacactgg tgtgtctcat aagtgacttc 420
 5 taccggggag ccgtgacagt ggcctggaag gcagatagca gccccgtcaa ggcgggagtg 480
 gagaccacca caccctccaa acaaagcaac aacaagtacg cggccagcag ctatctgagc 540
 ctgacgcctg agcagtggaa gtcccacaga agctacagct gccaggtcac gcatgaaggg 600
 10 agcaccgtgg agaagacagt ggcccctaca gaatgttca 639

<210> 43
 <211> 5
 <212> PRT
 15 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic
 peptide
 20
 <400> 43
 Asn Tyr Trp Ile Gly
 1 5

<210> 44
 <211> 17
 <212> PRT
 <213> Artificial Sequence

 <220>
 30 <223> Description of Artificial Sequence: Synthetic
 peptide

 <400> 44
 Arg Ile Asp Pro Gly Glu Ser Leu Thr Asn Tyr Ala Pro Ser Phe Gln
 35 1 5 10 15

Gly

<210> 45
 <211> 12
 <212> PRT
 <213> Artificial Sequence
 45
 <220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

 <400> 45
 50 Thr Gly Val Ala Asp Val Asp Met Pro Phe Ala His
 1 5 10

<210> 46
 <211> 11
 <212> PRT
 55 <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 46

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

<210> 47

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 47

Gly Asp Ser Glu Arg Pro Ser
 1 5

<210> 48

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 48

Gly Ser Trp Asp Ile Thr Ser Phe
 1 5

<210> 49

<211> 121

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 49

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
 20 25 30

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

Gly Arg Ile Asp Pro Gly Glu Ser Leu Thr Asn Tyr Ala Pro Ser Phe
 50 55 60

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Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

5 Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

10 Ala Arg Thr Gly Val Ala Asp Val Asp Met Pro Phe Ala His Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

15 <210> 50
<211> 106
<212> PRT
<213> Artificial Sequence

20 <220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

25 <400> 50
Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys
1 5 10 15

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

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

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

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

45 Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Trp Asp Ile Thr Ser Phe Val
85 90 95

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

50 <210> 51
<211> 224
<212> PRT
<213> Artificial Sequence

55 <220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

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<400> 51

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

Gly Arg Ile Asp Pro Gly Glu Ser Leu Thr Asn Tyr Ala Pro Ser Phe
50 55 60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65 70 75 80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg Thr Gly Val Ala Asp Val Asp Met Pro Phe Ala His Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
210 215 220

<210> 52

<211> 212

<212> PRT

<213> Artificial Sequence

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<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 52

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

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

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

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

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

Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Trp Asp Ile Thr Ser Phe Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110

Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125

Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140

Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160

Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175

Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190

Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205

Thr Glu Cys Ser
210

<210> 53

<211> 363

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 53

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 cctggcaagg gcctggaatg gatgggcaga atcgaccccg gcgagtcctt gaccaactac 180
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 ctgcagtgga gcagcctgaa ggccagcgac accgccatgt actactgcgc cagaaccggc 300
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<210> 54

<211> 318

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 54

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 agctgcagcg gcgacaacct gggcagctac tacgtgaact ggtatcagca gaagcccggc 120
 caggctcccg tgctggtgat ctacggcgac agcgagaggc ctacggcat ccccgagcgg 180
 ttcagcggca gcaacagcgg caataccgcc accctgacca tctctagagc ccaggccggc 240
 gacgaggccg attactactg cggctcctgg gacatcacca gcttcgtgtt cggaggcgga 300
 acaaagttaa ccgtccta 318

<210> 55

<211> 672

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 55

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 cctggcaagg gcctggaatg gatgggcaga atcgaccccg gcgagtcctt gaccaactac 180
 gccccagct tccagggcca ggtgacaatc agcgccgaca agagcatcag caccgcctat 240

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	ctgcagtgga gcagcctgaa ggccagcgac accgccatgt actactgcgc cagaaccggc	300
	gtggccgacg tggacatgcc ttttggccac tggggccagg gcaccctggt gaccgtgagc	360
5	tcagcctcca ccaaggggtcc atcgggtcttc cccctggcac cctcctccaa gagcacctct	420
	gggggacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg	480
	tcgtggaact caggcgccct gaccagcggc gtgcacacct tcccggtgt cctacagtcc	540
10	tcaggactct actccctcag cagcgtggtg accgtgccct ccagcagctt gggcaccag	600
	acctacatct gcaacgtgaa tcacaagccc agcaacacca aggtggacaa gagagttgag	660
	cccaaattctt gt	672
15		
	<210> 56	
	<211> 636	
	<212> DNA	
20	<213> Artificial Sequence	
	<220>	
	<223> Description of Artificial Sequence: Synthetic polynucleotide	
25	<400> 56	
	agctacgtgc tgactcagcc cccttctgtg tctgtggccc ctggcaagac cgccagaatc	60
	agctgcagcg gcgacaacct gggcagctac tacgtgaact ggtatcagca gaagcccggc	120
30	caggctcccg tgctggtgat ctacggcgac agcgagaggc ctagcggcat ccccgagcgg	180
	ttcagcggca gcaacagcgg caataaccgcc accctgacca tctctagagc ccaggccggc	240
	gacgaggccg attactactg cggctcctgg gacatcacca gcttcgtgtt cggaggcgga	300
35	acaaagttaa ccgtcctagg tcagcccaag gctgccccct cggtcactct gttcccgccc	360
	tcctctgagg agcttcaagc caacaaggcc aactggtgt gtctcataag tgacttctac	420
	ccgggagccg tgacagtggc ctggaaggca gatagcagcc ccgtcaaggc gggagtggag	480
40	accaccacac cctccaaaca aagcaacaac aagtacggcg ccagcagcta tctgagcctg	540
	acgcctgagc agtggaaagc ccacagaagc tacagctgcc aggtcacgca tgaaggagc	600
	accgtggaga agacagtggc ccctacagaa tgttca	636
45		
	<210> 57	
	<211> 5	
	<212> PRT	
50	<213> Artificial Sequence	
	<220>	
	<223> Description of Artificial Sequence: Synthetic peptide	
55	<400> 57	
	Ser Tyr Ala Ile Ser	
	1 5	

<210> 58
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic peptide

<400> 58
 Arg Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
 1 5 10 15

Gly

<210> 59
 <211> 8
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic peptide

<400> 59
 His Gly Gly Tyr Ser Phe Asp Ser
 1 5

<210> 60
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic peptide

<400> 60
 Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val Asp
 1 5 10

<210> 61
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic peptide

<400> 61
 Ser Asp Asn Asn Arg Pro Ser
 1 5

<210> 62

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<211> 10
<212> PRT
<213> Artificial Sequence

5 <220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 62
Ala Thr Tyr Asp Ser Ser Pro Arg Thr Glu
1 5 10

<210> 63
<211> 117
<212> PRT
15 <213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

20 <400> 63
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

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

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

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

35 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

45 Ala Arg His Gly Gly Tyr Ser Phe Asp Ser Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

50 <210> 64
<211> 108
<212> PRT
<213> Artificial Sequence

55 <220>
<223> Description of Artificial Sequence: Synthetic polypeptide

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<400> 64

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val
20 25 30

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

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

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

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

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

<210> 65

<211> 220

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 65

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

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

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

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

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

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

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	Ala	Arg	His	Gly	Gly	Tyr	Ser	Phe	Asp	Ser	Trp	Gly	Gln	Gly	Thr	Leu	
				100					105					110			
5	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	
			115					120					125				
10	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	
		130					135					140					
15	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	
	145					150					155					160	
20	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	
					165					170					175		
25	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	
			180						185					190			
30	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	
		195						200					205				
35	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys					
		210					215					220					
40	<210> 66																
	<211> 214																
	<212> PRT																
	<213> Artificial Sequence																
45	<220>																
	<223> Description of Artificial Sequence: Synthetic polypeptide																
50	<400> 66																
	Ser	Tyr	Val	Leu	Thr	Gln	Pro	Pro	Ser	Val	Ser	Val	Ala	Pro	Gly	Lys	
	1				5					10					15		
55	Thr	Ala	Arg	Ile	Ser	Cys	Ser	Gly	Asp	Asn	Leu	Gly	Ser	Lys	Tyr	Val	
				20					25					30			
60	Asp	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr	
		35						40					45				
65	Ser	Asp	Asn	Asn	Arg	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser	
		50					55					60					
70	Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Gly	Thr	Gln	Ala	Met	
	65					70					75					80	

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

5 Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

<210> 67
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 67
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tcctgcaagg ccagcggcgg caccttcaac agctacgcca tcagctgggt gcgccaggct 120
cctggacagg gcctggaatg gatgggccgg atcatcccca tcttcggcac cgccaactac 180
gcccagaaat tccagggcag agtgaccatc accgccgacg agagcaccag caccgcctac 240
atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc ccggcacggc 300
ggctacagct togatagctg gggccagggc accctggtga ccgtgagctc a 351

<210> 68
<211> 324
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

5 <400> 68
 agctacgtgc tgactcagcc cccttctgtg tctgtggccc ctggcaagac cgccagaatc 60
 agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc 120
 10 caggctcccg tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg 180
 ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccatg 240
 gacgaggccg actactactg cgccacctac gacagcagcc ccagaaccga ggtgttcgga 300
 15 ggcggaacaa agttaaccgt ccta 324

<210> 69

<211> 660

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

25 <400> 69
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 tcctgcaagg ccagcggcgg caccttcaac agctacgcca tcagctgggt gcgccaggct 120
 30 cctggacagg gcctggaatg gatgggcccgg atcatcccca tcttcggcac cgccaactac 180
 gccagaaat tccagggcag agtgaccatc accgcccagc agagcaccag caccgcctac 240
 atggaactga gcagcctgag aagcgaggac accgcccgtgt actactgtgc ccggcacggc 300
 35 ggctacagct tcgatagctg gggccagggc accctggtga ccgtgagctc agcctccacc 360
 aagggtccat cggctcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 420
 gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 480
 40 ggcgccctga ccagcggcgt gcacaccttc ccggtgtcc tacagtctc aggactctac 540
 tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcaccagac ctacatctgc 600
 45 aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt 660

<210> 70

<211> 642

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

55 <400> 70
 agctacgtgc tgactcagcc cccttctgtg tctgtggccc ctggcaagac cgccagaatc 60

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agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc 120

caggctcccg tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg 180

5 ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccatg 240

gacgaggccg actactactg cgccacctac gacagcagcc ccagaaccga ggtgttcgga 300

ggcgggaacaa agttaaccgt cctaggtcag cccaaggctg cccctcgggt cactctgttc 360

10 ccgccctcct ctgaggagct tcaagccaac aaggccacac tgggtgtgtct cataagtgc 420

ttctacccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480

gtggagacca ccacaccctc caaacaagc aacaacaagt acgcggccag cagctatctg 540

15 agcctgacgc ctgagcagtg gaagtccac agaagctaca gctgccagggt cagcatgaa 600

gggagcaccg tggagaagac agtggcccct acagaatgtt ca 642

20 <210> 71
<211> 5
<212> PRT
<213> Artificial Sequence

25 <220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 71
Ser His Tyr Met His
1 5

30

<210> 72
<211> 17
<212> PRT
<213> Artificial Sequence

35

<220>
<223> Description of Artificial Sequence: Synthetic peptide

40

<400> 72
Asn Ile Asn Pro Val Asp Gly Gly Thr Glu Tyr Ala Gln Lys Phe Gln
1 5 10 15

45 Gly

50 <210> 73
<211> 17
<212> PRT
<213> Artificial Sequence

55 <220>
<223> Description of Artificial Sequence: Synthetic peptide

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<400> 73

Asp Gly Ile Glu His Gly Gly His Tyr Tyr Trp Gly Tyr Leu Phe Asp
1 5 10 15

5

Ile

<210> 74

<211> 11

<212> PRT

<213> Artificial Sequence

10

<220>

<223> Description of Artificial Sequence: Synthetic peptide

15

<400> 74

Ser Gly Asp Ser Ile Arg Glu Tyr Tyr Val His
1 5 10

20

<210> 75

<211> 7

<212> PRT

<213> Artificial Sequence

25

<220>

<223> Description of Artificial Sequence: Synthetic peptide

30

<400> 75

Asp Asp Thr Asn Arg Pro Ser
1 5

<210> 76

<211> 9

<212> PRT

<213> Artificial Sequence

35

<220>

<223> Description of Artificial Sequence: Synthetic peptide

40

<400> 76

Ala Ala Trp Asp Phe Ser Pro Ala Ile
1 5

45

<210> 77

<211> 126

<212> PRT

<213> Artificial Sequence

50

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

55

<400> 77

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

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

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

10 Gly Asn Ile Asn Pro Val Asp Gly Gly Thr Glu 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

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

20 Ala Arg Asp Gly Ile Glu His Gly Gly His Tyr Tyr Trp Gly Tyr Leu
100 105 110

Phe Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

25

<210> 78
<211> 107
<212> PRT
30 <213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

35 <400> 78
Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys
1 5 10 15

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

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

Asp Asp Thr Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

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

55 Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Phe Ser Pro Ala Ile
85 90 95

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

5 <210> 79
<211> 229
<212> PRT
<213> Artificial Sequence

10 <220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 79
15 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

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

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

25 Gly Asn Ile Asn Pro Val Asp Gly Gly Thr Glu Tyr Ala Gln Lys Phe
50 55 60

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

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
35 85 90 95

Ala Arg Asp Gly Ile Glu His Gly Gly His Tyr Tyr Trp Gly Tyr Leu
100 105 110

40 Phe Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
115 120 125

45 Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr
130 135 140

Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
50 145 150 155 160

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
165 170 175

55 His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
180 185 190

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Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile
195 200 205

5 Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val
210 215 220

Glu Pro Lys Ser Cys
225

10

<210> 80
<211> 213
<212> PRT
15 <213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

20 <400> 80
Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys
1 5 10 15

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

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

30 Asp Asp Thr Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

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

40 Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Phe Ser Pro Ala Ile
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
100 105 110

45 Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
115 120 125

50 Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
130 135 140

Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145 150 155 160

55 Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser

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	165	170	175
5	Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr 180 185 190		
	Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala 195 200 205		
10	Pro Thr Glu Cys Ser 210		
15	<210> 81 <211> 378 <212> DNA <213> Artificial Sequence		
20	<220> <223> Description of Artificial Sequence: Synthetic polynucleotide		
25	<400> 81 gaggtgcagc tggtgcagag cggagccgaa gtgaagaaac ctggcgccag cgtgaagggt tcctgcaagg ccagcgggcta caccttcacc agccactaca tgcaactgggt gcgccagggt ccaggacagg gcctggaatg gatgggcaac atcaacccccg tggacggcgg caccgagtac gcccagaaat tccagggcag agtgaccatg acccgggaca ccagcatcag caccgcctac atggaactga gcagcctgag aagcgaggac accgccgtgt actactgcgc cagggacggc atcgagcacg gcggccacta ctactggggc tacctgttcg acatctgggg ccagggcacc ctggtgaccg tgagctca	60 120 180 240 300 360 378	
40	<210> 82 <211> 321 <212> DNA <213> Artificial Sequence		
45	<220> <223> Description of Artificial Sequence: Synthetic polynucleotide		
50	<400> 82 tcctacgtgc tgactcagcc cccttctgtg tctgtggccc ctggcaagac cgccagaatc agctgcagcg gcgacagcat ccgggagtag tacgtgcact ggtatcagca gaagcccggc caggctcctg tgctggtgat cggcgacgac accaacagac ccagcggcat ccccgagaga ttcagcggca gcaacagcgg caataccgcc accctgacca tctctagagc ccaggccggc gacgaggccg attactactg cgccgcctgg gacttcagcc ctgccatcgt gttcggaggc ggaacaaaqt taaccgtcct a	60 120 180 240 300 321	

<210> 83
 <211> 687
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 polynucleotide

<400> 83
 gaggtgcagc tgggtgcagag cggagccgaa gtgaagaaac ctggcgccag cgtgaaggtg 60
 tcctgcaagg ccagcggcta caccttcacc agccactaca tgcactgggt gcgccaggct 120
 ccaggacagg gcctggaatg gatgggcaac atcaaccccg tggacggcgg caccgagtac 180
 gccagaaat tccagggcag agtgaccatg acccgggaca ccagcatcag caccgcctac 240
 atggaactga gcagcctgag aagcgaggac accgcctgt actactgcgc cagggacggc 300
 atcgagcacg gcggccacta ctactggggc tacctgttcg acatctgggg ccagggcacc 360
 ctggtgaccg tgagctcagc ctccaccaag ggtccatcgg tcttccccct ggcaccctcc 420
 tccaagagca cctctggggg cacagcggcc ctgggctgcc tggtaagga ctacttcccc 480
 gaaccggtga cgggtgctgt gaactcaggc gccctgacca gcggcggtgca caccttcccc 540
 gctgtcctac agtcctcagg actctactcc ctcagcagcg tggtgaccgt gccctccagc 600
 agcttgggca ccagaccta catctgcaac gtgaatcaca agcccagcaa caccaaggtg 660
 gacaagagag ttgagcccaa atcttgt 687

<210> 84
 <211> 639
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 polynucleotide

<400> 84
 tcttacgtgc tgactcagcc cccttctgtg tctgtggccc ctggcaagac cgccagaatc 60
 agctgcagcg gcgacagcat ccgggagtag tacgtgcact ggtatcagca gaagcccggc 120
 caggctcctg tgctggtgat cggcgacgac accaacagac ccagcggcat ccccgagaga 180
 ttacgcggca gcaacagcgg caataaccgcc accctgacca tctctagagc ccaggccggc 240
 gacgaggccg attactactg cgccgcctgg gacttcagcc ctgccatcgt gttcggaggc 300
 ggaacaaagt taaccgtcct aggtcagccc aaggctgccc cctcggtcac tctgttcccc 360
 ccctcctctg aggagcttca agccaacaag gccacactgg tgtgtctcat aagtgacttc 420
 taccggggag ccgtgacagt ggcctggaag gcagatagca gcccgtcaa ggcgggagtg 480
 gagaccacca caccctcaa acaaagcaac aacaagtacg cggccagcag ctatctgagc 540

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ctgacgcctg agcagtggaa gtcccacaga agctacagct gccaggtcac gcatgaaggg 600
agcacccgtgg agaagacagt ggcccctaca gaatgttca 639

5

<210> 85
<211> 5
<212> PRT
<213> Artificial Sequence

10

<220>
<223> Description of Artificial Sequence: Synthetic peptide

15

<400> 85
Ser Tyr Ala Ile Ser
1 5

20

<210> 86
<211> 17
<212> PRT
<213> Artificial Sequence

25

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 86
Arg Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

30

Gly

35

<210> 87
<211> 9
<212> PRT
<213> Artificial Sequence

40

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 87
His Gly Gly Tyr Ser Tyr Phe Asp Ser
1 5

45

<210> 88
<211> 11
<212> PRT
<213> Artificial Sequence

50

<220>
<223> Description of Artificial Sequence: Synthetic peptide

55

<400> 88
Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val Asp
1 5 10

<210> 89
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic peptide

<400> 89
 Ser Asp Asn Asn Arg Pro Ser
 1 5

<210> 90
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic peptide

<400> 90
 Gln Thr Tyr Thr Ser Gly Asn Asn Tyr Leu
 1 5 10

<210> 91
 <211> 117
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

<400> 91
 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15

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

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

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

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

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

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

Val Thr Val Ser Ser
115

<210> 92
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 92
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val
20 25 30

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

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

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

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

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

<210> 93
<211> 220
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 93
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

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

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	Ala	Ile	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	
			35					40					45				
5	Gly	Arg	Ile	Ile	Pro	Ile	Phe	Gly	Thr	Ala	Asn	Tyr	Ala	Gln	Lys	Phe	
		50					55					60					
	Gln	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Glu	Ser	Thr	Ser	Thr	Ala	Tyr	
10	65					70					75					80	
	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
				85						90					95		
15	Ala	Arg	His	Gly	Gly	Tyr	Tyr	Phe	Asp	Ser	Trp	Gly	Gln	Gly	Thr	Leu	
				100					105					110			
	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	
20				115					120					125			
	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	
25		130					135					140					
	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	
	145					150					155					160	
30	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	
					165					170					175		
	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	
35				180					185					190			
	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	
40			195					200					205				
	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys					
		210					215					220					
45																	
	<210>	94															
	<211>	214															
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	<213>	Artificial Sequence															
50																	
	<220>																
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		polypeptide															
55	<400>	94															
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	1				5					10					15		

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Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val
 20 25 30
 5 Asp Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
 35 40 45
 Ser Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
 50 55 60
 10 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
 65 70 75 80
 15 Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Thr Ser Gly Asn Asn Tyr
 85 90 95
 20 Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
 100 105 110
 Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
 115 120 125
 25 Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
 130 135 140
 30 Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
 145 150 155 160
 Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
 165 170 175
 35 Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
 180 185 190
 40 Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
 195 200 205
 45 Ala Pro Thr Glu Cys Ser
 210
 <210> 95
 <211> 351
 50 <212> DNA
 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: Synthetic
 polynucleotide
 55 <400> 95

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gaggtgcagc tgggtgcagag cggagccgaa gtgaagaaac ccggcagcag cgtgaagggtg 60
 tcctgcaagg ccagcggcgg caccttcagc agctacgcca tcagctgggt gcgccaggct 120
 5 cctggacagg gcctggaatg gatgggcccg atcatcccca tcttcggcac cgccaactac 180
 gccagaaat tccagggcag agtgaccatc accgcccagc agagcaccag caccgcctac 240
 atggaactga gcagcctgag aagcaggagc accgcccgtgt actactgtgc ccggcacggc 300
 10 ggctactact tcgatagctg gggccagggc accctgggtga ccgtgagctc a 351

<210> 96
 <211> 324
 <212> DNA
 15 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 polynucleotide

<400> 96
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 agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc 120
 25 caggctcccc tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg 180
 ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccgag 240
 gacgaggccg actactactg ccagacctac accagcggca acaactacct ggtgttcgga 300
 30 ggcggaacaa agttaaccgt ccta 324

<210> 97
 <211> 660
 <212> DNA
 35 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 polynucleotide

<400> 97
 gaggtgcagc tgggtgcagag cggagccgaa gtgaagaaac ccggcagcag cgtgaagggtg 60
 tcctgcaagg ccagcggcgg caccttcagc agctacgcca tcagctgggt gcgccaggct 120
 45 cctggacagg gcctggaatg gatgggcccg atcatcccca tcttcggcac cgccaactac 180
 gccagaaat tccagggcag agtgaccatc accgcccagc agagcaccag caccgcctac 240
 atggaactga gcagcctgag aagcaggagc accgcccgtgt actactgtgc ccggcacggc 300
 50 ggctactact tcgatagctg gggccagggc accctgggtga ccgtgagctc agcctccacc 360
 aaggggccat cgggtcttccc cctggcacc cctccaaga gcacctctgg gggcacagcg 420
 55 gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacgggtgc gtggaactca 480
 ggcgccctga ccagcggcgt gcacacctc ccggctgtcc tacagtcctc aggactctac 540

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tccctcagca gcggtgtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 600
aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt 660

5
<210> 98
<211> 642
<212> DNA
<213> Artificial Sequence

10
<220>
<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 98
15 agctacgagc tgactcagcc cccttctgtg tctgtggccc ctggccagac cgccagaatc 60
agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc 120
caggctcccc tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg 180
20 ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccgag 240
gacgaggccg actactactg ccagacctac accagcggca acaactacct ggtgttcgga 300
ggcggaacaa agttaaccgt cctaggtcag cccaaggctg cccctcggt cactctgttc 360
25 ccgccctcct ctgaggagct tcaagccaac aaggccacac tgggtgtgtct cataagtgc 420
ttctaccggg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480
gtggagacca ccacaccctc caaacaagc aacaacaagt acgcggccag cagctatctg 540
30 agcctgacgc ctgagcagtg gaagtccac agaagctaca gctgccaggt cacgcatgaa 600
gggagcaccg tggagaagac agtggcccct acagaatgtt ca 642

35
<210> 99
<211> 5
<212> PRT
<213> Artificial Sequence

40
<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 99
45 Ser Tyr Ala Ile Ser
1 5

<210> 100
<211> 17
50 <212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide
55

<400> 100

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Arg Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

5 Gly

<210> 101
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide
15

<400> 101
His Gly Gly Tyr Ile Phe Asp Ser
1 5

20
<210> 102
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide
25

<400> 102
Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val Asp
1 5 10

30
<210> 103
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide
40

<400> 103
Ser Asp Asn Asn Arg Pro Ser
1 5

45
<210> 104
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide
50

<400> 104
Gln Thr Tyr Thr Ser Gly Asn Asn Tyr Leu
1 5 10

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<210> 105
 <211> 117
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 polypeptide

<400> 105
 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
 20 25 30
 Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Arg Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg His Gly Gly Tyr Ile Phe Asp Ser Trp Gly Gln Gly Thr Leu
 100 105 110
 Val Thr Val Ser Ser
 115

<210> 106
 <211> 108
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 polypeptide

<400> 106
 Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1 5 10 15
 Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val
 20 25 30
 Asp Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
 35 40 45

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

5 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

10 Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Thr Ser Gly Asn Asn Tyr
85 90 95

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

15

<210> 107
<211> 220
<212> PRT
<213> Artificial Sequence

20

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

25

<400> 107
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

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

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

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

40 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg His Gly Gly Tyr Ile Phe Asp Ser Trp Gly Gln Gly Thr Leu
100 105 110

50 Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

55 Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

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	Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser	
	145	150 155 160
5	Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser	
		165 170 175
10	Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser	
		180 185 190
15	Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn	
		195 200 205
	Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys	
	210	215 220
20	<210> 108	
	<211> 214	
	<212> PRT	
	<213> Artificial Sequence	
25	<220>	
	<223> Description of Artificial Sequence: Synthetic polypeptide	
	<400> 108	
30	Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln	
	1	5 10 15
35	Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val	
		20 25 30
40	Asp Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr	
		35 40 45
45	Ser Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser	
		50 55 60
50	Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu	
		65 70 75 80
55	Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Thr Ser Gly Asn Asn Tyr	
		85 90 95
	Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys	
		100 105 110
	Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln	
		115 120 125

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Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

5 Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

10 Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

15 Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

20 Ala Pro Thr Glu Cys Ser
210

25 <210> 109
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

30 <400> 109
gaggtgcagc tgggtgcagag cggagccgaa gtgaagaaac ccggcagcag cgtgaaggtg 60
tcctgcaagg ccagcggcgg caccttcagc agctacgcca tcagctgggt gcgccaggct 120
35 cctggacagg gcctggaatg gatgggccgg atcatcccca tcttcggcac cgccaactac 180
gccagaaat tccagggcag agtgaccatc accgccgacg agagcaccag caccgcctac 240
atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc ccggcacggc 300
40 ggctacattt tcgatagctg gggccagggc accctggtga ccgtgagctc a 351

45 <210> 110
<211> 324
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

50 <400> 110
agctacgagc tgactcagcc cccttctgtg tctgtggccc ctggccagac cgccagaatc 60
55 agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc 120
caggctcccg tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg 180

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	ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccgag	240
	gacgaggccg actactactg ccagacctac accagcggca acaactacct ggtgttcgga	300
5	ggcggaaaca agttaaccgt ccta	324
	<210> 111	
	<211> 660	
	<212> DNA	
10	<213> Artificial Sequence	
	<220>	
	<223> Description of Artificial Sequence: Synthetic polynucleotide	
15	<400> 111	
	gaggtgcagc tgggtgcagag cggagccgaa gtgaagaaac ccggcagcag cgtgaaggtg	60
	tcctgcaagg ccagcggcgg caccttcagc agctacgcca tcagctgggt gcgccaggct	120
20	cctggacagg gcctggaatg gatgggccgg atcatcccca tcttcggcac cgccaactac	180
	gccagaaat tccagggcag agtgaccatc accgccgacg agagcaccag caccgcctac	240
	atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc ccggcacggc	300
25	ggctacattt tcgatagctg gggccagggc accctggtga ccgtgagctc agcctccacc	360
	aaggggccat cgggtcttccc cctggcacc cctccaaga gcacctctgg gggcacagcg	420
	gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacgggtgc gtggaactca	480
30	ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac	540
	tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcaccagac ctacatctgc	600
35	aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt	660
	<210> 112	
	<211> 642	
	<212> DNA	
40	<213> Artificial Sequence	
	<220>	
	<223> Description of Artificial Sequence: Synthetic polynucleotide	
45	<400> 112	
	agctacgagc tgactcagcc cccttctgtg tctgtggccc ctggccagac cgccagaatc	60
	agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc	120
50	caggctcccg tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg	180
	ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccgag	240
	gacgaggccg actactactg ccagacctac accagcggca acaactacct ggtgttcgga	300
55	ggcggaaaca agttaaccgt cctaggtcag cccaaggctg cccctcggt cactctgttc	360
	ccgccctcct ctgaggagct tcaagccaac aaggccacac tgggtgtgtct cataagtgc	420

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ttctacccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480
 gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 540
 5 agcctgacgc ctgagcagtg gaagtccac agaagctaca gctgccaggt cacgcatgaa 600
 gggagcaccg tggagaagac agtggcccct acagaatgtt ca 642

10 <210> 113
 <211> 5
 <212> PRT
 <213> Artificial Sequence

15 <220>
 <223> Description of Artificial Sequence: Synthetic peptide

20 <400> 113
 Ser Tyr Ala Ile Ser
 1 5

25 <210> 114
 <211> 17
 <212> PRT
 <213> Artificial Sequence

30 <220>
 <223> Description of Artificial Sequence: Synthetic peptide

35 <400> 114
 Arg Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
 1 5 10 15

40 Gly

45 <210> 115
 <211> 8
 <212> PRT
 <213> Artificial Sequence

50 <220>
 <223> Description of Artificial Sequence: Synthetic peptide

55 <400> 115
 His Gly Gly Tyr Val Phe Asp Ser
 1 5

<210> 116
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic

peptide

<400> 116

Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val Asp
 1 5 10

<210> 117

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
 peptide

<400> 117

Ser Asp Asn Asn Arg Pro Ser
 1 5

<210> 118

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
 peptide

<400> 118

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

<210> 119

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
 polypeptide

<400> 119

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

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

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

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

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

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

5 Ala Arg His Gly Gly Tyr Val Phe Asp Ser Trp Gly Gln Gly Thr Leu
100 105 110

10 Val Thr Val Ser Ser
115

<210> 120
<211> 108
<212> PRT
15 <213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

20 <400> 120
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15

25 Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val
20 25 30

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

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

35 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

40 Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Thr Ser Gly Asn Asn Tyr
85 90 95

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

<210> 121
<211> 220
<212> PRT
50 <213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

55 <400> 121
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser

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5	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Gly	Thr	Phe	Ser	Ser	Tyr
			20					25						30		
10	Ala	Ile	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
			35					40					45			
15	Gly	Arg	Ile	Ile	Pro	Ile	Phe	Gly	Thr	Ala	Asn	Tyr	Ala	Gln	Lys	Phe
		50					55					60				
20	Gln	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Glu	Ser	Thr	Ser	Thr	Ala	Tyr
	65					70					75					80
25	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85						90					95	
30	Ala	Arg	His	Gly	Gly	Tyr	Val	Phe	Asp	Ser	Trp	Gly	Gln	Gly	Thr	Leu
			100						105					110		
35	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu
			115					120					125			
40	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys
		130					135					140				
45	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser
	145					150					155				160	
50	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser
				165						170					175	
55	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser
			180						185					190		
60	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn
		195						200					205			
65	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys				
		210					215					220				
70	<210>	122														
75	<211>	214														
80	<212>	PRT														
85	<213>	Artificial Sequence														
90	<220>															
95	<223>	Description of Artificial Sequence: Synthetic polypeptide														

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<400> 122

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val
20 25 30

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

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

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

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

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

<210> 123

<211> 351

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 123

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 tcctgcaagg ccagcggcgg caccttcagc agctacgcca tcagctgggt gcgccaggct 120
 cctggacagg gcctggaatg gatgggcccgg atcatcccca tcttcggcac cgccaactac 180
 gccagaaat tccagggcag agtgaccatc accgccgacg agagcaccag caccgcctac 240
 atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc ccggcacggc 300
 ggctacgtct tcgatagctg gggccagggc accctggtga ccgtgagctc a 351

<210> 124

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 124

agctacgagc tgactcagcc cccttctgtg tctgtggccc ctggccagac cgccagaatc 60
 agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc 120
 caggctcccg tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg 180
 ttacgcggca gcaacagcgg caataaccgcc accctgacca tcagcggcac ccaggccgag 240
 gacgaggccg actactactg ccagacctac accagcggca acaactacct ggtgttcgga 300
 ggcggaacaa agttaaccgt ccta 324

<210> 125

<211> 660

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 125

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 tcctgcaagg ccagcggcgg caccttcagc agctacgcca tcagctgggt gcgccaggct 120
 cctggacagg gcctggaatg gatgggcccgg atcatcccca tcttcggcac cgccaactac 180
 gccagaaat tccagggcag agtgaccatc accgccgacg agagcaccag caccgcctac 240
 atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc ccggcacggc 300
 ggctacgtct tcgatagctg gggccagggc accctggtga ccgtgagctc agcctccacc 360

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	aaggggtccat cgggtcttccc cctggcacccc tcctccaaga gcacctctgg gggcacagcg	420
	gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca	480
5	ggcgccctga ccagcggcgt gcacaccttc ccggtgtcc tacagtcttc aggactctac	540
	tcctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc	600
	aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt	660
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	<211> 642	
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	agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc	120
	caggctcccc tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg	180
25	ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccgag	240
	gacgaggccg actactactg ccagacctac accagcggca acaactacct ggtgttcgga	300
	ggcgaacaa agttaaccgt cctaggtcag cccaaggctg cccctcgggt cactctgttc	360
30	ccgccctcct ctgaggagct tcaagccaac aaggccacac tgggtgtgtct cataagtgac	420
	ttctaccggg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga	480
35	gtggagacca ccacaccctc caaacaagc aacaacaagt acgcggccag cagctatctg	540
	agcctgacgc ctgagcagtg gaagtccac agaagctaca gctgccaggt cacgcatgaa	600
	gggagcaccg tggagaagac agtggcccct acagaatgtt ca	642
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	<211> 5	
	<212> PRT	
	<213> Artificial Sequence	
45		
	<220>	
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	Ser Tyr Ala Ile Ser	
	1 5	
55		
	<210> 128	
	<211> 17	
	<212> PRT	
	<213> Artificial Sequence	

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<220>

<223> Description of Artificial Sequence: Synthetic peptide

5

<400> 128

Arg Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

10

Gly

<210> 129

<211> 8

15

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

20

<400> 129

His Gly Gly Tyr Val Phe Asp Ser
1 5

25

<210> 130

<211> 11

<212> PRT

<213> Artificial Sequence

30

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 130

35

Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val Asp
1 5 10

<210> 131

<211> 7

40

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

45

<400> 131

Ser Asp Asn Asn Arg Pro Ser
1 5

50

<210> 132

<211> 10

<212> PRT

<213> Artificial Sequence

55

<220>

<223> Description of Artificial Sequence: Synthetic peptide

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<400> 132

Ala Thr Tyr Asp Ser Ser Pro Arg Thr Glu
1 5 10

<210> 133

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 133

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

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

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

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

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

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

Ala Arg His Gly Gly Tyr Ile Phe Asp Ser Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 134

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 134

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val

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		20		25		30										
5	Asp	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr
			35					40					45			
10	Ser	Asp	Asn	Asn	Arg	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser
		50					55					60				
15	Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Gly	Thr	Gln	Ala	Met
	65					70					75					80
20	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Ala	Thr	Tyr	Asp	Ser	Ser	Pro	Arg	Thr
				85						90					95	
25	Glu	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu				
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30	<210>	135														
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	<223>	Description of Artificial Sequence: Synthetic polypeptide														
45	<400>	135														
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50	Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Gly	Thr	Phe	Ser	Ser	Tyr
			20						25					30		
55	Ala	Ile	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
		35						40					45			
60	Gly	Arg	Ile	Ile	Pro	Ile	Phe	Gly	Thr	Ala	Asn	Tyr	Ala	Gln	Lys	Phe
	50						55					60				
65	Gln	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Glu	Ser	Thr	Ser	Thr	Ala	Tyr
	65					70					75					80
70	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
				85						90					95	
75	Ala	Arg	His	Gly	Gly	Tyr	Ile	Phe	Asp	Ser	Trp	Gly	Gln	Gly	Thr	Leu
			100						105					110		
80	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu
			115						120					125		

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	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	
	130						135					140					
5	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	
	145					150					155					160	
	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	
10					165					170					175		
	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	
				180					185					190			
15	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	
		195						200					205				
	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys					
20		210					215					220					
	<210>	136															
25	<211>	214															
	<212>	PRT															
	<213>	Artificial Sequence															
	<220>																
30	<223>	Description of Artificial Sequence: Synthetic polypeptide															
	<400>	136															
	Ser	Tyr	Val	Leu	Thr	Gln	Pro	Pro	Ser	Val	Ser	Val	Ala	Pro	Gly	Lys	
35	1				5					10					15		
	Thr	Ala	Arg	Ile	Ser	Cys	Ser	Gly	Asp	Asn	Leu	Gly	Ser	Lys	Tyr	Val	
				20					25					30			
40	Asp	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr	
			35					40					45				
	Ser	Asp	Asn	Asn	Arg	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser	
45		50					55					60					
	Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Gly	Thr	Gln	Ala	Met	
50	65					70					75					80	
	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Ala	Thr	Tyr	Asp	Ser	Ser	Pro	Arg	Thr	
					85					90					95		
55	Glu	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	Gly	Gln	Pro	Lys	
				100					105					110			

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Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

5 Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

10 Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

15 Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

20 Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

25

<210> 137
<211> 351
<212> DNA
<213> Artificial Sequence

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<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

35

<400> 137
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tcctgcaagg ccagcggcgg caccttcagc agctacgcca tcagctgggt gcgccaggct 120
cctggacagg gcctggaatg gatggggccgg atcatcccca tcttcggcac cgccaactac 180
40 gccagaaat tccagggcag agtgaccatc accgccgacg agagcaccag caccgcctac 240
atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc ccggcacggc 300
45 ggctacattt tcgatagctg gggccagggc accctggtga ccgtgagctc a 351

<210> 138
<211> 324
<212> DNA
<213> Artificial Sequence

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<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

55

<400> 138
agctacgtgc tgactcagcc cccttctgtg tctgtggccc ctggcaagac cgccagaatc 60

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	agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc	120
	caggctcccg tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg	180
5	ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccatg	240
	gacgaggccg actactactg cgccacctac gacagcagcc ccagaaccga ggtgttcgga	300
	ggcgggaacaa agttaaccgt ccta	324
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	<210> 139	
	<211> 660	
	<212> DNA	
	<213> Artificial Sequence	
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	<220>	
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	gaggtgcagc tggtgcagag cggagccgaa gtgaagaaac ccggcagcag cgtgaagggtg	60
	tcctgcaagg ccagcggcgg caccttcagc agctacgcca tcagctgggt gcgccaggct	120
25	cctggacagg gcctggaatg gatgggcccg atcatcccca tcttcggcac cgccaactac	180
	gcccagaaat tccagggcag agtgaccatc accgcgcagc agagcaccag caccgcctac	240
	atggaactga gcagcctgag aagcgaggac accgcctgt actactgtgc ccggcacggc	300
30	ggctacattt tcgatagctg gggccagggc accctggtga ccgtgagctc agcctccacc	360
	aagggtccat cggctctccc cctggcacc cctccaaga gcacctctgg gggcacagcg	420
	gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca	480
35	ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcttc aggactctac	540
	tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcaccagac ctacatctgc	600
	aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt	660
40		
	<210> 140	
	<211> 642	
	<212> DNA	
	<213> Artificial Sequence	
45		
	<220>	
	<223> Description of Artificial Sequence: Synthetic polynucleotide	
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	agctacgtgc tgactcagcc cccttctgtg tctgtggccc ctggcaagac cgccagaatc	60
	agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc	120
55	caggctcccg tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg	180
	ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccatg	240

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gacgaggccg actactactg cgccacctac gacagcagcc ccagaaccga ggtgttcgga 300

ggcggaacaa agttaaccgt cctaggtcag cccaaggctg cccctcgggt cactctgttc 360

5 cgcacctcct ctgaggagct tcaagccaac aaggccacac tgggtgtgtct cataagtac 420

ttctaccggg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480

gtggagacca ccacaccctc caaacaagc aacaacaagt acgcggccag cagctatctg 540

10 agcctgacgc ctgagcagtg gaagtccac agaagctaca gctgccaggt cacgcatgaa 600

gggagcaccg tggagaagac agtggcccct acagaatggt ca 642

15 <210> 141
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
20 <223> Description of Artificial Sequence: Synthetic peptide

<400> 141
Ser Tyr Ala Ile Ser
1 5

25

<210> 142
<211> 17
<212> PRT
30 <213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

35 <400> 142
Arg Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

40 Gly

<210> 143
<211> 8
45 <212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

50

<400> 143
His Gly Gly Tyr Tyr Phe Asp Ser
1 5

55 <210> 144
<211> 11

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<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 144

Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val Asp
1 5 10

<210> 145

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 145

Ser Asp Asn Asn Arg Pro Ser
1 5

<210> 146

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 146

Ala Thr Tyr Asp Ser Ser Pro Arg Thr Glu
1 5 10

<210> 147

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 147

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

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

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

Gly Arg Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe

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	50		55		60	
5	Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr					
	65		70		75	80
	Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys					
		85		90		95
10	Ala Arg His Gly Gly Tyr Tyr Phe Asp Ser Trp Gly Gln Gly Thr Leu					
		100		105		110
15	Val Thr Val Ser Ser					
		115				
	<210> 148					
	<211> 108					
20	<212> PRT					
	<213> Artificial Sequence					
	<220>					
	<223> Description of Artificial Sequence: Synthetic					
25	polypeptide					
	<400> 148					
	Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys					
	1	5		10		15
30	Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val					
		20		25		30
	Asp Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr					
35		35		40		45
	Ser Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser					
	50		55		60	
40	Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met					
	65		70		75	80
45	Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Tyr Asp Ser Ser Pro Arg Thr					
		85		90		95
	Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu					
50		100		105		
	<210> 149					
	<211> 220					
	<212> PRT					
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	<220>					

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<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 149

5	Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser	1	5	10	15
10	Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr	20	25	30	
15	Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met	35	40	45	
20	Gly Arg Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe	50	55	60	
25	Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr	65	70	75	80
30	Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys	85	90	95	
35	Ala Arg His Gly Gly Tyr Tyr Phe Asp Ser Trp Gly Gln Gly Thr Leu	100	105	110	
40	Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu	115	120	125	
45	Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys	130	135	140	
50	Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser	145	150	155	160
55	Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser	165	170	175	
	Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser	180	185	190	
	Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn	195	200	205	
	Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys	210	215	220	
	<210> 150				
	<211> 214				
	<212> PRT				

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<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 150

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val
20 25 30

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

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

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

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

Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

<210> 151
 <211> 351
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 151
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 cctggacagg gcctggaatg gatgggccgg atcatcccca tcttcggcac cgccaactac 180
 gccagaaat tccagggcag agtgaccatc accgccgacg agagcaccag caccgcctac 240
 atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc ccggcacggc 300
 ggctactact tcgatagctg gggccagggc accctggtga ccgtgagctc a 351

<210> 152
 <211> 324
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 152
 agctacgtgc tgactcagcc cccttctgtg tctgtggccc ctggcaagac cgccagaatc 60
 agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc 120
 caggctcccg tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg 180
 ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccatg 240
 gacgaggccg actactactg cgccacctac gacagcagcc ccagaaccga ggtgttcgga 300
 ggcggaacaa agttaaccgt ccta 324

<210> 153
 <211> 660
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 153
 gaggtgcagc tgggtgcagag cggagccgaa gtgaagaaac ccggcagcag cgtgaaggtg 60
 tcctgcaagg ccagcggcgg caccttcagc agctacgcca tcagctgggt gcgccaggct 120
 cctggacagg gcctggaatg gatgggccgg atcatcccca tcttcggcac cgccaactac 180
 gccagaaat tccagggcag agtgaccatc accgccgacg agagcaccag caccgcctac 240

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atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc ccggcacggc 300

ggctactact tcgatagctg gggccagggc accctgggtga ccgtgagctc agcctccacc 360

5 aaggggtccat cgggtcttccc cctggcacc cctccaaga gcacctctgg gggcacagcg 420

gccctgggct gcctgggtcaa ggactacttc cccgaaccgg tgacgggtgtc gtggaactca 480

ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 540

10 tccctcagca gcgtgggtgac cgtgccctcc agcagcttgg gcaccagac ctacatctgc 600

aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt 660

15 <210> 154
<211> 642
<212> DNA
<213> Artificial Sequence

20 <220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 154

25 agctacgtgc tgactcagcc cccttctgtg tctgtggccc ctggcaagac cgccagaatc 60

agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc 120

caggctcccg tgctgggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg 180

30 ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccatg 240

gacgaggccg actactactg cgccacctac gacagcagcc ccagaaccga ggtgttcgga 300

ggcggaaaca agttaaccgt cctaggtcag cccaaggctg cccctcgggt cactctgttc 360

35 ccgccctcct ctgaggagct tcaagccaac aaggccacac tgggtgtgtct cataagtgc 420

ttctaccgga gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480

40 gtggagacca ccacaccctc caaacaagc aacaacaagt acgcggccag cagctatctg 540

agcctgacgc ctgagcagtg gaagtccac agaagctaca gctgccaggt cacgcatgaa 600

gggagcaccg tggagaagac agtggcccct acagaatgtt ca 642

45 <210> 155
<211> 5
<212> PRT
<213> Artificial Sequence

50 <220>
<223> Description of Artificial Sequence: Synthetic
peptide

55 <400> 155
Ser Tyr Ala Ile Ser
1 5

<210> 156
 <211> 17
 <212> PRT
 <213> Artificial Sequence

5

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

10

<400> 156
 Arg Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
 1 5 10 15

Gly

15

<210> 157
 <211> 8
 <212> PRT
 <213> Artificial Sequence

20

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

25

<400> 157
 His Gly Gly Tyr Val Phe Asp Ser
 1 5

30

<210> 158
 <211> 11
 <212> PRT
 <213> Artificial Sequence

35

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

40

<400> 158
 Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val Asp
 1 5 10

45

<210> 159
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

50

<400> 159
 Ser Asp Asn Asn Arg Pro Ser
 1 5

55

<210> 160
 <211> 10
 <212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 160

Ala Thr Tyr Asp Ser Ser Pro Arg Thr Glu
1 5 10

<210> 161

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 161

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

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

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

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

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

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

Ala Arg His Gly Gly Tyr Val Phe Asp Ser Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 162

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 162

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

5 Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val
20 25 30

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

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

15 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

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

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

25

<210> 163
<211> 220
<212> PRT
<213> Artificial Sequence

30

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

35

<400> 163
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

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

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

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

50 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

55

Ala Arg His Gly Gly Tyr Val Phe Asp Ser Trp Gly Gln Gly Thr Leu

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	100	105	110
5	Val Thr Val Ser Ser Ala Ser	Thr Lys Gly Pro Ser	Val Phe Pro Leu
	115	120	125
10	Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys		
	130	135	140
15	Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser		
	145	150	155
20	Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser		
	165	170	175
25	Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser		
	180	185	190
30	Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn		
	195	200	205
35	Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys		
	210	215	220
40	<210> 164		
	<211> 214		
	<212> PRT		
	<213> Artificial Sequence		
45	<220>		
	<223> Description of Artificial Sequence: Synthetic polypeptide		
50	<400> 164		
	Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys		
	1 5 10 15		
55	Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val		
	20 25 30		
60	Asp Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr		
	35 40 45		
65	Ser Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser		
	50 55 60		
70	Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met		
	65 70 75 80		
75	Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Tyr Asp Ser Ser Pro Arg Thr		
	85 90 95		

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Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

5 Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

10 Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

15 Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

20 Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

25 Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

30 <210> 165
<211> 351
<212> DNA
<213> Artificial Sequence

35 <220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

40 <400> 165
gaggtgcagc tgggtgcagag cggagccgaa gtgaagaaac ccggcagcag cgtgaagggtg 60
tcctgcaagg ccagcggcgg caccttcagc agctacgcca tcagctgggt gcgccaggct 120
cctggacagg gcctggaatg gatgggcccgg atcatcccca tcttcggcac cgccaactac 180
45 gccagaaat tccagggcag agtgaccatc accgccgacg agagcaccag caccgcctac 240
atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc ccggcacggc 300
ggctacgtct tcgatagctg gggccagggc accctggtga ccgtgagctc a 351

50

55 <210> 166
<211> 324
<212> DNA
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 166

5 agctacgtgc tgactcagcc cccttctgtg tctgtggccc ctggcaagac cgccagaatc 60
 agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc 120
 caggctcccc tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg 180
 10 ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccatg 240
 gacgaggccg actactactg cgccacctac gacagcagcc ccagaaccga ggtgttcgga 300
 ggcggaacaa agttaaccgt ccta 324

<210> 167

<211> 660

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 167

25 gaggtgcagc tgggtgcagag cggagccgaa gtgaagaaac ccggcagcag cgtgaagggtg 60
 tcctgcaagg ccagcggcgg caccttcagc agctacgcca tcagctgggt gcgccaggct 120
 cctggacagg gcctggaatg gatgggccgg atcatcccca tcttcggcac cgccaactac 180
 30 gcccagaaat tccagggcag agtgaccatc accgccgacg agagcaccag caccgcctac 240
 atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc ccggcacggc 300
 ggctacgtct tcgatagctg gggccagggc accctggtga ccgtgagctc agcctccacc 360
 35 aagggtccat cgggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 420
 gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 480
 ggcgccctga ccagcggcgt gcacaccttc ccggtgtcc tacagtcctc aggactctac 540
 40 tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 600
 aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt 660

<210> 168

<211> 642

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 168

55 agctacgtgc tgactcagcc cccttctgtg tctgtggccc ctggcaagac cgccagaatc 60
 agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc 120

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caggctcccg tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg 180
 ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccatg 240
 5 gacgaggccg actactactg cgccacctac gacagcagcc ccagaaccga ggtgttcgga 300
 ggcggaacaa agttaaccgt cctagggtcag cccaaggctg cccctcgggt cactctgttc 360
 ccgccctcct ctgaggagct tcaagccaac aaggccacac tgggtgtgtct cataagtgac 420
 10 ttctaccggg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480
 gtggagacca ccacaccctc caaacaagc aacaacaagt acgcgccag cagctatctg 540
 agcctgacgc ctgagcagtg gaagtccac agaagctaca gctgccaggt cacgcatgaa 600
 15 gggagcaccg tggagaagac agtggcccct acagaatggt ca 642

<210> 169
 <211> 5
 20 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 25 peptide

<400> 169
 Ser Tyr Ala Ile Ser
 1 5

30 <210> 170
 <211> 17
 <212> PRT
 <213> Artificial Sequence

35 <220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

<400> 170
 40 Arg Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
 1 5 10 15

Gly

45 <210> 171
 <211> 8
 <212> PRT
 50 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

55 <400> 171
 His Gly Gly Tyr Ser Phe Asp Ser

1 5

<210> 172
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic peptide

<400> 172
 Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val Asp
 1 5 10

<210> 173
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic peptide

<400> 173
 Ser Asp Asn Asn Arg Pro Ser
 1 5

<210> 174
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic peptide

<400> 174
 Gln Thr Tyr Thr Ser Gly Asn Asn Tyr Leu
 1 5 10

<210> 175
 <211> 117
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

<400> 175
 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15

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

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	Ala	Ile	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	
			35					40					45				
5	Gly	Arg	Ile	Ile	Pro	Ile	Phe	Gly	Thr	Ala	Asn	Tyr	Ala	Gln	Lys	Phe	
			50				55					60					
	Gln	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Glu	Ser	Thr	Ser	Thr	Ala	Tyr	
10		65				70					75					80	
	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
					85					90					95		
15	Ala	Arg	His	Gly	Gly	Tyr	Ser	Phe	Asp	Ser	Trp	Gly	Gln	Gly	Thr	Leu	
				100					105					110			
	Val	Thr	Val	Ser	Ser												
20				115													
	<210>	176															
	<211>	108															
25	<212>	PRT															
	<213>	Artificial Sequence															
	<220>																
	<223>	Description of Artificial Sequence: Synthetic															
		polypeptide															
30	<400>	176															
	Ser	Tyr	Glu	Leu	Thr	Gln	Pro	Pro	Ser	Val	Ser	Val	Ala	Pro	Gly	Gln	
	1				5					10					15		
	Thr	Ala	Arg	Ile	Ser	Cys	Ser	Gly	Asp	Asn	Leu	Gly	Ser	Lys	Tyr	Val	
35				20					25					30			
	Asp	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr	
40			35					40					45				
	Ser	Asp	Asn	Asn	Arg	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser	
		50					55					60					
45	Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Gly	Thr	Gln	Ala	Glu	
		65				70					75					80	
	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Thr	Tyr	Thr	Ser	Gly	Asn	Asn	Tyr	
50					85					90					95		
	Leu	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu					
55				100					105								
	<210>	177															

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<211> 220
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 177

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

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

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

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

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

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

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

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
210 215 220

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<210> 178
 <211> 214
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

<400> 178
 Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1 5 10 15
 Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val
 20 25 30
 Asp Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
 35 40 45
 Ser Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
 50 55 60
 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
 65 70 75 80
 Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Thr Ser Gly Asn Asn Tyr
 85 90 95
 Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
 100 105 110
 Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
 115 120 125
 Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
 130 135 140
 Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
 145 150 155 160
 Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
 165 170 175
 Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
 180 185 190
 Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
 195 200 205

Ala Pro Thr Glu Cys Ser
210

5 <210> 179
 <211> 351
 <212> DNA
 <213> Artificial Sequence

10 <220>
 <223> Description of Artificial Sequence: Synthetic
 polynucleotide

<400> 179
 gaggtgcagc tgggtgcagag cggagccgaa gtgaagaaac ccggcagcag cgtgaaggtg 60
 15 tcctgcaagg ccagcggcgg caccttcagc agctacgcca tcagctgggt gcgccaggct 120
 cctggacagg gcctggaatg gatggggcgg atcatcccca tcttcggcac cgccaactac 180
 20 gccagaaat tccagggcag agtgaccatc accgccgacg agagcaccag caccgcctac 240
 atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc ccggcacggc 300
 ggctacagct tcgatagctg gggccagggc accctggtga ccgtgagctc a 351

25 <210> 180
 <211> 324
 <212> DNA
 <213> Artificial Sequence

30 <220>
 <223> Description of Artificial Sequence: Synthetic
 polynucleotide

<400> 180
 35 agctacgagc tgactcagcc cccttctgtg tctgtggccc ctggccagac cgccagaatc 60
 agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc 120
 caggctcccg tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg 180
 40 ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccgag 240
 gacgaggccg actactactg ccagacctac accagcggca acaactacct ggtgttcgga 300
 45 ggcggaacaa agttaaccgt ccta 324

<210> 181
 <211> 660
 <212> DNA
 50 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 polynucleotide

55 <400> 181
 gaggtgcagc tgggtgcagag cggagccgaa gtgaagaaac ccggcagcag cgtgaaggtg 60

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	tccctgcaagg ccagcggcgg caccttcagc agctacgcca tcagctgggt gcgccaggct	120
	cctggacagg gcctggaatg gatggggccgg atcatcccca tcttcggcac cgccaactac	180
5	gcccagaaat tccagggcag agtgaccatc accgccgacg agagcaccag caccgcctac	240
	atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc ccggcacggc	300
	ggctacagct tcgatagctg gggccagggc accctggtga ccgtgagctc agcctccacc	360
10	aaggggtccat cggctcttccc cctggcacccc tccctccaaga gcacctctgg gggcacagcg	420
	gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca	480
	ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac	540
15	tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc	600
	aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt	660
20	<210> 182 <211> 642 <212> DNA <213> Artificial Sequence	
25	<220> <223> Description of Artificial Sequence: Synthetic polynucleotide	
	<400> 182 agctacgagc tgactcagcc cccttctgtg tctgtggccc ctggccagac cgccagaatc	
30	agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc	120
	caggctcccg tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg	180
35	ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccgag	240
	gacgaggccg actactactg ccagacctac accagcggca acaactacct ggtgttcgga	300
	ggcggaacaa agttaaccgt cctaggtcag cccaaggctg cccctcggt cactctgttc	360
40	ccgccctcct ctgaggagct tcaagccaac aaggccacac tgggtgtgtct cataagtgac	420
	ttctacccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga	480
	gtggagacca ccacaccctc caaacaagc aacaacaagt acgcgccag cagctatctg	540
45	agcctgacgc ctgagcagtg gaagtccac agaagctaca gctgccaggt cacgcatgaa	600
	gggagcaccg tggagaagac agtggcccct acagaatggt ca	642
50	<210> 183 <211> 5 <212> PRT <213> Artificial Sequence	
55	<220> <223> Description of Artificial Sequence: Synthetic peptide	

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<400> 183
Ser Tyr Ala Ile Ser
1 5

5

<210> 184
<211> 17
<212> PRT
<213> Artificial Sequence

10

<220>
<223> Description of Artificial Sequence: Synthetic peptide

15

<400> 184
Arg Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

20

<210> 185
<211> 8
<212> PRT
<213> Artificial Sequence

25

<220>
<223> Description of Artificial Sequence: Synthetic peptide

30

<400> 185
His Gly Gly Tyr Ser Phe Asp Ser
1 5

35

<210> 186
<211> 11
<212> PRT
<213> Artificial Sequence

40

<220>
<223> Description of Artificial Sequence: Synthetic peptide

45

<400> 186
Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val Asp
1 5 10

50

<210> 187
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

55

<400> 187
Ser Asp Asn Asn Arg Pro Ser
1 5

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<210> 188
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic peptide

<400> 188
 Gln Thr Tyr Thr Ser Gly Asn Asn Tyr Leu
 1 5 10

<210> 189
 <211> 117
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

<400> 189
 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15

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

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

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

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

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

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

Val Thr Val Ser Ser
 115

<210> 190
 <211> 108
 <212> PRT
 <213> Artificial Sequence

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<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 190

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val
20 25 30

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

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

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

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

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

<210> 191

<211> 220

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 191

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

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

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

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

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

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

5 Ala Arg His Gly Gly Tyr Ser Phe Asp Ser Trp Gly Gln Gly Thr Leu
100 105 110

10 Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

15 Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

20 Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

25 Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

30 Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
210 215 220

35 <210> 192
<211> 214
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

40 <400> 192
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15

45 Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val
20 25 30

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

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

55 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu

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	65		70		75		80									
5	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Thr	Tyr	Thr	Ser	Gly	Asn	Asn	Tyr
				85					90					95		
10	Leu	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	Gly	Gln	Pro	Lys
			100						105					110		
15	Ala	Ala	Pro	Ser	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu	Leu	Gln
			115					120					125			
20	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp	Phe	Tyr	Pro	Gly
		130					135					140				
25	Ala	Val	Thr	Val	Ala	Trp	Lys	Ala	Asp	Ser	Ser	Pro	Val	Lys	Ala	Gly
	145					150					155					160
30	Val	Glu	Thr	Thr	Thr	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys	Tyr	Ala	Ala
					165					170					175	
35	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Glu	Gln	Trp	Lys	Ser	His	Arg	Ser
			180						185					190		
40	Tyr	Ser	Cys	Gln	Val	Thr	His	Glu	Gly	Ser	Thr	Val	Glu	Lys	Thr	Val
		195						200					205			
45	Ala	Pro	Thr	Glu	Cys	Ser										
		210														
50	<210>	193														
	<211>	351														
	<212>	DNA														
	<213>	Artificial Sequence														
55	<220>															
	<223>	Description of Artificial Sequence: Synthetic polynucleotide														
60	<400>	193														
			gaggtgcagc	tggtgcagag	cggagccgaa	gtgaagaaac	ccggcagcag	cgtgaaggtg								60
			tcctgcaagg	ccagcggcgg	caccttccaa	agctacgcca	tcagctgggt	gcgccaggct								120
			cctggacagg	gcctggaatg	gatgggccgg	atcatcccca	tcttcggcac	cgccaactac								180
			gccagaaat	tccagggcag	agtgaccatc	accgccgacg	agagcaccag	caccgcctac								240
			atggaactga	gcagcctgag	aagcgaggac	accgccgtgt	actactgtgc	ccggcacggc								300
			ggctacagct	tcgatagctg	gggccagggc	accctggtga	ccgtgagctc	a								351
55	<210>	194														

<211> 324
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 194
 agctacgagc tgactcagcc cccttctgtg tctgtggccc ctggccagac cgccagaatc 60
 agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc 120
 caggctcccg tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg 180
 ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccgag 240
 gacgaggccg actactactg ccagacctac accagcggca acaactacct ggtgttcgga 300
 ggcggaacaa agttaaccgt ccta 324

<210> 195
 <211> 660
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 195
 gaggtgcagc tgggtgcagag cggagccgaa gtgaagaaac ccggcagcag cgtgaaggtg 60
 tcctgcaagg ccagcggcgg caccttccaa agctacgcca tcagctgggt gcgccaggct 120
 cctggacagg gcctggaatg gatgggcccg atcatcccca tcttcggcac cgccaactac 180
 gcccgaaat tccagggcag agtgaccatc accgcccagc agagcaccag caccgcctac 240
 atggaactga gcagcctgag aagcaggac accgccgtgt actactgtgc ccggcacggc 300
 ggctacagct tcgatagctg gggccagggc accctggtga ccgtgagctc agcctccacc 360
 aagggtccat cggctcttccc cctggcacc cctccaaga gcacctctgg gggcacagcg 420
 gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 480
 ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 540
 tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 600
 aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt 660

<210> 196
 <211> 642
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polynucleotide

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<400> 196
 agctacgagc tgactcagcc cccttctgtg tctgtggccc ctggccagac cgccagaatc 60
 agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc 120
 5 caggctcccg tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg 180
 ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccgag 240
 10 gacgaggccg actactactg ccagacctac accagcggca acaactacct ggtgttcgga 300
 ggcggaacaa agttaaccgt cctaggtcag cccaaggctg cccctcggt cactctgttc 360
 ccgccctcct ctgaggagct tcaagccaac aaggccacac tgggtgtgtct cataagtga 420
 15 ttctaccggg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480
 gtggagacca ccacaccctc caaacaagc aacaacaagt acgcggccag cagctatctg 540
 agcctgacgc ctgagcagtg gaagtccac agaagctaca gctgccaggt cacgcatgaa 600
 20 gggagcaccg tggagaagac agtggcccct acagaatgtt ca 642

<210> 197
 <211> 5
 25 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 30 peptide

<400> 197
 Ser Tyr Ala Ile Ser
 1 5

35 <210> 198
 <211> 17
 <212> PRT
 <213> Artificial Sequence

40 <220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

45 <400> 198
 Arg Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
 1 5 10 15

Gly

50
 <210> 199
 <211> 8
 <212> PRT
 55 <213> Artificial Sequence

<220>

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 199

His Gly Gly Tyr Ser Phe Asp Ser
1 5

<210> 200

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 200

Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val Asp
1 5 10

<210> 201

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 201

Ser Asp Asn Asn Arg Pro Ser
1 5

<210> 202

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 202

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

<210> 203

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 203

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

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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Asn Ala Tyr
 20 25 30
 5 Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 10 Gly Arg Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 15 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 20 Ala Arg His Gly Gly Tyr Ser Phe Asp Ser Trp Gly Gln Gly Thr Leu
 100 105 110
 Val Thr Val Ser Ser
 115
 25
 <210> 204
 <211> 108
 <212> PRT
 30 <213> Artificial Sequence
 <220>
 <223> Description of Artificial Sequence: Synthetic
 polypeptide
 35
 <400> 204
 Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1 5 10 15
 40 Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val
 20 25 30
 Asp Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
 35 40 45
 Ser Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
 50 55 60
 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
 65 70 75 80
 55 Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Thr Ser Gly Asn Asn Tyr
 85 90 95

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

5 <210> 205
<211> 220
<212> PRT
<213> Artificial Sequence

10 <220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 205
15 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

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

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

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

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
30 65 70 75 80

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

35 Ala Arg His Gly Gly Tyr Ser Phe Asp Ser Trp Gly Gln Gly Thr Leu
100 105 110

40 Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

45 Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

50 Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

55 Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn

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	195		200		205
5	Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys				
	210		215		220
10	<210> 206 <211> 214 <212> PRT <213> Artificial Sequence				
	<220>				
	<223> Description of Artificial Sequence: Synthetic polypeptide				
15	<400> 206				
	Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln				
	1		5	10	15
20	Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val				
		20	25		30
25	Asp Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr				
		35	40		45
30	Ser Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser				
		50	55		60
35	Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu				
			70	75	80
40	Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Thr Ser Gly Asn Asn Tyr				
		85	90		95
45	Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys				
		100	105		110
50	Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln				
		115	120		125
55	Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly				
		130	135	140	
	Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly				
		145	150	155	160
	Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala				
		165	170		175
	Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser				
		180	185		190

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Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

5 Ala Pro Thr Glu Cys Ser
210

<210> 207

<211> 351

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 207

gaggtgcagc tggtgcagag cggagccgaa gtgaagaaac ccggcagcag cgtgaagggtg 60

tcctgcaagg ccagcggcgg caccttcaac gcctacgcca tcagctgggt gcgccaggct 120

cctggacagg gcctggaatg gatgggcccgg atcatcccca tcttcggcac cgccaactac 180

gcccagaaat tccagggcag agtgaccatc accgccgacg agagcaccag caccgcctac 240

atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc ccggcacggc 300

ggctacagct tcgatagctg gggccagggc accctggtga ccgtgagctc a 351

<210> 208

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 208

agctacgagc tgactcagcc cccttctgtg tctgtggccc ctggccagac cgccagaatc 60

agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc 120

caggctcccg tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg 180

ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccgag 240

gacgaggccg actactactg ccagacctac accagcggca acaactacct ggtgttcgga 300

ggcggaaaca agttaaccgt ccta 324

<210> 209

<211> 660

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic

polynucleotide

<400> 209

gaggtgcagc tgggtgcagag cggagccgaa gtgaagaaac ccggcagcag cgtgaagggtg 60
 5 tcctgcaagg ccagcggcgg caccttcaac gcctacgcca tcagctgggt gcgccaggct 120
 cctggacagg gcctggaatg gatgggccgg atcatcccca tcttcggcac cgccaactac 180
 10 gccagaaat tccagggcag agtgaccatc accgccgacg agagcaccag caccgcctac 240
 atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc ccggcacggc 300
 ggctacagct tcgatagctg gggccagggc accctggtga ccgtgagctc agcctccacc 360
 15 aaggggtccat cgggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg 420
 gccctgggct gcctgggtcaa ggactacttc cccgaaccgg tgacgggtgtc gtggaactca 480
 ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 540
 20 tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcaccagac ctacatctgc 600
 aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt 660

<210> 210

<211> 642

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
 polynucleotide

<400> 210

agctacgagc tgactcagcc cccttctgtg tctgtggccc ctggccagac cgccagaatc 60
 35 agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccgcc 120
 caggctcccc tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg 180
 ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccgag 240
 40 gacgaggccg actactactg ccagacctac accagcggca acaactacct ggtgttcgga 300
 ggcggaacaa agttaaccgt cctaggtcag cccaaggctg cccctcgggt cactctgttc 360
 ccgccctcct ctgaggagct tcaagccaac aaggccacac tgggtgtgtc cataagtgac 420
 45 ttctaccggg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480
 gtggagacca ccacaccctc caaacaagc aacaacaagt acgcggccag cagctatctg 540
 agcctgacgc ctgagcagtg gaagtccac agaagctaca gctgccaggt cacgcatgaa 600
 50 gggagcaccg tggagaagac agtggcccct acagaatgtt ca 642

<210> 211

<211> 5

<212> PRT

<213> Artificial Sequence

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<220>
 <223> Description of Artificial Sequence: Synthetic peptide
 5
 <400> 211
 Ser Tyr Ala Ile Ser
 1 5
 10
 <210> 212
 <211> 17
 <212> PRT
 <213> Artificial Sequence
 15
 <220>
 <223> Description of Artificial Sequence: Synthetic peptide
 <400> 212
 Arg Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
 1 5 10 15
 20
 Gly
 25
 <210> 213
 <211> 8
 <212> PRT
 <213> Artificial Sequence
 30
 <220>
 <223> Description of Artificial Sequence: Synthetic peptide
 <400> 213
 His Gly Gly Tyr Ser Phe Asp Ser
 1 5
 35
 <210> 214
 <211> 11
 <212> PRT
 <213> Artificial Sequence
 40
 <220>
 <223> Description of Artificial Sequence: Synthetic peptide
 45
 <400> 214
 Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val Asp
 1 5 10
 50
 <210> 215
 <211> 7
 <212> PRT
 <213> Artificial Sequence
 55
 <220>
 <223> Description of Artificial Sequence: Synthetic

peptide

<400> 215

Ser Asp Asn Asn Arg Pro Ser
 1 5

<210> 216

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
 peptide

<400> 216

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

<210> 217

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic
 polypeptide

<400> 217

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

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

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

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

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

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

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

Val Thr Val Ser Ser
 115

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<210> 218
 <211> 108
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

<400> 218
 Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
 1 5 10 15

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val
 20 25 30

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

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

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

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

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

<210> 219
 <211> 220
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

<400> 219
 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15

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

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

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

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

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

10 Ala Arg His Gly Gly Tyr Ser Phe Asp Ser Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

15 Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

20 Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

25 Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

30 Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

35 Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
210 215 220

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40 <211> 214
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45 <223> Description of Artificial Sequence: Synthetic
polypeptide

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50 Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val
20 25 30

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

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

5 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

10 Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Thr Ser Gly Asn Asn Tyr
85 90 95

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

15 Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

20 Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

25 Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

30 Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

35 Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

40 <210> 221
<211> 351
<212> DNA
<213> Artificial Sequence

45 <220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

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cctggacagg gcctggaatg gatgggccgg atcatcccca tcttcggcac cgccaactac 180
gcccagaaat tccagggcag agtgaccatc accgccgacg agagcaccag caccgcctac 240
55 atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc ccggcacggc 300

ggctacagct tcgatagctg gggccagggc accctggtga ccgtgagctc a 351

<210> 222

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 222

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agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc 120

caggtccccg tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg 180

ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccgag 240

gacgaggccg actactactg ccagacctac accagcggca acaactacct ggtgttcgga 300

ggcggaacaa agttaaccgt ccta 324

<210> 223

<211> 660

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 223

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tcctgcaagg ccagcggcgg caccttcggc agctacgcca tcagctgggt gcgccaggct 120

cctggacagg gcctggaatg gatgggcccgg atcatcccca tcttcggcac cgccaactac 180

gcccagaaat tccagggcag agtgaccatc accgcgcagc agagcaccag caccgcctac 240

atggaactga gcagcctgag aagcgaggac accgcctgt actactgtgc ccggcacggc 300

ggctacagct tcgatagctg gggccagggc accctggtga ccgtgagctc agcctccacc 360

aaggttccat cggctcttccc cctggcacc cctccaaga gcacctctgg gggcacagcg 420

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 480

ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcttc aggactctac 540

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aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt 660

<210> 224

<211> 642

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 224

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caggctcccg tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg      180
ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccgag      240
gacgaggccg actactactg ccagacctac accagcggca acaactacct ggtgttcgga      300
ggcggaaaca agttaaccgt cctaggtcag cccaaggctg cccctcgggt cactctgttc      360
ccgccctcct ctgaggagct tcaagccaac aaggccacac tgggtgtgtct cataagtgac      420
ttctaccogg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga      480
gtggagacca ccacaccctc caaacaagc aacaacaagt acgcggccag cagctatctg      540
agcctgacgc ctgagcagtg gaagtccac agaagctaca gctgccaggt cagcatgaa      600
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<210> 225

<211> 5

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

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<210> 226

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 226

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Arg Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
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Gly

<210> 227

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

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 <220>
 <223> Description of Artificial Sequence: Synthetic peptide

<400> 227
 His Gly Gly Tyr Ser Phe Asp Ser
 1 5

<210> 228
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic peptide

<400> 228
 Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val Asp
 1 5 10

<210> 229
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic peptide

<400> 229
 Ser Asp Asn Asn Arg Pro Ser
 1 5

<210> 230
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic peptide

<400> 230
 Gln Thr Tyr Thr Ser Gly Asn Asn Tyr Leu
 1 5 10

<210> 231
 <211> 117
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

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<400> 231

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

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

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

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

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

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

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

Val Thr Val Ser Ser
115

<210> 232

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 232

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val
20 25 30

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

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

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

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

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

10 <210> 233
<211> 220
<212> PRT
<213> Artificial Sequence

15 <220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

20 <400> 233
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

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

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

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

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

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

40 Ala Arg His Gly Gly Tyr Ser Phe Asp Ser Trp Gly Gln Gly Thr Leu
100 105 110

45 Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

50 Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

55 Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

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Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

5 Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

10 Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
210 215 220

<210> 234
<211> 214
<212> PRT
15 <213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

20 <400> 234
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1 5 10 15

25 Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val
20 25 30

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

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

35 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

40 Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Thr Ser Gly Asn Asn Tyr
85 90 95

Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

45 Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

50 Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

55 Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala

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35	<210> 236 <211> 324 <212> DNA <213> Artificial Sequence		
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55	<210> 237 <211> 660		

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

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cctggacagg gcctggaatg gatgggcccgg atcatcccca tcttcggcac cgccaactac 180

gcccagaaat tccagggcag agtgaccatc accgccgacg agagcaccag caccgcctac 240

atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc ccggcacggc 300

ggctacagct tcgatagctg gggccagggc accctggtga ccgtgagctc agcctccacc 360

aaggggtccat cggctcttccc cctggcacc cctccaaga gcacctctgg gggcacagcg 420

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacgggtgc gtggaactca 480

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<210> 238

<211> 642

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 238

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caggctcccc tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg 180

ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccgag 240

gacgaggccg actactactg ccagacctac accagcggca acaactacct ggtgttcgga 300

ggcggaacaa agttaaccgt cctaggtcag cccaaggctg cccctcggt cactctgttc 360

ccgccctcct ctgaggagct tcaagccaac aaggccacac tgggtgtgtct cataagtgc 420

ttctacccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480

gtggagacca ccacaccctc caaacaagc aacaacaagt acgcggccag cagctatctg 540

agcctgacgc ctgagcagtg gaagtccac agaagctaca gctgccaggt cagcatgaa 600

gggagcaccg tggagaagac agtggcccct acagaatgtt ca 642

<210> 239
 <211> 5
 <212> PRT
 <213> Artificial Sequence

5

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

10

<400> 239
 Ser Tyr Ala Ile Ser
 1 5

15

<210> 240
 <211> 17
 <212> PRT
 <213> Artificial Sequence

20

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

25

<400> 240
 Arg Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
 1 5 10 15

Gly

30

<210> 241
 <211> 8
 <212> PRT
 <213> Artificial Sequence

35

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

40

<400> 241
 His Gly Gly Tyr Ser Phe Asp Ser
 1 5

45

<210> 242
 <211> 11
 <212> PRT
 <213> Artificial Sequence

50

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

<400> 242
 Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val Asp
 1 5 10

55

<210> 243
 <211> 7

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<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 243
Ser Asp Asn Asn Arg Pro Ser
1 5

<210> 244
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 244
Ala Thr Tyr Asp Ser Ser Pro Arg Thr Glu
1 5 10

<210> 245
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 245
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Thr Ser Tyr
20 25 30

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

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

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

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

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

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Val Thr Val Ser Ser
115

5 <210> 246
<211> 108
<212> PRT
<213> Artificial Sequence

10 <220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 246
Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys
1 5 10 15

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val
20 25 30

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

25 Ser Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

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

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

40 <210> 247
<211> 220
<212> PRT
<213> Artificial Sequence

45 <220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 247
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

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

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

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	Gly	Arg	Ile	Ile	Pro	Ile	Phe	Gly	Thr	Ala	Asn	Tyr	Ala	Gln	Lys	Phe	
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	65					70					75					80	
10	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
				85						90					95		
15	Ala	Arg	His	Gly	Gly	Tyr	Ser	Phe	Asp	Ser	Trp	Gly	Gln	Gly	Thr	Leu	
				100					105					110			
20	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	
			115					120					125				
25	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	
		130					135					140					
30	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	
	145					150					155					160	
35	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	
					165					170					175		
40	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	
			180						185					190			
45	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	
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50	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys					
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	Asp	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr	
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	Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Gly	Thr	Gln	Ala	Met	
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	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Ala	Thr	Tyr	Asp	Ser	Ser	Pro	Arg	Thr	
					85					90					95		
15	Glu	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	Gly	Gln	Pro	Lys	
				100					105					110			
	Ala	Ala	Pro	Ser	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu	Leu	Gln	
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	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp	Phe	Tyr	Pro	Gly	
25		130				135					140						
	Ala	Val	Thr	Val	Ala	Trp	Lys	Ala	Asp	Ser	Ser	Pro	Val	Lys	Ala	Gly	
	145				150					155					160		
30	Val	Glu	Thr	Thr	Thr	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys	Tyr	Ala	Ala	
					165					170					175		
	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Glu	Gln	Trp	Lys	Ser	His	Arg	Ser	
35				180				185					190				
	Tyr	Ser	Cys	Gln	Val	Thr	His	Glu	Gly	Ser	Thr	Val	Glu	Lys	Thr	Val	
			195					200					205				
40	Ala	Pro	Thr	Glu	Cys	Ser											
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	gccagaaat tccagggcag agtgaccatc accgccgacg agagcaccag caccgcctac	240
5	atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc ccggcacggc	300
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15	<220> <223> Description of Artificial Sequence: Synthetic polynucleotide	
	<400> 250 agctacgtgc tgactcagcc cccttctgtg tctgtggccc ctggcaagac cgccagaatc	60
20	agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc	120
	caggctcccg tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg	180
	ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccatg	240
25	gacgaggccg actactactg cgccacctac gacagcagcc ccagaaccga ggtgttcgga	300
	ggcggaaaca agttaaccgt ccta	324
30	<210> 251 <211> 660 <212> DNA <213> Artificial Sequence	
35	<220> <223> Description of Artificial Sequence: Synthetic polynucleotide	
	<400> 251 gaggtgcagc tggtgcagag cggagccgaa gtgaagaaac ccggcagcag cgtgaagggtg	60
40	tcctgcaagg ccagcggcgg caccttcacc agctacgcca tcagctgggt gcgccaggct	120
	cctggacagg gcctggaatg gatgggccgg atcatcccca tcttcggcac cgccaactac	180
	gccagaaat tccagggcag agtgaccatc accgccgacg agagcaccag caccgcctac	240
45	atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc ccggcacggc	300
	ggctacagct tcgatagctg gggccagggc accctggtga ccgtgagctc agcctccacc	360
	aaggggtccat cgggtcttccc cctggcacc cctccaaga gcacctctgg gggcacagcg	420
50	gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca	480
	ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac	540
55	tcctcagca gcgtggtgac cgtgccctcc agcagcttgg gcaccagac ctacatctgc	600
	aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt	660

<210> 252
 <211> 642
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 polynucleotide

<400> 252
 agctacgtgc tgactcagcc cccttctgtg tctgtggccc ctggcaagac cgccagaatc 60
 agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc 120
 caggctcccg tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg 180
 ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccatg 240
 gacgaggccg actactactg cgccacctac gacagcagcc ccagaaccga ggtgttcgga 300
 ggcggaacaa agttaaccgt cctaggtcag cccaaggctg cccctcgggt cactctgttc 360
 ccgccctcct ctgaggagct tcaagccaac aaggccacac tgggtgtgtct cataagtgac 420
 ttctaccggg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 480
 gtggagacca ccacaccctc caaacaagc aacaacaagt acgcggccag cagctatctg 540
 agcctgacgc ctgagcagtg gaagtccac agaagctaca gctgccaggt cacgcatgaa 600
 gggagcaccg tggagaagac agtggcccct acagaatgtt ca 642

<210> 253
 <211> 5
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

<400> 253
 Ser Tyr Ala Ile Ser
 1 5

<210> 254
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

<400> 254
 Arg Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
 1 5 10 15

Gly

5 <210> 255
 <211> 8
 <212> PRT
 <213> Artificial Sequence

 10 <220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

 <400> 255
 His Gly Gly Tyr Ser Phe Asp Ser
 1 5
 15

 <210> 256
 <211> 11
 <212> PRT
 20 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

 25 <400> 256
 Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val Asp
 1 5 10

 30 <210> 257
 <211> 7
 <212> PRT
 <213> Artificial Sequence

 <220>
 35 <223> Description of Artificial Sequence: Synthetic
 peptide

 <400> 257
 Ser Asp Asn Asn Arg Pro Ser
 1 5
 40

 <210> 258
 <211> 10
 <212> PRT
 45 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

 50 <400> 258
 Ala Thr Tyr Asp Ser Ser Pro Arg Thr Glu
 1 5 10

 55 <210> 259
 <211> 117
 <212> PRT

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<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 259

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

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

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

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

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

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

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

Val Thr Val Ser Ser
115

<210> 260

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 260

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val
20 25 30

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

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

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Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
 65 70 75 80

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

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

<210> 261
 <211> 220
 <212> PRT
 15 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 polypeptide

20 <400> 261
 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15

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

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

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

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

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

45 Ala Arg His Gly Gly Tyr Ser Phe Asp Ser Trp Gly Gln Gly Thr Leu
 100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
 115 120 125

50 Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
 130 135 140

55 Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
 145 150 155 160

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Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
 165 170 175
 5 Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
 180 185 190
 10 Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
 195 200 205
 Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys
 210 215 220
 15
 <210> 262
 <211> 214
 <212> PRT
 <213> Artificial Sequence
 20
 <220>
 <223> Description of Artificial Sequence: Synthetic
 polypeptide
 25
 <400> 262
 Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys
 1 5 10 15
 30 Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val
 20 25 30
 Asp Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
 35 35 40 45
 Ser Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
 50 55 60
 40 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
 65 70 75 80
 45 Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Tyr Asp Ser Ser Pro Arg Thr
 85 90 95
 Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
 100 105 110
 50 Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
 115 120 125
 55 Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
 130 135 140

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Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

5 Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

10 Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

15 Ala Pro Thr Glu Cys Ser
210

20 <210> 263
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
25 <223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 263
gaggtgcagc tgggtgcagag cggagccgaa gtgaagaaac ccggcagcag cgtgaaggtg 60
30 tcctgcaagg ccagcggcgg caccttccaa agctacgcca tcagctgggt gcgccaggct 120
cctggacagg gcctggaatg gatggggccg atcatcccca tcttcggcac cgccaactac 180
gcccagaaat tccagggcag agtgaccatc accgcccagc agagcaccag caccgcctac 240
35 atggaactga gcagcctgag aagcgaggac accgcccgtgt actactgtgc ccggcacggc 300
ggctacagct tcgatagctg gggccagggc accctggtga ccgtgagctc a 351

40 <210> 264
<211> 324
<212> DNA
<213> Artificial Sequence

45 <220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

<400> 264
agctacgtgc tgactcagcc cccttctgtg tctgtggccc ctggcaagac cgccagaatc 60
50 agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc 120
caggctcccg tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg 180
55 ttacagcgga gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccatg 240
gacgaggccg actactactg cgccacctac gacagcagcc ccagaaccga ggtgttcgga 300

ggcggaaaca agttaaccgt ccta

324

<210> 265

<211> 660

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 265

gaggtgcagc tgggtgcagag cggagccgaa gtgaagaaac ccggcagcag cgtgaaggtg 60

tcctgcaagg ccagcggcgg caccctccaa agctacgcca tcagctgggt gcgccaggct 120

cctggacagg gcctggaatg gatgggcccg atcatcccca tcttcggcac cgccaactac 180

gcccagaaat tccagggcag agtgaccatc accgccgacg agagcaccag caccgcctac 240

atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc ccggcacggc 300

ggctacagct tcgatagctg gggccagggc accctggtga ccgtgagctc agcctccacc 360

aaggttccat cggctctccc cctggcacc cctccaaga gcacctctgg gggcacagcg 420

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 480

ggcgccctga ccagcggcgt gcacacctc ccggtgtcc tacagtctc aggactctac 540

tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcaccagac ctacatctgc 600

aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt 660

<210> 266

<211> 642

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 266

agctacgtgc tgactcagcc cccttctgtg tctgtggccc ctggcaagac cgccagaatc 60

agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc 120

caggctcccg tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg 180

ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccatg 240

gacgaggccg actactactg cgccacctac gacagcagcc ccagaaccga ggtgttcgga 300

ggcggaaaca agttaaccgt cctaggtcag cccaaggctg cccctcggt cactctgttc 360

ccgccctcct ctgaggagct tcaagccaac aaggccacac tgggtgtgtc cataagtgac 420

ttctacccgg gagccgtgac agtggcctgg aaggcagata gcagcccgt caagcgggga 480

gtggagacca ccacaccctc caaacaagc aacaacaagt acgcggccag cagctatctg 540

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agcctgacgc ctgagcagtg gaagtccac agaagctaca gctgccaggt cacgcatgaa 600
 gggagcaccg tggagaagac agtggcccct acagaatggt ca 642

5

<210> 267
 <211> 5
 <212> PRT
 <213> Artificial Sequence

10

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

15

<400> 267
 Ser Tyr Ala Ile Ser
 1 5

20

<210> 268
 <211> 17
 <212> PRT
 <213> Artificial Sequence

25

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

30

<400> 268
 Arg Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
 1 5 10 15

Gly

35

<210> 269
 <211> 8
 <212> PRT
 <213> Artificial Sequence

40

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

45

<400> 269
 His Gly Gly Tyr Ser Phe Asp Ser
 1 5

50

<210> 270
 <211> 11
 <212> PRT
 <213> Artificial Sequence

55

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

<400> 270
 Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val Asp

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1 5 10

5

<210> 271
<211> 7
<212> PRT
<213> Artificial Sequence

10

<220>
<223> Description of Artificial Sequence: Synthetic peptide

15

<400> 271
Ser Asp Asn Asn Arg Pro Ser
1 5

20

<210> 272
<211> 10
<212> PRT
<213> Artificial Sequence

25

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 272
Ala Thr Tyr Asp Ser Ser Pro Arg Thr Glu
1 5 10

30

<210> 273
<211> 117
<212> PRT
<213> Artificial Sequence

35

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

40

<400> 273
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

45

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

50

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

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

55

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

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

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

Val Thr Val Ser Ser
115

<210> 274
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 274
Ser Tyr Val Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Lys
1 5 10 15

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Tyr Val
20 25 30

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

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

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

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

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

<210> 275
<211> 220
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr

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	20	25	30
5	Ala Ile Ser Trp Val Arg Gln	Ala Pro Gly Gln Gly	Leu Glu Trp Met
	35	40	45
10	Gly Arg Ile Ile Pro Ile Phe	Gly Thr Ala Asn Tyr	Ala Gln Lys Phe
	50	55	60
15	Gln Gly Arg Val Thr Ile Thr	Ala Asp Glu Ser Thr	Ser Thr Ala Tyr
	65	70	75
20	Met Glu Leu Ser Ser Leu Arg	Ser Glu Asp Thr Ala Val	Tyr Tyr Cys
	85	90	95
25	Ala Arg His Gly Gly Tyr Ser	Phe Asp Ser Trp Gly Gln	Gly Thr Leu
	100	105	110
30	Val Thr Val Ser Ser Ala Ser	Thr Lys Gly Pro Ser Val	Phe Pro Leu
	115	120	125
35	Ala Pro Ser Ser Lys Ser Thr	Ser Gly Gly Thr Ala Ala	Leu Gly Cys
	130	135	140
40	Leu Val Lys Asp Tyr Phe Pro	Glu Pro Val Thr Val Ser	Trp Asn Ser
	145	150	155
45	Gly Ala Leu Thr Ser Gly Val	His Thr Phe Pro Ala Val	Leu Gln Ser
	165	170	175
50	Ser Gly Leu Tyr Ser Leu Ser	Ser Val Val Thr Val Pro	Ser Ser Ser
	180	185	190
55	Leu Gly Thr Gln Thr Tyr Ile	Cys Asn Val Asn His Lys	Pro Ser Asn
	195	200	205
60	Thr Lys Val Asp Lys Arg Val	Glu Pro Lys Ser Cys	
	210	215	220
65	<210> 276		
	<211> 214		
70	<212> PRT		
	<213> Artificial Sequence		
75	<220>		
	<223> Description of Artificial Sequence: Synthetic polypeptide		
80	<400> 276		
85	Ser Tyr Val Leu Thr Gln Pro	Pro Ser Val Ser Val Ala	Pro Gly Lys
	1	5	10
			15

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	Thr	Ala	Arg	Ile	Ser	Cys	Ser	Gly	Asp	Asn	Leu	Gly	Ser	Lys	Tyr	Val	
				20					25					30			
5	Asp	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr	
			35					40					45				
10	Ser	Asp	Asn	Asn	Arg	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser	
		50					55					60					
15	Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Gly	Thr	Gln	Ala	Met	
	65					70					75					80	
20	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Ala	Thr	Tyr	Asp	Ser	Ser	Pro	Arg	Thr	
				85						90					95		
25	Glu	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	Gly	Gln	Pro	Lys	
				100					105					110			
30	Ala	Ala	Pro	Ser	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu	Leu	Gln	
			115					120					125				
35	Ala	Asn	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp	Phe	Tyr	Pro	Gly	
		130					135					140					
40	Ala	Val	Thr	Val	Ala	Trp	Lys	Ala	Asp	Ser	Ser	Pro	Val	Lys	Ala	Gly	
	145					150					155					160	
45	Val	Glu	Thr	Thr	Thr	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys	Tyr	Ala	Ala	
					165					170					175		
50	Ser	Ser	Tyr	Leu	Ser	Leu	Thr	Pro	Glu	Gln	Trp	Lys	Ser	His	Arg	Ser	
				180					185					190			
55	Tyr	Ser	Cys	Gln	Val	Thr	His	Glu	Gly	Ser	Thr	Val	Glu	Lys	Thr	Val	
			195					200					205				
60	Ala	Pro	Thr	Glu	Cys	Ser											
				210													
65	<210>	277															
	<211>	351															
	<212>	DNA															
	<213>	Artificial Sequence															
70	<220>																
	<223>	Description of Artificial Sequence: Synthetic polynucleotide															

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	<400> 277	
	gaggtgcagc tgggtgcagag cggagccgaa gtgaagaaac ccggcagcag cgtgaaggtg	60
5	tcctgcaagg ccagcggcgg caccttcagc agctacgcca tcagctgggt gcgccaggct	120
	cctggacagg gcctggaatg gatgggccgg atcatcccca tcttcggcac cgccaactac	180
	gcccagaaat tccagggcag agtgaccatc accgccgacg agagcaccag caccgcctac	240
10	atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc ccggcacggc	300
	ggctacagct tcgatagctg gggccagggc accctggtga ccgtgagctc a	351
	<210> 278	
15	<211> 324	
	<212> DNA	
	<213> Artificial Sequence	
	<220>	
20	<223> Description of Artificial Sequence: Synthetic polynucleotide	
	<400> 278	
	agctacgtgc tgactcagcc cccttctgtg tctgtggccc ctggcaagac cgccagaatc	60
25	agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc	120
	caggctcccc tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg	180
	ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccatg	240
30	gacgaggccg actactactg cgccacctac gacagcagcc ccagaaccga ggtgttcgga	300
	ggcgggaacaa agttaaccgt ccta	324
	<210> 279	
35	<211> 660	
	<212> DNA	
	<213> Artificial Sequence	
	<220>	
40	<223> Description of Artificial Sequence: Synthetic polynucleotide	
	<400> 279	
	gaggtgcagc tgggtgcagag cggagccgaa gtgaagaaac ccggcagcag cgtgaaggtg	60
45	tcctgcaagg ccagcggcgg caccttcagc agctacgcca tcagctgggt gcgccaggct	120
	cctggacagg gcctggaatg gatgggccgg atcatcccca tcttcggcac cgccaactac	180
	gcccagaaat tccagggcag agtgaccatc accgccgacg agagcaccag caccgcctac	240
50	atggaactga gcagcctgag aagcgaggac accgccgtgt actactgtgc ccggcacggc	300
	ggctacagct tcgatagctg gggccagggc accctggtga ccgtgagctc agcctccacc	360
	aaggggtccat cggctctccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg	420
55	gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacgggtgtc gtggaactca	480

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	ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcttc aggactctac	540
	tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc	600
5	aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt	660
	<210> 280	
	<211> 642	
	<212> DNA	
10	<213> Artificial Sequence	
	<220>	
	<223> Description of Artificial Sequence: Synthetic polynucleotide	
15	<400> 280	
	agctacgtgc tgactcagcc cccttctgtg tctgtggccc ctggcaagac cgccagaatc	60
	agctgcagcg gcgacaacct gggcagcaaa tacgtggact ggtatcagca gaagcccggc	120
20	caggctcccg tgctggtgat ctacagcgac aacaaccggc ccagcggcat ccctgagcgg	180
	ttcagcggca gcaacagcgg caataccgcc accctgacca tcagcggcac ccaggccatg	240
	gacgaggccg actactactg cgccacctac gacagcagcc ccagaaccga ggtgttcgga	300
25	ggcggaaaca agttaaccgt cctaggtcag cccaaggctg cccctcggt cactctgttc	360
	ccgccctcct ctgaggagct tcaagccaac aaggccacac tgggtgtgtct cataagtgc	420
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 20 25 30
 Ala Phe Ala Tyr Gln Lys Arg Ser Gly Gly Leu Cys Gln Pro Cys Arg
 35 40 45
 40 Ser Pro Arg Trp Ser Leu Trp Ser Thr Trp Ala Pro Cys Ser Val Thr
 50 55 60
 45 Cys Ser Glu Gly Ser Gln Leu Arg Tyr Arg Arg Cys Val Gly Trp Asn
 65 70 75 80
 Gly Gln Cys Ser Gly Lys Val Ala Pro Gly Thr Leu Glu Trp Gln Leu
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 Gln Ala Cys Glu Asp Gln Gln Cys Cys Pro Glu Met Gly Gly Trp Ser
 100 105 110
 55 Gly Trp Gly Pro Trp Glu Pro Cys Ser Val Thr Cys Ser Lys Gly Thr
 115 120 125

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10	Val	Cys	Pro	Thr	His	Gly	Ala	Trp	Ala	Thr	Trp	Gly	Pro	Trp	Thr	Pro	
					165					170					175		
15	Cys	Ser	Ala	Ser	Cys	His	Gly	Gly	Pro	His	Glu	Pro	Lys	Glu	Thr	Arg	
				180					185					190			
20	Ser	Arg	Lys	Cys	Ser	Ala	Pro	Glu	Pro	Ser	Gln	Lys	Pro	Pro	Gly	Lys	
			195					200					205				
25	Pro	Cys	Pro	Gly	Leu	Ala	Tyr	Glu	Gln	Arg	Arg	Cys	Thr	Gly	Leu	Pro	
		210					215					220					
30	Pro	Cys	Pro	Val	Ala	Gly	Gly	Trp	Gly	Pro	Trp	Gly	Pro	Val	Ser	Pro	
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					245					250					255		
40	Asn	His	Pro	Val	Pro	Gln	His	Gly	Gly	Pro	Phe	Cys	Ala	Gly	Asp	Ala	
				260					265					270			
45	Thr	Arg	Thr	His	Ile	Cys	Asn	Thr	Ala	Val	Pro	Cys	Pro	Val	Asp	Gly	
			275					280					285				
50	Glu	Trp	Asp	Ser	Trp	Gly	Glu	Trp	Ser	Pro	Cys	Ile	Arg	Arg	Asn	Met	
	290						295					300					
55	Lys	Ser	Ile	Ser	Cys	Gln	Glu	Ile	Pro	Gly	Gln	Gln	Ser	Arg	Gly	Arg	
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60	Thr	Cys	Arg	Gly	Arg	Lys	Phe	Asp	Gly	His	Arg	Cys	Ala	Gly	Gln	Gln	
					325					330					335		
65	Gln	Asp	Ile	Arg	His	Cys	Tyr	Ser	Ile	Gln	His	Cys	Pro	Leu	Lys	Gly	
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70	Ser	Trp	Ser	Glu	Trp	Ser	Thr	Trp	Gly	Leu	Cys	Met	Pro	Pro	Cys	Gly	
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	385		390		395	400
	Val Thr Phe Trp Gly Arg Pro Leu Pro Arg Cys Glu Glu Leu Gln Gly					
		405		410		415
10	Gln Lys Leu Val Val Glu Glu Lys Arg Pro Cys Leu His Val Pro Ala					
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15	Cys Lys Asp Pro Glu Glu Glu Glu Leu					
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		20		25		30
30	Phe Thr Gln Tyr Glu Glu Ser Ser Gly Lys Cys Lys Gly Leu Leu Gly					
		35		40		45
	Gly Gly Val Ser Val Lys Asp Cys Cys Leu Asn Thr Ala Tyr Ala Tyr					
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	Gln Glu Arg Asn Gly Gly Leu Cys Gln Pro Cys Arg Ser Pro Arg Trp					
	65		70		75	80
40	Ser Leu Trp Ser Thr Trp Ala Pro Cys Ser Val Thr Cys Ser Glu Gly					
		85		90		95
45	Ser Gln Leu Arg Tyr Arg Arg Cys Val Gly Trp Asn Gly Gln Cys Ser					
		100		105		110
	Glu Arg Val Ala Leu Gly Thr Leu Glu Trp Gln Leu Gln Ala Cys Glu					
50		115		120		125
	Asp Lys Gln Cys Cys Pro Glu Met Gly Gly Trp Ser Asp Trp Gly Pro					
		130		135		140
55	Trp Glu Pro Cys Ser Val Thr Cys Ser Lys Gly Met Arg Thr Arg Arg					
		145		150		155
						160

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	Arg	Ala	Cys	Asn	His	Pro	Ala	Pro	Lys	Cys	Gly	Gly	His	Cys	Pro	Gly
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5	Glu	Ala	Gln	Glu	Ser	Glu	Ala	Cys	Asp	Thr	Gln	Gln	Val	Cys	Pro	Thr
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10	His	Gly	Ala	Trp	Ala	Ala	Trp	Gly	Pro	Trp	Ser	Pro	Cys	Ser	Gly	Ser
			195					200					205			
15	Cys	His	Gly	Gly	Pro	His	Glu	Pro	Lys	Glu	Thr	Arg	Ser	Arg	Thr	Cys
		210					215					220				
20	Ser	Ala	Pro	Glu	Pro	Ser	Gln	Lys	Pro	Pro	Gly	Lys	Pro	Cys	Pro	Gly
	225					230					235					240
25	Pro	Ala	Tyr	Glu	His	Arg	Lys	Cys	Thr	Gly	Leu	Pro	Pro	Cys	Pro	Val
					245					250					255	
30	Ala	Gly	Gly	Trp	Gly	Pro	Trp	Gly	Pro	Val	Ser	Pro	Cys	Pro	Val	Thr
				260					265					270		
35	Cys	Gly	Leu	Gly	Gln	Thr	Ile	Glu	Arg	Arg	Thr	Cys	Asn	Arg	Pro	Val
			275					280					285			
40	Pro	Gln	His	Gly	Gly	Pro	Ser	Cys	Ala	Gly	Asp	Ala	Thr	Arg	Thr	His
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45	Ile	Cys	Asn	Thr	Ala	Ala	Pro	Cys	Pro	Val	Asp	Gly	Glu	Trp	Asp	Leu
	305					310					315					320
50	Trp	Gly	Gln	Trp	Ser	Thr	Cys	Val	Arg	Arg	Asn	Met	Lys	Ser	Ile	Ser
					325					330					335	
55	Cys	Glu	Glu	Ile	Pro	Gly	Gln	Gln	Ser	Arg	Trp	Arg	Thr	Cys	Lys	Gly
				340					345					350		
60	Arg	Lys	Phe	Asp	Gly	His	Arg	Cys	Thr	Gly	Gln	Gln	Gln	Asp	Ile	Arg
			355					360					365			
65	His	Cys	Tyr	Ser	Ile	Gln	His	Cys	Pro	Leu	Lys	Gly	Ser	Trp	Ser	Glu
		370					375					380				
70	Trp	Ser	Thr	Trp	Gly	Leu	Cys	Met	Pro	Pro	Cys	Gly	Pro	Asn	Pro	Thr
	385					390					395					400
75	Arg	Ala	Arg	Gln	Arg	Leu	Cys	Thr	Pro	Leu	Leu	Pro	Lys	Tyr	Pro	Pro

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	405	410	415
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15	Val Glu Glu Lys Arg Pro Cys Leu His Val Pro Ala Cys Lys Asp Pro 450 455 460		
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40	Val Glu Asp Cys Cys Leu Asn Thr Ala Tyr Ala Phe Gln Glu His Asp 50 55 60		
45	Gly Gly Leu Cys Gln Ser Cys Arg Ser Pro Gln Trp Ser Ala Trp Ser 65 70 75 80		
50	Ser Trp Gly Pro Cys Ser Val Thr Cys Ser Glu Gly Ser Gln Leu Arg 85 90 95		
55	His Arg Arg Cys Val Gly Arg Gly Gly Gln Cys Ser Glu Lys Ala Ala 100 105 110		
	Pro Gly Thr Leu Glu Trp Gln Leu Gln Ala Cys Glu Asp Gln Leu Cys 115 120 125		
	Cys Pro Glu Met Gly Gly Trp Ser Glu Trp Gly Pro Trp Gly Pro Cys 130 135 140		
	Ser Val Thr Cys Ser Lys Gly Thr Gln Thr Arg Gln Arg Leu Cys Asp 145 150 155 160		

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				180					185					190			
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15	Ala	Gln	Glu	Pro	Lys	Glu	Thr	Arg	Ser	Arg	Ser	Cys	Ser	Ala	Pro	Ala	
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25	His	Arg	Gly	Cys	Ser	Gly	Leu	Pro	Pro	Cys	Pro	Val	Ala	Gly	Gly	Trp	
					245					250					255		
30	Gly	Pro	Trp	Gly	Pro	Ser	Ser	Pro	Cys	Pro	Val	Thr	Cys	Gly	Leu	Gly	
				260					265					270			
35	Gln	Thr	Leu	Glu	Arg	Arg	Thr	Cys	Asp	His	Pro	Val	Pro	Arg	His	Gly	
			275					280					285				
40	Gly	Pro	Phe	Cys	Ala	Gly	Asp	Ala	Thr	Arg	Lys	His	Val	Cys	Asn	Thr	
		290					295					300					
45	Ala	Met	Pro	Cys	Pro	Val	Asn	Gly	Glu	Trp	Glu	Ala	Trp	Gly	Lys	Trp	
	305					310					315					320	
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65	Ile	His	Asn	Cys	Val	Leu	Lys	Gly	Ser	Trp	Ser	Gln	Trp	Ser	Thr	Trp	
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70	Gly	Leu	Cys	Thr	Pro	Pro	Cys	Gly	Pro	Asn	Pro	Thr	Arg	Val	Arg	Gln	
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					405					410					415	
5	Val	Glu	Gly	Gln	Gly	Glu	Lys	Asn	Val	Thr	Phe	Trp	Gly	Ile	Pro	Arg
				420					425					430		
10	Pro	Leu	Cys	Glu	Val	Leu	Gln	Gly	Gln	Lys	Leu	Val	Val	Glu	Glu	Lys
			435					440					445			
15	Arg	Pro	Cys	Leu	His	Val	Pro	Ser	Cys	Arg	Asp	Pro	Glu	Glu	Lys	Lys
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				180					185					190			
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15	Gly	Gly	Pro	Gln	Val	Pro	Lys	Glu	Thr	Arg	Ser	Arg	Thr	Cys	Ser	Ala	
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25	Tyr	Glu	Glu	Gln	Ser	Cys	Ala	Gly	Leu	Pro	Pro	Cys	Pro	Val	Ala	Gly	
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30	Gly	Trp	Gly	Pro	Trp	Gly	Pro	Val	Ser	Ser	Cys	Ser	Val	Thr	Cys	Gly	
				260					265					270			
35	Leu	Gly	Lys	Thr	Leu	Glu	Lys	Arg	Thr	Cys	Asp	His	Pro	Val	Pro	Gln	
			275					280					285				
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		290					295					300					
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	370						375					380					
70	Ser	Trp	Gly	Leu	Cys	Thr	Pro	Pro	Cys	Gly	Pro	Ser	Pro	Thr	Arg	Thr	
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75	Arg	Gln	Arg	Leu	Cys	Thr	Ala	Leu	Leu	Pro	Lys	Phe	Pro	Pro	Thr	Ile	

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10	Pro	Trp	Pro	Gln	Cys	Glu	Gln	Leu	Gln	Gly	Gln	Lys	Leu	Val	Val	Glu	
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		130					135					140					
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	145					150					155					160	

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	Asn	Pro	Ala	Pro	Lys	Cys	Gly	Gly	His	Cys	Pro	Gly	Glu	Ala	Gln	Gln	
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5	Ser	Gln	Ala	Cys	Asp	Thr	Gln	Lys	Thr	Cys	Pro	Thr	His	Gly	Ala	Trp	
				180					185					190			
10	Ala	Ser	Trp	Gly	Pro	Trp	Ser	Pro	Cys	Ser	Gly	Ser	Cys	Leu	Gly	Gly	
			195					200					205				
15	Ala	Gln	Glu	Pro	Lys	Glu	Thr	Arg	Ser	Arg	Ser	Cys	Ser	Ala	Pro	Ala	
		210					215					220					
20	Pro	Ser	His	Gln	Pro	Pro	Gly	Lys	Pro	Cys	Ser	Gly	Pro	Ala	Tyr	Glu	
	225					230					235					240	
25	His	Lys	Ala	Cys	Ser	Gly	Leu	Pro	Pro	Cys	Pro	Val	Ala	Gly	Gly	Trp	
					245					250					255		
30	Gly	Pro	Trp	Ser	Pro	Leu	Ser	Pro	Cys	Ser	Val	Thr	Cys	Gly	Leu	Gly	
				260					265					270			
35	Gln	Thr	Leu	Glu	Gln	Arg	Thr	Cys	Asp	His	Pro	Ala	Pro	Arg	His	Gly	
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40	Gly	Pro	Phe	Cys	Ala	Gly	Asp	Ala	Thr	Arg	Asn	Gln	Met	Cys	Asn	Lys	
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45	Ala	Val	Pro	Cys	Pro	Val	Asn	Gly	Glu	Trp	Glu	Ala	Trp	Gly	Lys	Trp	
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50	Ser	Asp	Cys	Ser	Arg	Leu	Arg	Met	Ser	Ile	Asn	Cys	Glu	Gly	Thr	Pro	
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				340					345					350			
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65	His	Asn	Cys	Ile	Met	Lys	Gly	Ser	Trp	Ser	Gln	Trp	Ser	Thr	Trp	Ser	
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70	Leu	Cys	Thr	Pro	Pro	Cys	Ser	Pro	Asn	Ala	Thr	Arg	Val	Arg	Gln	Arg	
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	405	410	415
5	Glu Gly Gln Gly Glu Lys Asn Val Thr Phe Trp Gly Thr Pro Arg Pro 420 425 430		
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<212> PRT

<213> Mus musculus

<400> 409

5 Val Asn Gly Glu Trp Glu Ala Trp Gly Lys Trp Ser Asp Cys Ser Arg
1 5 10 15

10 Leu Arg Met Ser Ile Asn Cys Glu Gly Thr Pro Gly Gln Gln Ser Arg
20 25 30

Ser Arg Ser Cys Gly Gly Arg Lys Phe Asn Gly Lys Pro Cys Ala Gly
35 40 45

15 Lys Leu Gln Asp Ile Arg His Cys Tyr Asn Ile His Asn Cys Ile
50 55 60

<210> 410

20 <211> 5

<212> PRT

<213> Artificial Sequence

<220>

25 <223> Description of Artificial Sequence: Synthetic
peptide

<400> 410

30 Ser Tyr Ala Ile Ser
1 5

<210> 411

<211> 17

<212> PRT

<213> Artificial Sequence

35

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

<400> 411

40 Gly Ile Gly Pro Phe Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

45

<210> 412

<211> 7

<212> PRT

<213> Artificial Sequence

50

<220>

<223> Description of Artificial Sequence: Synthetic
peptide

55

<400> 412

Asp Thr Pro Tyr Phe Asp Tyr

1 5

<210> 413
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic peptide

<400> 413
 Ser Gly Asp Ser Ile Pro Asn Tyr Tyr Val Tyr
 1 5 10

<210> 414
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic peptide

<400> 414
 Asp Asp Ser Asn Arg Pro Ser
 1 5

<210> 415
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic peptide

<400> 415
 Gln Ser Phe Asp Ser Ser Leu Asn Ala Glu Val
 1 5 10

<210> 416
 <211> 116
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polypeptide

<400> 416
 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15

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

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	Ala	Ile	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met	
			35						40					45			
5	Gly	Gly	Ile	Gly	Pro	Phe	Phe	Gly	Thr	Ala	Asn	Tyr	Ala	Gln	Lys	Phe	
		50					55					60					
	Gln	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Glu	Ser	Thr	Ser	Thr	Ala	Tyr	
10		65				70					75					80	
	Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
					85					90					95		
15	Ala	Arg	Asp	Thr	Pro	Tyr	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	
				100					105						110		
	Thr	Val	Ser	Ser													
20				115													
	<210>	417															
	<211>	108															
25	<212>	PRT															
	<213>	Artificial Sequence															
	<220>																
	<223>	Description of Artificial Sequence: Synthetic															
		polypeptide															
30	<400>	417															
	Ser	Tyr	Glu	Leu	Thr	Gln	Pro	Leu	Ser	Val	Ser	Val	Ala	Leu	Gly	Gln	
	1				5					10					15		
35	Thr	Ala	Arg	Ile	Thr	Cys	Ser	Gly	Asp	Ser	Ile	Pro	Asn	Tyr	Tyr	Val	
				20					25					30			
	Tyr	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr	
40			35					40					45				
	Asp	Asp	Ser	Asn	Arg	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser	
		50					55					60					
45	Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Arg	Ala	Gln	Ala	Gly	
		65				70					75					80	
	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Ser	Phe	Asp	Ser	Ser	Leu	Asn	Ala	
50					85					90					95		
	Glu	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu					
55				100					105								
	<210>	418															

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<211> 446
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 418

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

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	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser	Val	Phe	
	225					230					235					240	
5	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	
					245					250					255		
10	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	
				260					265					270			
15	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	
			275					280					285				
20	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	
		290					295					300					
25	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	
	305					310					315					320	
30	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	
				325					330						335		
35	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	
				340					345					350			
40	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	
			355					360					365				
45	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	
		370					375					380					
50	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	
	385					390					395					400	
55	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	
				405						410					415		
60	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	
				420					425					430			
65	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys			
			435					440					445				
70	<210>	419															
75	<211>	214															
80	<212>	PRT															
85	<213>	Artificial Sequence															

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<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 419

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

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

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

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

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

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

Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys
100 105 110

Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln
115 120 125

Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly
130 135 140

Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly
145 150 155 160

Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala
165 170 175

Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser
180 185 190

Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val
195 200 205

Ala Pro Thr Glu Cys Ser
210

<210> 420

<211> 348

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 420

gaggtgcaat tggttcagtc tggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagtg 60
 agctgcaaag cctccggagg cactttttct tcttatgcca tttcttgggt gcgccaagcc 120
 cctgggcagg gtctcgagtg gatgggcggt atcgggccgt tttttggcac tgcgaattac 180
 gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240
 atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtgatact 300
 ccttattttg attattgggg ccaaggcacc ctggtgacgg ttagctca 348

<210> 421

<211> 324

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 421

tcctatgaac tcacacagcc cctgagcgtg agcgtggccc tgggccagac cgcccggatc 60
 acctgctccg gcgacagcat ccccaactac tacgtgtact ggtaccagca gaagcccggc 120
 caggcccccg tgctggtgat ctacgacgac agcaaccggc ccagcggcat ccccgagcgg 180
 ttcagcggca gcaacagcgg caacaccgcc accctgacca tttccagagc acaggcaggc 240
 gacgaggccg actactactg ccagagcttc gacagcagcc tgaacgccga ggtgttcggc 300
 ggagggacca agttaaccgt ccta 324

<210> 422

<211> 1338

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 422

gaggtgcaat tggttcagtc tggcgcggaa gtgaaaaaac cgggcagcag cgtgaaagtg 60
 agctgcaaag cctccggagg cactttttct tcttatgcca tttcttgggt gcgccaagcc 120
 cctgggcagg gtctcgagtg gatgggcggt atcgggccgt tttttggcac tgcgaattac 180
 gcgcagaagt ttcagggccg ggtgaccatt accgcggatg aaagcaccag caccgcgtat 240
 atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtgatact 300

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	ccttatttttg attattgggg ccaaggcacc ctggtgacgg ttagctcagc ctccaccaag	360
	ggtccatcgg tcttccccct ggcaccctcc tccaagagca cctctggggg cacagcggcc	420
5	ctgggctgcc tgggtcaagga ctacttcccc gaaccgggtga cgggtgtcgtg gaactcaggc	480
	gccctgacca gcggcgtgca caccttcccc gctgtcctac agtcctcagg actctactcc	540
	ctcagcagcg tgggtgaccgt gccctccagc agcttgggca cccagaccta catctgcaac	600
10	gtgaatcaca agcccagcaa caccaagggtg gacaagagag ttgagcccaa atcttgtgac	660
	aaaactcaca catgcccacc gtgcccagca cctgaagcag cgggggggacc gtcagtcttc	720
	ctcttcccc caaaacccaa ggacaccctc atgatctccc ggaccctga ggtcacatgc	780
15	gtgggtgggg acgtgagcca cgaagaccct gaggtcaagt tcaactggta cgtggacggc	840
	gtggagggtgc ataatgccaa gacaaagccg cgggaggagc agtacaacag cacgtaccgg	900
20	gtgggtcagcg tcctcaccgt cctgcaccag gactgggtga atggcaagga gtacaagtgc	960
	aagggtctcca acaaagccct cccagcccc atcgagaaaa ccatctccaa agccaaaggg	1020
	cagccccgag aaccacaggt gtacaccctg ccccatccc gggaggagat gaccaagaac	1080
25	caggtcagcc tgacctgcct ggtcaaaggc ttctatccca gcgacatcgc cgtggagtgg	1140
	gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccggtgct ggactccgac	1200
	ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac	1260
30	gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc	1320
	tcctgtctc cgggtaaa	1338
35	<210> 423 <211> 642 <212> DNA <213> Artificial Sequence	
40	<220> <223> Description of Artificial Sequence: Synthetic polynucleotide	
	<400> 423 tcctatgaac tcacacagcc cctgagcgtg agcgtggccc tgggccagac cggccggtc	
45	acctgctccg gcgacagcat ccccaactac tacgtgtact ggtaccagca gaagcccggc	120
	caggcccccg tgctggtgat ctacgacgac agcaaccggc ccagcggcat cccgagcgg	180
50	ttcagcggca gcaacagcgg caacaccgcc accctgacca tttccagagc acaggcaggc	240
	gacgaggccg actactactg ccagagcttc gacagcagcc tgaacgccga ggtgttcggc	300
	ggagggacca agttaaccgt cctaggtcag cccaaggctg cccctcgggt cactctgttc	360
55	ccgccctcct ctgaggagct tcaagccaac aaggccacac tgggtgtgtct cataagtgac	420
	ttctaccggg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga	480

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	gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg	540
	agcctgacgc ctgagcagtg gaagtccac agaagctaca gctgccaggt cacgcatgaa	600
5	gggagcaccg tggagaagac agtggcccct acagaatggt ca	642
	<210> 424	
	<211> 1338	
10	<212> DNA	
	<213> Artificial Sequence	
	<220>	
	<223> Description of Artificial Sequence: Synthetic polynucleotide	
15	<400> 424	
	gaggtgcagc tgggtgcagag cggagccgag gtgaagaagc cggtagcag cgtcaagggtg	60
	tcctgcaagg ccagcggcgg caccttcagc agctacgcca tcagctgggt gcggcaggcc	120
20	ccaggccagg gcctggagtg gatgggcggc atcggcccat tcttcggcac cgccaactac	180
	gcccagaagt tccagggcag ggtcaccatc accgccgacg agagcaccag caccgcctac	240
	atggagctgt ccagcctgag aagcgaggac accgccgtgt actactgcgc cagagacacc	300
25	ccctacttcg actactgggg ccagggcacc ctggtgaccg tgagcagcgc tagcaccaag	360
	ggccccagcg tgttccccct ggcccccagc agcaagagca cctccggcgg cacagccgcc	420
30	ctgggctgcc tgggtgaagga ctacttcccc gagcccgtga ccgtgtcctg gaacagcgga	480
	gccctgacca gcggcgtgca caccttcccc gccgtgctgc agagcagcgg cctgtacagc	540
	ctgtccagcg tgggtgacagt gcccagcagc agcctgggca cccagaccta catctgcaac	600
35	gtgaaccaca agcccagcaa caccaagggtg gacaagagag tggagcccaa gagctgcgac	660
	aagaccaca cctgcccccc ctgcccagcc cccgaagctg caggcggccc ttccgtgttc	720
	ctgttcccc ccaagcccaa ggacaccctg atgatcagca ggacccccga ggtgacctgc	780
40	gtggtggtgg acgtgagcca cgaggacca gaggtgaagt tcaactggta cgtggacggc	840
	gtggaggtgc acaacgcaa gaccaagccc agagaggagc agtacaacag cacctacagg	900
	gtggtgtccg tgctgaccgt gctgcaccag gactggctga acggcaaaga atacaagtgc	960
45	aaggtctcca acaaggccct gcctgcccc atcgaaaaga ccatcagcaa ggccaagggc	1020
	cagccacggg agccccaggt gtacaccctg ccccttctc gggaggagat gaccaagaac	1080
	cagggtgtcc tgacctgtct ggtgaagggc ttctacccca gcgacatcgc cgtggagtgg	1140
50	gagagcaacg gccagcccga gaacaactac aagaccaccc cccagtgct ggacagcgac	1200
	ggcagcttct tcctgtacag caagctgacc gtggacaaga gcagggtggca gcagggaac	1260
55	gtgttcagct gcagcgtgat gcacgaggcc ctgcacaacc actacacca gaagagcctg	1320
	agcctgtcac ccggcaag	1338

<210> 425
 <211> 642
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 polynucleotide

<400> 425
 agctacgagc tgacccagcc cctgagcgtg agcgtggccc tgggccagac cgccaggatc 60
 acctgcagcg gcgacagcat ccccaactac tacgtgtact ggtatcagca gaagcccggc 120
 caggcccccg tgctgggtgat ctacgacgac agcaacaggc ccagcggcat ccccagagag 180
 ttcagcggca gcaacagcgg caacaccgcc accctgacca tcagcagagc ccaggccggc 240
 gacgaggccg actactactg ccagagcttc gacagctcac tgaacgccga ggtgttcggc 300
 ggagggacca agctgaccgt gctgggccag cctaaggctg ccccagcgt gaccctgttc 360
 ccccccagca gcgaggagct gcaggccaac aaggccaccc tgggtgtgcct gatcagcgac 420
 ttctaccag gcgccgtgac cgtggcctgg aaggccgaca gcagccccgt gaaggccggc 480
 gtggagacca ccacccccag caagcagagc aacaacaagt acgccgccag cagctacctg 540
 agcctgaccc ccgagcagtg gaagagccac aggtcctaca gctgccaggt gaccacagag 600
 ggcagcaccg tggaaaagac cgtggcccca accgagtgcg gc 642

<210> 426
 <211> 4
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

<400> 426
 Asn Tyr Ile Ser
 1

<210> 427
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

<400> 427
 Ile Ile Asp Pro Asp Asp Ser Tyr Thr Glu Tyr Ser Pro Ser Phe Gln
 1 5 10 15

Gly

5 <210> 428
 <211> 8
 <212> PRT
 <213> Artificial Sequence

 10 <220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

 <400> 428
 Tyr Glu Tyr Gly Gly Phe Asp Ile
 1 5
 15

 <210> 429
 <211> 11
 <212> PRT
 20 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

 25 <400> 429
 Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val His
 1 5 10

 30 <210> 430
 <211> 7
 <212> PRT
 <213> Artificial Sequence

 <220>
 35 <223> Description of Artificial Sequence: Synthetic
 peptide

 <400> 430
 Lys Asp Asn Asp Arg Pro Ser
 1 5
 40

 <210> 431
 <211> 9
 <212> PRT
 45 <213> Artificial Sequence

 <220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

 50 <400> 431
 Gly Thr Tyr Asp Ile Glu Ser Tyr Val
 1 5

 55 <210> 432
 <211> 116
 <212> PRT

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<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 432

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

Ile Ile Asp Pro Asp Asp Ser Tyr Thr Glu Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 433

<211> 106

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 433

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

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

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

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

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

5 Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Tyr Asp Ile Glu Ser Tyr Val
 85 90 95

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

<210> 434
 <211> 446
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 polypeptide

20 <400> 434
 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15

25 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
 20 25 30

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

35 Ile Ile Asp Pro Asp Asp Ser Tyr Thr Glu Tyr Ser Pro Ser Phe Gln
 50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
 65 70 75 80

40 Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
 85 90 95

45 Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
 100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
 115 120 125

50 Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
 130 135 140

55 Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
 145 150 155 160

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	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	
					165					170					175		
5	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	
				180					185					190			
10	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	
			195					200					205				
	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	
		210					215					220					
15	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser	Val	Phe	
	225					230					235					240	
20	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	
					245					250					255		
	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	
25				260					265					270			
	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	
			275					280					285				
30	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	
		290					295					300					
35	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	
	305					310					315					320	
	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	
				325						330					335		
40	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	
				340					345					350			
45	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	
			355					360					365				
	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	
50		370					375					380					
	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	
	385					390					395					400	
55	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	
				405						410					415		

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Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

5 Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

10 <210> 435
<211> 212
<212> PRT
<213> Artificial Sequence

15 <220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

20 <400> 435
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15

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

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

30 Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

35 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

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

40 Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala Ala
100 105 110

45 Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala Asn
115 120 125

50 Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala Val
130 135 140

Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val Glu
145 150 155 160

55 Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser Ser
165 170 175

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Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr Ser
180 185 190

5 Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala Pro
195 200 205

10 Thr Glu Cys Ser
210

<210> 436

<211> 348

<212> DNA

15 <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

20 <400> 436

gaggtgcaat tgggtcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttcctttact aattatatatt cttgggtgcg ccagatgcct 120

25 gggaagggtc tcgagtggat gggcattatt gatcctgatg attcttatac tgagtattct 180

ccttcttttc agggtcaggt caccattagc gcggataaaa gcattagcac cgcgtatctt 240

caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300

30 ggtgggttttg atatttgggg ccaaggcacc ctgggtgacgg ttagctca 348

<210> 437

<211> 318

<212> DNA

35 <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

40 <400> 437

agttacgaac tgaccagacc gccttcagtg agcgttgac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg 120

45 caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgc caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgc attattattg cggctacttat gatattgagt cttatgtgtt tggcggcggc 300

50 acgaagttaa ccgtccta 318

<210> 438

<211> 1338

<212> DNA

55 <213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

5 <400> 438
gaggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60
agctgcaaag gttccggata ttcttttact aattatatatt cttgggtgcg ccagatgcct 120
10 gggaagggtc tcgagtggat gggcattatt gatcctgatg attcttatac tgagtattct 180
ccttcttttc agggtcaggt caccattagc gcggataaaa gcattagcac cgcgtatctt 240
caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat 300
15 ggtggttttg atatttgggg ccaaggcacc ctggtgacgg ttagctcagc ctccaccaag 360
ggtccatcgg tcttccccct ggcaccctcc tccaagagca cctctggggg cacagcggcc 420
ctgggctgcc tgggtcaagga ctacttcccc gaaccgggtga cgggtgctgtg gaactcaggc 480
20 gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc 540
ctcagcagcg tggtgaccgt gccctccagc agcttgggca cccagacctc catctgcaac 600
gtgaatcaca agcccagcaa caccaagggtg gacaagagag ttgagcccaa atcttgtgac 660
25 aaaactcaca catgcccacc gtgcccagca cctgaagcag cgggggggacc gtcagtcttc 720
ctcttcccc caaaacccaa ggacaccctc atgatctccc ggaccctga ggtcacatgc 780
30 gtggtggtgg acgtgagcca cgaagaccct gaggtcaagt tcaactggta cgtggacggc 840
gtggaggtgc ataatgccaa gacaaagccg cgggaggagc agtacaacag cacgtaccgg 900
gtggtcagcg tcctcaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc 960
35 aaggtctcca acaaagccct cccagcccc atcgagaaaa ccatctccaa agccaaaggg 1020
cagccccgag aaccacaggt gtacaccctg ccccatccc gggaggagat gaccaagaac 1080
caggtcagcc tgacctgcct ggtcaaaggc ttctatocca gcgacatcgc cgtggagtgg 1140
40 gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccggtgct ggactccgac 1200
ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1260
gtcttctcat gtcctgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1320
45 tccctgtctc cgggtaaa 1338

<210> 439

<211> 636

50 <212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

55

<400> 439

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	agttacgaac tgaccagcc gccttcagtg agcgttgac caggtcagac cgcgcgtatc	60
	tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg	120
5	caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc	180
	tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa	240
	gacgaagcgg attattattg cgggtacttat gatattgagt cttatgtgtt tggcggcggc	300
10	acgaagttaa ccgtcctagg tcagcccaag gctgccccct cggtcactct gttcccgccc	360
	tcctctgagg agcttcaagc caacaaggcc aactggtgt gtctcataag tgacttctac	420
	ccgggagccg tgacagtggc ctggaaggca gatagcagcc ccgtcaaggc gggagtggag	480
15	accaccacac cctccaaaca aagcaacaac aagtacgagg ccagcagcta tctgagcctg	540
	acgcctgagc agtggaagtc ccacagaagc tacagctgcc aggtcacgca tgaaggagc	600
20	accgtggaga agacagtggc ccctacagaa tgttca	636
	<210> 440	
	<211> 1338	
	<212> DNA	
25	<213> Artificial Sequence	
	<220>	
	<223> Description of Artificial Sequence: Synthetic polynucleotide	
30	<400> 440	
	gaggtgcagc tgggtgcagag cggagccgag gtgaaaaagc ccggtgagag cctgaagatc	60
	agctgcaagg gcagcggcta cagcttcacc aactacatca gctgggtgag gcagatgccc	120
35	ggcaagggcc tggagtggat gggcatcatc gaccccgacg acagctacac cgagtacagc	180
	cccagcttcc agggccaggt gaccatcagc gccgacaaga gcatcagcac cgcctacctg	240
	cagtggagca gcctgaaggc cagcgacacc gccatgtact actgcgccag atacgagtac	300
40	ggcggcttcg acatctgggg ccagggcacc ctggtgaccg tcagctcagc tagcaccaag	360
	ggccccagcg tgttccccct ggccccagc agcaagagca cctccggcgg cacagccgcc	420
	ctgggctgcc tggatgaagga ctacttcccc gagcccgatga ccgtgtcctg gaacagcggg	480
45	gccctgacca gcggcgtgca caccttcccc gccgtgctgc agagcagcgg cctgtacagc	540
	ctgtccagcg tgggtgacagt gccagcagc agcctgggca ccagaccta catctgcaac	600
	gtgaaccaca agcccagcaa caccaagggtg gacaagagag tggagcccaa gagctgcgac	660
50	aagaccaca cctgcccccc ctgcccagcc cccgaagctg caggcggccc ttccgtgttc	720
	ctgttcccc ccaagcccaa ggacaccctg atgatcagca ggacccccga ggtgacctgc	780
55	gtgggtggtg acgtgagcca cgaggaccca gaggtgaagt tcaactggtg cgtggacggc	840
	gtggaggtgc acaacgcaa gaccaagccc agagaggagc agtacaacag cacctacagg	900

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	gtggtgtccg tgctgaccgt gctgcaccag gactggctga acggcaaaga atacaagtgc	960
	aaggtctcca acaaggccct gcctgcccc atcgaaaaga ccatcagcaa ggccaagggc	1020
5	cagccacggg agccccaggt gtacaccctg ccccttctc gggaggagat gaccaagaac	1080
	caggtgtccc tgacctgtct ggtgaagggc ttctaccca gcgacatcgc cgtggagtgg	1140
	gagagcaacg gccagcccga gaacaactac aagaccaccc cccagtgct ggacagcgac	1200
10	ggcagcttct tcctgtacag caagctgacc gtggacaaga gcaggtggca gcagggcaac	1260
	gtgttcagct gcagcgtgat gcacgaggcc ctgcacaacc actacacca gaagagcctg	1320
	agcctgtcac ccggcaag	1338
15		
	<210> 441	
	<211> 636	
	<212> DNA	
20	<213> Artificial Sequence	
	<220>	
	<223> Description of Artificial Sequence: Synthetic polynucleotide	
25	<400> 441	
	agctacgagc tgaccagcc cccagcgtg agcgtggccc caggccagac cgccaggatc	60
	agctgcagcg gcgacaacat cggcaacagc tacgtgcaact ggtatcagca gaagcccggc	120
30	caggcccccg tgctggtgat ctacaaggac aacgacaggc ccagcggcat ccccgagagg	180
	ttcagcggca gcaactccg caacaccgcc accctgacca tcagcggcac ccaggccgag	240
	gacgaggccg actactactg cggcacctac gacatcgagt catacgtgtt cggcggaggg	300
35	accaagctga ccgtgctggg ccagcctaag gctgccccca gcgtgaccct gttccccccc	360
	agcagcgagg agctgcaggc caacaaggcc accctggtgt gcctgatcag cgacttctac	420
	ccaggcgccg tgaccgtggc ctggaaggcc gacagcagcc ccgtgaaggc cggcgtggag	480
40	accaccaccc ccagcaagca gagcaacaac aagtacgccg ccagcagcta cctgagcctg	540
	acccccgagc agtggaaagag ccacaggtcc tacagctgcc aggtgacca cgagggcagc	600
	accgtggaaa agaccgtggc cccaaccgag tgcagc	636
45		
	<210> 442	
	<211> 7	
	<212> PRT	
50	<213> Artificial Sequence	
	<220>	
	<223> Description of Artificial Sequence: Synthetic peptide	
55	<400> 442	
	Thr Ser Gly Gly Gly Val Ser	
	1 5	

<210> 443
 <211> 16
 <212> PRT
 <213> Artificial Sequence

5

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

10

<400> 443
 Asn Ile Asp Asp Ala Asp Ile Lys Asp Tyr Ser Pro Ser Leu Lys Ser
 1 5 10 15

15

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

20

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

<400> 444
 Gly Pro Tyr Gly Phe Asp Ser
 1 5

25

<210> 445
 <211> 14
 <212> PRT
 <213> Artificial Sequence

30

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

35

<400> 445
 Thr Gly Thr Ser Ser Asp Ile Gly Thr Tyr Asn Tyr Val Ser
 1 5 10

40

<210> 446
 <211> 7
 <212> PRT
 <213> Artificial Sequence

45

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

<400> 446
 Asp Asp Ser Asn Arg Pro Ser
 1 5

50

<210> 447
 <211> 9
 <212> PRT
 <213> Artificial Sequence

55

<220>

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 447

Gln Ser Tyr Asp Ser Gln Ser Ile Val
1 5

<210> 448

<211> 117

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 448

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

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

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

Trp Leu Ala Asn Ile Asp Asp Ala Asp Ile Lys Asp Tyr Ser Pro Ser
50 55 60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65 70 75 80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Gly Pro Tyr Gly Phe Asp Ser Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 449

<211> 109

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 449

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

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Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Ile Gly Thr Tyr
 20 25 30
 5 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
 35 40 45
 10 Met Ile Tyr Asp Asp Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
 50 55 60
 Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
 65 70 75 80
 15 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Gln
 85 90 95
 20 Ser Ile Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105
 25 <210> 450
 <211> 447
 <212> PRT
 <213> Artificial Sequence
 30 <220>
 <223> Description of Artificial Sequence: Synthetic
 polypeptide
 <400> 450
 Glu Val Thr Leu Lys Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
 1 5 10 15
 35 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
 20 25 30
 40 Gly Gly Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
 35 40 45
 45 Trp Leu Ala Asn Ile Asp Asp Ala Asp Ile Lys Asp Tyr Ser Pro Ser
 50 55 60
 50 Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
 65 70 75 80
 Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
 85 90 95
 55 Cys Ala Arg Gly Pro Tyr Gly Phe Asp Ser Trp Gly Gln Gly Thr Leu
 100 105 110

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

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	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	
	370						375					380					
5	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	
	385					390					395					400	
10	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	
				405						410					415		
15	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	
				420					425					430			
20	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys		
			435					440					445				
25	<210>	451															
	<211>	215															
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	<213>	Artificial Sequence															
30	<220>																
	<223>	Description of Artificial Sequence: Synthetic															
		polypeptide															
	<400>	451															
	Glu	Ser	Ala	Leu	Thr	Gln	Pro	Ala	Ser	Val	Ser	Gly	Ser	Pro	Gly	Gln	
	1			5						10					15		
35	Ser	Ile	Thr	Ile	Ser	Cys	Thr	Gly	Thr	Ser	Ser	Asp	Ile	Gly	Thr	Tyr	
				20					25					30			
40	Asn	Tyr	Val	Ser	Trp	Tyr	Gln	Gln	His	Pro	Gly	Lys	Ala	Pro	Lys	Leu	
			35					40					45				
45	Met	Ile	Tyr	Asp	Asp	Ser	Asn	Arg	Pro	Ser	Gly	Val	Ser	Asn	Arg	Phe	
		50					55					60					
50	Ser	Gly	Ser	Lys	Ser	Gly	Asn	Thr	Ala	Ser	Leu	Thr	Ile	Ser	Gly	Leu	
	65					70					75					80	
55	Gln	Ala	Glu	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Gln	Ser	Tyr	Asp	Ser	Gln	
					85					90					95		
60	Ser	Ile	Val	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	Gly	Gln	Pro	
				100					105					110			
65	Lys	Ala	Ala	Pro	Ser	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu	Leu	
			115					120					125				

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Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
130 135 140

5 Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145 150 155 160

10 Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
165 170 175

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
180 185 190

15 Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
195 200 205

20 Val Ala Pro Thr Glu Cys Ser
210 215

25 <210> 452
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

30 <400> 452
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acctgtacct tttccggatt tagcctgtct acttctggtg gtggtgtgtc ttggattcgc 120
35 cagccgcctg ggaaagccct cgagtggctg gctaattattg atgatgctga tattaaggat 180
tattctcctt ctcttaagtc tcgtctgacc attagcaaag atacttcgaa aaatcagggtg 240
gtgctgacta tgaccaacat ggacccggtg gatacggcca cctattattg cgcgcggtgtg 300
40 ccttatgggtt ttgattcttg gggccaaggc accctggtga cggttagctc a 351

45 <210> 453
<211> 327
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polynucleotide

50 <400> 453
gaaagcgcac tgaccagacc agcttcagtg agcggctcac caggtcagag cattaccatc 60
55 tcgtgtacgg gtactagcag cgatattggt acttataatt atgtgtcttg gtaccagcag 120
catcccggga aggcgccgaa acttatgatt tatgatgatt ctaatcgtcc ctcaggcgtg 180

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	agcaaccggtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg	240
	caagcggaag acgaagcggg ttattattgc cagtcttatg attctcagtc tattgtgttt	300
5	ggcggcggca cgaagttaac cgtccta	327
	<210> 454	
	<211> 1341	
10	<212> DNA	
	<213> Artificial Sequence	
	<220>	
	<223> Description of Artificial Sequence: Synthetic polynucleotide	
15	<400> 454	
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	acctgtacct tttccggatt tagcctgtct acttctggtg gtggtgtgtc ttggattcgc	120
20	cagccgcctg ggaaagccct cgagtggctg gctaattattg atgatgctga tattaaggat	180
	tattctcctt ctcttaagtc tcgtctgacc attagcaaag atacttcgaa aaatcaggtg	240
	gtgctgacta tgaccaacat ggacccggtg gatacggcca cctattattg cgcgcgtggt	300
25	ccttatgggt ttgattcttg gggccaaggc accctggtga cggttagctc agcctccacc	360
	aaggggccat cggctctccc cctggcacc cctccaaga gcacctctgg gggcacagcg	420
30	gccctgggct gcctgggcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca	480
	ggcgccctga ccagcggcgt gcacaccttc ccggtgtcc tacagtctc aggactctac	540
	tcctcagca gcgtggtgac cgtgccctcc agcagcttg gcacccagac ctacatctgc	600
35	aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt	660
	gacaaaactc acacatgccc accgtgccc gcacctgaag cagcgggggg accgtcagtc	720
	ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca	780
40	tgctgtgtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac	840
	ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac	900
	cgggtgtgca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag	960
45	tgcaaggctc ccaacaaagc cctcccagcc cccatcgaga aaacctctc caaagccaaa	1020
	gggcagcccc gagaaccaca ggtgtacacc ctgccccat cccgggagga gatgaccaag	1080
50	aaccaggtca gcctgacctg cctgggtcaaa ggcttctatc ccagcgacat cgcctggag	1140
	tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc	1200
	gacggctcct tcttctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg	1260
55	aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc	1320
	ctctccctgt ctccgggtaa a	1341

<210> 455
 <211> 645
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 455
 gaaagcgcac tgaccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60
 tcgtgtacgg gtactagcag cgatattggt acttataatt atgtgtcttg gtaccagcag 120
 catcccggga aggcgccgaa acttatgatt tatgatgatt ctaatcgtcc ctcaggcgtg 180
 agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240
 caagcggaag acgaagcgga ttattattgc cagtcttatg attctcagtc tattgtgttt 300
 ggcggcggca cgaagttaac cgtcctaggt cagcccaagg ctgccccctc ggtcactctg 360
 ttcccgcctt cctctgagga gcttcaagcc aacaaggcca cactggtgtg tctcataagt 420
 gacttctacc cgggagccgt gacagtggcc tggaaggcag atagcagccc cgtcaaggcg 480
 ggagtggaga ccaccacacc ctccaaacaa agcaacaaca agtacgcggc cagcagctat 540
 ctgagcctga cgcctgagca gtggaagtcc cacagaagct acagctgccg ggtcacgcat 600
 gaagggagca ccgtggagaa gacagtggcc cctacagaat gttca 645

<210> 456
 <211> 1341
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 456
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 acttgcacct tcagcggctt cagcctgagc accagcggag ggggcgtgag ctggatcagg 120
 cagccccag gtaaggccct ggagtggctg gccaatatcg acgacgccga tatcaaggac 180
 tacagcccca gcctgaagag caggctgacc atcagcaagg acaccagcaa gaaccagggtg 240
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 ccctacggct tcgacagctg gggccagggc accctggtga ccgtcagctc agctagcacc 360
 aagggcccca gcgtgttccc cctggccccc agcagcaaga gcacctccgg cggcacagcc 420
 gccctgggct gcctggtgaa ggactacttc cccgagcccg tgaccgtgtc ctggaacagc 480
 ggagccctga ccagcggcgt gcacaccttc cccgcctgtc tgcagagcag cggcctgtac 540
 agcctgtcca gcgtggtgac agtgcccagc agcagcctgg gcaccagac ctacatctgc 600

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	aacgtgaacc acaagcccag caacaccaag gtggacaaga gagtggagcc caagagctgc	660
	gacaagaccc acacctgccc cccctgccc a gccccgaag ctgcaggcgg cccttcctgt	720
5	ttcctgttcc cccccaagcc caaggacacc ctgatgatca gcaggacccc cgaggtgacc	780
	tgcgtgggtg tggacgtgag ccacgaggac ccagaggtga agttcaactg gtacgtggac	840
	ggcgtggagg tgcacaacgc caagaccaag ccagagagg agcagtacaa cagcacctac	900
10	agggtgggtgt ccgtgctgac cgtgctgcac caggactggc tgaacggcaa agaatacaag	960
	tgcaaggtct ccaacaaggc cctgcctgcc cccatcgaaa agaccatcag caaggccaag	1020
	ggccagccac gggagcccca ggtgtacacc ctgccccctt ctcgaggagga gatgaccaag	1080
15	aaccaggtgt ccctgacctg tctggtgaag ggcttctacc ccagcgacat cgccgtggag	1140
	tgggagagca acggccagcc cgagaacaac tacaagacca cccccccagt gctggacagc	1200
20	gacggcagct tcttcctgta cagcaagctg accgtggaca agagcaggtg gcagcagggc	1260
	aacgtgttca gctgcagcgt gatgcacgag gccctgcaca accactacac ccagaagagc	1320
	ctgagcctgt caccgga g	1341
25	<210> 457 <211> 645 <212> DNA <213> Artificial Sequence	
30	<220> <223> Description of Artificial Sequence: Synthetic polynucleotide	
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	agctgcaccg gcacctccag cgatatcggc acctacaact acgtgagctg gtatcagcag	120
	caccgga agggcccaa gctgatgatc tacgacgaca gcaacaggcc cagcggcgtg	180
40	agcaacaggt tcagcggcag caagagcggc aacaccgcca gcctgacaat cagcggcctg	240
	caggccgagg acgaggccga ctactactgc cagagctacg acagccagtc aatcgtgttc	300
	ggcggaggga ccaagctgac cgtgctgggc cagcctaagg ctgccccag cgtgaccctg	360
45	ttcccccca gcagcgagga gctgcaggcc aacaaggcca ccctgggtgtg cctgatcagc	420
	gacttctacc caggcgccgt gaccgtggcc tggaaggccg acagcagccc cgtgaaggcc	480
50	ggcgtggaga ccaccacccc cagcaagcag agcaacaaca agtacgccgc cagcagctac	540
	ctgagcctga ccccgagca gtggaagagc cacaggctcct acagctgcca ggtgaccac	600
	gagggcagca ccgtggaaaa gaccgtggcc ccaaccgagt gcagc	645
55	<210> 458 <211> 17	

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<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 458
Ile Ile Asp Pro Asp Asp Ser Tyr Thr Arg Tyr Ser Pro Ser Phe Gln
1 5 10 15

Gly

<210> 459
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 459
Ala Thr Trp Gly Ser Glu Asp Gln Val
1 5

<210> 460
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 460
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

Ile Ile Asp Pro Asp Asp Ser Tyr Thr Arg Tyr Ser Pro Ser Phe Gln
50 55 60

Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu
65 70 75 80

Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala
85 90 95

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Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> 461
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 461
Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1 5 10 15

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

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

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

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

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

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

<210> 462
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 462
Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
20 25 30

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

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	275		280		285
5	Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val				
	290		295		300
10	Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys				
	305		310		315
					320
15	Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser				
			325		330
					335
20	Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro				
			340		345
					350
25	Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val				
			355		360
					365
30	Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly				
			370		375
					380
35	Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp				
			385		390
					395
40	Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp				
			405		410
					415
45	Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His				
			420		425
					430
50	Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys				
			435		440
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	<211> 212				
	<212> PRT				
	<213> Artificial Sequence				
	<220>				
	<223> Description of Artificial Sequence: Synthetic				
	polypeptide				
	<400> 463				
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					15
	Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val				
			20		25
					30
	His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr				
			35		40
					45

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	Lys	Asp	Asn	Asp	Arg	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser	
	50						55					60					
5	Asn	Ser	Gly	Asn	Thr	Ala	Thr	Leu	Thr	Ile	Ser	Gly	Thr	Gln	Ala	Glu	
	65				70					75					80		
	Asp	Glu	Ala	Asp	Tyr	Tyr	Cys	Ala	Thr	Trp	Gly	Ser	Glu	Asp	Gln	Val	
10				85					90					95			
	Phe	Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	Gly	Gln	Pro	Lys	Ala	Ala	
				100				105					110				
15	Pro	Ser	Val	Thr	Leu	Phe	Pro	Pro	Ser	Ser	Glu	Glu	Leu	Gln	Ala	Asn	
			115				120						125				
	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ile	Ser	Asp	Phe	Tyr	Pro	Gly	Ala	Val	
20		130				135					140						
	Thr	Val	Ala	Trp	Lys	Ala	Asp	Ser	Ser	Pro	Val	Lys	Ala	Gly	Val	Glu	
25	145			150						155					160		
	Thr	Thr	Thr	Pro	Ser	Lys	Gln	Ser	Asn	Asn	Lys	Tyr	Ala	Ala	Ser	Ser	
				165				170					175				
30	Tyr	Leu	Ser	Leu	Thr	Pro	Glu	Gln	Trp	Lys	Ser	His	Arg	Ser	Tyr	Ser	
				180				185					190				
	Cys	Gln	Val	Thr	His	Glu	Gly	Ser	Thr	Val	Glu	Lys	Thr	Val	Ala	Pro	
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	Thr	Glu	Cys	Ser													
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	<211>	348															
	<212>	DNA															
45	<213>	Artificial Sequence															
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	<223>	Description of Artificial Sequence: Synthetic															
		polynucleotide															
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55	gggaagggtc	tcgagtggat	gggcattatc	gatccggatg	atagctatac	ccgttattct										180	
	ccgagctttc	agggacaggt	gaccattagc	gcggataaaa	gcattagcac	cgcgtatctt										240	

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	caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat	300
	ggtgggttttg atatttgagg ccaaggcacc ctggtgacgg ttagctca	348
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10	<220> <223> Description of Artificial Sequence: Synthetic polynucleotide	
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	caggcgccag ttcttgtgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc	180
20	tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa	240
	gacgaagcgg attattattg cgctacttgg ggttctgagg atcaggtgtt tggcggcggc	300
25	acgaagttaa ccgtccta	318
30	<210> 466 <211> 1338 <212> DNA <213> Artificial Sequence	
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40	gggaagggtc tcgagtggat gggcattatc gatccggatg atagctatac ccgttattct	180
	ccgagctttc agggacaggt gaccattagc gcggataaaa gcattagcac cgcgtatctt	240
	caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat	300
45	ggtgggttttg atatttgagg ccaaggcacc ctggtgacgg ttagctcagc ctccaccaag	360
	ggtccatcgg tcttccccct ggcaccctcc tccaagagca cctctggggg cacagcggcc	420
	ctgggctgcc tgggtcaagga ctacttcccc gaaccgggtga cgggtgcgtg gaactcaggc	480
50	gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc	540
	ctcagcagcg tggtgaccgt gccctccagc agcttgggca ccagaccta catctgcaac	600
55	gtgaatcaca agcccagcaa caccaagggtg gacaagagag ttgagcccaa atcttgtgac	660
	aaaactcaca catgcccacc gtgcccagca cctgaagcag cgggggggacc gtcagtcttc	720

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ctcttccccc caaaacccaa ggacaccctc atgatctccc ggaccctga ggtcacatgc 780
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 15 ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1260
 gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1320
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 20

<210> 467

<211> 636

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 467

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 caggcgcagc ttcttctgat ttataaggat aatgatcgtc cctcaggcat cccggaacgc 180
 35 tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240
 gacgaagcgg attattattg cgctacttgg ggttctgagg atcaggtgtt tggcggcggc 300
 acgaagttaa ccgtcctagg tcagcccaag gctgccccct cggtcactct gttcccggcc 360
 40 tcctctgagg agcttcaagc caacaaggcc aactgggtgt gtctcataag tgacttctac 420
 ccgggagccg tgacagtggc ctggaaggca gatagcagcc ccgtcaaggc gggagtggag 480
 accaccacac cctccaaaca aagcaacaac aagtacgagg ccagcagcta tctgagcctg 540
 45 acgcctgagc agtggaagtc ccacagaagc tacagctgcc aggtcacgca tgaagggagc 600
 accgtggaga agacagtggc ccctacagaa tgttca 636
 50

<210> 468

<211> 1338

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic

polynucleotide

<400> 468

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 ggcaagggcc tggagtggat gggcatcatc gaccccgacg acagctacac caggtacagc 180
 10 cccagcttcc agggccaggt gaccatcagc gccgacaaga gcatcagcac cgcctacctg 240
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 15 ggccccagcg tgttccccct ggccccagc agcaagagca cctccggcgg cacagccgcc 420
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 gccctgacca gggcgctgca caccttcccc gccgtgctgc agagcagcgg cctgtacagc 540
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 gtgaaccaca agcccagcaa caccaaggtg gacaagagag tggagcccaa gagctgcgac 660
 aagaccaca cctgcccccc ctgcccagcc cccgaagctg caggcggccc ttccgtgttc 720
 25 ctgttcccc ccaagcccaa ggacaccctg atgatcagca ggacccccga ggtgacctgc 780
 gtggtggtgg acgtgagcca cgaggaccca gaggtgaagt tcaactggtc cgtggacggc 840
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 30 gtggtgtccg tgctgaccgt gctgcaccag gactggctga acggcaaaga atacaagtgc 960
 aaggtctcca acaaggccct gcctgcccc atcgaaaaga ccatcagcaa ggccaagggc 1020
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 gagagcaacg gccagcccga gaacaactac aagaccaccc cccagtgct ggacagcgac 1200
 40 ggcagcttct tcctgtacag caagctgacc gtggacaaga gcaggtggca gcagggaac 1260
 gtgttcagct gcagcgtgat gcacgaggcc ctgcacaacc actacacca gaagagcctg 1320
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<210> 469

<211> 636

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 469

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caggcccccg tgctggtgat ctacaaggac aacgacaggc ccagcggcat ccccgagagg 180
 ttcagcggca gcaactccg caacaccgcc accctgacaa tcagcggcac ccaggccgag 240
 5 gacgaggccg actactactg cgccacctgg ggctcagagg accaggtgtt cggcggaggg 300
 accaagctga ccgtgctggg ccagcctaag gctgccccca gcgtgaccct gttccccccc 360
 agcagcgagg agctgcaggc caacaaggcc accctggtgt gcctgatcag cgacttctac 420
 10 ccaggcggccg tgaccgtggc ctggaaggcc gacagcagcc ccgtgaaggc cggcgtggag 480
 accaccaccc ccagcaagca gagcaacaac aagtaacgcc ccagcagcta cctgagcctg 540
 acccccgagc agtgggaagag ccacaggtcc tacagctgcc aggtgaccca cgagggcagc 600
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<210> 470
 <211> 5
 20 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 25 peptide

<400> 470
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 1 5

30 <210> 471
 <211> 17
 <212> PRT
 <213> Artificial Sequence

35 <220>
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 peptide

40 <400> 471
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Gly

45 <210> 472
 <211> 8
 <212> PRT
 50 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

55 <400> 472
 Tyr Met Met Arg Gly Phe Asp His

1 5

<210> 473
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

<400> 473
 Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala Tyr
 1 5 10

<210> 474
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

<400> 474
 Lys Asp Asn Asn Arg Pro Ser
 1 5

<210> 475
 <211> 10
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 peptide

<400> 475
 Gln Thr Trp Asp Thr Gly Glu Ser Gly Val
 1 5 10

<210> 476
 <211> 117
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 polypeptide

<400> 476
 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
 20 25 30

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Tyr Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 5 Gly Ile Ile Asp Pro Thr Asp Ser Gln Thr Ala Tyr Ser Pro Ser Phe
 50 55 60
 10 Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 15 Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
 85 90 95
 20 Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu
 100 105 110
 Val Thr Val Ser Ser
 115
 <210> 477
 <211> 107
 <212> PRT
 25 <213> Artificial Sequence
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 polypeptide
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 1 5 10 15
 35 Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala
 20 25 30
 40 Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
 35 40 45
 Lys Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
 50 55 60
 45 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
 65 70 75 80
 50 Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Trp Asp Thr Gly Glu Ser Gly
 85 90 95
 Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
 100 105
 55 <210> 478

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<211> 447
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 478

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15			20					25						30		
	Tyr	Ile	Gly	Trp	Val	Arg	Gln	Met	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Met
		35					40						45			
20	Gly	Ile	Ile	Asp	Pro	Thr	Asp	Ser	Gln	Thr	Ala	Tyr	Ser	Pro	Ser	Phe
	50						55					60				
	Gln	Gly	Gln	Val	Thr	Ile	Ser	Ala	Asp	Lys	Ser	Ile	Ser	Thr	Ala	Tyr
25	65				70					75						80
	Leu	Gln	Trp	Ser	Ser	Leu	Lys	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
				85						90					95	
30	Ala	Arg	Tyr	Met	Met	Arg	Gly	Phe	Asp	His	Trp	Gly	Gln	Gly	Thr	Leu
				100					105					110		
	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu
35			115					120						125		
	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys
40		130					135					140				
	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser
	145					150					155					160
45	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser
					165					170					175	
	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser
50				180					185					190		
	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn
			195					200					205			
55	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His
		210					215						220			

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	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser	Val	
	225						230				235					240	
5	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	
					245					250					255		
	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	
10				260					265					270			
	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	
			275					280					285				
15	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	
	290						295					300					
	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	
20	305					310					315					320	
	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	
25					325					330					335		
	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	
				340					345					350			
30	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	
			355					360					365				
	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	
35		370					375					380					
	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	
40	385					390					395				400		
	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	
				405						410					415		
45	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	
				420					425					430			
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	<211>	213															
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<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 479

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

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

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

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

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

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro Lys Ala
100 105 110

Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu Gln Ala
115 120 125

Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro Gly Ala
130 135 140

Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val
145 150 155 160

Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser
165 170 175

Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr
180 185 190

Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala
195 200 205

Pro Thr Glu Cys Ser
210

<210> 480

<211> 351

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 480

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cctgggaagg gtctcgagt gatgggcatt attgatccta ctgattctca gactgcttat 180

tctccttctt ttcaggggtca ggtgaccatt agcgcggaata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300

atgcgtgggt ttgatcattg gggccaaggc accctggtga cggttagctc a 351

<210> 481

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 481

agttacgaac tgaccagacc gccttcagt agcgttgac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctct tggtgattat tatgcttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgag accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagacttgg gatactggtg agtctggtgt gtttggcggc 300

ggcacgaagt taaccgtcct a 321

<210> 482

<211> 1341

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polynucleotide

<400> 482

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cctgggaagg gtctcgagt gatgggcatt attgatccta ctgattctca gactgcttat 180

tctccttctt ttcaggggtca ggtgaccatt agcgcggaata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatatg 300

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	atgcgtgggtt ttgatcattg gggccaaggc accctgggtga cggttagctc agcctccacc	360
	aagggtccat cggctcttccc cctggcacccc tccccaaga gcacctctgg gggcacagcg	420
5	gccctgggct gcctgggtcaa ggactacttc cccgaaccgg tgacgggtgtc gtggaactca	480
	ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac	540
	tccctcagca gcgtgggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc	600
10	aacgtgaatc acaagcccag caacaccaag gtggacaaga gagttgagcc caaatcttgt	660
	gacaaaactc acacatgccc accgtgcccga gcacctgaag cagcgggggg accgtcagtc	720
	ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca	780
15	tgcgtgggtg tggacgtgag ccacgaagac cctgagggtca agttcaactg gtacgtggac	840
	ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac	900
20	cgggtgggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag	960
	tgcaaggctc ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa	1020
	gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag	1080
25	aaccagggtca gcctgacctg cctgggtcaaa ggcttctatc ccagcgacat cgccgtggag	1140
	tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccggt gctggactcc	1200
	gacggctcct tcttctctta cagcaagctc accgtggaca agagcagggtg gcagcagggg	1260
30	aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc	1320
	ctctccctgt ctccgggtaa a	1341
35	<210> 483 <211> 639 <212> DNA <213> Artificial Sequence	
40	<220> <223> Description of Artificial Sequence: Synthetic polynucleotide	
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45	tcgtgtagcg gcgattctct tgggtgattat tatgcttatt ggtaccagca gaaacccggg	120
	caggcgccag ttcttgtgat ttataaggat aataatcgtc cctcaggcat cccggaacgc	180
50	tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa	240
	gacgaagcgg attattattg ccagacttgg gatactgggtg agtctgggtgt gtttggcggc	300
	ggcacgaagt taaccgtcct aggtcagccc aaggctgccc cctcggtcac tctgttcccg	360
55	ccctcctctg aggagcttca agccaacaag gccacactgg tgtgtctcat aagtgacttc	420
	tacccgggag ccgtgacagt ggcttgggaag gcagatagca gcccgtcaa ggcgggagtg	480

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	gagaccacca caccctccaa acaaagcaac aacaagtacg cggccagcag ctatctgagc	540
	ctgacgcctg agcagtggaa gtcccacaga agctacagct gccaggtcac gcatgaaggg	600
5	agcaccgtgg agaagacagt ggcccctaca gaatgttca	639
	<210> 484	
	<211> 1341	
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	<213> Artificial Sequence	
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	<223> Description of Artificial Sequence: Synthetic polynucleotide	
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	agctgcaagg gcagcggcta cagcttcacc agctactaca tcggctgggt gcggcagatg	120
20	cccggcaagg gcctggagtg gatgggcatc atcgacccca ccgacagcca gaccgcctac	180
	agccccagct tccagggcca ggtgaccatc agcgccgaca agagcatcag caccgcctac	240
	ctgcagtgga gcagcctgaa ggccagcgac accgccatgt actactgcgc ccggtacatg	300
25	atgaggggct tcgaccactg gggtcagggc accctgggtga ccgtcagctc agctagcacc	360
	aagggcccca gcgtgttccc cctggccccc agcagcaaga gcacctccgg cggcacagcc	420
30	gccctgggct gcctggtgaa ggactacttc cccgagcccg tgaccgtgtc ctggaacagc	480
	ggagccctga ccagcggcgt gcacaccttc cccgccgtgc tgcagagcag cggcctgtac	540
	agcctgtcca gcgtggtgac agtgcccagc agcagcctgg gcacccagac ctacatctgc	600
35	aacgtgaacc acaagcccag caacaccaag gtggacaaga gagtggagcc caagagctgc	660
	gacaagaccc acacctgccc cccctgcccga gccccogaag ctgcaggcgg cccttccgtg	720
	ttcctgttcc cccccaagcc caaggacacc ctgatgatca gcaggacccc cgaggtgacc	780
40	tgctgtgtgg tggacgtgag ccacgaggac ccagaggtga agttcaactg gtacgtggac	840
	ggcgtggagg tgcacaacgc caagaccaag cccagagagg agcagtacaa cagcacctac	900
	aggggtggtg ccgtgctgac cgtgctgcac caggactggc tgaacggcaa agaatacaag	960
45	tgcaaggtct ccaacaaggc cctgcctgcc cccatcgaaa agaccatcag caaggccaag	1020
	ggccagccac gggagcccca ggtgtacacc ctgccccctt ctggggagga gatgaccaag	1080
50	aaccaggtgt ccctgacctg tctggtgaag ggcttctacc ccagcgacat cgccgtggag	1140
	tgggagagca acggccagcc cgagaacaac tacaagacca cccccccagt gctggacagc	1200
	gacggcagct tcttctgtga cagcaagctg accgtggaca agagcaggtg gcagcagggc	1260
55	aacgtgttca gctgcagcgt gatgcacgag gccctgcaca accactacac ccagaagagc	1320
	ctgagcctgt caccggcaa g	1341

<210> 485
 <211> 639
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: Synthetic
 polynucleotide

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 agctgcagcg ggcacagcct gggcgactac tacgcctact ggtatcagca gaagcccggc 120
 caggcccccg tgctggtgat ctacaaggac aacaacaggc ccagcggcat ccccgagagg 180
 ttcagcggca gcaacagcgg caacaccgcc accctgacaa tcagcggcac ccaggccgag 240
 gacgaggccg actactactg ccagacctgg gacaccggcg agtcaggcgt gttcggcgga 300
 gggaccaagc tgaccgtgct gggtcagcct aaggctgccc ccagcgtgac cctgttcccc 360
 cccagcagcg aggagctgca ggccaacaag gccaccctgg tgtgcctgat cagcgacttc 420
 taccagggcg ccgtgaccgt ggctggaag gccgacagca gccccgtgaa ggccggcggtg 480
 gagaccacca cccccagcaa gcagagcaac aacaagtacg ccgccagcag ctacctgagc 540
 ctgacccccg agcagtggaa gagccacagg tcctacagct gccaggtgac ccacgagggc 600
 agcaccgtgg aaaagaccgt ggccccaacc gagtgcagc 639

<210> 486
 <211> 68
 <212> PRT
 <213> Homo sapiens

<400> 486
 Pro Val Asp Gly Glu Trp Asp Ser Trp Gly Glu Trp Ser Pro Cys Ile
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Arg Arg Asn Met Lys Ser Ile Ser Cys Gln Glu Ile Pro Gly Gln Gln
 20 25 30

Ser Arg Gly Arg Thr Cys Arg Gly Arg Lys Phe Asp Gly His Arg Cys
 35 40 45

Ala Gly Gln Gln Gln Asp Ile Arg His Cys Tyr Ser Ile Gln His Cys
 50 55 60

Pro Leu Lys Gly
 65

<210> 487
 <211> 67

<212> PRT

<213> Mus musculus

<400> 487

Pro Val Asn Gly Glu Trp Glu Ala Trp Gly Lys Trp Ser Asp Cys Ser
 1 5 10 15

Arg Leu Arg Met Ser Ile Asn Cys Glu Gly Thr Pro Gly Gln Gln Ser
 20 25 30

Arg Ser Arg Ser Cys Gly Gly Arg Lys Phe Asn Gly Lys Pro Cys Ala
 35 40 45

Gly Lys Leu Gln Asp Ile Arg His Cys Tyr Asn Ile His Asn Cys Ile
 50 55 60

Met Lys Gly
 65

Claims

1. An antibody, or antigen binding fragment thereof, that binds a region of Factor P comprising SEQ ID NO: 408.
2. An antibody, or antigen binding fragment thereof, that binds a region of Factor P comprising SEQ ID NO: 407.
3. The antibody, or antigen binding fragment of any preceding claim that binds Factor P with a KD of less than or equal to 1.2 nM as measured by solution equilibrium titration.
4. The antibody, or antigen binding fragment of any preceding claim that binds Factor P with a KD of less than or equal to 500 pM.
5. The antibody, or antigen binding fragment of any preceding claim that binds Factor P with a KD of less than or equal to 200 pM.
6. The antibody, or antigen binding fragment, of any preceding claim, wherein said antibody binds human Factor P.
7. The antibody, or antigen binding fragment, any preceding claim that also binds cynomologous monkey, rabbit or rat Factor P.
8. The isolated antibody, or antigen binding fragment, of any preceding claim that further inhibits the alternative complement pathway as measured by an *in vitro* hemolytic assay with an IC50 of less than or equal to 25 nM.
9. The isolated antibody, or antigen binding fragment, of any preceding claim, wherein said antibody binds Human Factor P and inhibits the alternative complement pathway as measured by an *in vitro* hemolytic assay with an IC50 of less than or equal to 16 nM.
10. The isolated antibody, or antigen binding fragment thereof, of any preceding claim that further inhibits the alternative complement pathway as measure by an *in vitro* C3b deposition assay with an IC50 of less than or equal to 10 nM.
11. The antibody, or antigen binding fragment of claim 10, wherein said antibody binds Human Factor P and inhibits the alternative complement pathway as measured by an *in vitro* C3b deposition assay with an IC50 of less than or equal to 3 nM.
12. The isolated antibody, or antigen binding fragment of any preceding claim, that further inhibits the alternative com-

plement pathway as measure by an *in vitro* MAC deposition assay with an IC50 of less than or equal to 25 nM.

13. The antibody, or antigen binding fragment of any preceding claim, wherein said antibody binds Human Factor P and inhibits the alternative complement pathway as measure by an *in vitro* MAC deposition assay with an IC50 of less than or equal to 25 nM.

14. The isolated antibody, or antigen binding fragment, of any preceding claim that further inhibits the alternative complement pathway as measured by an *in vitro* hemolytic assay with an IC50 of less than or equal to 25 nM, an *in vitro* C3b deposition assay with an IC50 of less than or equal to 10 nM and an *in vitro* MAC deposition assay with an IC50 of less than or equal to 25 nM.

15. An isolated antibody, or antigen binding fragment thereof, that binds Factor P and competes with an antibody described in Table 1.

16. An isolated antibody, or antigen binding fragment, that binds Factor P, said antibody or antigen binding fragment comprising:

a) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 1, 2, and 3, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 4, 5, and 6, respectively;

b) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 15, 16, and 17, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 18, 19, and 20, respectively;

c) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 29, 30, and 31, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 32, 33, and 34, respectively;

d) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 43, 44, and 45, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 46, 47, and 48, respectively;

e) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 57, 58, and 59, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 60, 61, and 62, respectively;

f) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 71, 72, and 73, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 74, 75, and 76, respectively;

g) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 85, 86, and 87, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 88, 89, and 90, respectively;

h) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 99, 100, and 101, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 102, 103, and 104, respectively;

i) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 113, 114, and 115, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 116, 117, and 118, respectively;

j) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 127, 128, and 129, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 130, 131, and 132, respectively;

k) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 141, 142, and 143, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 144, 145, and 146, respectively;

l) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 155, 156, and 157, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 158, 159, and 160, respectively;

m) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 169, 170, and 171, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 172, 173, and 174, respectively;

n) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 183, 184, and 185, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 186, 187, and 188, respectively;

o) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 197, 198, and 199, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 200, 201, and 202, respectively;

p) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 211, 212, and 213, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 214, 215, and 216, respectively;

q) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 225, 226, and 227, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 228, 229, and 230, respectively;

r) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 239, 240, and 241, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 242, 243, and 244, respectively;

s) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 253, 254, and 255, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 256, 257, and 258, respectively; or

t) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 267, 268, and 269, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 270, 271, and 272, respectively.

17. The antibody, or antigen binding fragment, of any preceding claim comprising heavy and light chain variable regions having amino acid sequences at least 90% identical to SEQ ID NOs: 7 and 8; SEQ ID NOs: 21 and 22; SEQ ID NOs: 35 and 36; SEQ ID NOs: 49 and 50; SEQ ID NOs: 63 and 64; SEQ ID NOs: 77 and 78; SEQ ID NOs: 91 and 92; SEQ ID NOs: 105 and 106; SEQ ID NOs: 119 and 120; SEQ ID NOs: 133 and 134; SEQ ID NOs: 147 and 148; SEQ ID NOs: 161 and 162; SEQ ID NOs: 175 and 176; SEQ ID NOs: 189 and 190; SEQ ID NOs: 203 and 204; SEQ ID NOs: 217 and 218; SEQ ID NOs: 231 and 232; SEQ ID NOs: 245 and 246; SEQ ID NOs: 259 and 260; or SEQ ID NOs: 273 and 274, respectively.

18. An isolated antibody, or antigen binding fragment, which comprises a heavy chain variable region comprising SEQ ID NO: 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175, 189, 203, 217, 231, 245, 259, or 273 and further comprising a light chain variable region, wherein said heavy chain variable region and said light chain variable region combine to form an antigen binding site to Factor P.

19. An isolated antibody, or antigen binding fragment, which comprises a light chain variable domain comprising SEQ ID NO: 8, 22, 36, 50, 64, 78, 92, 106, 120, 134, 148, 162, 176, 190, 204, 218, 232, 246, 260, or 274 and further comprising a heavy chain variable domain, wherein the light chain variable domain and the heavy chain variable domain combine to form an antigen binding site to Factor P.

20. The isolated antibody, or antigen binding fragment, of any preceding claim wherein said light chain variable domain region comprises SEQ ID NO: 8, 22, 36, 50, 64, 78, 92, 106, 120, 134, 148, 162, 176, 190, 204, 218, 232, 246, 260, or 274.

21. An isolated antibody, or antigen binding fragment, which comprises a heavy chain of SEQ ID NO: 9, 23, 37, 51, 65, 79, 93, 107, 121, 135, 149, 163, 177, 191, 205, 219, 233, 247, 261 or 275 and further comprising a light chain, wherein the heavy chain and the light chain combine to form an antigen binding site to Factor P.

22. An isolated antibody, or antigen binding fragment, which comprises a light chain of SEQ ID NO: 10, 24, 38, 52, 66, 80, 94, 108, 122, 136, 150, 164, 178, 192, 206, 220, 234, 248, 262 or 276 and further comprising a heavy chain, wherein the light chain and the heavy chain combine to form an antigen binding site to Factor P.

23. The isolated antibody, or antigen binding fragment, of any preceding claim wherein said light chain comprises SEQ ID NO: 10, 24, 38, 52, 66, 80, 94, 108, 122, 136, 150, 164, 178, 192, 206, 220, 234, 248, 262 or 276.

24. An isolated antibody, or antigen binding fragment, that binds Factor P comprising a heavy chain with an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 9, 23, 37, 51, 65, 79, 93, 107, 121, 135, 149, 163, 177, 191, 205, 219, 233, 247, 261 or 275 and further comprising a light chain with an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 10, 24, 38, 52, 66, 80, 94, 108, 122, 136, 150, 164, 178, 192, 206, 220, 234, 248, 262 or 276.

25. An isolated antibody, or antigen binding fragment, that binds Factor P comprising a heavy chain and a light chain with an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 9 and 10, 23 and 24, 37 and 38, 51 and 52, 65 and 66, 79 and 80, 93 and 94, 107 and 108, 121 and 122, 135 and 136, 149 and 150, 163 and 164, 177 and 178, 191 and 192, 205 and 206, 219 and 220, 233 and 234, 247 and 248, 261 and 262, or 275 and 276.
26. The antibody or antigen binding fragment of any preceding claim, wherein said antibody is a human antibody, a chimeric antibody, a monoclonal antibody, a single chain antibody, Fab, Fab', F(ab')₂, Fv or scFv.
27. The antibody or antigen binding fragment of any preceding claim, wherein said antibody is an IgG isotype.
28. An isolated nucleic acid molecule comprising a nucleotide encoding the antibody or fragment of any preceding claim.
29. An isolated nucleic acid molecule encoding a polypeptide comprising the heavy chain variable region of any preceding claim.
30. The nucleic acid molecule of any preceding claim, wherein said nucleic acid has at least 95% sequence identity to a sequence selected from SEQ ID NOs: 11, 25, 39, 53, 67, 81, 95, 109, 123, 137, 151, 165, 179, 193, 207, 221, 235, 249, 263, and 277.
31. An isolated nucleic acid molecule encoding a polypeptide comprising the light chain variable region of any preceding claim.
32. The nucleic acid molecule of any preceding claim wherein said nucleic acid sequence has 95% sequence identity to SEQ ID NO: 12, 26, 40, 54, 68, 82, 96, 110, 124, 138, 152, 166, 180, 194, 208, 222, 236, 250, 264, and 278.
33. An isolated nucleic acid molecule encoding a polypeptide comprising the heavy chain of any preceding claim.
34. The nucleic acid molecule of any preceding claim wherein said nucleic acid sequence has 95% sequence identity to SEQ ID NO: 13, 27, 41, 55, 69, 83, 97, 111, 125, 139, 153, 167, 181, 195, 209, 223, 237, 251, 265 and 279.
35. An isolated nucleic acid molecule encoding a polypeptide comprising the light chain of any preceding claim.
36. The nucleic acid molecule of any preceding claim wherein said nucleic acid sequence has 95% sequence identity to SEQ ID NO: 14, 28, 42, 56, 70, 84, 98, 112, 126, 140, 154, 168, 182, 196, 210, 224, 238, 252, 266 and 280.
37. A vector comprising the nucleic acid molecule of any one of claims 28-36.
38. An isolated host cell comprising the vector of claim 37.
39. A composition comprising the antibody or antigen binding fragment of any preceding claim and a pharmaceutically acceptable diluent or carrier.
40. A method of treating age related macular degeneration in a subject comprising administering to said subject, an effective amount of a composition comprising the antibody or antigen binding fragment of any preceding claim.
41. The method of claim 40 wherein the subject is human.
42. A method of inhibiting the alternative complement pathway in a subject comprising administering to said subject an effective amount of a composition comprising the antibody or antigen binding fragment of any preceding claim.
43. The method of claim 42 wherein the subject is human.
44. A method of inhibiting complement mediated cell death, comprising contacting a cell with a composition comprising the antibody or antigen binding fragment of any preceding claim.
45. A method of inhibiting the formation of C3b in a cell, comprising contacting a cell with a composition comprising the antibody or antigen binding fragment of any preceding claim.

46. A method of inhibiting the formation of the Membrane Attack Complex in a cell, comprising contacting a cell with a composition comprising the antibody or antigen binding fragment of any preceding claim.

47. A method of inhibiting the alternative complement pathway in a cell, comprising contacting a cell with a composition comprising the antibody or antigen binding fragment of any preceding claim and measuring said pathway activity by an *in vitro* hemolytic assay, an *in vitro* C3b deposition assay, or an *in vitro* MAC deposition assay, wherein a decrease in pathway activity is measured by a 10% decrease in hemolysis, C3b deposition and/or MAC deposition.

48. A composition comprising a first antibody, or antigen binding fragment thereof, that binds Factor P, and a second antibody, or antigen binding fragment thereof, that binds C5, wherein said combination inhibits the alternative complement pathway.

49. The composition of claim 48, wherein said combination inhibits ocular inflammation.

50. The composition of any of claims 48-49, wherein said ocular inflammation is determined by measuring neutrophil accumulation and/or macrophage recruitment in the retina.

51. The combination of any of claims 48-50, wherein said combination inhibits neutrophil accumulation in the retina.

52. The combination of any of claims 48-51, wherein said combination inhibits macrophage recruitment in the retina.

53. The composition of any of claims 48-52, wherein said antibody that binds Factor P, binds a region of Factor P comprising SEQ ID NO: 408.

54. The composition of any of claims 48-52, wherein said antibody that binds Factor P, binds a region of Factor P comprising SEQ ID NO: 407.

55. The composition of any of claims 48-54, wherein said first antibody, or antigen binding fragment thereof, is an antibody selected from Table 1 and said second antibody or antigen-binding fragment thereof is an antibody or antigen binding fragment selected from Table 2.

56. The composition of any of claims 48-55, wherein the first antibody, or antigen binding fragment thereof binds the same epitope as is an antibody described in Table 1 and the second antibody, or antigen binding fragment thereof, binds the same epitope as is an antibody described in Table 2.

57. The composition of any of claims 48-56 wherein the first antibody, or antigen binding fragment thereof comprises a heavy chain CDR1, 2, 3, and a light chain CDR1, 2, 3, selected from the group consisting of:

a) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 1, 2, and 3, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 4, 5, and 6, respectively;

b) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 15, 16, and 17, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 18, 19, and 20, respectively;

c) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 29, 30, and 31, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 32, 33, and 34, respectively;

d) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 43, 44, and 45, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 46, 47, and 48, respectively;

e) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 57, 58, and 59, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 60, 61, and 62, respectively;

f) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 71, 72, and 73, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 74, 75, and 76, respectively;

g) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 85, 86, and 87, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 88, 89, and 90, respectively;

- h) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 99, 100, and 101, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 102, 103, and 104, respectively;
- 5 i) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 113, 114, and 115, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 116, 117, and 118, respectively;
- j) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 127, 128, and 129, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 130, 131, and 132, respectively;
- 10 k) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 141, 142, and 143, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 144, 145, and 146, respectively;
- l) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 155, 156, and 157, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 158, 159, and 160, respectively;
- 15 m) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 169, 170, and 171, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 172, 173, and 174, respectively;
- n) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 183, 184, and 185, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 186, 187, and 188, respectively;
- 20 o) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 197, 198, and 199, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 200, 201, and 202, respectively;
- 25 p) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 211, 212, and 213, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 214, 215, and 216, respectively;
- q) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 225, 226, and 227, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 228, 229, and 230, respectively;
- 30 r) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 239, 240, and 241, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 242, 243, and 244, respectively;
- s) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 253, 254, and 255, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 256, 257, and 258, respectively; and
- 35 t) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 267, 268, and 269, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 270, 271, and 272, respectively;
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and wherein the second antibody or antigen binding fragment thereof comprises a heavy chain CDR1, 2, 3 and light chain CDR1, 2, 3 selected from the group consisting of:

- 45 a) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 410, 411, and 412, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 413, 414, and 415, respectively;
- b) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 426, 427, and 428, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 429, 430, and 431, respectively;
- 50 c) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 442, 443, and 444, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 445, 446, and 447, respectively;
- d) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 426, 458, and 428, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 429, 430, and 459, respectively; and
- 55 e) heavy chain variable region HCDR1, HCDR2 and HCDR3 as set forth in SEQ ID NOs: 470, 471, and 472, respectively, and light chain variable region LCDR1, LCDR2, and LCDR3 as set forth in SEQ ID NOs: 473, 474 and 475, respectively.

58. The composition of any of claims 48-57, wherein the first antibody or antigen binding fragment thereof comprises heavy and light chain variable regions having amino acid sequences at least 90% identical to SEQ ID NOs: 7 and 8; SEQ ID NOs: 21 and 22; SEQ ID NOs: 35 and 36; SEQ ID NOs: 49 and 50; SEQ ID NOs: 63 and 64; SEQ ID NOs: 77 and 78; SEQ ID NOs: 91 and 92; SEQ ID NOs: 105 and 106; SEQ ID NOs: 119 and 120; SEQ ID NOs: 133 and 134; SEQ ID NOs: 147 and 148; SEQ ID NOs: 161 and 162; SEQ ID NOs: 175 and 176; SEQ ID NOs: 189 and 190; SEQ ID NOs: 203 and 204; SEQ ID NOs: 217 and 218; SEQ ID NOs: 231 and 232; SEQ ID NOs: 245 and 246; SEQ ID NOs: 259 and 260; or SEQ ID NOs: 273 and 274, respectively, and wherein the second antibody or antigen binding fragment thereof comprises heavy and light chain variable regions having amino acid sequences at least 90% identical to SEQ ID NOs: 416 and 417; SEQ ID NOs: 432 and 433; SEQ ID NOs: 448 and 449; SEQ ID NOs: 460 and 461; or SEQ ID NOs: 476 and 477, respectively.
59. The composition of any of claims 48-58 wherein (a) the first antibody, or antigen binding fragment thereof comprises a heavy chain variable region comprising SEQ ID NO: 7, 21, 35, 49, 63, 77, 91, 105, 119, 133, 147, 161, 175, 189, 203, 217, 231, 245, 259, or 273 and further comprises a light chain variable region, wherein said heavy chain variable region and said light chain variable region combine to form an antigen binding site to Factor P and (b) wherein the second antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising SEQ ID NO: 416, 432, 448, 460 or 476 and further comprises a light chain variable region, wherein said heavy chain variable region and said light chain variable region combine to form an antigen binding site to C5.
60. The composition of any of claims 48-59, wherein the first antibody, or antigen binding fragment thereof (a) comprises a light chain variable domain comprising SEQ ID NO: 8, 22, 36, 50, 64, 78, 92, 106, 120, 134, 148, 162, 176, 190, 204, 218, 232, 246, 260, or 274 and further comprises a heavy chain variable domain, wherein the light chain variable domain and the heavy chain variable domain combine to form an antigen binding site to Factor P and (b) wherein the second antibody or antigen binding fragment thereof comprises a light chain variable region comprising a light chain variable domain comprising SEQ ID NO: 417, 433, 449, 461 or 477 and further comprises a heavy chain variable domain, wherein the light chain variable domain and the heavy chain variable domain combine to form an antigen binding site to C5.
61. The composition of claim 59, wherein the first antibody or antigen binding fragment thereof comprises the light chain variable region sequence of SEQ ID NO: 8, 22, 36, 50, 64, 78, 92, 106, 120, 134, 148, 162, 176, 190, 204, 218, 232, 246, 260, or 274, and wherein the second antibody or antigen binding fragment thereof comprises the light chain variable region sequence of SEQ ID NO: 417, 433, 449, 461 or 477.
62. The composition of any of claims 48-61 wherein (a) the first antibody, or antigen binding fragment thereof comprises a heavy chain of SEQ ID NO: 9, 23, 37, 51, 65, 79, 93, 107, 121, 135, 149, 163, 177, 191, 205, 219, 233, 247, 261 or 275 and further comprises a light chain, wherein the heavy chain and the light chain combine to form an antigen binding site to Factor P and (b) wherein the second antibody or antigen binding fragment thereof comprises a heavy chain of SEQ ID NO: 418, 434, 450, 462, or 478 and further comprises a light chain, wherein the heavy chain and the light chain combine to form an antigen binding site to C5.
63. The composition of any of claims 48-62, wherein (a) the first antibody, or antigen binding fragment thereof comprises a light chain of SEQ ID NO: 10, 24, 38, 52, 66, 80, 94, 108, 122, 136, 150, 164, 178, 192, 206, 220, 234, 248, 262 or 276 and further comprises a heavy chain, wherein the light chain and the heavy chain combine to form an antigen binding site to Factor P and (b) wherein the second antibody or antigen binding fragment thereof comprises a light chain of SEQ ID NO: 419, 435, 451, 463, or 479 and further comprises a heavy chain, wherein the light chain and the heavy chain combine to form an antigen binding site to C5.
64. The composition of claim 62, wherein the first antibody or antigen binding fragment thereof comprises a light chain of SEQ ID NO: 10, 24, 38, 52, 66, 80, 94, 108, 122, 136, 150, 164, 178, 192, 206, 220, 234, 248, 262 or 276, and wherein the second antibody or antigen binding fragment thereof comprises a light chain of SEQ ID NO: 419, 435, 451, 463, or 479.
65. The composition of claim 48-64, wherein the first antibody, or antigen binding fragment thereof comprises a heavy chain with an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 9, 23, 37, 51, 65, 79, 93, 107, 121, 135, 149, 163, 177, 191, 205, 219, 233, 247, 261 or 275 and further comprises a light chain with an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 10, 24, 38, 52, 66, 80, 94, 108, 122, 136, 150, 164, 178, 192, 206, 220, 234, 248, 262 or 276 and wherein the second antibody or antigen binding fragment thereof comprises a heavy chain with an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 418,

434, 450, 462, or 478 and further comprises a light chain with an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 419, 435, 451, 463, or 479.

- 5 66. The composition of any of claims 48-65, wherein the first antibody, or antigen binding fragment thereof comprises a heavy chain and a light chain with an amino acid sequence having at least 90% sequence identity, respectively, to SEQ ID NO: 9 and 10, 23 and 24, 37 and 38, 51 and 52, 65 and 66, 79 and 80, 93 and 94, 107 and 108, 121 and 122, 135 and 136, 149 and 150, 163 and 164, 177 and 178, 191 and 192, 205 and 206, 219 and 220, 233 and 234, 247 and 248, 261 and 262, or 275 and 276; and wherein the second antibody or antigen binding fragment thereof comprises a heavy chain and a light chain with an amino acid sequence having at least 90% sequence identity, respectively, to SEQ ID NOs: 418 and 419, 434 and 435; 450 and 451; 462 and 463; or 478 and 479.
- 10 67. An isolated nucleic acid molecule comprising a nucleotide sequence encoding the first antibody or fragment of any of claims 48-66.
- 15 68. An isolated nucleic acid molecule comprising nucleotide sequence encoding the second antibody or antigen binding fragment thereof of any of claims 48-66.
69. A vector comprising the nucleic acid molecule of claim 67 or 68
- 20 70. An isolated host cell comprising the vector of claim 69.
71. A method of treating age related macular degeneration in a subject comprising administering to said subject, an effective amount of the composition of any of claims 48-66.
- 25 72. The method of claim 71 wherein the subject is human.
73. A method of inhibiting the alternative complement pathway in a subject comprising administering to said subject an effective amount of the composition of any of claims 48-66.
- 30 74. The method of claim 73, wherein said subject is human.
75. The antibody or antigen binding fragment thereof of claim 1 for use as a medicament.
76. The composition of claim 48 for use as a medicament.
- 35 77. The antibody or antigen binding fragment thereof of any of claims 1-27 for use in the treatment of age related macular degeneration.
78. The antibody or antigen binding fragment thereof of any of claims 1-27 for use in the inhibition of the alternative complement pathway.
- 40 79. The antibody or antigen binding fragment thereof of any of claims 1-27 for use in the inhibition of complement mediated cell death.
- 45 80. The antibody or antigen binding fragment thereof of any of claims 1-27 for use in the inhibition of the formation of C3b in a cell.
81. The antibody or antigen binding fragment thereof of any of claims 1-27 for use in the inhibition of the formation of the Membrane Attack Complex in a cell.
- 50 82. The composition of any of claims 48-66 for use in the treatment of age related macular degeneration.
83. The composition of any of claims 48-66 for use in the inhibition of the alternative complement pathway in a subject.
- 55 84. A method of treating age related macular degeneration in a subject comprising administering to said subject, an effective amount of the composition of claim 48.
85. The method of claim 84 wherein the subject is human.

86. A method of inhibiting the alternative complement pathway in a subject comprising administering to said subject an effective amount of the composition of claim 48.

87. The method of claim 86, wherein said subject is human.

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FIG 1A



FIG 1B



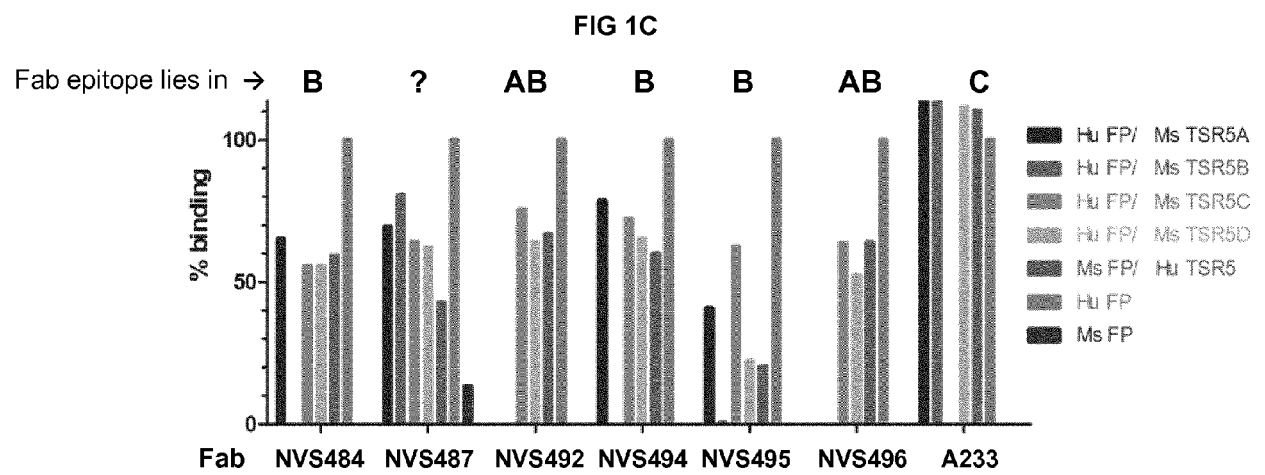


Figure 2

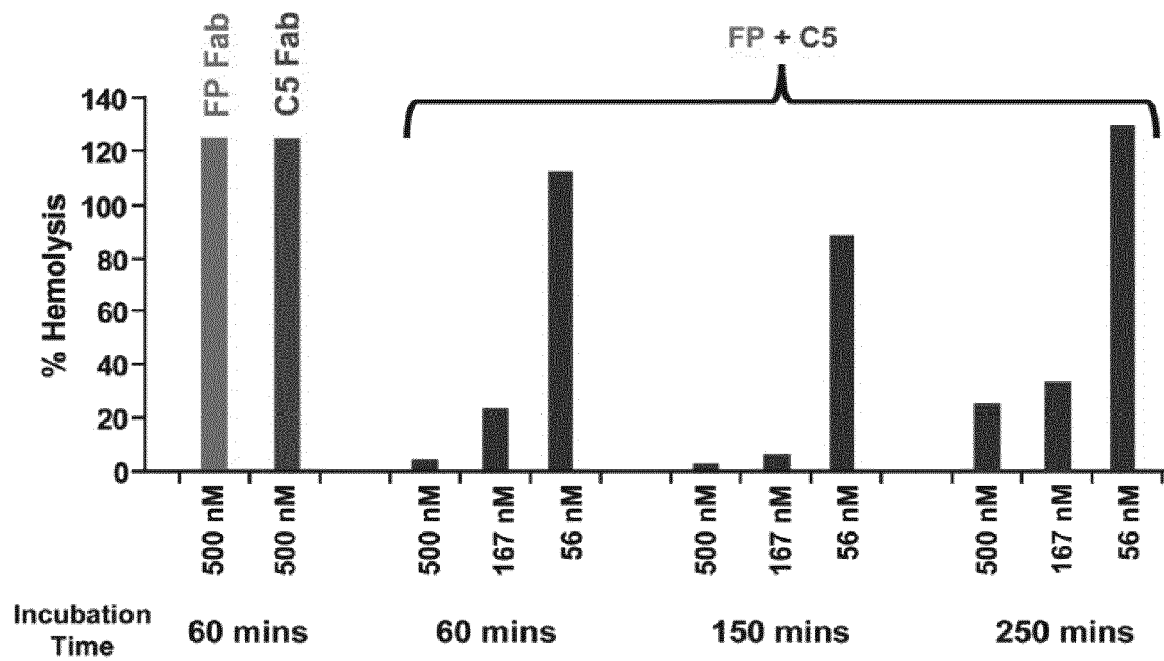


Figure 3

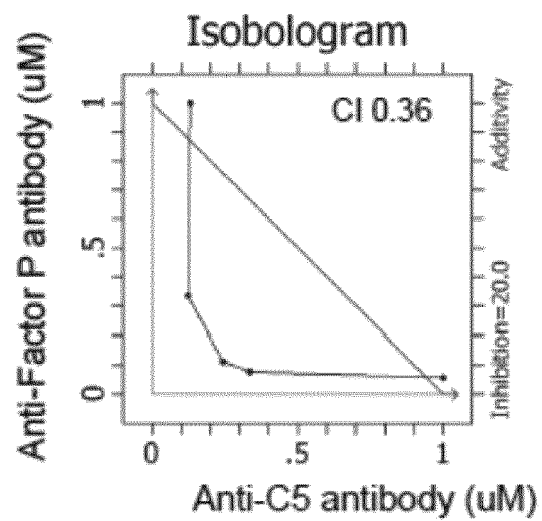


Figure 4

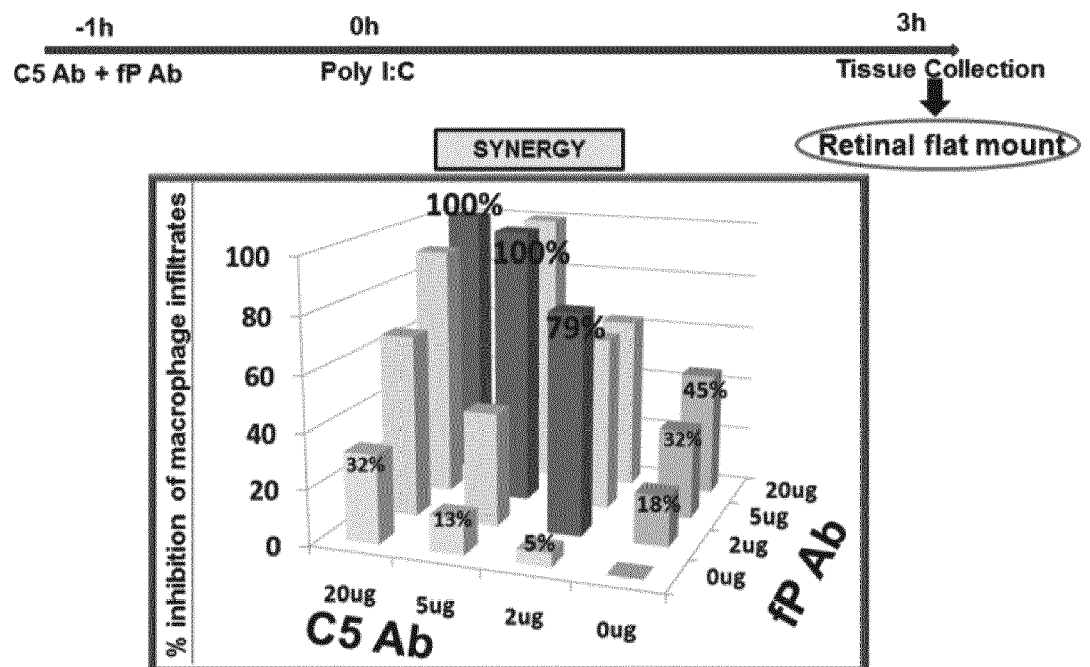
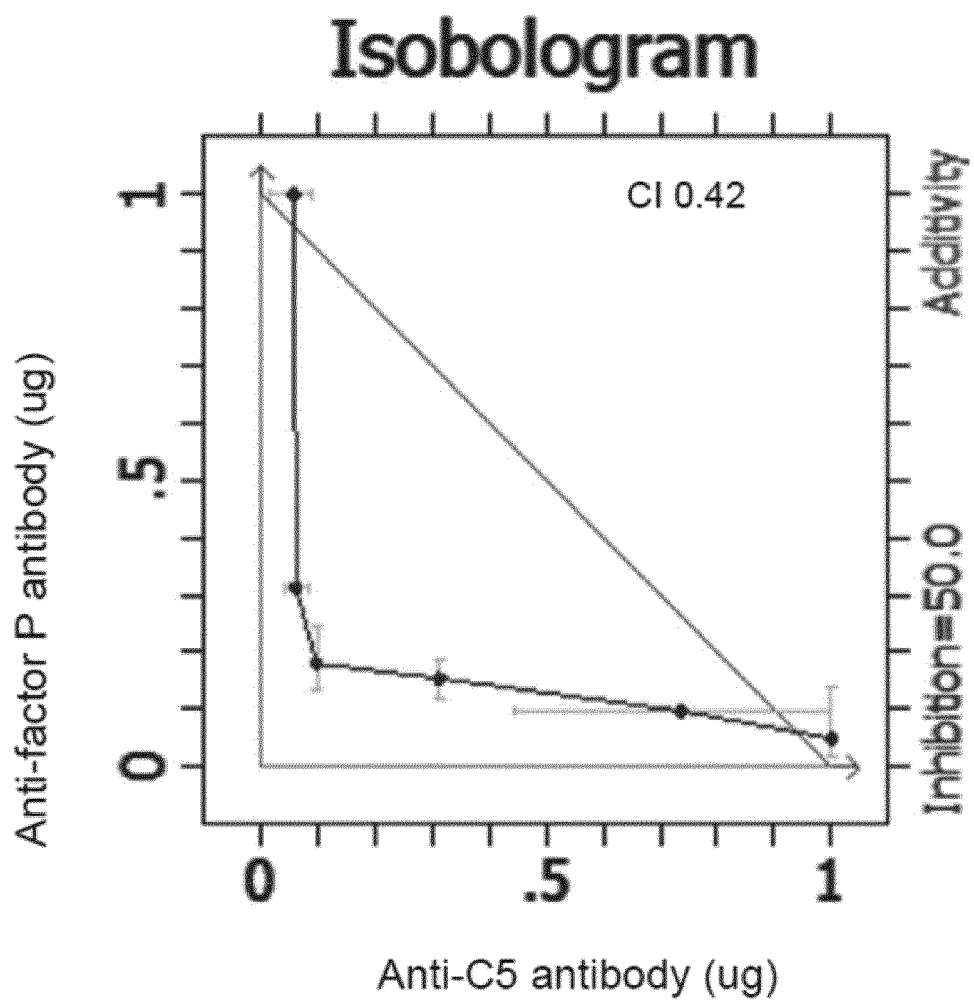


Figure 5





EUROPEAN SEARCH REPORT

Application Number
EP 17 20 8690

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
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摘要

本发明涉及结合补体P因子的抗体或其抗原结合片段及其用途，以及抗P因子抗体与结合补体组分5 (C5)的抗体或其抗原结合片段的组合。